Conformational Analysis. 37. Gauche-Repulsive Interactions in 5-Methoxy- and 5-Methylthio-1,3-dithianes[1]

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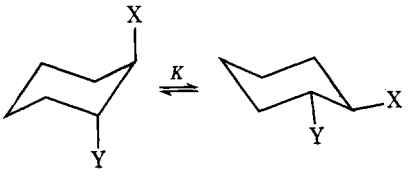
Received August 25, 1977

Abstract: Cis-trans equilibria in 2-*tert*-butyl-5-methoxy- and 2-*tert*-butyl-5-methylthio-1,3-dithianes, in dilute acetonitrile, indicate the trans (equatorial) isomers to be preferred by 1.22 and 1.57 kcal/mol, respectively. Smaller free-energy differences are found in other solvents and solvent combinations. The preferences for the equatorial positions of OCH_3 and SCH_3 are greater than what one calculates on the basis of classical steric and polar interactions. The results support the existence of a repulsive S/S or S/O gauche effect over and above that predicted on the basis of van der Waals and dipolar forces, as previously postulated by Zefirov and co-workers.

In a series of publications,[3,4] Zefirov and co-workers have shown that repulsive interactions beyond those readily accounted for by steric and polar factors are encountered in molecules when two atoms of the third (or lower) row of the periodic system are gauche to each other. The combination S/S has been particularly extensively studied and the most convincing demonstration of repulsive effects was obtained by studying conformational equilibria in trans-1,2-disubstituted cyclohexanes (Scheme I) by means of vicinal ($J^3_{H/H}$) coupling constants. A special repulsive effect was deemed to exist when K was smaller than calculated. The calculations were effected by estimating the conformational free energy of the diaxial conformer as the sum of the conformational energies $\Delta G^\circ_X + \Delta G^\circ_Y$ whereas that of the diequatorial conformer was deemed to be the sum of a steric component (X/Y interaction as calculated by the Hill equation[5]) and a polar component (charge/charge repulsion[6]). The steric calculations are based on the assumption that the normal van der Waals parameters for sulfur[5] are appropriate, an assumption which has recently been put in doubt.[7] Also, for the calculations of the dipole interactions a dielectric constant of 1 was assumed. The special repulsive effects vary between ca. 0.5 kcal/mol (Cl/Cl) and 1.5 kcal/mol (S/S); no special repulsive effect was found for Cl/I, O/I, O/Cl, or O/Br and an attractive effect actually exists for O/O and F/I.[4] The repulsive effect was called "hockey sticks effect" in Zefirov's earlier publications,[3] but recently he has adopted[4] the term "gauche-repulsive effect."

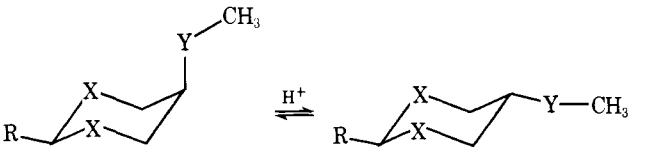
In independent investigations involving 5-substituted 1,3-dioxanes[8] and 1,3-dithianes (Scheme II) we have also found gauche-repulsive (as well as gauche-attractive) effects. We have previously described[9] the evidence for attractive effects; this paper will deal largely with gauche/gauche repulsions.

Scheme I



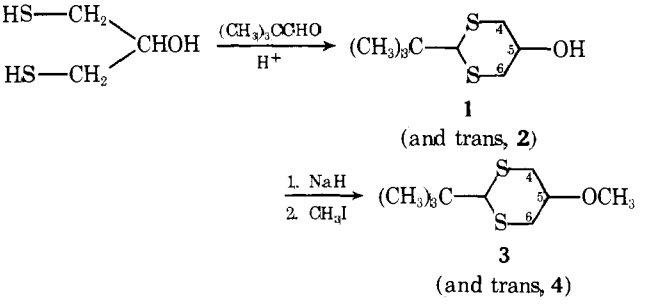
X = S, Y = S, Br, Cl, O;
X = Y = Br; X = Y = Cl

Scheme II



X = O or S; Y = O or S

Scheme III



1
(and trans, **2**)

3
(and trans, **4**)

separated by column chromatography

Results

The synthesis of the anancomeric[10] 2-*tert*-butyl-5-methoxy-1,3-dithianes (**3, 4**) was readily accomplished from commercially available 2-hydroxypropane-1,3-dithiol (Scheme III). Separation was effected at the hydroxydithiane (**1, 2**) stage by column or dry-column chromatography. The intramolecularly hydrogen-bonded cis isomer (**1**) was eluted first. Assignment of configuration was made in several different ways: (1) In dilute solution **1** showed the IR stretching frequency for an intramolecularly bonded OH at 3541 cm^{-1} whereas **2** only displayed free OH at 3640 cm^{-1}. (2) ^1H NMR vicinal coupling constants of $H_{4,6}$ and H_5 showed the expected large J_{anti} in the case of the trans isomers **2** (J^3_{H4H5} = 10.4 and 4.3 Hz) and **4** (J^3_{H4H5} = 10.4 and 3.6 Hz) whereas the corresponding coupling constants for the cis isomer were much smaller (**1**, J^3_{H4H5} = 4.5, 1.7 Hz; **3**, J^3_{H4H5} = 4, 4 Hz). (3) The dipole moment was greater for the cis isomer (2.08 D) than for the trans (1.40 D). (4) The structure of **3** was confirmed by X-ray structure analysis.[11]

A rather interesting difference between **3** and **4** was seen in the shifts induced by $Eu(fod)_3$ which are shown (for a mole ratio shift reagent/substrate of 0.8) in Table I. The biggest difference is for H_2, which is shifted substantially in **3** but only feebly in **4**. This suggests a "double complexing mechanism" in **3** as shown in Scheme IV.

The synthesis of the diastereomeric 2-*tert*-butyl-5-methylthio-1,3-dithianes (**7, 8**) was accomplished by the sequence of steps shown in Scheme V. 2-*tert*-Butyl-1,3-dithian-5-one[12] was converted to the corresponding mercaptans (diastereomeric mixture of **5** and **6**) by a method[13] which we had previously used in the cyclohexyl series.[14] Methylation gave a mixture of **7** and **8**; after separation of the major part of **7** by

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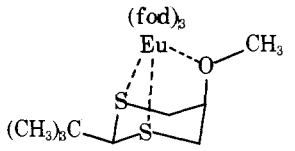
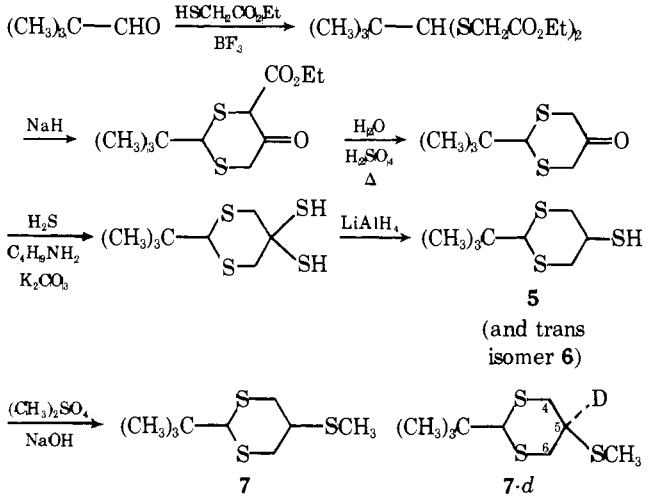
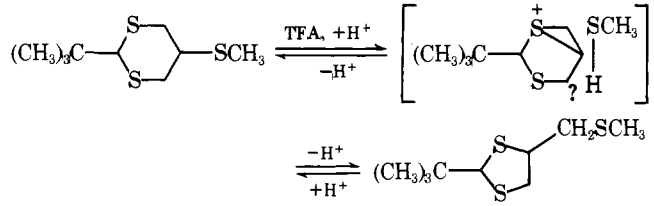
Scheme IV



Scheme V



Scheme VI



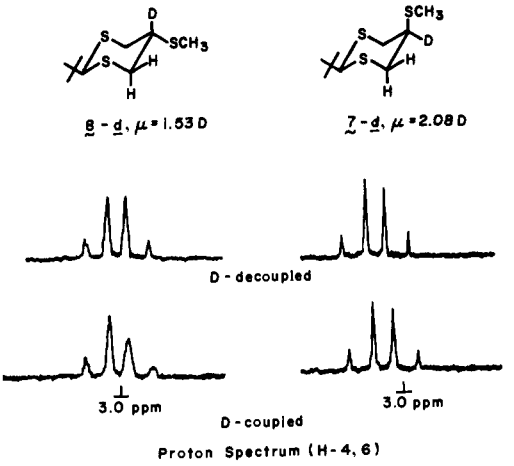


Figure 1. ^{1}H NMR spectra (3-ppm region) of 7-*d* and 8-*d*.

Table I. Proton Shifts (ppm) upon Addition of 0.8 mol of Eu(fod)$_3$

	H_2	$H_{4,6}$	H_5	OCH_3
3	42	70	63	39
4	18	56	57	47

Table II. Conformational Equilibria in 2-*tert*-Butyl-5-methoxy-1,3-dithianes (**4**/**3**)

solvents (mole ratio)	K^a	$-\Delta G^\circ_{25}$, kcal/mol (25 °C)^a
TFA-$CHCl_3$ (1:1)	3.44 ± 0.22	0.73 ± 0.05
(1:3)	4.00 ± 0.32	0.82 ± 0.05
(1:19)	6.34 ± 0.63	1.09 ± 0.06
TFA-CH_3CN (1:3)	4.35 ± 0.25	0.87 ± 0.03
(1:9)	5.63 ± 0.62	1.02 ± 0.07
(1:57)	8.22 ± 2.42	1.22 ± 0.18

^{a} Standard deviations[18] indicated.

crystallization, **8** was purified by either gas–liquid partition or column (adsorption) chromatography. Two other attempted syntheses of **7** and **8**, one unsuccessful and the other inefficient, are indicated in the Experimental Section.

Assignment of configuration to **7** and **8** on the basis of ^{1}H NMR spectroscopy foundered initially because the AA'BB'X system at $C_{4,5,6}$ is quite degenerate. We therefore synthesized the 5-*d* analogues **7**-*d* and **8**-*d* shown in Scheme V by replacing $LiAlD_4$ for $LiAlH_4$ in the synthesis. The $C_{4,6}$ region of these deuterated isomers showed an AB pattern, the upfield leg of which was broadened in one of the two isomers (**8**-*d*) but not in the other (**7**-*d*). The broadening was shown to be due to the deuterium in the antiperiplanar (axial) position at C_5 (the expected $J^3_{H,D}$ coupling for this case being ca. 1.5 Hz) for when the deuterium at C_5 was decoupled in **8**-*d*, the signal of the axial proton at $C_{4,6}$ sharpened (Figure 1). The isomer which showed the broadening was therefore assigned the trans configuration **8**-*d*. Additional evidence for the configurational assignment came from measurement of dipole moments (**7**, 2.08 D; **8**, 1.53 D) and, ultimately, from an X-ray structural investigation of **7**.[11]

Equilibration of **3**, **4**, **7**, and **8** was readily performed by means of trifluoroacetic acid (TFA), in preference to weaker acids, such as BF_3,[15,16] or Amberlyst-15,[9] which promote equilibration of dithianes only very slowly or not at all. A disadvantage of TFA is that it also promotes cleavage of the ether group and/or rearrangements;[12] in the case of **7** and **8** we found that pure TFA promotes the reaction shown in Scheme VI with equilibrium (established after about 4 days) being nearly entirely on the side of the five-membered ring system.[17] This problem could be largely avoided by diluting the TFA.

Equilibrium constants (trans/cis) and the corresponding free-energy differences for **3** and **4** are summarized in Table II, and those for **7** and **8** in Table III.

Discussion

In all cases studied, the equatorial 5-methoxy or 5-methylthio compound is the more stable. Its stability, relative to its axial epimer, increases with increasing dilution of the TFA. This is not a dielectric effect, for the dielectric constant of TFA (8.2) is intermediate between that of $CHCl_3$ (4.7) and CH_3CN (38.8); thus the dielectric constant of solutions of TFA in CH_3CN increases, but that of solutions in $CHCl_3$ decreases as the solutions are made more dilute. We ascribe the effect to a stabilization of the axial isomer (**3** or **7**) through protonation; the protonated species can be stabilized through intramolecular hydrogen bonding only in the case of the axial substituent (Scheme VII). [The analogy for the picture postulated for Eu(fod)$_3$ complexation—Scheme IV—might be noted; the axial isomers **3** and **7** may well turn out to be good polydentate complexing agents.]

The very substantial preference of the equatorial **4** over the axial **3** or the equatorial **8** over the axial **7** in dilute solution in CH_3CN contrasts with the equilibrium of 2-isopropyl-5-methoxy-1,3-dioxane (**9**, **10**)[9,19] in the same solvent but compares to that of 2-isopropyl-5-methylthio-1,3-dioxanes (**11**, **12**)[8] (Scheme VIII). The data are collected in Table IV (see also Table V, line 1). Since $-\Delta G^\circ_{ax \rightleftharpoons eq}$ for methoxycyclohexane

Table III. Conformational Equilibria in 2-*tert*-Butyl-5-methylthio-1,3-dithianes (**8**/**7**)

solvent (mole ratio)		K^a	$-\Delta G°$, kcal/mol (25 °C)[a]
TFA		3.53 ± 0.33	0.75 ± 0.06
TFA-H_2O	(1:1)	3.73 ± 0.38	0.78 ± 0.06
TFA-$CHCl_3$	(1:1)	6.01 ± 0.31	1.06 ± 0.03
	(1:3)	7.90 ± 0.48	1.22 ± 0.04
	(1:19)	12.27 ± 1.17	1.49 ± 0.06
TFA-CH_3CN	(1:3)	10.71 ± 0.64	1.40 ± 0.04
	(1:9)	12.77 ± 1.37	1.51 ± 0.07
	(1:57)	14.46 ± 3.88	1.57 ± 0.17
TFA-CH_2Cl_2	(1:3)	7.52 ± 0.53	1.20 ± 0.05

[a] Standard deviations indicated.[18]

Table IV. Equilibria of *cis*- and *trans*-5-Methoxy- and 5-Methylthio-Substituted 1,3-Dioxanes and 1,3-Dithianes in Acetonitrile

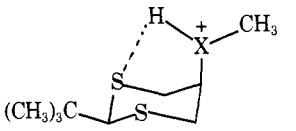
heteroatoms			
ring	exocyclic	compds	$-\Delta G°$, kcal/mol
O	O	**9** ⇌ **10**	−0.01
O	S	**11** ⇌ **12**	1.13
S	O	**3** ⇌ **4**	1.22
S	S	**7** ⇌ **8**	1.57

(**13**) is 0.60 kcal/mol[20] and for methylthiocyclohexane (**14**) 1.07 kcal/mol[14,20] it would appear that the O/O interaction in **9** is attractive[21] and the O/S and S/S interactions in **3** and **7** repulsive; the situation for **11** is ambiguous. To put this tentative conclusion on a firm footing, we calculated the difference in steric interactions between axial and equatorial groups for the various pairs of compounds (**3, 4; 7, 8; 9, 10; 11, 12; 13-e, 13-a; 14-e, 14-a**) from the Hill equation.[5b] The results are shown in Table V, second line. It must be emphasized that, since no energy minimization was attempted, these differences should be *maximum* values; any energy minimization would reduce the calculated difference between the less stable and more stable isomers. Indeed, for cyclohexyl methyl sulfide we calculate a repulsive energy much in excess of that found (Table V, line 4) whereas Allinger[22] obtains good agreement between calculated and experimental conformational energies for cyclohexyl mercaptan by energy minimization.

For the dioxane (**9–12**) and dithiane (**3, 4, 7, 8**) derivatives, electrostatic as well as steric interactions must be taken into account. Charge-charge interactions were calculated by Abraham's formula[6] assuming the (least favorable) dielectric constant of unity. The results are shown in Table V, line 2, and the sum of the steric and electrostatic interactions in line 3.

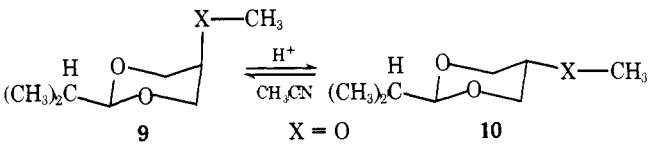
Comparison with the experimental data in line 4 shows poor agreement in at least three of the four cases. For **10**/**9** the axial isomer is far more abundant at equilibrium than calculation leads one to predict (cf. line 5). This is probably a manifestation of the previously observed gauche-attractive effect in this system.[4,8] In contrast, for **4**/**3** and especially **8**/**7** the opposite occurs: the equatorial isomer is strongly preferred at equilibrium whereas calculation suggests either a slight preference for this isomer (**3, 4**) or actually a preference for the axial isomer (**7, 8**) (see Table V, line 5). Raising the dielectric constant above unity to a more realistic value would further increase the discrepancy between calculated and experimental $\Delta G°$; minimizing the energy would slightly reduce the discrepancy inasmuch as the axial isomers **3** and **7** are slightly favored, sterically, over the equatorial **4** and **8**; however, this effect would be small since $\Delta G°_{steric}$ is itself small. The conclusion that there is repulsion over and above that calculated by steric and polar effects in **3** and **7** thus appears firm as is the inference of attraction in **9**; only in the case of **11** is the situation ambiguous.[24]

Scheme VII



X = O (**3**) or S (**7**)

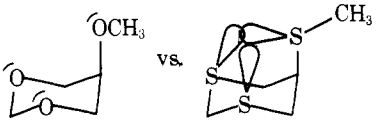
Scheme VIII



9 X = O **10**
11 X = S **12**

$-\Delta G°$ (**9** ⟶ **10**) −0.01 kcal/mol[9]
$-\Delta G°$ (**11** ⟶ **12**) 1.13 kcal/mol[8]

Scheme IX



In summary, then, we agree with Zefirov[4] that an S/S gauche interaction and (less certainly) an S/O gauche interaction give rise to repulsion over and above that estimated on the basis of steric and classical polar effects. We agree, also, that this repulsion is probably due to repulsive overlap of the filled 3p orbital on sulfur with the 3p orbital on another sulfur or the $2sp^3$ filled orbital on oxygen; the much greater extension of the 3p orbital (as compared to a $2sp^3$ orbital on O or N) appears to be responsible for this repulsion (Scheme IX).

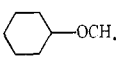
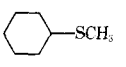
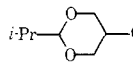
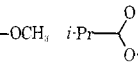
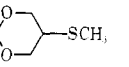
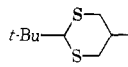
Experimental Section

^1H NMR spectra were recorded on JEOL C-60 HL and Varian XL-100 spectrometers in CW or FT mode, and ^{13}C spectra on the XL-100 instrument in FT mode. The solvent was $CDCl_3$ and the standard Me_4Si. Mass spectra were recorded by a Hitachi Perkin-Elmer RMU-6E mass spectrometer; deuterium analyses were carried out at low voltage (13–15 V) by comparing the M, M + 1, M + 2, etc., parent peaks. Gas chromatographic analyses were carried out on a Hewlett-Packard Model 5750 instrument equipped with a dual thermal conductivity detector, a Moseley Model 7127A 1.0-mV recorder, and a Disc Instrument Co. peak area integrator. Columns were ⅛ in. stainless steel or aluminum. The injector block was at 220 °C, the detector at 250 °C. Helium pressure was 40–50 psi. Infrared spectra were recorded on Perkin-Elmer Model 257 or 421 grating infrared spectrophotometers. Liquid samples were run as neat films, solids, as KBr pellets. Melting points were determined in an Electrothermal melting point apparatus.

***cis*- and *trans*-2-*tert*-Butyl-5-hydroxy-1,3-dithiane (1, 2).**[25] Pivalaldehyde (86.1 g, 1 mol) and 124.2 g (1 mol) of 2-hydroxy-1,3-propanedithiol were dissolved in 300 mL of methanol to which 10 mL of concentrated hydrochloric acid was added. After standing for 2 days in a stoppered container at room temperature the solution was neutralized and partitioned between chloroform and water. The chloroform layer was cleared with water, dried, and concentrated to give 182.7 g (95%) of a mixture of **1** and **2** in a ratio of 2:1. The mixture was analyzed by GLC on a 4 × ⅛ in. column packed with 20% FFAP on Chromosorb W (80/100 mesh) with programmed heating; retention time cis, 12 min at 160 °C; trans, 26 min at 195 °C; rate of heating 10 °C/min.

The mixture (ca. 22 g) was separated by column chromatography on a 45 × 3 cm column packed with neutral aluminum oxide. Elution with hexane afforded a very small amount of what appeared to be a mixture of *cis*- and *trans*-2-*tert*-butyl-5-methylmercapto-1,3-oxathiolane: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.97 (s, 9 H), 1.56 (t, J = 8.5 Hz, 1 H), 2.82 (m, 4 H), 4.0 (m, 1 H), 4.90 (s, 1 H). This was followed

Table V. Experimental and Calculated Energy Differences (a ⇌ e) for Pairs of Cyclohexanes, 1,3-Dioxanes, and 1,3-Dithianes Axially and Equatorially Substituted with CH_3O or CH_3S Groups

line	system compds	 13a,c	 14a,c	 9,10	 11,12	 3,4	 7,8
1	$-\Delta G°_{steric}$[a]	+0.55	+3.24	+0.18	+0.01	−0.37	−1.05
2	$-\Delta G°_{electrostat}$[b]	0	0	+2.22	+1.49	+0.64	+0.36
3	$-\Delta G°_{total}$ (1 + 2)	+0.55	+3.24	+2.40	+1.50	+0.27	−0.69
4	$-\Delta G°_{exptl}$[c]	+0.55	+1.07	−0.01	+1.13	+1.22	+1.57
5	4 − 3	0.00	−2.17	−2.41	−0.37	+0.95	+2.26

[a] In kcal/mol. [b] Difference between conformational energies of equatorial and axial groups calculated by Hill equation.[5b] For the equatorial isomer, the interaction of the exocyclic heteroatom with the four gauche hydrogens was computed; for the axial isomer the interaction of the same heteroatom with the two gauche and the two anti hydrogen atoms, the two gauche ring heteroatoms and (in the case of **13a** and **14a**) the syn-axial hydrogen atoms. The geometries used for **3** and **7** were those actually determined;[17] those for the other systems were taken from the known ring geometries[23] with standard bond angles and bond distances for the substituents. The OMe and SMe groups were assumed to be gauche (τ = 60°). [c] From Table IV and ref 20.

Table VI. Chemical Shifts in ^{13}C NMR Spectra of Compounds **3**, **4**, **7**, and **8**[a]

compd	C(2)	C(4,6)	C(5)	CMe_3	$(CH_3)_3C$	CH_3X
3	60.48	33.28	68.16	36.28	27.82	56.14
4	61.31	34.08	76.84	35.29	28.23	56.17
7	59.81	34.84	41.04	36.48	27.70	14.68
8	61.42	35.95	43.95	35.43	28.02	13.92

[a] Downfield in parts per million from Me_4Si.

by 13 g of **1** and (upon elution with hexane–ether, 9:1) 7.1 g of **2.** The recovery of **1** and **2** as judged by analytical gas chromatography of the original mixture (10% UC-W98 on Chromosorb W, 80/100 mesh) was ca. 90%.

The cis isomer (**1**) was recrystallized from hexane at −20 °C and sublimed at reduced pressure: mp 49–49.5 °C (lit.[12] mp 46–47 °C); IR (CCl_4, 5 × 10^{-3} M) 3541 cm^{-1}; IR (KBr) 3473 (m), 2962 (vs), 2922 (s), 1463 (s), 1422 (s), 1400 (s), 1364 (s), 1307 (m), 1238 (m), 1183 (s), 1049 (vs), 1028 (m), 787 cm^{-1} (s); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.14 (s, 9 H), 2.91 (A_2B_2X, J_{AB} = 13.5, J_{AX} = 4.5 Hz, 2 H), 3.14 (A_2B_2X, J_{AB} = 13.5, J_{BX} = 1.7 Hz, 2 H), 3.46 (s, 1 H), 3.86 (A_2B_2X, J_{AX} = 4.5, J_{BX} = 1.7 Hz, 1 H). Acetate, mp 32–33.5 °C.

The trans isomer (**2**) was similarly purified: mp 82–83 °C (lit.[12] mp 81–82 °C); IR (CCl_4, 5 × 10^{-3} M) 3640 cm^{-1}; IR (KBr) 3280 (broad, vs), 2963 (s), 2870 (m), 1475 (s), 1434 (s), 1414 (s), 1398 (s), 1370 (s), 1302 (w), 1188 (m), 1039 (s), 1019 (vs), 985 (s), 784 cm^{-1} (s); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.145 (s, 9 H), 2.31 (s, 1 H), 2.77 (A_2B_2X, J_{AB} = 13.3, J_{AX} = 10.4 Hz, 2 H), 2.93 (A_2B_2X, J_{AB} = 13.3, J_{BX} = 4.3 Hz, 2 H), 3.90 (s, 1 H), 4.01 (A_2B_2X, J_{AX} = 10.4, J_{BX} = 4.3 Hz, 1 H). Acetate, mp 80–81 °C.

***cis*-2-*tert*-Butyl-5-methoxy-1,3-dithiane (3).** Methylation of 3.6 g (18.75 mmol) of **1** with 3.63 g (21.9 mmol) of CH_3I by the method of Diner, Sweet, and Brown[26] afforded, after recrystallization from methanol at −20 °C, 3.4 g (88%) of **3** as white needles: mp 48.5–49.5 °C (lit.[25] 47–48 °C); IR (KBr) 2969 (s), 2921 (s), 2823 (s), 1462 (s), 1395 (m), 1370 (s), 1358 (s), 1241 (m), 1196 (m), 1098 (vs), 1008 (m), 784 cm^{-1} (m); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.13 (s, 9 H), 3.01 (d, J = 4 Hz), 3.43 (s, 3 H), 3.48 (quintet, J = 4 Hz, 1 H), 3.96 (s, 1 H); ^{13}C NMR spectrum, Table VI.

Anal. Calcd for $C_9H_{18}OS_2$: C, 52.38; H, 8.79. Found: C, 52.75; H, 8.77.

***trans*-2-*tert*-Butyl-5-methoxy-1,3-dithiane (4)** was similarly prepared from **2** and was purified by distillation: bp 65 °C (0.2 mm) (lit.[25] bp 94–96 °C (0.65 mm)); yield 77.5%; IR (neat) 2965 (s), 2915 (s), 2828 (m), 1466 (s), 1400 (m), 1374 (s), 1250 (w), 1192 (s), 1116 (s), 1092 (vs), 959 (m), 773 cm^{-1} (w); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.14 (s, 9 H), 2.69 (distorted A_2B_2X, J_{AB} = 13.5, J_{AX} = 10.4 Hz, 2 H), 3.0 (distorted A_2B_2X, J_{AB} = 13.5, J_{BX} = 3.6 Hz, 2 H), 3.40 (s, 3 H), 3.53 (distorted A_2B_2X, J_{AX} = 10.4, J_{BX} = 3.6 Hz, 1 H), 3.94 (s, 1 H); ^{13}C NMR spectrum, Table VI.

Anal. Found: C, 52.43; H, 8.89.

2-*tert*-Butyl-1,3-dithian-5-one. The procedure of Atkinson et al.[12] was modified as follows. Boron trifluoride etherate (20 mL, 23.1 g, 0.15 mol) was added to 48 g (0.4 mol) of ethyl mercaptoacetate and 13 g (0.15 mol) of trimethylacetaldehyde and the solution kept at room temperature for 12 h. Ether was added and the solution was extracted with 2 N aqueous NaOH, followed by water; it was dried and concentrated (rotary evaporator) to give 39 g (91%) of crude diethyl 4-*tert*-butyl-3,5-dithiapimelate which was not purified but dissolved in 90 mL of dry ether and added dropwise to a stirred suspension of sodium hydride in mineral oil (11.6 g, 57% NaH, 0.28 mol), diluted with 240 mL of dry ether. The mixture was stirred for an additional 3 h and set aside overnight. It was then cautiously diluted with an equal volume of water, acidified with dilute HCl, and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 28.3 g of crude 2-*tert*-butyl-5-ethoxycarbonyl-1,3-dithian-5-one which was hydrolyzed by boiling at reflux for 3 h with 360 mL of water containing 40 mL of concentrated sulfuric acid. The solution was cooled and extracted with ether and the combined ether extracts were washed with aqueous $NaHCO_3$ followed by water, dried over anhydrous $MgSO_4$, filtered, and concentrated (rotary evaporator). Distillation yielded 17.1 g (60% overall) of product, bp 60°C (0.05 mm), which crystallized slowly upon standing, mp 29–31 °C (lit.[25] 30–31.5 °C), oxime mp 122 °C (lit.[12] 121–122 °C).

^1H NMR ($CDCl_3$, 60 MHz): δ 1.15 (s, 9 H), 3.53 (s, 4 H), 4.36 (s, 1 H).

2-*tert*-Butyl-1,3-dithiane-5,5-dithiol. 2-*tert*-Butyl-1,3-dithian-5-one (9.5 g, 0.05 mol) and 0.44 g (0.006 mol) of *n*-butylamine were dissolved in 15 mL of tetrahydrofuran. Anhydrous potassium carbonate (5 g) was added and the mixture cooled with stirring to −20 °C. Hydrogen sulfide from a cylinder was bubbled into this solution for 1 h at −20 °C and then for 5 h at room temperature. The potassium carbonate was filtered (some foaming occurred) and washed with ether. The washings were added to the reaction mixture which was then cooled to −20 °C, acidified with 5 N hydrochloric acid, and let stand overnight. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ether layers were washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting solid was recrystallized from hexane to furnish 7.8 g (65%) of 2-*tert*-butyl-1,3-dithiane-5,5-dithiol: mp 83–84 °C; IR (KBr) 2953 (s), 2920 (m), 2860 (m), 2524 (m), 1457 (s), 1430 (s), 1396 (s), 1367 (vs), 1277 (w), 1231 (m), 1208 (s), 1029 (w), 779 cm^{-1} (s); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.16 (s, 9 H), 2.78 (distorted s, 1 H), 3.02 (distorted A_2B_2, J_{AB} = 13.5 Hz, 2 H), 3.92 (s, 1 H), 4.53 (distorted s, 1 H). Note: $^4J_{H\text{-}4,6/SH} \simeq 1.5$, $^4J_{H\text{-}4,6/SH} \simeq 1.0$ Hz.

MS (70 V) *m/e* 41 (100%), 45 (60%), 47 (14.7%), 53 (26.7%), 55 (12.7%), 57 (58%), 59 (80%), 69 (34.7%), 71 (13%), 74 (34.7%), 87 (20%), 102 (60%), 103 (9.3%), 111 (5.3%), 116 (13.3%), 117 (21.3%),

149 (53.5%), 150 (6.7%), 151 (9.3%), 206 ($M^+ - 32$, 17.3%).

***cis*- and *trans*-2-*tert*-Butyl-5-methylthio-1,3-dithianes (7, 8).** Lithium aluminum hydride (1.67 g, 0.044 mol) was placed in a three-necked flask provided with magnetic stirrer, pressure-equalized addition funnel, and protected reflux condenser. Anhydrous ether (70 mL) was added with stirring and cooling. The slurry was stirred for an additional 1 h after which a solution of 10.5 g (0.044 mol) of 2-*tert*-butyl-1,3-dithiane-5,5-dithiol in 50 mL of anhydrous ether was added at a rate to maintain gentle reflux. After addition was complete, the stirred mixture was refluxed for 1 h more and cooled. Excess hydride was destroyed by cautious dropwise addition of 10 mL of water followed by 10% aqueous sulfuric acid until the solution was clear. The ether layer was separated and the aqueous layer extracted three times with ether. The combined ether layers were washed with 5% aqueous $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 8.8 g (96.7%) of the crude thiols. Without purification the thiols were dissolved in ca. 10 mL of ethanol to which a solution of 4.2 of NaOH in 21 mL of water was added, followed, after 10 min, by 5.32 g of dimethyl sulfate, with stirring. The temperature of the mixture rose spontaneously; when it had returned to room temperature, the solution was extracted with three 50-mL portions of ether which were combined, cleared with water, dried over anhydrous $MgSO_4$, and concentrated to give 9 g (96%) of a mixture of **7** and **8**.

Cis Isomer. Repeated recrystallization from methanol afforded the pure cis isomer: mp 78–79 °C; IR (KBr) 2957 (vs), 2903 (s), 2865 (s), 1463 (m), 1419 (s), 1404 (s), 1372 (s), 1290 (s), 1266 (s), 1243 (m), 1190 (s), 1165 (m), 1031 (w), 968 (s), 790 cm^{-1} (s); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.12 (s, 9 H), 2.14 (s, 3 H), 3.09 (m, 5 H), 3.92 (s, 1 H); MS (70 V) *m/e* 41 (30.1%), 45 (15.8%), 55 (5.3%), 57 (7.1%), 59 (8.2%), 61 (5.7%), 69 (6.6%), 73 (15.6%), 74 (7.5%), 87 (11.7%), 93 (13.3%), 101 (5.8%), 117 (24.5%), 119 (9.8%), 165 (100%), 166 (5.3%), 167 (8.9%), 207 (1.4%), 222 (M^+, 16.7%); ^{13}C NMR spectrum, Table VI.

Anal. Calcd for $C_9H_{18}S_3$: C, 48.64; H, 8.16. Found: C, 48.54; H, 8.22.

Trans Isomer. The mixture from the mother liquors of crystallizing the cis isomer was separated either by preparative GLC (6 ft × 3/8 in. i.d., 20% FFAP on Carbowax W, 60/80 mesh column at 160 °C; Varian-Aerograph 2700 instrument; **7** comes off first) or by column chromatography on neutral aluminum oxide (65 × 3 cm column). The trans isomer (**8**) was eluted first (eluent hexane–benzene, 9:1) followed by the cis (**7**) (hexane–benzene, 8:2). The separation could be readily monitored by analytical GLC (20 ft 30% QF-1 on Chromosorb W, 60/80 mesh column at 160 °C) or by thin layer chromatography (hexane–acetone (9:1) on silica gel, R_f (**7**) 0.4, R_f (**8**) 0.55). The physical constants for the trans isomer are as follows: IR (neat) 2962 (vs), 2919 (s), 2865 (m), 1474 (m), 1430 (m), 1371 (s), 1237 (w), 1184 (m), 920 (w), 784 cm^{-1} (m); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.12 (s, 9 H), 2.15 (s, 3 H), 2.96 (m, 5 H), 4.0 (s, 1 H); MS (70 V) *m/e* 41 (43.5%), 45 (23.3%), 55 (6.5%), 57 (9.5%), 59 (11.0%), 61 (8.5%), 69 (8.75%), 73 (23.5%), 74 (10.4%), 87 (18.2%), 101 (6.3%), 117 (42.3%), 119 (17%), 165 (100%), 166 (8.3%), 167 (14.3%), 207 (2.1%), 222 (M^+, 22.5%); ^{13}C NMR spectrum, Table VI.

Alternative Synthesis of 7 and 8. A. The ethylene monothioketals of 2-*tert*-butyl-1,3-dithian-5-one were prepared by the standard method[27] from the ketone and β-mercaptoethanol. There resulted a mixture of the two diastereomeric ketals in a 57:43 ratio, mp 131–133 °C (for separation, see ref 11). However, attempts to reduce the mixed ketal with lithium aluminum hydride–aluminum chloride in the expectation of obtaining a β-hydroxythioether[28] were fruitless, even when the Soxhlet extraction technique[29] of the relatively insoluble monothioketal mixture was employed. It appeared that this treatment simply led to preferential destruction of the trans isomer and recovery of the pure cis isomer, mp 159–160 °C (lit.[11] 158–159.5 °C) (17%). See Scheme X.

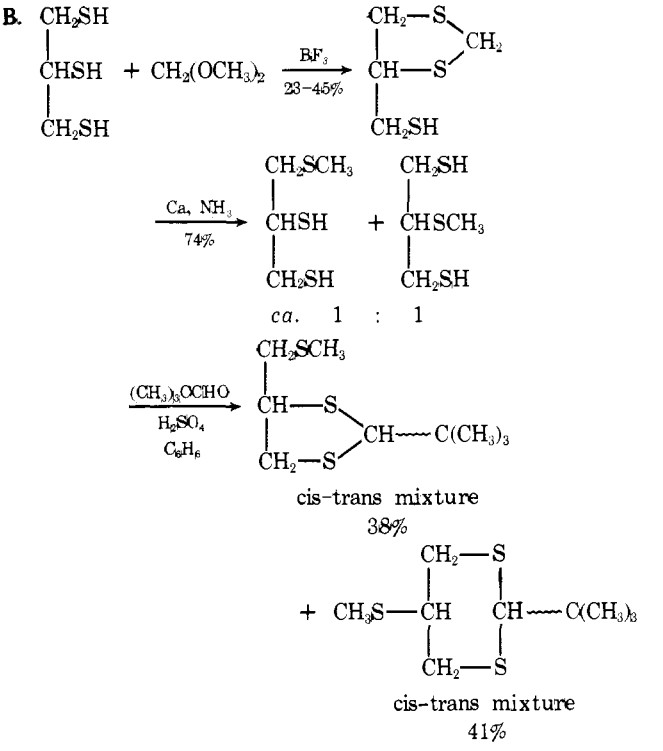
The two dithiolanes were not separated but gas chromatography on a 6-ft 20% FFAP on Chromosorb W 60/80 mesh column at 160 °C separated the two dithianes from each other and from the dithiolane mixture. The properties of the dithianes **7** and **8** so obtained were identical with those of the compounds described above. Details of this synthesis may be found elsewhere.[2]

Equilibrations and Analyses. The dithiane (ca. 30 mg) was placed in a 1-mL ampule and dissolved in ca. 500 mg of the solvent–catalyst mixture (e.g., TFA–$CHCl_3$, 1:9). The ampule was sealed and submerged in a constant temperature bath at 25 °C until equilibrium was reached, i.e., till samples *initially* rich in one or other diastereomer reached the same composition. This might take from 15 min to 3 months. (In some cases preliminary studies were carried out in NMR tubes to record the progress of equilibration by viewing the ^1H NMR spectrum at intervals.) The ampules were broken and the contents poured into a suspension of potassium carbonate in the inert solvent. Two drops of phenolphthalein was added and the suspension stirred until the red color of the indicator persisted. Alternatively the equilibrating solution was extracted three times with 0.5 N aqueous NaOH which was back-extracted with chloroform. The combined chloroform solutions were dried and concentrated and the residue was subjected to GLC. The preferred column for **3/4** was a 6-ft 5% FFAP on Chromosorb W, 80/100 mesh column at 130 °C whereas **7/8** were best analyzed on a 20-ft, 30% QF-1 on Chromosorb W, 80/100 mesh at 160 °C or a 6-ft 20% FFAP on Chromosorb A, 60/80 mesh column at 200 °C.

In all cases, response ratios were determined from known mixtures of the two components and the areas (measured by disc integrator or planimetrically) corrected accordingly. Standard deviations were estimated by the usual procedure.[18]

Dipole Moments. Dielectric constants of cyclohexane solutions were measured using a Wissenschaftlich-Technische Werkstätten Dipolemeter DM 01 equipped with a measuring cell DFL 2/D thermostated at 25 °C. The measuring scale was calibrated with pure cyclohexane, $\epsilon = 2.0148$ at 25 °C.[30] From the dielectric constants at varying concentrations the dipole moment was calculated[31] by the equation $\mu = \beta[(d\epsilon/dw)(M_1/M_2)]^{1/2}$ where $d\epsilon/dw$ is the slope of the plot of the dielectric constant of the cyclohexane solution vs. weight fraction of solute, M_1 is the molecular weight of the solvent (84.163 for cyclohexane), M_2 is the molecular weight of the solute, and $\beta = 0.9955$ for cyclohexane solutions.

Scheme X



Acknowledgment. This work was supported under NSF Grant CHE75-20052. We are grateful to Dr. A. A. Hartmann for first carrying out the preparation of compounds **1–4** and to Professor A. Streitwieser, Jr., for the use of his Tektroniz Model 4051 computer.

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Mechanism of Carbanion Addition to Carbonyl Compounds. Equilibria and Kinetics of Substituted Cyanohydrin Cleavage and Formation in Aqueous Solution. Substituted Cyanohydrin Proton Dissociation Constants

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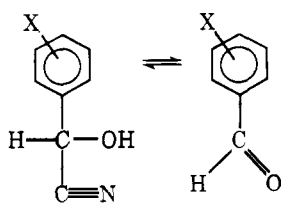
Abstract: The reactions of cyanohydrin formation and cleavage in dilute aqueous solution have been studied at 25 °C, ionic strength 1.0 M. The compounds studied include 4-NO_2-; 3-Cl-, 4-Cl; 4-Cl-; 4-H-; 4-CH_3-; 4-CH_3O-; and 4-$(CH_3)_2N$-substituted benzaldehydes. The equilibrium constants $K_1 = [>C(OH)CN]/[HCN][>C{=}O]$ and $K_1' = [>C(O^-)CN]/[CN^-][>C{=}O]$ have been determined from the pH dependence of the apparent cyanohydrin formation constants for this series of compounds and are correlated by ρ^+ values of 1.01 ± 0.04 and 1.49 ± 0.14, respectively. The K_a^T values ($K_a^T = [>C(O^-)CN]a_{H^+}/[>C(OH)CN]$), calculated from $K_a^T = K_a^{HCN}K_1'/K_1$, where K_a^{HCN} is the proton dissociation constant for HCN, are correlated by a ρ value of 0.70 ± 0.08. The rates of cyanohydrin formation and breakdown exhibit no significant general-base-catalyzed contribution, and are accounted for by the rate laws $v = k_1[HCN][>C{=}O][OH^-]$ and $v = k_{-1}[>C(OH)CN][OH^-] = k_{-1}'[>C(O^-)CN]$ where $k_{-1}' = k_{-1}K_w/K_a^T$ for the forward and reverse reactions, respectively, in the pH range 2.5–7.4. The ρ^+ values for k_1 and k_{-1} are 1.18 ± 0.06 and 0.27 ± 0.07, respectively. The ρ^+ value for the carbon–carbon bond cleavage step of the oxyanionic cyanohydrin, k_{-1}', is −0.19 ± 0.06. The absence of a detectable pH-independent pathway for cyanohydrin breakdown indicates that complete proton removal to form the oxy anion is necessary for the CN^- moiety to depart.

Introduction

Substituted cyanohydrin breakdown is a simple carbonyl group reaction (eq 1) which bears a formal similarity with



(1)

X = 4-$(CH_3)_2N$-; 4-CH_3O-; 4-CH_3-; H-; 4-Cl-; 3-Cl, 4-Cl-; 4-NO_2-

dealdolization reactions of substituted β-hydroxy-α-amino acids to form substituted benzaldehydes and α-amino acids.[1-3]

In the absence of adequate data on nonenzymatic dealdolization reactions of α-amino-β-hydroxy derivatives,[4] cyanohydrin breakdown appeared to offer a model system worthy of comparison with our studies of serine hydroxymethylase (E.C.2.1.2.1.).[3,37] However, both the earlier studies, which involved 95% ethanol as solvent and pyridine and other bases as catalysts, and more recent studies of the reaction in aqueous solution, published while the present study was in progress, have provided insufficient data for this purpose.[5] Furthermore, a strong solvent dependence of the rate of cyanohydrin formation has been reported.[5i,j] In this paper are reported sub-

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