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Enthalpic Anomeric Effect in 2-Y-1,3-Dithianes (Y = SC_6H_5, $CO_2CH_2CH_3$, and COC_6H_5). Experimental and Theoretical Evaluation. Solvent Effects.

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Abstract. The conformational behavior of 2-substituted 1,3-dithianes **1-3** (Y = SC_6H_5, CO_2Et, COC_6H_5) was studied by ^{13}C NMR spectroscopy in the 228-318 K temperature range. Plots of ln *K versus* 1/T are linear, permitting evaluation of the enthalpic and entropic contributions to the S-C-Y anomeric effects in these heterocycles. *Ab initio* Density Functional Theory calculations in the gas phase and in solution were carried out on slightly simplified models with Y = SCH_3, CO_2CH_3, and $COCH_3$. The influence of the solvent was simulated with a self-consistent reaction field (SCRF) continuum model. The axial preference observed for **1-3** is reproduced by calculation.

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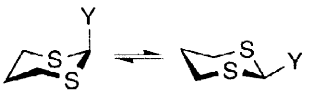
INTRODUCTION

Several years ago, low-temperature (-90 to -100°C) ^{13}C NMR spectra of several mobile 2-substituted 1,3-dithianes afforded the conformational free energy differences summarized in Scheme 1. Sizable anomeric effects (axial preferences) were found, and comparison with the corresponding *A* values suggested that the relative magnitude of the observed anomeric effects is $COC_6H_5 > CO_2CH_3 > SC_6H_5 > SCH_3$.[3,4]



Y	Solvent	T(°C)	$\Delta G^{\circ a}$ (kcal/mol)
SCH_3	CD_2Cl_2	-100	0.64
SC_6H_5	CD_2Cl_2	-100	0.92
CO_2CH_3	CD_2Cl_2	-100	0.83
COC_6H_5	CD_2Cl_2	-90	1.16

[a] Positive ΔG° values indicate axial preference.

Scheme 1

Nevertheless, Booth *et al.*[5,6] have stressed that in studies of the anomeric effect it is the ΔH° values, rather than the ΔG° values, that correlate with the steric, electrostatic, and stereoelectronic interactions of interest. Thus, the present NMR study was undertaken in order to determine the enthalpic and entropic contributions to the conformational equilibria. Interpretation of the experimental data was aided by *ab initio* Density Functional Theory calculations.[7]

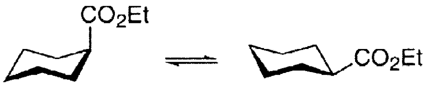
RESULTS AND DISCUSSION

2-Substituted-1,3-dithianes **1**, **2**, and **3** were prepared according to the literature procedure,[3] and ax $\rightleftharpoons$ eq equilibrium data were derived by application of Eliel's equation, eq. 1,

$$K = (\delta_{eq} - \delta)/(\delta - \delta_{ax}) \qquad (1)$$

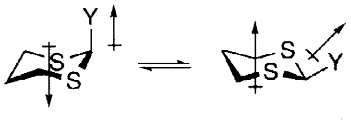
to ^{13}C NMR chemical shifts in the 228-318 K temperature range. ^{13}C NMR data below coalescence ($T \leq 183$ K) afforded the required reference NMR data for the axial and equatorial conformers. Particularly useful were C(2) and C(4,6) since these carbons provided the largest differences in axial *versus* equatorial chemical shifts. Tables 1-3 summarize the relevant data, Figures 1-3 present the corresponding plots of ln K versus 1/T, and the thermodynamic parameters derived from these plots by use of a weighted nonlinear least-squares program are listed in Table 4.

The thermodynamical data collected in Table 4 provide strong evidence that the predominance of the axial conformer in **1-3** is of enthalpic origin. Indeed, $\Delta H°(SC_6H_5)$ varies from +1.35 to +1.51 kcal/mol, $\Delta H°(CO_2Et)$ varies from +1.03 to +2.13 kcal/mol, and $\Delta H°(COC_6H_5)$ varies from +0.63 to +1.67 kcal/mol, depending on the solvent. These large and positive values indicate that the axial conformers are favored on enthalpy terms, which overcome the entropy contributions favoring the equatorial conformers. (Table 4). By contrast, $\Delta H°(ax \rightleftharpoons eq)$ for the substituents of interest in monosustituted cyclohexanes are substantially negative.[8] For example $\Delta H°(CO_2Et)$ in cyclohexane is -1.09 kcal/mol in solvent ethanol (eq 2).[9] Therefore, the present results confirm the existence of a large *enthalpic* S-C-CO$_2$Et anomeric effect in **2**: 1.68 + (0.6 x 1.09) = 2.33 kcal/mol.[10]



(2)

The observed decrease of $\Delta H°$ values in going from toluene ($\varepsilon = 2.4$) to methylene chloride ($\varepsilon = 8.9$) (Table 4) can be explained in terms of the repulsive electrostatic (dipole-dipole) interaction present in equatorial **1-3** (eq. 3). Thus, polar solvents stabilize the more polar (equatorial) conformation, leading to diminished axial preference and smaller $\Delta H°(ax \rightleftharpoons eq)$ values.

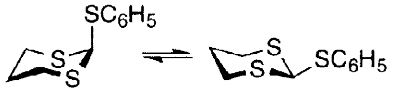


(3)

On the other hand, the positive values of $\Delta S°$ in **1-3** (Table 4) indicate that, as anticipated, the axial substituent must exist largely with the phenyl (in **1** and **3**) or ethoxy group (in **2**) pointing out. By contrast, equatorial substituents are apparently free to fully rotate around the C(2)-X bond.

The following section describes the results of *ab initio* Density Functional Theory (DFT) calculations showing good agreement with experiment in the case of toluene and methylene chloride solvents.

Table 1. Temperature-dependent Variation in the Chemical shift of C(2) and C(4,6) in 2-Phenylthio-1,3-dithiane (**1**), and Estimated Free Energy Differences.



1-ax **1-eq**

Solvent, Toluene-d_8 [δC(2)$_{ax}$ = 48.8; δC(2)$_{eq}$ = 55.6; δC(4,6)$_{ax}$ = 24.1; δC(4,6)$_{eq}$ = 32.5][a]

T(K)	δ(C2)	δC(4,6)	K[b]	$\Delta G°$ (kcal/mol)[c]
318	51.0	26.8	0.46	0.49
303	50.8	26.6	0.41	0.53
298	50.7	26.5	0.40	0.54
288	50.6	26.3	0.36	0.58
273	50.4	26.1	0.31	0.63
258	50.3	25.9	0.27	0.67
243	50.1	25.6	0.22	0.73

Solvent, CD_2Cl_2 [δC(2)$_{ax}$ = 49.5; δC(2)$_{eq}$ = 51.1; δC(4,6)$_{ax}$ = 24.5; δC(4,6)$_{eq}$ = 33.1][a]

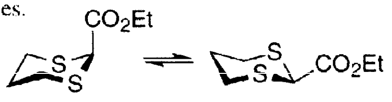
T(K)	δ(C2)	δC(4,6)	K[b]	$\Delta G°$ (kcal/mol)[c]
300	50.8	27.2	0.45	0.48
288	50.7	27.1	0.42	0.50
273	50.6	26.8	0.36	0.55
258	50.4	26.6	0.32	0.59
228	50.1	26.1	0.22	0.69

[a] Chemical Shifts in ppm, δax and δeq recorded at 173 K or 183 K, below coalescence.

[b] When several nuclei are useful for incorporation into Eliel's equation, K values are averaged.

[c] Positive $\Delta G°$ values indicate axial preference.

Table 2. Temperature-dependent Variation in the Chemical shift of C(2) and C(4,6) in 2-carboethoxy-1,3-dithiane (**2**), and Estimated Free Energy Differences.



2-ax **2**-eq

Solvent, Toluene-d_8 [$\delta C(2)_{ax}$ = 37.3; $\delta C(2)_{eq}$ = * ; $\delta C(4,6)_{ax}$ = 24.8; $\delta C(4,6)_{eq}$ = 30.2][a]

T(K)	δ(C2)	δC(4,6)	K[b]	$\Delta G°$ (kcal/mol)[c]
318	39.9	25.9	0.26	0.86
298	39.6	25.7	0.20	0.95
288	39.4	25.7	0.18	0.97
273	39.2	25.5	0.14	1.06
258	38.9	25.4	0.12	1.09
243	38.5	25.3	0.09	1.16

Solvent, CD_2Cl_2 [$\delta C(2)_{ax}$ = 37.4; $\delta C(2)_{eq}$ = 49.5; $\delta C(4,6)_{ax}$ = 25.0; $\delta C(4,6)_{eq}$ = 31.0][a]

T(K)	δ(C2)	δC(4,6)	K[b]	$\Delta G°$ (kcal/mol)[c]
300	40.8	26.6	0.34	0.63
288	40.7	26.5	0.32	0.65
273	40.5	26.4	0.30	0.66
258	40.3	26.3	0.27	0.67
243	40.0	26.2	0.24	0.68
228	39.3	26.0	0.20	0.74

Solvent, CH_3OD [$\delta C(2)_{ax}$ = 37.8; $\delta C(2)_{eq}$ = 48.3; $\delta C(4,6)_{ax}$ = 25.4; $\delta C(4,6)_{eq}$ = 30.0][a]

T(K)	δ(C2)	δC(4,6)	K[b]	$\Delta G°$ (kcal/mol)[c]
308	41.5	27.1	0.54	0.38
300	41.3	27.0	0.50	0.41
288	41.1	26.9	0.45	0.46
273	40.7	26.7	0.38	0.52
258	40.4	26.6	0.32	0.57

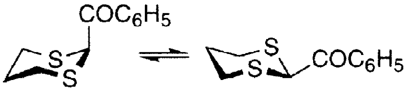
[a] Chemical Shifts in ppm, δax and δeq recorded at 173 K or 183 K, below coalescence.

[b] When several nuclei are useful for incorporation into Eliel's equation, K values are averaged.

[c] Positive $\Delta G°$ values indicate axial preference.

* Obscured by base-line noise.

Table 3. Temperature-dependent Variation in the Chemical shift of C(2) and C(4,6) in 2-Benzoyl-1,3-dithiane (**3**), and Estimated Free Energy Differences.



3-ax **3**-eq

Solvent, Toluene-d_8 [$\delta C(2)_{ax}$ = 39.4; $\delta C(2)_{eq}$ = 55.6; $\delta C(4,6)_{ax}$ = 24.9; $\delta C(4,6)_{eq}$ = 30.5][a]

T(K)	δ(C2)	δC(4,6)	*K*[b]	Δ*G*° (kcal/mol)[c]
318	42.0	26.3	0.19	1.04
303	41.7	26.1	0.17	1.07
300	41.6	26.1	0.17	1.09
288	41.4	26.0	0.14	1.11
273	41.1	25.9	0.12	1.17

Solvent, CD_2Cl_2 [$\delta C(2)_{ax}$ = 40.0; $\delta C(2)_{eq}$ = * ; $\delta C(4,6)_{ax}$ = 24.9; $\delta C(4,6)_{eq}$ = 21.2][a]

T(K)	δ(C2)	δC(4,6)	*K*[b]	Δ*G*° (kcal/mol)[c]
318	44.2	27.3	0.62	0.30
308	44.0	27.3	0.59	0.32
298	43.9	27.2	0.57	0.33
288	43.7	27.1	0.54	0.35
273	43.6	27.1	0.52	0.35
258	43.4	27.0	0.49	0.37

[a] Chemical Shifts in ppm, δax and δeq recorded at 173 K or 183 K, below coalescence.

[b] When several nuclei are useful for incorporation into Eliel's equation, *K* values are averaged.

[c] Positive Δ*G*° values indicate axial preference.

* Obscured by base-line noise.

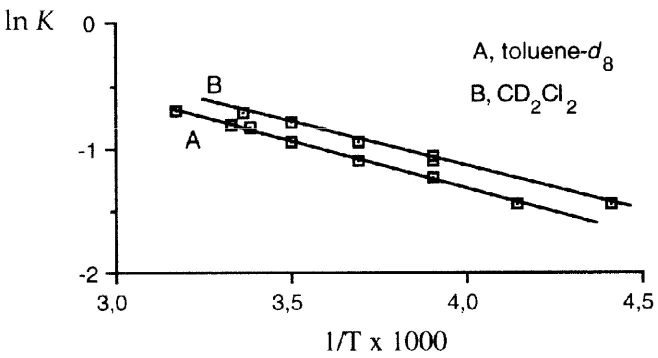


Figure 1 . ln*K* as a function of 1/T for 2-phenylthio-1,3-dithiane (**1**).

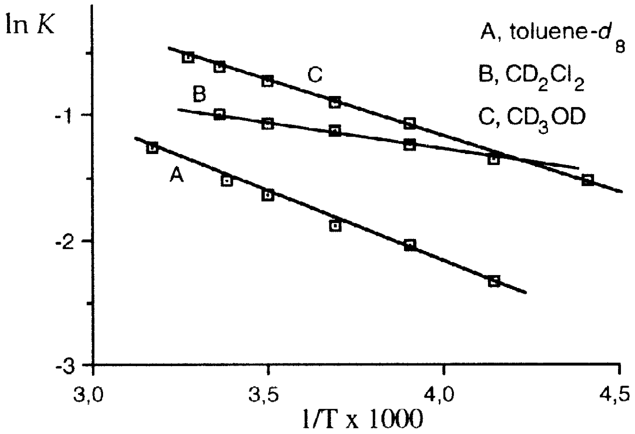


Figure 2. ln*K* as a function of 1/T for 2-carboethoxy-1,3-dithiane (**2**).

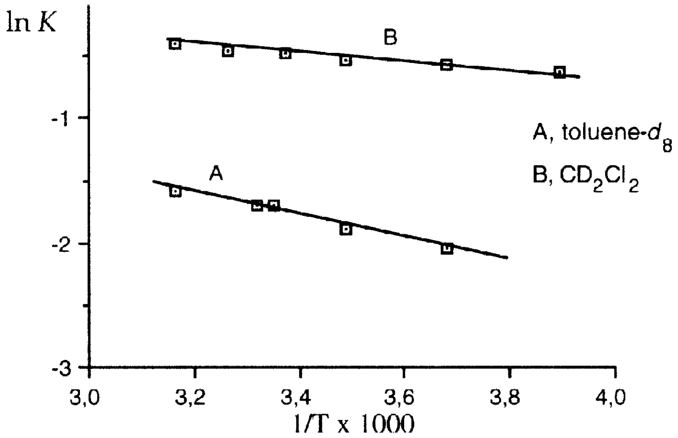


Figure 3. ln*K* as a function of 1/T for 2-benzoyl-1,3-dithiane (**3**).

Table 4. Thermodynamic Parameters for **1**-**3**.

Compd.	Y	Solvent	$\Delta H^{\circ a}$ (kcal/mol)	$\Delta S^{\circ b}$ (cal/mol·K)
1	SC_6H_5	toluene-d_8	1.51 ± 0.4	3.23 ± 0.8
1	SC_6H_5	CD_2Cl_2	1.35 ± 0.5	2.94 ± 0.8
2	CO_2Et	toluene-d_8	2.13 ± 0.4	3.99 ± 0.8
2	CO_2Et	CD_2Cl_2	1.03 ± 0.4	1.32 ± 0.6
2	CO_2Et	CD_3OD	1.68 ± 0.3	4.25 ± 1.0
3	COC_6H_5	toluene-d_8	1.67 ± 0.4	1.92 ± 0.6
3	COC_6H_5	CD_2Cl_2	0.63 ± 0.3	1.01 ± 0.6

[a] Positive values indicate that the axial conformer is favored enthalpically.
[b] Positive values indicate that the equatorial conformer is favored entropically.

Computational Methods and Results

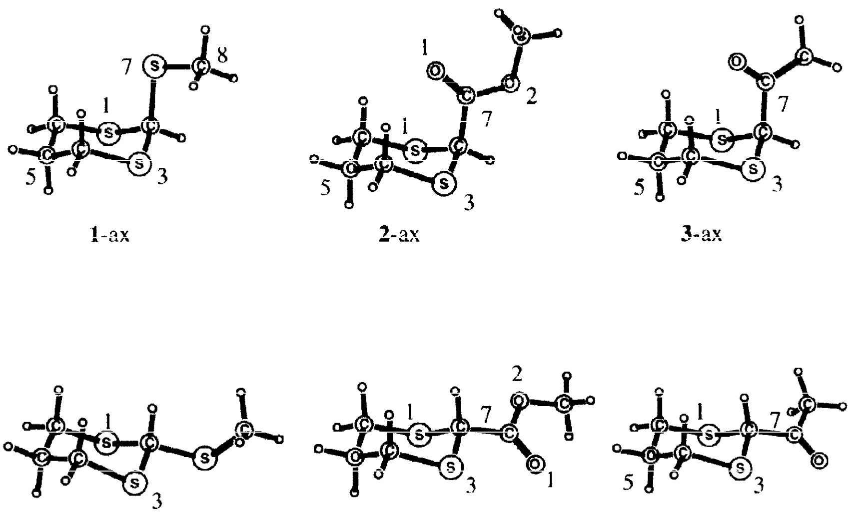
Complete geometry optimization (without symmetry constraints) was performed on the complete structures of 2-methylthio (as model of phenyl substituted **1**), 2-carbomethoxy- (as model of carboethoxy analogue **2**), and 2-acetyl-1,3-dithiane (as model of 2-benzoyl analogue **3**) at the *ab initio* level and within the frame of DFT at the Becke3LYP/6-31G(*d,p*) level with the Gaussian 92 program (G92).[11]

The Becke3LYP hybrid functional defines the exchange functional as a linear combination of Hartree-Fock, local, and gradient-corrected exchange terms.[12] The exchange functional is combined with a local and gradient-corrected correlation functional. The correlation functional used is actually $CE_C^{LYP} + (1 - C)E_C^{VWN}$, where LYP is the correlation functional of Lee, Yang, and Parr,[13] which includes both local and nonlocal terms, and VWN is the Vosko, Wilk, and Nusair 1980 correlation functional fitting the RPA solution to the uniform gas, often referred to as local spin density (LSD) correlation.[14] VWN is used to provide the excess local correlation required, since LYP contains a local term essentially equivalent to VWN.[12] The orbital basis set used was 6-31G(*d,p*), which adds polarization functions to heavy atoms and hydrogens.

The role of the solvent has been taken into account by means of a general self-consistent reaction field (SCRF) model proposed for quantum chemical computations on solvated molecules.[15] In this model, the solvent is represented by an infinite dielectric continuum, characterized by its dielectric relative permittivity ε, in which a cavity is created and the solute is placed in it. The charge distribution of the solute polarizes the continuum which in turn creates an electrostatic field inside the cavity. A spherical cavity of fixed radius a_0 has been used.[16]

Figure 4 shows the *ab initio* DFT calculated most stable structures for the axial and equatorial conformer 2-Y-1,3-dithianes (Y = SCH_3, CO_2CH_3, $COCH_3$) and Table 5 list the energetic results, and Tables 6-8 summarize the calculated structural data in solvents of increasing polarity.

It is appreciated (Figure 4) that both in the axial and equatorial isomers, the substituent (Y = SCH_3, CO_2CH_3, COC_6H_5) adopts less congested positions, pointing outside the dithiane ring. By contrast, from the results of PM3 semiempirical calculations, Aviyente and coworkers [7] conclude that the conformer of minimum energy in axial 2-methylthio-1,3-dithiane presents the methyl group inside the ring.



1-ax **2**-ax **3**-ax

1-eq **2**-eq **3**-eq

Figure 4. The *ab initio* DFT calculated most stable axial and equatorial conformers of 2-Y-1,3-dithianes.

Table 5. Calculated Total and Relative Energies for Axial and Equatorial 2-Methylthio-, 2-Carbomethoxy-, and 2-Acetyl-1,3-dithiane in Solvents of Different Polarity.

Y = SCH_3	axial (Hartrees)	equatorial (Hartrees)	ΔE (kcal/mol)	ΔH_{exptl} (kcal/mol)
$\varepsilon = 1$	-1391.13176	-1391.12819	2.24	
$\varepsilon = 2.4$	-1391.13202	-1391.12898	1.91	1.51
$\varepsilon = 8.9$	-1391.13226	-1391.12966	1.63	1.35
$\varepsilon = 20.6$	-1391.13232	-1391.12986	1.54	2.68
$\varepsilon = 32.7$	-1391.13234	-1391.12992	1.52	
Y = CO_2CH_3				
$\varepsilon = 1$	-1181.50637	-1391.12819	4.10	
$\varepsilon = 2.4$	-1181.50647	-1391.12898	3.77	2.13
$\varepsilon = 8.9$	-1181.50656	-1391.12966	3.46	1.03
$\varepsilon = 20.6$	-1181.50658	-1391.12986	3.38	1.42
$\varepsilon = 32.7$	-1181.50659	-1391.12992	3.35	1.68
Y = $COCH_3$				
$\varepsilon = 1$	-1106.27561	-1106.27037	3.29	
$\varepsilon = 2.4$	-1106.27564	-1106.27160	2.54	1.67
$\varepsilon = 8.9$	-1106.27567	-1106.27273	1.84	0.63
$\varepsilon = 20.6$	-1106.27567	-1106.27304	1.65	0.72
$\varepsilon = 32.7$	-1106.27568	-1106.37313	1.60	

The total energy of the rotamers of minimum energy in the axial and equatorial conformers is compared in Table 5. In agreement with experiment, the axial conformers are estimated to be more stable than the equatorial. Calculation seems to reproduce the experimentally observed decrease of S-C-Y anomeric effect (i.e., diminished axial preference) in going from the less polar solvent toluene to the more polar methylene chloride.

The structural data collected in Tables 6-8 are useful in the analysis of precise bond length and angle variations with substitution. Interestingly, these structural parameters are essentially unaffected by the change in the dielectric constant of the medium.

Table 6. Selected Structural data for Axial 2-Methylthio-1,3-dithiane in Solvents of Different Polarity.

	$\varepsilon = 1.0$		$\varepsilon = 2.4$		$\varepsilon = 8.9$		$\varepsilon = 20.6$		$\varepsilon = 32.7$	
	ax.	eq.	ax.	eq.	ax.	eq.	ax.	eq.	ax.	eq.
S_1-C_2	1.835	1.839	1.835	1.839	1.835	1.839	1.836	1.839	1.836	1.839
C_2-S_3	1.838	1.842	1.837	1.842	1.837	1.841	1.836	1.841	1.836	1.841
S_3-C_4	1.836	1.840	1.836	1.840	1.836	1.841	1.837	1.841	1.837	1.841
C_2-S_7	1.851	1.831	1.851	1.832	1.851	1.832	1.851	1.832	1.851	1.832
S_7-C_8	1.828	1.829	1.828	1.829	1.828	1.829	1.828	1.829	1.828	1.829
S_1-C_2-S_3	114.0	114.5	114.0	114.4	114.1	114.4	114.2	114.4	114.2	114.4
C_2-S_3-C_4	100.2	99.2	100.2	99.1	100.3	98.9	100.3	98.9	100.3	98.9
S_3-C_4-C_5	114.1	113.7	114.1	113.7	114.0	113.7	114.0	113.7	114.0	113.7
S_1-C_2-S_7	108.7	107.3	108.5	107.5	108.4	107.7	108.4	107.7	108.4	107.7
C_2-S_7-C_8	101.4	99.6	101.5	99.5	101.6	99.4	101.6	99.4	101.6	99.4
S_1-C_2-S_3-C_4	57.0	59.5	57.1	59.9	57.0	60.2	57.0	60.3	57.0	60.3
C_2-S_3-C_4-C_5	58.8	59.2	58.8	59.3	58.8	59.4	58.7	59.4	58.7	59.4
S_1-C_2-S_7-C_8	175.4	152.3	175.7	152.4	176.5	152.6	176.7	152.6	176.8	152.6
C_4-S_3-C_2-S_7	70.4	179.8	70.3	179.1	70.4	178.6	70.4	179.4	70.4	178.4

Experimental Section

For a description of general laboratory manipulations, see ref. 17. 2-Substituted 1,3-dithianes **1-3** were prepared as described in reference 3. Variable temperature ^{13}C NMR spectra were recorded on a Jeol GSX-270 (67.8 MHz) spectrometer. The temperature indicator was calibrated by using the known C-H/O-H shift for assessment of temperature.

Table 7. Selected Structural data for Axial 2-Carboethoxy-1,3-dithiane in Solvents of Different Polarity.

	$\varepsilon = 1.0$		$\varepsilon = 2.4$		$\varepsilon = 8.9$		$\varepsilon = 20.6$		$\varepsilon = 32.7$	
	ax.	eq.	ax.	eq.	ax.	eq.	ax.	eq.	ax.	eq.
S_1-C_2	1.838	1.850	1.838	1.850	1.838	1.850	1.838	1.850	1.838	1.850
C_2-S_3	1.838	1.832	1.838	1.838	1.838	1.832	1.838	1.832	1.838	1.832
S_3-C_4	1.840	1.837	1.841	1.838	1.841	1.839	1.841	1.839	1.841	1.839
C_2-C_7	1.521	1.525	1.521	1.525	1.521	1.524	1.521	1.523	1.821	1.523
C_7-O_1	1.215	1.209	1.215	1.210	1.215	1.210	1.215	1.210	1.215	1.210
C_7-O_2	1.347	1.345	1.346	1.345	1.346	1.345	1.346	1.345	1.346	1.345
O-CH_3	1.440	1.440	1.441	1.439	1.441	1.438	1.441	1.438	1.441	1.438
S_1-C_2-S_3	115.0	114.8	115.0	114.7	114.9	114.5	114.9	114.4	114.9	114.4
C_2-S_3-C_4	100.5	97.9	100.5	97.7	100.5	97.5	100.5	97.4	100.5	97.4
S_3-C_4-C_5	114.2	114.6	114.1	114.6	114.2	114.6	114.2	114.6	114.2	114.6
S_1-C_2-C_7	111.2	109.2	111.2	109.1	111.2	109.0	111.2	109.0	111.2	109.0
C_2-C_7-O_1	125.6	124.9	125.6	125.0	125.5	125.3	125.5	125.4	125.5	125.4
C_2-C_7-O_2	110.6	110.7	100.7	110.5	110.7	110.3	110.7	110.3	110.7	110.3
S_1-C_2-S_3-C_4	55.5	60.4	55.6	60.9	55.7	61.6	55.8	61.8	55.8	61.8
C_2-S_3-C_4-C_5	57.0	59.5	57.0	59.6	57.0	59.6	57.0	59.6	57.0	59.6
S_1-C_2-C_7-O_1	64.9	116.8	64.6	113.5	64.8	108.8	64.7	106.8	64.7	106.8
S_1-C_2-C_7-O_2	115.1	63.9	115.4	67.0	115.3	72.5	115.3	73.3	115.3	73.3

Table 8. Selected Structural data for Axial 2-Acetyl-1,3-dithiane in Solvents of Different Polarity.

	$\varepsilon = 1.0$		$\varepsilon = 2.4$		$\varepsilon = 8.9$		$\varepsilon = 20.6$		$\varepsilon = 32.7$	
	ax.	eq.	ax.	eq.	ax.	eq.	ax.	eq.	ax.	eq.
S_1-C_2	1.848	1.851	1.848	1.851	1.848	1.852	1.848	1.852	1.848	1.852
C_2-S_3	1.830	1.830	1.830	1.830	1.830	1.831	1.830	1.831	1.830	1.831
S_3-C_4	1.842	1.838	1.842	1.839	1.842	1.840	1.842	1.840	1.842	1.841
C_2-C_7	1.534	1.537	1.534	1.536	1.534	1.534	1.534	1.534	1.534	1.534
C_7-CH_3	1.516	1.516	1.516	1.515	1.516	1.515	1.516	1.515	1.516	1.515
C_7-O	15.18	1.213	1.218	1.214	1.218	1.215	1.218	1.215	1.218	1.215
S_1-C_2-S_3	115.1	114.7	115.0	114.5	115.1	114.2	115.1	114.2	115.1	114.2
C_2-S_3-C_4	101.3	97.8	101.3	97.6	101.3	97.4	101.3	97.4	101.3	97.3
S_3-C_4-C_5	114.3	114.9	114.3	114.9	114.3	114.8	114.3	114.8	114.3	114.8
S_1-C_2-C_7	107.7	109.6	107.6	109.5	107.5	109.1	107.5	109.1	107.5	109.1
C_2-C_7-CH_3	115.8	117.2	115.8	117.0	115.8	116.6	115.8	116.6	115.8	116.6
S_1-C_2-S_3-C_4	54.9	60.3	54.9	60.8	54.7	61.7	54.7	61.7	54.7	61.8
C_2-S_3-C_4-C_5	55.1	59.3	55.1	59.4	55.0	59.6	55.0	59.6	55.0	59.6
S_1-C_2-C_7-O_1	82.5	124.0	83.4	121.1	84.1	114.4	84.2	114.1	84.3	113.7

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REFERENCES

[1] Instituto Politécnico Nacional.

[2] Universidad Nacional Autónoma de México.

[3] Juaristi, E.; Tapia, J.; Méndez, R. *Tetrahedron* **1986**, *42*, 1253-1264.

[4] Juaristi, E.; *Acc. Chem. Res.* **1989**, *22*, 357-364.

[5] Booth, H.; Khedhair, K.A. *J. Chem. Soc., Chem. Commun.* **1985**, 467-468. Booth, H.; Khedhair, K.A.; Readshaw, S.A. *Tetrahedron*, **1987**, *43*, 4699-4723.

[6] See, also: (a) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, **1995**. (b) Juaristi, E.; González, E.A.; Pinto, B.M.; Johnston, B.D.; Nagelkerke, R. *J. Am. Chem. Soc.* **1989**, *111*, 6745-6749. (c) Juaristi, E.; Cuevas, G. *Tetrahedron Lett.* **1992**, *33*, 2271-2274.

[7] Semiempirical (PM3) molecular orbital calculations for axial *versus* equatorial energies for **1-4** have recently been reported by Aviyente, *et al.*: Selcuki, C.; Aviyente, V.; Varnali, T.; López Rodríguez, R. *J. Mol. Struct. (Theochem)* **1997**, *418*, 41-47.

[8] Bushweller, C.H. In *Conformational Behavior* of *Six-Membered Rings*, Juaristi, E., Ed.; VCH Publishers: New York, **1995**; Chapter 2.

[9] (a) Ouellette, R.J.; Booth, G.E. *J. Org. Chem.* **1966**, *31*, 587-588. (b) Allinger, N.L.; Freiberg, L.A. *J. Org. Chem.* **1966**, *31*, 894 - 897.

[10] Consideration of the relative steric requirements of an axial substituent at C(2) of the 1,3-dithiane *vis a vis* in cyclohexane suggests that the effective size of the carboethoxy group in **2** should be *ca.* 60% of 1.09 kcal/mol: see, ref. 6a, section 7.3.3.

[11] Gaussian 92/DFT, Revision G.2. M.J. Frisch, G.W. Trucks, H.B. Schlegel, P.M.W. Gill, B.G. Johnson, M.W. Wong, J.B. Foresman, M.A. Robb, M. Head-Gordon, E.S. Replogle, R. Gomperts, J.L. Andres, K. Raghavachari, J.S. Binkley, C. Gonzalez, R.L. Martin, D.J. Fox, D.J. Defrees, J. Baker, J.J.P. Stewart, J.A. Pople, Gaussian, Inc., Pittsburgh PA, **1993**.

[12] Stephens, P.J.; Devlin, F.J.; Chabalowski, C.F.; Frisch, M.J. *J. Phys. Chem.* **1994**, *98*, 11623- 11627. Becke, A.D. *J. Chem. Phys.* **1993**, *98*, 1372-1377 , 5648-5652.

[13] Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev.* **1988**, *B37*, 785-789. Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200-206.

[14] Vosko, S.H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200-1211.

[15] Rivail, J.L.; Rinaldi, D. *Chem. Phys.* **1976**, *18*, 233-242

[16] (a) Onsager, L. *J. Am. Chem. Soc.* **1938**, *60*, 1486-1489. (b) Wong, M.W.; Frisch, M.; Wiberg, K.B. *J. Am. Chem. Soc.* **1991**, *113*, 4776-4782.

[17] Ordóñez, M.; Juaristi, E. *Tetrahedron*. **1998**, *54*, 1375-1380.