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STUDY OF THE ANOMERIC EFFECT IN 2-SUBSTITUTED 1,3-DITHIANES[1]

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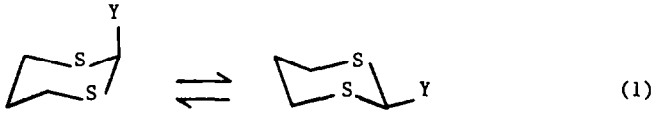
Abstract. The conformational analysis of several 2-substituted 1,3-dithianes made possible the evaluation of S-C-Y anomeric interactions, where Y = SCH_3, SC_6H_5, CO_2CH_3, COC_6H_5, CO_2H and $N(CH_3)_2$. The relative magnitude of the effects observed for these groups [$\Delta G°_{dithiane}(Y) - \Delta G°_{cyclohexane}(Y)$] can be explained in terms of the combined influence of dipole/dipole and two-electron stabilizing interactions (stereoelectronic effect).

The tendency of electronegative substituents to assume the axial rather than equatorial orientation at C(1) of a pyranoid ring (i.e., the anomeric effect) was discovered more than 25 years ago.[2] This conformational effect has been observed in many other heterocyclic systems,[3] and its more general chemical implications have been realized.[4,5] Nevertheless, and despite the recent appearance of several reviews,[6,7] the nature of the phenomenon is not well understood. In this respect, while much work has been dedicated to the study of models possessing oxygen, much less effort has been devoted to systems containing second-row elements.[8,9]

Herein we report the conformational analysis of certain 2-substituted 1,3-dithianes [Eqn. 1; Y = SCH_3, SC_6H_5, CO_2H, CO_2CH_3, COC_6H_5, $N(CH_3)_2$]; these results complement those obtained in thiane rings[13,14] [Eqn. 2; Y = Cl, OR, SR] and 1,3,5-trithiane rings[15] [Eqn. 3; Y = CO_2H, CO_2CH_3, SCH_3, SC_6H_5, $OCOC_6H_5$], and reveal the interplay of steric, electrostatic and stereoelectronic interactions.



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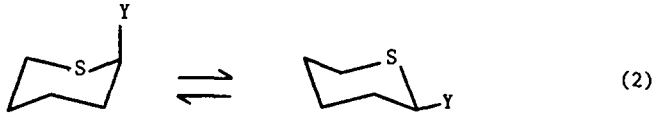

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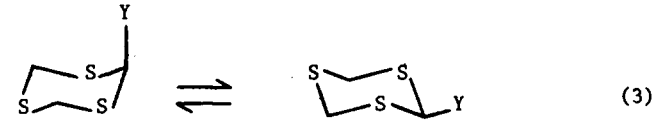

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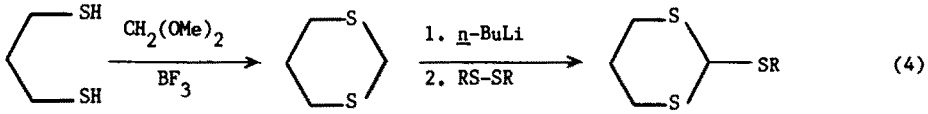
RESULTS AND DISCUSSION

A. Preparation of the 2-Substituted 1,3-Dithianes.

2-Methylthio- (3) and 2-phenylthio-1,3-dithiane (4) were prepared by the slow addition of the lithium salt of 1,3-dithiane[16] to two equivalents of methyl or phenyl disulfide (Eqn. 4).



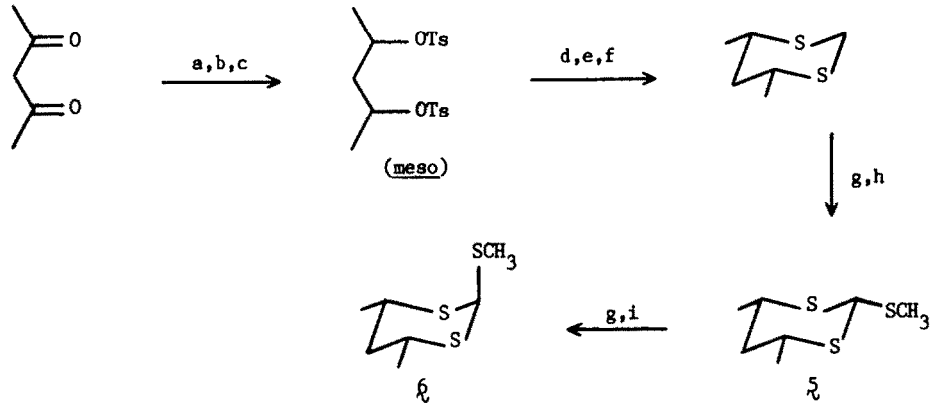
(4)

3: R = CH_3

4: R = C_6H_5

The conformationally rigid models 5 and 6 were similarly prepared from cis-4,6-dimethyl-1,3-dithiane[17] making use of the highly stereoselective reaction of 2-lithio-1,3-dithianes with electrophiles (Scheme I).[18]

SCHEME I[a]

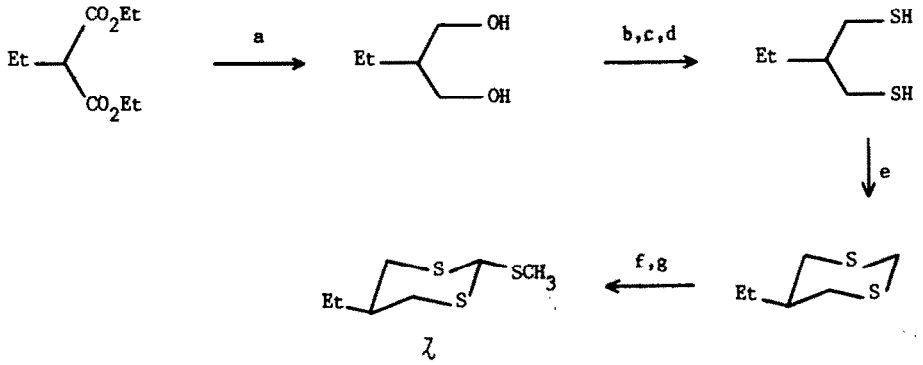


6 5

[a](a) $NaBH_4$. (b) p-TsCl (2 equiv.), pyridine. (c) Fractional crystallization. (d) AcS^-K^+ (2 equiv.), EtOH. (e) $(CH_2NH_2)_2$. (f) $CH_2(OCH_3)_2$, $BF_3 \cdot Et_2O$. (g) n-BuLi, THF. (h) $(MeS)_2$ (excess). (i) NH_4Cl, H_2O.

trans-5-Ethyl-2-methylthio-1,3-dithiane (7) was similarly obtained starting with 2-ethyl-1,3-propanediol (Scheme II). The ethyl group in 7 serves as a counterpoise group in the determination of conformational equilibria (vide infra).

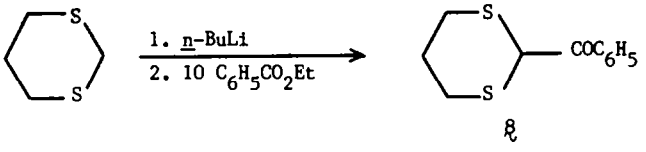
SCHEME II[a]



7

[a](a) $LiAlH_4$, Et_2O; (b) p-TsCl (2 equiv), pyridine; (c) AcS^-K^+ (2 equiv), EtOH; (d) $(CH_2NH_2)_2$; (e) $CH_2(OCH_3)_2$, $BF_3 \cdot OEt_2$; (f) n-BuLi, THF; -78°C; (g) $(CH_3S)_2$.

2-Benzoyl-1,3-dithiane (8) was prepared by the reaction of 2-[1,3]dithianyllithium with excess ethyl benzoate (Eqn. 5),[19] and 2-carbomethoxy-1,3-dithiane (9) was made by the methylation of carboxylic acid 10 (Eqn. 6).



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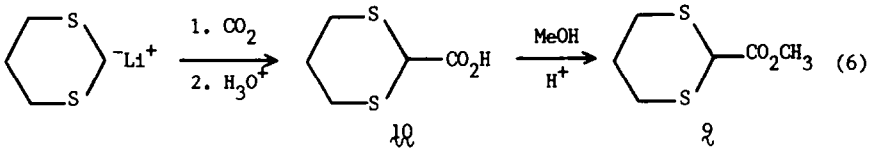

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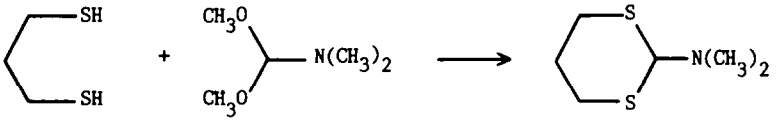
Finally, 2-N,N-dimethylamino-1,3-dithiane (11) was prepared by condensation of 1,3-propanedithiol with N,N-dimethylformamide dimethyl acetal (Eqn. 7).



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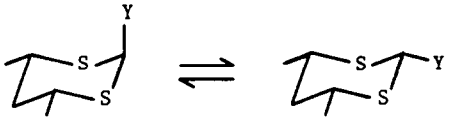
B. Determination of the Conformational Equilibria.

The low-temperature (-90° to -100°C) C-13 NMR spectra of mobile dithianes 3, 4, 8-10 give rise to two sets of signals, which correspond to the axial and equatorial conformers. The assignment of the spectra was based on anticipated substituent shifts.[20] Table I lists the chemical shifts for 3, 4, 8-11 at various temperatures and in different solvents.

Integration of the peak areas for each of the conformers in the spectra recorded well below the coalescence temperature afforded the equilibrium constants, K,[21] and the conformational free energy differences, $\Delta G° = -RT \ln K$, which are summarized in Table II. Sizable anomeric effects (axial preferences) were apparent for 3 (Y = SCH_3), 4 (Y = SC_6H_5), 8 (Y = COC_6H_5), 9 (Y = CO_2CH_3) and 10 (Y = CO_2H).

The SCH_3 and CO_2CH_3 values agree well with those obtained by Hartmann in the chemical equilibration of the anancomeric models shown in Eqn. 8:[22] $\Delta G°_{30°C}(SCH_3) = 0.73 \pm 0.02$ kcal/mol in CCl_4; $\Delta G°_{23°C}(CO_2CH_3) = 0.81 \pm 0.02$ kcal/mol in $CDCl_3$.



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By contrast, the room-temperature C-13 NMR data for aminodithiane 11 (Table I) shows that this compound exists in a highly predominant (≥95%) equatorial conformation. In particular, the chemical shift for C(4,6) is slightly downfield relative to that in the parent system: 29.86 ppm;[20] the absence of any shielding γ-gauche effect suggests that the conformation with an axial dimethylamino group is not significantly populated.[23]

C. Relative Magnitude of the Anomeric Effect.

The magnitude of the anomeric effect is usually defined as the difference of the free energy difference for the equilibrium studied and the conformational energy for the same substituent in cyclohexane.[24] There is, however, a well recognized difficulty with evaluation in this fashion:[25] the steric requirements of a group in the anomeric position of the heterocycle are different to those encountered in a cyclohexane. In the system at hand, because of the long C-S bonds, the

Table I. Room and Low Temperature C-13 Signal Assignments in Compounds 3, 4, 8-11 (ppm from TMS).

Compound	Solvent	C(2)	C(4,6)	C(5)	C_{ipso}	C_{ortho}	C_{meta}	C_{para}	Other
3	$CDCl_3$[a]	48.06	26.58	25.19	---	---	---	---	$S\underline{C}H_3$: 16.75
3	CD_2Cl_2[a]	48.64	27.20	25.72	---	---	---	---	16.89
3ax	CD_2Cl_2[b]	47.52	24.32	25.67	---	---	---	---	18.66
3eq	CD_2Cl_2[b]	c	32.63	25.67	---	---	---	---	12.90
3	CD_3NO_2[a]	49.25	28.16	26.31	---	---	---	---	16.68
3ax	CD_3COCD_3/CD_3OD (1:1)[d]	c	24.42	26.36	---	---	---	---	17.98
3eq	CD_3COCD_3/CD_3OD (1:1)[d]	c	32.30	26.36	---	---	---	---	12.50
4	$CDCl_3$[a]	50.35	26.66	25.00	134.14	128.60	132.98	127.94	---
4	CD_2Cl_2[a]	50.95	27.33	25.62	135.02	129.30	133.75	128.65	---
4ax	CD_2Cl_2[b]	49.48	24.47	25.48	135.66	129.45	133.67	128.76	---
4eq	CD_2Cl_2[b]	51.04	33.02	25.48	135.66	129.45	133.67	128.76	---
4	CD_3NO_2[a]	51.13	27.99	26.14	135.71	130.18	134.13	129.38	---
4ax	CD_3COCD_3/CD_3OD (1:1)[d]	c	24.65	26.25	136.53	129.99	133.37	128.71	---
4eq	CD_3COCD_3/CD_3OD (1:1)[d]	c	32.80	26.25	136.53	129.99	133.37	128.71	---
4	CD_3SOCD_3[a]	48.73	26.08	24.68	134.05	128.54	131.71	127.36	---
8	$C_6D_5CD_3$[a]	41.59	26.11	25.51	f	f	f	f	$\underline{C}O$: e
9	$CDCl_3$[a]	39.78	25.94	25.00	---	---	---	---	$\underline{C}O_2$: 169.84[g]
9	CD_2Cl_2[a]	40.73	26.60	25.54	---	---	---	---	$\underline{C}O_2$: 170.60 $\underline{C}H_3$: 52.85
9ax	CD_2Cl_2[b]	37.76	25.17	24.95	---	---	---	---	$\underline{C}O_2$: 171.00 $\underline{C}H_3$: 53.56
9eq	CD_2Cl_2[b]	49.18	30.93	24.95	---	---	---	---	$\underline{C}O_2$: 169.17 $\underline{C}H_3$: c
9	CD_3NO_2[a]	42.06	27.45	26.13	---	---	---	---	$\underline{C}O_2$: 171.53 $\underline{C}H_3$: 53.33
9ax	CD_3COCD_3[d]	36.88	24.84	25.33	---	---	---	---	$\underline{C}O_2$: 171.29 $\underline{C}H_3$: 52.88
9eq	CD_3COCD_3[d]	48.87	c	25.33	---	---	---	---	$\underline{C}O_2$: 169.35 $\underline{C}H_3$: 53.63
9ax	CD_3COCD_3/CD_3OD (1:1)[d]	c	25.15	25.63	---	---	---	---	$\underline{C}O_2$: 171.69 $\underline{C}H_3$: 52.98
9eq	CD_3COCD_3/CD_3OD (1:1)[d]	c	c	25.63	---	---	---	---	$\underline{C}O_2$: 169.80 $\underline{C}H_3$: 53.74
10ax	CD_2Cl_2[d]	36.90	24.20	23.80	---	---	---	---	$\underline{C}O_2$: e
11	$CDCl_3$[a]	74.96	30.11	25.65	---	---	---	---	41.35[h]

[a]At room temperature. [b]At -100°C. [c]Sample signal masked by solvent signal. [d]At -90°C. [e]Sample signal masked by baseline noise. [f]Overlapped by toluene-$\underline{d}_8$ peaks. [g]$\underline{C}H_3$: 52.43 ppm. [h]$N(\underline{C}H_3)_2$.

steric congestion of an axial 2-substituent in 1,3-dithiane should be smaller to that of the same substituent in cyclohexane; therefore, the magnitude of the anomeric effect tends to be overestimated. One way out of this difficulty would be through evaluation of the steric part of the interaction by force-field calculation,[26] but unfortunately, such calculations have so far had limited success for oxygen- and sulfur-containing saturated heterocycles. Nevertheless, in order to esti-

Table II. Low-temperature Conformational Equilibria of 2-Substituted 1,3-Dithianes (Eqn. 1); by Integration of C-13 NMR Signal Areas below Coalescence.

Substituent	Solvent	Temperature (°C)	K	ΔG° (kcal/mol)
SCH_3	Toluene-$\underline{d}_8$	-100[a]	9.3	0.77
	CD_2Cl_2	-100[a]	6.5	0.64
	$CD_3OD/(CD_3)_2CO$ (1:1)	- 90[a]	5.7	0.63
SC_6H_5	CD_2Cl_2	-100[b]	14.7	0.92
	$CD_3OD/(CD_3)_2CO$ (1:1)	- 90[c]	10.4	0.85
CO_2CH_3[i]	CD_2Cl_2	-100[d]	11.1	0.83
	$(CD_3)_2CO$	- 90[e]	12.6	0.92
	$CD_3OD/(CD_3)_2CO$ (1:1)	- 90[f]	19.9	1.09
	CD_3OD	- 90[g]	22.3	1.13
COC_6H_5	Toluene-$\underline{d}_8$	- 90[g]	24.0	1.16
CO_2H	CD_2Cl_2	- 90[h]	$\geq$32.3	$\geq$1.26

[a]C(4,6) and C(Me) considered; [b]C(2) and C(4,6) considered; [c]C(4,6) considered; [d]C(2), C(4,6) and C(C=O) considered; [e]C(2), C(C=O) and C(Me) considered; [f]C(C=O) and C(Me) considered; [g]By H-1 NMR: H(2) considered; [h]no signals for the equatorial conformer were detected ($\leq$3%); [i]Arai, Iwamura and Oki[15a] have done a low-temperature NMR measurement of 2-carbomethoxy-1,3-dithiane and get 0.87 kcal/mol (in favor of the axial conformer) in acetone-$\underline{d}_6/CDCl_3$ and 1.15 kcal/mol in $CS_2/CDCl_3$: the solvent effect seems to be in the opposite direction.

mate the relative magnitude of the anomeric effects present in 3, 4, 8-11, the usual convention[24] was followed. Table III summarizes the calculated values for the anomeric effect in solvent CD_2Cl_2 (with the exception of 8, which was measured in toluene-$\underline{d}_8$, and 11, which was recorded in $CDCl_3$).[32]

The relative magnitude of the anomeric effects observed are (in order of decreasing importance): $CO_2H > COC_6H_5 > CO_2CH_3 > SC_6H_5 > SCH_3 >>> N(CH_3)_2$ ($\leq$ 0). This is a tentative sequence since Table III compares ΔG° values for 2-substituted-1,3-dithianes obtained at low temperature (-90 or -100°C) with ΔG° values for substituted cyclohexanes obtained by measurements at or near +25°C; non-zero ΔS° contributions to ΔG°'s would alter the data, perhaps substantially.[35]

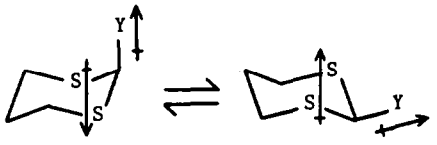
Table III. Magnitude of the Anomeric Effect in 2-Substituted 1,3-Dithianes (Eqn. 1), in kcal/mol.

Group	ΔG°(dithiane)[a]	-ΔG°(cyclohexane)	Anomeric Effect[h]
SCH_3	0.64	1.00[b]	1.64
SC_6H_5	0.92	ca 1.1[c]	ca 2.02
CO_2CH_3	0.83	1.27[d]	2.10
COC_6H_5	1.16	ca 1.3[e]	ca 2.46
CO_2H	$\geq$1.26	1.39[f]	$\geq$2.65
$N(CH_3)_2$	ca -2.0	2.1[g]	ca 0

[a]In CD_2Cl_2 except for 8 (Y = COC_6H_5), which was measured in CD_3OD and 11 [Y = $N(CH_3)_2$], which was recorded in $CDCl_3$. [b]Reference 27. [c]Estimated to be ca. 0.1 kcal/mol greater than that for SCH_3: Reference 28. [d]Reference 29. [e]Assuming a conformational energy close to that of COCl: Reference 30. [f]Reference 30. [g]Reference 31. [h]Defined as in Text.

D. Interpretation of the Results: Dipole/dipole Interaction.

According to the interpretation of the anomeric effect given by Edward,[36] electrostatic dipole/dipole repulsion should disfavor the equatorial conformer, while dipole/dipole attraction favors the axial conformer in the equilibria depicted by Eqn. 9.[38] If dipole/dipole interactions



(9)

were dominant in the conformational equilibria of 3, 4, 8-11, it would be expected that the contribution of the equatorial form should increase with increasing dielectric constant of the medium.[40] The low-temperature $\Delta G°$ measurements summarized in Table II are in agreement with this prediction for the case of Y = SCH_3 and Y = SC_6H_5; for example, the ratio 3-ax/3-eq increases in going from $CD_3OD/(CD_3)_2CO$ (1:1 $\varepsilon \geq 20.7$; K = 5.71) to CD_2Cl_2 (ε = 2.4; K = 8.22).[41] An opposite solvent effect is, however, observed for Y = CO_2CH_3: the 9-ax/9-eq ratio increases with increasing solvent polarity (Table II). In view of this conflicting information, the solvent effect on the conformational behavior of 3, 8 and 9 was also studied at room temperature.

Solvent effects on the magnitude of the anomeric effect for the methylthio group were determined by proton NMR spectroscopic application of Eliel's equation[42] [$K = (\delta_{eq} - \delta_{mobile}) / (\delta_{mobile} - \delta_{ax})$] to the mobile trans-5-ethyl-2-methylthio-1,3-dithiane (7) and the anancomeric models 5 and 6. The ethyl group in 7 serves as a counterpoise,[43] so that equilibrium lies close to unity and permits a more precise calculation of $\Delta G°$ than would be possible in 3. For 7, the most convenient signals to incorporate in Eliel's equation are those for $SC\underline{H}_3$ since they are sharp singlets and also provide an adequate spread of chemical shifts ($\delta_{eq} - \delta_{ax}$) so as to make the calculations reliable. Table IV summarizes the results in four solvents of different polarity. Although the precision of these $\Delta G°$ values is only of the order of $\pm$ 0.1 kcal/mol, the observed trend clearly confirms the expected[40] solvent effect; i.e., a stronger anomeric effect in the less polar media.[44,45]

Table IV. Solvent Effect on the Conformational Energies ($\Delta G°$) of the Thiomethyl Group in 7.[a]

Solvent	Dielectric Constant (ε)[b]	$\Delta G°$ (kcal/mol)[c]
CCl_4	2.2	0.95
$CDCl_3$	4.7	0.88
DMF-$\underline{d}_7$	36.7	0.77
DMSO-$\underline{d}_6$	48.9	0.65

[a]At 39°C. [b]For protiated solvents. [c]Estimated standard deviation: $\pm$ 0.1 kcal/mol.

In the course of assignment of several H-1 NMR spectra of 1,3-dithianes with polar substituents at C-2 we observed that the chemical shift difference between axial and equatorial protons at C(4,6) increases with increasing population of the axial conformer.[8a,46] Table V lists $\Delta\delta_{ax/eq}(H_{4,6})$ for 4, 8 and 9 in different solvents. The results indicate that all three systems behave as expected:[40] smaller amounts of the axial conformer in more polar media. For 9, there is thus a marked contrast with the low-temperature behavior which is difficult to explain. However, on the reasonable assumption that the axial conformer of 9 presents a smaller molar volume than

Table V. Solvent Effect on the Chemical Shift Difference ($\Delta\delta_{ax/eq}$) for the C(4,6) Methylene Protons in 4, 8 and 9, in ppm.

Solvent (ε)	Δδ for 4	Δδ for 8	Δδ for 9
CCl_4 (2.2)	0.72	0.92	1.00
$CDCl_3$ (4.7)	0.65	0.71	0.80
CD_3COCD_3 (20.7)	0.57	0.50	0.69
CD_3OD (32.6)	0.51-0.59[a]	—	—
DMF-d_7 (36.7)	—	0.41	—
CD_3CN (37.5)	—	0.44	0.62
DMSO-d_6 (48.9)	0.40	0.32	0.47

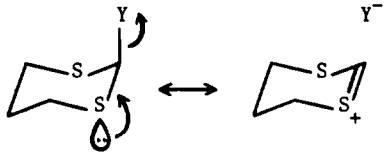
[a]Obscured by overlap with residual protiated solvent signal.

the equatorial isomer, a solvent compression effect[47] (dominant at low temperature) could be advanced to reconcile the apparent contradiction.

Despite the evidence in this Section that supports the participation of a dipole/dipole mechanism in the conformational equilibria for 3, 4, 8-11, some of the results in Table III are not in accord with that rationalization. In particular, the absence of an anomeric effect in 11 despite the sizable dipole of the dimethylamino group[48] requires of an alternative explanation. In addition, although the methylthio and phenylthio substituents are expected to have fairly similar group dipoles,[48] the anomeric effect in 4 is definitively greater than in 3. An alternative (or additional) explanation is thus called for.

E. Interpretation of the Results: the Stereoelectronic Effect.

Structural[49,50] and theoretical[37,50] studies on X-C-Y segments can usually[51] be accounted for in terms of lone pair/antibonding orbital interactions, of which the n→σ* type appears to be the more important. For 3, 4, 8-11 "double bond/no bond" resonance structures can thus be written for the axial conformers, where a lone pair of electrons on each sulfur is antiperiplanar (app) to the C-Y bond (Eqn. 10). In principle, the relative magnitudes of the anomeric effect can therefore be



(10)

predicted from the relative energies of the σ^*_{C-Y} orbitals, since n_S should be essentially constant in 3, 4, 8-11. On this basis, the greater axial preferences of SC_6H_5 and COC_6H_5 relative to SCH_3 and CO_2CH_3 may be anticipated when one considers that electronegative substituents lower the σ* molecular orbital level, and increase the overlap with the donor orbitals.[5]

No simple rationalization can be advanced at the moment for the (greatest) anomeric effect observed in 10 (Y = CO_2H; Table III), for which dimer formation in the weakly polar CD_2Cl_2 could obscure the normal electrostatic and stereoelectronic effects. Finally, the "abnormal" equatorial preference of the dimethylamino group in 11 must mean that in the equatorial conformer the app $n_N \rightarrow \sigma^*$ interaction is more important (best combination of orbital overlap and energetic difference) than app $n_S \rightarrow \sigma^*_{C-N}$ in the axial isomer; i.e., there is a stereoelectronic preference for the conformation in which the best donor lone pair is antiperiplanar to the best acceptor bond.[7,52]

Comparison of the results obtained in this work (Eqn. 1) with those of Öki in 2-substituted 1,3,5-trithianes[15] (Eqn. 3) is pertinent in this respect because the photoelectron spectroscopy

studies of Turner, et al.,[53] have shown that the HOMO energy in 1,3,5-trithiane is lower than that in 1,3-dithiane. It is then expected (vide supra and ref. 15a) that the anomeric effect will be stronger in the dithiane series. Indeed, Table VI clearly shows this trend. (The decreased axial populations in the trithiane series are difficult to explain on dipole/dipole arguments alone in view of the similarity of the dipoles involved).[54]

Table VI. Comparison of $-\Delta G^\circ$ Values (kcal/mol) in 2-Substituted 1,3-Dithianes (This Work) and 2-Substituted 1,3,5-Trithianes (Ref. 15).

Substituent	Solvent	T(°C)	$-\Delta G^\circ_{dithiane}$	$-\Delta G^\circ_{trithiane}$
CH_3S	toluene	-90	0.77	—
	$CDCl_3$-CS_2 (1:1)	-83	—	0.44
	CD_2Cl_2	-100	0.64	—
	CD_3COCD_3	-83	—	0.07
C_6H_5S	$CDCl_3$-CS_2 (1:1)	-83	—	0.79
	CD_2Cl_2	-100	0.92	—
	CD_3COCD_3	-83	—	0.18
	CD_3COCD_3/CD_3OD (1:1)	-90	0.85	—
CO_2CH_3	CD_2Cl_2	-100	0.83	—
	CD_3COCD_3	-90	0.92	—
	CD_3COCD_3	-80	—	0.43
	$CD_3COCD_3/CDCl_3$ (1:1)	-80	—	0.54
CO_2H	CD_2Cl_2	-100	$\geq$1.26	—
	CD_3COCD_3	-80	—	0.15

EXPERIMENTAL SECTION

General Information. Proton NMR spectra were recorded on Varian EM-360 (60 MHz), Varian EM-390 (90 MHz) or Bruker Spectrospin WM-250 (250 MHz) spectrometers. Carbon-13 NMR spectra were recorded on Varian XL-100 (25.12 MHz) or Bruker Spectrospin WM-250 (62.89 MHz) instruments operated in pulsed Fourier transform mode and locked on solvent deuterium. Samples were prepared as 8-15% solutions in CD_2Cl_2, $CDCl_3$, CD_3CN, CD_3CN, CD_3SOCD_3, CD_3COCD_3, CD_3OD or CD_3COCD_3/CD_3OD (1:1) mixture with 2-5% Me_4Si as internal reference in 5- or 10-mm o.d. tubes. The temperature indicator of the Bruker WM-250 spectrometer was calibrated by recording low-temperature proton spectra of acidified methanol and using the known C-H/O-H shift for assessment of temperature.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37291.

Flasks, stirring bars and hypodermic needles used for the generation and reactions of alkyllithiums were dried for ca. 12 h at 120°C and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[56] The n-butyllithium employed was titrated according to the methods of Kofron and Baclawski[57] or Juaristi, et al.[58] Melting points and boiling points are uncorrected.

2-Substituted 1,3-dithianes. General Procedure. 1,3-Dithiane (freshly sublimed, 600 mg, 5 mmol) was placed in a 50-mL flask provided with rubber septa and under nitrogen. Tetrahydrofuran (THF, ca. 35 mL) was added via cannula, and the flask was immersed in a CCl_4/dry ice bath (ca. -20°C) before the addition of 3.5 mL (5.25 mmol) of n-BuLi 1.5 M in hexane. The reaction mixture was then

stirred at -20°C for 90 minutes and transferred under positive pressure of nitrogen to another flask containing the electrophile (in excess, see Text). The mixture was stirred at -20°C for 1 h and at room temperature for an additional hour before it was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ether and worked up in the usual way.

2-Methylthio-1,3-dithiane (3). The general procedure was followed, with 2 equiv. of dimethyl disulfide as the electrophile. The product (clear oil) was purified by distillation at reduced pressure; bp 50°C/0.02 mm (lit.[59] bp 74°C/0.35 mm), yield 36.3%. ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.02 (m, 2 H), 2.25 (s, 3 H), 2.65 (d of t, J_{gem} = 14.4 Hz, J_{gauche} = 5.1 Hz, 2 H), 3.14 (d of d of d, J_{gem} = J_{anti} = 14.4 Hz, J_{gauche} = 5.1 Hz, 2 H), 4.82 (s, 1 H). ^{13}C NMR in Table I.

2-Phenylthio-1,3-dithiane (4). The general procedure was followed, with 2 equiv. of diphenyl disulfide as the electrophile. The product was purified by flash chromatography and recrystallized from methanol/acetone (9:1) to afford white crystals in 29% yield; mp 60-61°C (lit.[15d] mp 59-60°C). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.03 (m, 2 H), 2.63 (d of t, J_{gem} = 14.4 Hz, J_{gauche} = 5.1 Hz, 2 H), 3.28 (d of d of d, J_{gem} = J_{anti} = 14.4 Hz, J_{gauche} = 5.1 Hz, 2 H), 5.10 (s, 1 H), 7.39 (m, 5 H). ^{13}C NMR in Table I.

r-2-Thiomethyl-c-4,c-6-dimethyl-1,3-dithiane (5). The general procedure was carried out with 200 mg (1.35 mmol) of cis-4,6-dimethyl-1,3-dithiane[17] and 2 equiv. of dimethyl disulfide to afford 5 as a colorless oil, which was distilled on a Kugelrohr apparatus; bp 55-56°C/0.15 mm. This material crystallized upon standing at room temperature; mp 46-47°C (lit.[22] mp 48°C). ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.25 (d, J_{vic} = 6.6 Hz, 6 H), 1.26 (d of t, J_{gem} = J_{anti} = 14.1 Hz, 1 H), 2.03 (d of t, J_{gem} = 14.1 Hz, J_{gauche} = 3.0 Hz, 1 H), 2.35 (s, 3 H), 2.95 (d of d of q, J_{anti} = 14.1 Hz, J_{vic} = 6.6 Hz, J_{gauche} = 3.0 Hz, 2 H), 4.89 (s, 1 H). ^{13}C NMR (25.12 MHz, $CDCl_3$) δ 13.10 ($S\underline{C}H_3$), 21.12 ($\underline{C}H_3C$), 41.27 ($CH_3\underline{C}$), 42.28 ($\underline{C}H_2$), 49.65 ($S\underline{C}HS$). Yield 231 mg (88%).

r-2-Thiomethyl-t-4,t-6-dimethyl-1,3-dithiane (6). One hundred milligrams (0.67 mmol) of 5 was placed in a 50-mL round bottom flask provided with rubber septa before the addition of 20 mL of THF under nitrogen. The flask was immersed in a carbon tetrachloride/dry ice bath (ca. -20°C) and then 0.5 mL of 1.45 M n-BuLi in hexane (5% excess) was added. The reaction mixture was stirred at -20°C for 1.5 h and then quenched with saturated ammonium chloride. Extraction with ether and the usual work-up procedure yielded the crude product, which was purified by column chromatography [silica gel, hexane/ethyl acetate (95:5) eluent]. Recrystallization from methanol/water (9:1) afforded 50 mg (50% yield) of 6 as white crystals; mp 48-49°C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.21 (d, J_{vic} = 6.6 Hz, 6 H), ca. 1.35 (d of t, J_{gem} = J_{anti} = 14.1 Hz, 1 H), 2.10 (d of t, J_{gem} = 14.1 Hz, J_{gauche} = 3.0 Hz, 1 H), 2.20 (s, 3 H), 3.37 (d of d of q, J_{anti} = 14.1 Hz, J_{vic} = 6.6 Hz, J_{gauche} = 3.0 Hz, 2 H), 4.89 (s, 1 H). ^{13}C NMR (25.12 MHz, $CDCl_3$) δ 18.56 ($S\underline{C}H_3$), 21.05 ($\underline{C}H_3C$), 33.99 ($CH_3\underline{C}$), 44.02 ($C\underline{C}H_2C$), 50.98 ($S\underline{C}HS$).

Anal. Calcd for $C_7H_{14}S_3$: C, 43.25; H, 7.26. Found: C, 43.30; H, 7.35.

5-Ethyl-1,3-dithiane. A solution of 3.63 g (0.0267 mol) of 2-ethyl-1,3-propanedithiol[17] and 2.19 g (0.0288 mol) of dimethoxymethane in 8 mL of chloroform was added dropwise to a boiling solution of 8.17 g (0.0575 mol) of boron trifluoride etherate in 20 mL of chloroform. The reaction mixture was refluxed during 2 h and then washed with water, aqueous 20% potassium carbonate, and water again. The usual work-up procedure afforded the desired product as a clear liquid, which was distilled in a Kugelrohr apparatus; bp 48-49°C/0.25 mm (lit.[60] bp 85°C), yield 2.5 g (63%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.96 (t, J_{vic} = 5.8 Hz, 3 H), 1.42 (d of q, J_{vic} = 5.8 Hz, 2 H), 1.79 (t of t of t, J_{vic} = 5.8 Hz, 1 H), 2.68 (m, 4 H), 3.51 (AB, J_{gem} = 12.9 Hz, J_w = 1.8 Hz, 1 H), 3.88 (AB, J_{gem} = 12.9 Hz, 1 H).

trans-2-Methylthio-5-ethyl-1,3-dithiane (7). The general procedure was carried out with 200 mg

(1.35 mmol) of 5-ethyl-1,3-dithiane (vide supra) and 2 equiv. of dimethyl disulfide, to afford mainly (≥92%) the trans isomer of the expected product. Distillation from a Kugelrohr apparatus (bp 82-85°C/0.25 mm) yielded 147 mg (56.1%) of 7. ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.93 (t, J_{vic} = 6.3 Hz, 3 H), 1.4-1.9 (m, 3 H), 2.30 (s, 3 H), 2.4-3.3 (m, 4 H), 4.83 (s, 1 H). ^{13}C NMR (25.12 MHz, $CDCl_3$) δ 11.29 ($\underline{C}H_3CH_2$), 15.37 ($S\underline{C}H_3$), 25.82 ($\underline{C}H_2CH_3$), 33.28 ($CH_2\underline{C}H_2S$), 33.90 (Et$\underline{C}$), 48.35 ($S\underline{C}HS$).

Anal. Calcd for $C_7H_{14}S_3$: C, 43.25; H, 7.26. Found: C, 43.51; H, 7.25.

2-Benzoyl-1,3-dithiane (8). The general procedure was carried out with 10 equivalents of ethyl benzoate.[19] Since the crude product was contaminated with bis[2-(1,3)dithianyl]phenylmethanol, the desired product (8) was obtained in 48% yield by fractional crystallization from chloroform/hexane (8:2); mp 97-98.5°C (lit.[61] mp 98.4-99.4°C). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.13 (m, 2 H), 2.67 (d of t, J_{gem} = 14.1 Hz, J_{gauche} = 3.2 Hz, 2 H), 3.37 (d of d of d, J_{gem} = J_{anti} = 14.1 Hz, J_{gauche} = 3.2 Hz, 2 H), 5.13 (s, 1 H), 7.35-8.1 (m, 5 H). ^{13}C NMR in Table I.

2-[1,3]Dithianylcarboxylic acid (10). The general procedure was carried out with excess CO_2 (dry ice) as the electrophile. The product (10) was recrystallized from hexane; mp 114-116°C (lit.[62] mp 114-116°C), yield 66%. ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.10 (m, 2 H), 2.58 (d of t, J_{gem} = 15.0 Hz, J_{gauche} = 4 Hz, 2 H), 3.40 (d of d of d, J_{gem} = J_{anti} = 15.0 Hz, J_{gauche} = 4.0 Hz, 2 H), 4.18 (s, 1 H), 10.6 (s, 1 H). ^{13}C NMR in Table I.

2-Carbomethoxy-1,3-dithiane (9). Hydrochloric acid was bubbled during 5 minutes into a methanolic solution of 0.5 g (3 mmol) of carboxylic acid 10. The reaction mixture was concentrated and the product distilled in a Kugelrohr apparatus. The desired ester (9, 0.26 g, 48% yield) crystallized upon standing at room temperature; mp 28°C (lit.[62] mp 28°C). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.14 (m, 2 H), 2.60 (d of t, J_{gem} = 15.0 Hz, J_{gauche} = 3.6 Hz, 2 H), 3.41 (d of d of d, J_{gem} = J_{anti} = 15.0 Hz, J_{gauche} = 3.6 Hz, 2 H), 3.83 (s, 3 H), 4.22 (s, 1 H). ^{13}C NMR in Table I.

2-N,N-Dimethylamino-1,3-dithiane (11). 1,3-Propanedithiol[63] (5.1 mL, 50 mmol) and 6.6 mL (50 mmol) of N,N-dimethylformamide dimethyl acetal[63] was placed in a round-bottom flask adapted for distillation. The reaction mixture was warmed to 30-35°C and the methanol produced was distilled at reduced pressure (100 mmHg). When the theoretical amount of methanol had been collected (2-3 h), the desired product (11) was distilled (bp 73-74°C/1 mm); yield 4.67 g (57.3%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.92 (m, 2 H), 2.52 (s, 6 H), 2.93 (m, 4 H), 5.29 (s, 1 H). ^{13}C NMR in Table I. Compound 11 was not analyzed owing to its lability.

cis- and trans-2-tert-Butyl-5-ethyl-1,3-dithianes (12 and 13). 2-Ethyl-1,3-propanedithiol[17] (see Scheme II, 1.36 g, 0.01 mmol) and 0.861 g (8.8 mmol) of pivalaldehyde[63] was added to a flask containing 30 mL of benzene. A few crystals of p-toluenesulfonic acid was added and the reaction mixture heated to reflux during 5 h, condensing the water generated in a Dean-Stark trap. The reaction mixture was washed with 10% aqueous sodium hydroxide and three times with water. The usual work-up procedure afforded a brownish liquid, which was distilled at reduced pressure, bp 69-70°C/0.2 mm, to provide 1.50 g (74% yield) of the desired mixture (ca. 1:3) of isomers 12 and 13. ^{13}C NMR (12): δ 11.05 ($CH_2\underline{C}H_3$), 22.10 ($\underline{C}H_2CH_3$), 27.47 [$C(\underline{C}H_3)_3$], 30.85 (Et$\underline{C}$H), 35.45 [$\underline{C}(CH_3)_3$], 37.83 ($CH\underline{C}H_2S$), 61.21 ($S\underline{C}HS$). 13: δ 10.74 ($CH_2\underline{C}H_3$), 27.65 [$C(\underline{C}H_3)_3$], 28.95 ($\underline{C}H_2CH_3$), 34.64 (Et$\underline{C}$H), 35.00 [$\underline{C}(CH_3)_3$], 35.87 ($CH\underline{C}H_2S$), 61.21 ($S\underline{C}HS$).

Anal. Calcd for $C_{10}H_{20}S_2$: C, 58.76; H, 9.86. Found: C, 59.15; H. 9.84.

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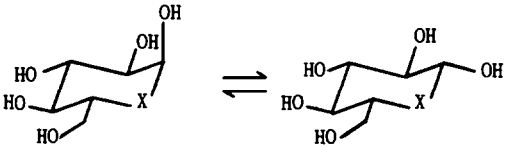

1α: X = O 1β: X = O
2α: X = S 2β: X = S

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45. There is a small but systematic difference between the $\Delta G°(SCH_3)$ values obtained for 3 and those obtained for 7. It could be that the effective dielectric constant for the more hydrophobic 7 is a little lower than for 3, leading to a stronger anomeric effect.
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