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Conformational Analysis of 3-Aminothiacyclohexane and Derivatives by Low-Temperature ^{13}C NMR(*)

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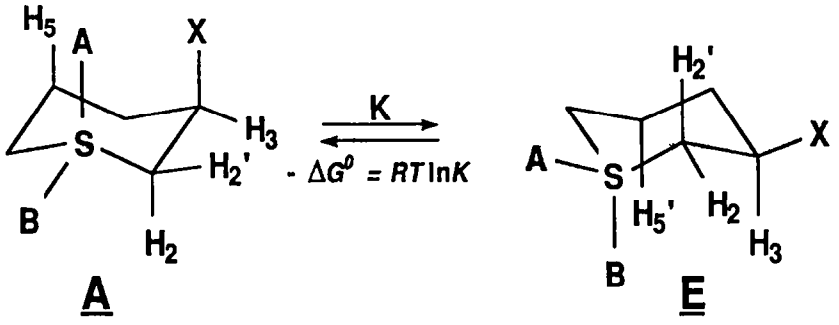
Abstract. Several *gauche* interactions between sulfur and nitrogen functions are determined from measurement of conformational equilibria of 3-(X)-thiacyclohexanes (X = NH_2, NMe_2, NHPh and $NHCO_2Bu^t$), their epimeric sulfoxides, and the corresponding sulfones, by low-temperature carbon-13 and proton NMR spectroscopy. The (RNH/S)*gauche* interaction is 0.18 (R=H), -0.04 (R=Ph) and -0.31 (R=CO_2Bu^t) kcal/mol. The (Me_2N/S)*gauche* interaction is 0.70 kcal/mol, of which 0.26 kcal/mol is estimated to arise from the *gauche* repulsive effect between the electron lone pairs. The (RNH/SOx)*gauche* interactions in the *trans*-sulfoxides (x=1) are approximately as destabilizing as expected on simple steric grounds, whereas in their *cis* epimers and in the sulfones they are 0.65 (R=H, x=1), 0.28 (R=H, x=2), -0.78 (R=Ph, x=1), -0.22 (R=Ph, x=2), < -1.94 (R=CO_2Bu^t, x=1) and <-1.41 (R=CO_2Bu^t, x=2) kcal/mol. Concentration and solvent effects in the RNH- series are small, intermediate and large, respectively, when R is H, Ph or CO_2Bu^t. The effect of protonation upon conformational equilibria is also discussed.

INTRODUCTION

We report in this paper the conformational analysis of 3-amino-thiacyclohexane and some derivatives listed in Scheme I, with a view to measuring the interactions between the sulfur and nitrogen functions in these compounds. Previous work related to this topic was confined to several acyclic systems, in which only semiquantitative conclusions could be reached.[1] In contrast, the recent conformational study of 3-oxygenated thiacyclohexanes[2] lead to quantitative values for various interactions between oxygen and sulfur functions. In the present paper we continue the systematic study of 3-substituted thiacyclohexanes with polar substituents by low temperature NMR. The interaction of three different nitrogen functions, NH_2, NHPh and $NHCO_2Bu^t$, with sulfide, sulfoxide and sulfone groups has been studied and compared with corresponding interactions of oxygen functions.[2b] In addition, study of 3-dimethylaminothiacyclohexane has led to an evaluation of the N/S *gauche* repulsive effect earlier seen in acyclic systems.

(*) *Dedicated to Prof. Ernest L. Eliel on the occasion of his 65th birthday.*



Compound	A	B	X
1	:	:	NH_2
2(*t*)	:	O	NH_2
3(*c*)	O	:	NH_2
4	O	O	NH_2
5	:	:	NHPh
6(*t*)	:	O	NHPh
7(*c*)	O	:	NHPh
8	O	O	NHPh
9	:	:	$NHCO_2But^t$
10(*t*)	:	O	$NHCO_2But^t$
11(*c*)	O	:	$NHCO_2But^t$
12	O	O	$NHCO_2But^t$
13	:	:	NMe_2

(*t* = trans; *c* = cis; : = lone pair)

Scheme I

SYNTHESIS AND NMR SPECTRA

Reduction of 3-thianone oxime[3] with $LiALH_4$ and of 3-thiacyclohexylidene-phenylamine with $NaBH_4$ yielded the corresponding sulfides 1 and 5 which, in turn, were converted to 9 and 13 by treatment with an equivalent of di-*t*-butyl carbonate or by methylation with formic acid/formaldehyde.[4] Oxidation of sulfides 5 (by H_2O_2/trifluoroacetic acid) and 9 (by $NaIO_4$ or *m*-chloroperbenzoic acid) yielded the corresponding sulfoxides 6-7 and 10-11 (mixture of *cis* and *trans* diastereomers) or sulfones (8, 12) by treatment, respectively, with one mole or excess of oxidant. Sulfoxides 10 and 11 were separated by flash chromatography and converted to the free amines 2 and 3 by mild acid hydrolysis. Sulfone 12 required basic hydrolysis for conversion to 4.

Table I summarizes the results of the first-order analysis, at room temperature, of the C(2)-C(3) fragment (Scheme I) whose protons were in general easily discerned by simple double resonance decoupling experiments. The table also contains the approximate populations of axial and equatorial conformers, calculated from the averaged coupling constants as previously described.[2b,5]

Table I.- First-Order Coupling Constants (Hz) and Chemical Shifts (ppm) of the Protons in Positions 2 and 3 for some of the Compounds in Scheme I at 25°C and Approximate Mole fractions of the Conformers in Scheme I (see text).

			Chemical shifts			Coupling Constants		Mole fract.[c]	
compd	solv[a]	conc[b]	H2	H2'	H3	J2,3	J2',3	x_A	x_E
1	A	1.79	2.52	2.23	2.81	3.3	9.4	0.28	0.72
	A	0.01	2.67	2.38	2.97	3.4	9.3	0.30	0.70
	A+B	*10*	2.99	2.71	3.77	2.6	6.8	0.63	0.37
3	A	2.60	2.88	-	2.58	3.3	10.2	0.17	0.83
	A	0.02	2.90	-	2.69	3.2	10.0	0.20	0.80
	A+B	*8*	3.72	2.84	4.25	2.4	3.2	≈1.00	≈0.00
4	A	0.51	3.15	2.72	3.29	3.6	10.5	0.11	0.89
	A	0.001	3.44	2.79	-	3.6	10.4	0.12	0.88
	A+B	*20*	3.68	3.48	4.17	-	8.9	0.29	0.71
5	A	1.00	2.88	2.42	3.53	3.0	8.1	0.44	0.56
	A	0.01	2.98	2.44	3.64	3.1	8.1	0.44	0.56
	A+B	*100*	2.83	2.66	3.94	2.8	8.0	0.46	0.54
7	A	0.54	-	-	3.92	-	≈6.1	0.67	0.33
	A	0.01	-	-	4.09	-	≈5.5	0.74	0.26
	A+B	*5*	2.90	3.60	4.33	2.9	≈4.0	≈0.96	≈0.04
8	A	0.02[d]	3.48	2.92	4.08	-	9.8	0.19	0.81

[a] Solvent A is $CDCl_3$; A+B, $CDCl_3$ + TFA. [b] Mol/l; the numbers in italics refer to the thiane:TFA molar ratio (thiane concentration ≤ 0.1M) [c] Mole fractions of conformers with axial (x_A) and equatorial (x_E) nitrogen group (Scheme I). [d] Very low solubility; the spectra in $CDCl_3$/TFA were deceptively simple.

Room- and low-temperature ^{13}C chemical shifts on one hand, and conformational parameters (equilibrium constants and free energies) under several conditions on the other, are indicated in Tables II and III, respectively. The numbers in parenthesis in Table II correspond to the difference between the observed chemical shifts and shifts calculated by parametric addition, the shift parameters to be added being derived from the spectra of the thiacyclohexane ring systems[6] and of various cyclohexylamines.[7,8] The linear regression of the plot of observed *vs.* calculated shifts in general gave excellent correlation coefficients[9] and we have thus assigned configurations of the *cis*- and *trans*-sulfoxides, **2-3**, **6-7** and **10-11** on the basis of the data in Table II. The finding that the conformational equilibria in the *trans* isomers (**2**, **6**, **10**) are strongly biased (*cf.* Table III) toward one side (*e*-NHR/*a*-SO), in contrast to those of their epimers **3**, **7**, **11** (see below), supports this assignment.

Table II.- Room- and Low-Temperature ^{13}C NMR Chemical Shifts (ppm) of Thiane Ring Carbons for the Compounds Studied in This Work (See Scheme I)[a]

[b]	[c,d]	C(2)	C(3)	C(4)	C(5)	C(6)	coef[e]
1	E	36.1(-3.2)	49.9(-2.2)	34.6(-2.3)	[27.0(+0.4)]	[27.6(-0.4)]	
	A	32.1(-3.7)	42.6(-4.3)		20.2(-0.8)		0.993
	RT	[35.2]	48.7	[36.7]	[26.3]	[27.8]	
2	E	52.2(-3.1)	40.4(+1.0)	34.1(-0.6)	15.8(+1.9)	43.8(0.0)	0.997
	RT	53.4	41.3	34.5	16.1	45.3	
3	E	59.1(-3.0)	46.4(-0.8)	33.2(-1.5)	19.0(-2.7)	50.0(-0.8)	
	A			27.2(-4.0)	8.4(+0.1)	44.8(0.0)	0.996
	RT	58.5	47.2	34.4	18.1	50.4	
4	E	58.4(-4.2)	48.0(-1.0)	32.6(-1.7)	20.4(-3.1)	49.2(-2.1)	
	A	55.4(-3.7)	46.4(+3.2)	30.8(0.0)	17.8(-0.1)	51.2(-1.1)	0.990
	RT	59.6	48.7	34.0	21.0	50.7	
5	E	32.5(+2.7)	50.4(-0.8)	32.4(+5.0)	27.6(+2.1)	28.1(+1.1)	
	A	32.9(+2.7)	42.9(-3.4)	27.7(-0.1)	20.7(0.0)	26.7(-0.3)	0.973
	RT	33.7	49.2	31.7	26.1	28.2	
6	E	47.8(-2.3)	40.9(+2.4)	31.5(+1.8)	16.3(+3.5)	44.2(+1.4)	0.995
	RT	50.3	43.0	32.6	16.7	45.8	
7	E	54.7(-2.4)	46.5(+0.2)	30.2(+0.5)	18.9(-0.7)	50.2(+0.4)	
	A	[45.6(-0.4)]	[44.5(+10.9)]	24.8(-0.8)	9.1(+1.0)	[44.9(+2.1)]	0.996[f]
	RT	50.3	47.6	28.8	13.6	47.9	
8	E		48.5(+0.4)	30.1(+0.7)	20.5(-1.9)	49.8(0.0)	
	A		44.7(+1.5)	24.7(-0.5)	18.2(+0.6)		0.997
	RT	55.9	49.7	30.0	20.4	51.2	
9	E	32.8(-1.7)	48.5(-2.3)	31.9(-0.2)	[26.9(+1.7)]	[28.9(+1.8)]	
	A		41.8(-3.4)	29.2(+0.2)	21.1(+0.5)		0.994
	RT	33.8	46.5	31.7	25.3	28.0	
10	E	48.5(-1.8)	40.1(+2.0)	31.1(+1.2)	16.3(+3.8)	43.5(+0.6)	0.998
	RT	50.4	42.0	31.6	16.5	45.6	
11	E	55.9(-1.4)	45.1(-0.8)	30.3(+0.4)	18.9(-1.4)	50.0(+0.1)	
	A	[44.5(-2.7)]	44.3(+11.8)	28.8(+2.0)	9.8(+1.9)	[44.8(+1.5)]	0.996[f]
	RT	49.5	44.8	29.6	13.0	47.0	
12	E	55.6(-2.2)	46.8(-0.9)	29.8(+0.3)	20.4(-1.7)	49.5(-0.9)	
	A	53.4(-1.3)	44.9(+2.8)	27.9(+1.5)	19.8(+2.3)	51.1(+0.3)	0.994
	RT	55.2	46.5	29.4	19.9	50.9	
13	E	[28.2(-2.8)]	62.3(-3.0)	[27.6(-1.0)]	[26.7(-0.4)]	[27.8(-0.9)]	
	A		57.6(-4.3)		18.9(-3.1)		0.998
	RT	[28.9]	63.5	[28.8]	[28.5]	[28.7]	

[a] Chemical shifts for carbons different from those of the thiane ring are not included in the table for the sake of simplicity. Nevertheless, compounds **5-8** showed the phenyl ring signals at 113.3±0.4, 118.1±0.7, 129.4±0.2, 145.6±0.6 ppm; compounds **9-12** the CO_2Bu^t signals at 28.1±0.2, 79.3±0.5, 154.6±0.2 ppm; and compound **13** the NMe_2 signal at 40.4 ppm; close-by values in brackets may be exchanged. [b] Compound number (see Squeme I). [c] Low-temperature spectra in CD_2Cl_2: A (axial) and E (equatorial) are referred to the position of the nitrogen function. [d] RT, averaged spectrum in $CDCl_3$ at room temperature. [e] Correlation coefficient for linear regression analysis of observed *vs.* calculated values. [f] The regression does not include C(3).

Table III.- Conformational Free Energy (kcal/mol) for the Equilibrium of the Compounds Studied in This Work (See Squeme I)

compd	solv[a](conc)[b]	signals measured[c]	K[E]/[A]	-ΔG°[d]
1	A (0.16)	3C	13.75 ± 2.25	0.88 ± 0.05
	C (1.9)	3C	15.06 ± 2.08	1.03 ± 0.05
2	A (0.32)		>50.0	>1.40
3	A (1.13)	3C	31.83 ± 3.10	1.24 ± 0.03
	A (0.4)	3C	27.98 ± 3.52	1.27 ± 0.04
	C (2.0)	1C	28.04 ± 3.16	1.27 ± 0.04
4	A (0.51)	3C	28.30 ± 7.47	1.20 ± 0.08
	C (0.5)		>50.0	>1.40
5	A (0.9)	4C	3.91 ± 0.04	0.56 ± 0.04
	C (0.2)		>50.0	>1.40
6	A (0.2)		>50.0	>1.40
7	A (1.0)	2C	0.76 ± 0.01	-0.10 ± 0.01
	A (0.2)	2C	0.56 ± 0.03	-0.22 ± 0.02
	B (0.2)	1C	2.00	0.27
	C (0.2)		>50.0	>1.40
8	A (0.1)[e]	2C	4.82 ± 0.18	0.64 ± 0.02
9	A (0.2)	2C + 2H	2.08 ± 0.22	0.25 ± 0.03
	A (0.002)	2H	2.16 ± 0.03	0.26 ± 0.01
	C (0.2)	2H	20.41 ± 4.02	1.01 ± 0.06
10	A (0.77)	2H	26.32 ± 4.10	1.24 ± 0.06
	A (0.01)	1H	21.28	1.16
	C (1.0)		>50.0	>1.40
11	A (1.24)	4C + 1H	0.84 ± 0.03	-0.07 ± 0.02
	A (0.003)	1H	0.02	-1.49
	B (0.8)	3C	0.97 ± 0.01	-0.01 ± 0.02
	B (0.04)	1H	0.58	-0.21
	C (0.9)	2C	10.33 ± 0.42	0.89 ± 0.01
	C (0.03)	1H	10.77	0.90
12	A (0.78)	2C	4.74 ± 0.04	0.59 ± 0.01
	A (0.0001)	2H	0.37 ± 0.05	-0.38 ± 0.05
	B (0.02)	2H	28.57 ± 4.76	1.27 ± 0.06
	C (0.02)		>50.0	>1.40
13	A (0.91)	2C	52.63 ± 5.01	1.42 ± 0.03
	C (0.86)	2C	≈125	≈1.8

[a] Solvent A is CD_2Cl_2; B, acetone-d_6; C, CD_3OD. [b] Mol/l. [c] Number of signal pairs used to evaluate K: C, ^{13}C signals; H, ^1H signals. [d] Temperature was set between 170 and 203K, depending on the solubility of the compound, to attain the best possible s/n ratio; [e] Insoluble in methanol at low temperature.

RESULTS AND DISCUSSION

Table IV summarizes the *gauche* interactions between different X groups and the studied sulfur functions estimated, assuming additivity of the interactions present in each conformer of Scheme I, by means of the following equations: i) $(X/S) = -\Delta G^0 - (X/CH_2)_{gauche}$; ii) $trans\text{-}(X/SO) = -\Delta G^0 - (X/CH_2)_{gauche} + a + b$;

iii) *cis*-*(X/OS)* = $-\Delta G^0$ - *(X/CH2)gauche* - *a*; iv) *(X/O2S)* = $-\Delta G^0$ - *(X/CH2)gauche* + *b*, where *a* is the (SO/H5a) interaction [similar to that in thiane *S*-oxide (-0.08 kcal/mol)[10]], and *b* is the (SO/H3a) interaction. The latter depends on X and is taken to be that in 1,4-oxathiane *S*-oxide (-0.34 kcal/mol)[11] for X = OH, OAc, OMe, in 1,4-thiamorpholine *S*-oxide (-0.22 kcal/mol)[12] for X = NH_2, NHPh, and in *N*-*t*-butoxycarbonyl-1,4-thiamorpholine *S*-oxide (-0.49 kcal/mol)[12] for X = $NHCO_2Bu^t$. The numbers in parenthesis (Δ) correspond to the difference between these interactions and their values calculated from an "exclusively steric" point of view.[13,14,15] Therefore, a negative value of Δ indicates that the interaction between the heteroatomic functions is smaller (attractive) than expected on steric grounds. Although these numbers have a limited quantitative meaning due to the neccesary approximations made, they will be useful to guide the discussion and to give an indication of the presence of interactions between the heteroatoms other than steric, such as dipolar interactions, lone pair/lone pair repulsions and *intra*molecular hydrogen bonding.

Table IV.- Comparison Among the Heteroatomic Interactions in CD_2Cl_2 (kcal/mol) for Several 3-(X)-Thiacyclohexanes and their Sulfoxides and Sulfones (see text).[a]

	X(compd)						
interact.[b]	OH[c]	OAc[c]	OMe[c]	NH_2	NHPh	$NHCO_2Bu^t$	NMe_2
(X/S)	-0.08	0.91	0.79	0.18(**1**)	-0.04(**5**)	-0.31(**9**)	0.70(**13**)
(Δ)	(-0.26)	(0.67)	(0.61)	(-0.25)	(-0.43)	(-0.64)	(0.26)
(X/SO)t		-0.25	-0.39	>0.40(**2**)	>0.46(**6**)	0.13(**10**)	
(Δ)		(-0.52)	(-0.59)	(>-0.08)	(>0.02)	(-0.24)	
(X/OS)c	<-1.50	>1.00	1.13	0.65(**3**)	-0.78(**7**)	<-1.94(**11**)	
(Δ)	(<-1.93)	(>0.44)	(0.71)	(-0.35)	(-1.80)	(<-2.68)	
(X/O2S)	<-0.80	>0.57	>0.67	0.28(**4**)	-0.22(**8**)	<-1.41(**12**)	
(Δ)	(<-1.23)	(>0.01)	(>0.25)	(-0.82)	(-1.14)	(<-2.29)	

[a] The numbers in parenthesis (Δ) correspond to the difference between the heteroatomic interactions and their values calculated from an "exclusive steric" point of view (see text) [b] Subscripts *t* and *c* refer to *trans* and *cis*, respectively. [c] Estimated from - G^0 values of ref. 2b.

Let us first focus on the thioethers. It may be seen in Table IV that the (X/S)*gauche* interaction is lower than expected on steric grounds when X is OH (Δ = -0.26 kcal/mol), NH_2 (**1**; Δ = -0.25 kcal/mol), NHPh (**5**; Δ = -0.43 kcal/mol) and $NHCO_2Bu^t$ (**13**; Δ = -0.64 kcal/mol), *i.e.* in compounds where *intra*molecular hydrogen bonding can take place. Unfortunately, the strength of the hydrogen bond cannot be evaluated since the dipole/dipole interaction between C-S and C-O or C-N bonds is not known. However, room-temperature ^1H NMR spectra in $CDCl_3$ of compounds **1** and **5** (Table I), and low-temperature ^{13}C NMR spectra in CD_2Cl_2 of carbamate **9** (Table III) show that the conformational

equilibria of these compounds are insensitive, over a relatively wide range, to concentration, *i.e.* there is no competition between *inter*- and *intra*molecular interactions. This contrasts with the situation in 3-hydroxythiane, in which $-\Delta G^{o}$ changes by *ca.* 1 kcal/mol from 3.5M to 10^{-3}M solutions in CD_2Cl_2 or $CDCl_3$[2b] and suggests that hydrogen bonding in the aminothianes is much weaker than in the analogous hydroxy derivative. When *inter*molecular interactions with solvent become important, as in methanol-d_4 (which may act as acceptor as well as donor in hydrogen bonding) equilibrium in the three thioethers **1**, **5** and **9** does shift to the equatorial side (Table III). On the other hand, the (X/S)*gauche* interaction is higher than expected from a steric viewpoint when X is OAc (Δ = 0.67 kcal/mol), OMe (Δ = 0.61 kcal/mol) and NMe_2 (**13**; Δ = 0.26 kcal/mol; cf. Table IV), *i.e.* in those cases where the heteroatom turns a pair into the ring in the A conformer (Scheme I) to avoid the strong steric interactions that would otherwise result. Taking into account that the C-N bond is less polar than the C-O bond and that dipolar repulsion is already small in 3-hydroxythiane[2b], one may take the energy excess of the (Me_2N/S)*gauche* interaction (0.26 kcal/mol; *cf.* Table IV) as an estimate for the "*gauche*-repulsive" effect[16] between nitrogen and sulfur in **13**.

In the *trans*-sulfoxides **2** and **6** in solvent CD_2Cl_2 (Table III) the mole fraction of the conformer with axial sulfinyl and equatorial nitrogen is higher than 95% ($-\Delta G^{0}$ > 1.4 kcal/mol). The estimated values of Δ (Table IV), >-0.08 and >0.02 kcal/mol for **2** and **6**, respectively, are close to zero but they can be higher. This suggests that the *trans*-(NHR/SO) interaction is at least as repulsive as it should be expected on steric grounds when R is H or Ph. In contrast, the interaction of sulfinyl sulfur with axial OAc and OMe groups (Δ = -0.52 and -0.59 kcal/mol, respectively; *cf.* Table IV) is attractive, presumably by electrostatic $O^{\delta-}/S^{\delta+}$ interaction. In the case of the carbamate **10**, the (*e*-NHR/*a*-SO) conformer, for unknown reasons, appears to be less stable than expected in view of the negative Δ value calculated for this compound (-0.24 kcal/mol; *cf.* Table IV). In this case we cannot postulate an attractive interaction between $S^{\delta+}$ and nitrogen in the (*a*-NHR/*e*-SO) conformer since the amido nitrogen is also electron deficient due to resonance with carbonyl.

The population of the diaxial conformer in the *cis*-3-(X)-thiane *S*-oxide series in CD_2Cl_2 (dilute solution) varies (see Table III and ref. 2b) from less than 3% in **3** (X = NH_2; $-\Delta G^{0}$ = 1.27 kcal/mol) and the 3-methoxy derivative (X = OMe; $-\Delta G^{0}$ > 1.3 kacl/mol[2b]), to at least[17] 64% in **7** (R = NHPh; $-\Delta G^{0}$ = -0.22 kcal/mol), and to more than 97% in both **11** (X = $NHCO_2Bu^{t}$; $-\Delta G^{0}$ < -1.49 kcal/mol) and the 3-hydroxy derivative (X = OH; $-\Delta G^{0}$ < -1.3 kcal/mol[2]). The (X/OS)*gauche* interaction in the *cis* isomers is much more complex than in their *trans*

counterparts since there may be attractive components [both electrostatic ones ($X^{\delta-}/S^{\delta+}$ when X = OR[18] and $N^{\delta+}/O^{\delta-}$--S in 11) and X-H...O-S hydrogen bonding] as well as repulsive parts [both electrostatic ($X^{\delta-}/O^{\delta-}$--S when X = NH_2 (3), NHPh (7), and $N^{\delta+}/S^{\delta+}$ in 11) and steric]. Estimation of the total interaction (Table IV) gave a value of +0.65 kcal/mol for 3 (X = NH_2), -0.78 kcal/mol or less[17] for 7 (X = NHPh), less than -1.94 kcal/mol for 11 (X = $NHCO_2Bu^t$), and less than -1.5 kcal/mol for X = OH. In all these cases, the estimated values for Δ are negative suggesting that the attractions are more important than the repulsions, in contrast with the 3-methoxyderivative in which the (MeO/OS)*gauche* interaction is repulsive (1.13 kcal/mol; Δ = 0.71 kcal/mol; *cf.* Table IV). Unfortunately, the picture is too complex to evaluate the exact contribution of all the components. Nevertheless, the concentration dependence of $-\Delta G^0$ in CD_2Cl_2 shown by compounds 7 and 11 (Table III), but not by 3 ($J_{2',3}$ changed very little, by *ca.* 0.2 Hz, when 3 was diluted 130 times in $CDCl_3$, whereas the same coupling constant in 7 changed by *ca.* 0.6 Hz when 7 was diluted 54 times in the same solvent; see Table I), strongly suggests that *intra*molecular R-NH...O-S interaction is a very important stabilizing factor for the diaxial conformer of the compounds studied when R is Ph or CO_2Bu^t. The competition between this *intra*molecular attraction and solute-solute (at high concentrations in CD_2Cl_2) or solute-solvent associations (in acetone-d_6 or methanol-d_4) - which favor the diequatorial conformer[2] for steric reasons - explains why the conformational equilibria of compounds 7 and 11 are shifted to the diequatorial side in concentrated solutions in CD_2Cl_2, or in acetone-d_6 or methanol-d_4 (Table III).

The sulfones 4, 8[19] and 12 also showed different behavior among each other but similar, for corresponding nitrogen substituents, to that of the aforediscussed *cis*-sulfoxides. Thus, the axial conformation becomes more populated in CD_2Cl_2 as one goes down in Table III (3% in 4, *ca.* 17% in 8, and 73% in 12 at high dilution), *i.e.* from NH_2 to NHPh to $NHCO_2Bu^t$ groups, and the (X/O$_2$S)*gauche* interactions (Table IV) showed a similar trend: 0.28 (4, X=NH_2), -0.22 (8, X=NHPh) and <-1.41 (12, X=$NHCO_2Bu^t$) kcal/mol. The lower population of the axial conformer in 8 and 12 compared to that of 7 and 11 under similar conditions (*cf.* Table IV) suggests that the sulfone group interacts less favorably with the phenylamino or carbamate group than does the *cis*-sulfoxide. This is in agreement with the known, weaker hydrogen-bonding ability of sulfones compared to the more polar sulfoxides.

Finally, the effect of protonation at nitrogen was studied. It may be seen from Table I that, in the case of compounds 1, 3, 4 and 7, the addition of an excess of trifluoracetic acid (TFA) shifted the equilibrium toward the conformer with axial nitrogen (Scheme I), suggesting that the attractions between the

heteroatomic functional groups are enhanced by protonation. Thus, compound **1** displayed a change in x_A from 28% in $CDCl_3$ to *ca.* 63%, when a ten-molar excess of TFA was added to the solution, *i.e.* $-\Delta G^0$ changed by -0.9 kcal/mol from nonprotonated to protonated NH_2 in **1**. In contrast, the population of the axial conformer in the phenylamine **5** hardly changes with protonation (*cf.* Table I), suggesting that the inductive effect of the phenyl group plays an important role in minimizing the $(^+N/S)_{gauche}$ interaction.[20] The shift in equilibrium of the *cis*-sulfoxide **3** upon protonation is, in turn, striking: the nitrogen changes its axial preference from *ca.* 17% in $CDCl_3$ to virtualy 100% at a 8:1 TFA/substrate molar ratio, suggesting a very strong $(^+NH_3/SO)_{gauche}$ interaction, presumably due to hydrogen bonding as well as to electrostatic $^+N/O^{\delta-}$ attraction. In contrast, the equilibrium of the corresponding sulfone **4** changed very little (by *ca.* 18%) which is reasonable in view of the lower polarity of sulfone group compared to sulfoxide.

EXPERIMENTAL SECTION

^1H (200 MHz) and ^{13}C NMR (50 MHz) were recorded on either Bruker WP-200-SY (UAM, Spain) or AC-200 (UNC, USA) instruments (coupled to ASPECT 2000 and 3000 computers, respectively) equipped with 5 mm dual $^1H/^{13}C$ probes, operated in pulse FT mode and locked on solvent deuterium. Low temperature spectra were controlled in both spectrometers with a Bruker B-VT-1000 unit previously calibrated by standard procedures. The ^{13}C spectral parameters were set as described elsewhere.[2b] Mass spectra (MS) were recorded on a Hewlett-Packard 5985 spectrometer (UAM, Spain) at electron impact (70 eV). Mass data are reported in mas units (m/z) and the values in brackets regard the relative intensity from base peak (as 100%). Boiling and melting points are uncorrected. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ, USA). IR spectra were recorded on a Nicolet FT-20DX instrument (UNC, USA).

3-Aminothiacyclohexane (1). To a suspension of 2.47 g (65 mmol) of $LiAlH_4$ in 85 ml of anhydrous ethyl ether was slowly added 4.25 g (32 mmol) of 3-oxothiacyclohexane oxime[3] in 130 ml of anydrous ethyl ether. The reaction mixture was stirred and refluxed for 2 h and the excess of reducing agent carefully destroyed with ethyl acetate at 0-5°C. The residue was treated with water until the two phases separated and extracted with CH_2Cl_2. Standard workup of the extracts yielded 3.78 g (99%) of crude **1** which was purified by crystallization, from ethanol, of the corresponding oxalate (mp 226°C) or picrate (mp 175-176°C) obtained by standard methods: IR (film) 3314, 2923, 2848, 1590, 1450, 1437 and 1423 cm^{-1}.; ^1H NMR ($CDCl_3$) δ 1.22 (m, 1 H), 1.66 (s broad, 2 H), 1.75 (m, 1 H), 1.90 (m, 1 H), 2.05 (m, 1 H), 2.39 (m, 1 H), 2.48 (m, 2 H), 2.67 (m, 1 H) and 2.98 (m, 1H); MS 117 M^+ (88.8), 100 (4.3), 85 (6.8), 74 (11.1), 56 (78.8), 43 (100), 42 (24.7). Anal. Calcd. for $C_{11}H_{14}N_4O_7S$ (picrate): C, 38.16, H, 4.08. Found: C, 37.92, H, 4.19.

***N*-*t*-Butoxycarbonyl-3-aminothiacyclohexane (9).** To a solution of **1** in anhydrous CH_2Cl_2 was added slowly an equimolecular amount of di-*t*-butyl carbonate, used as received from Aldrich. Co., and the mixture was stirred overnight at room temperature. The solvent was then removed and the crude **5** crystallized from hexane (mp 80-81°C). Yield 85%. IR (nujol): 3343, 3290, 1682, 1524, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H) 1.46 (m, 1 H), 1.80 (m, 2 H), 1.96 (m, 1 H), 2.48 (m, 3 H), 2.87 (m, 1 H), 3.82 (m, 1 H), 5.05 (d broad, 1 H). MS 217 M^+ (11.6), 161 (7.8), 144 (7.1), 118 (9.3), 100 (100), 85 (6.6), 73 (5.6), 57 (41.8), 43 (34.0).

***N*-*t*-Butoxycarbonyl-3-aminothiacyclohexane *S*-Oxide (10, 11).** To a dispersion of tioether **9** in water was added an equimolecular amount of sodium metaperiodate at 0-5°C. The mixture was stirred overnight at room temperature, the solvent removed, and the resulting cake extracted with $CHCl_3$ in a Soxhlet apparatus. The mixture of diastereomers **10** and **11** was purified by flash chromatography on silica gel (acetone; yield 73%) and they were separated by a second flash chromatography [chloroform-methanol (10:1)] (mp **10**, 156-157°C; mp **11**, 85-89°C). IR **10** (0.1M $CDCl_3$): 3444, 2982, 2932, 2869, 1708, 1501, 1165, 1068, 1041, 1015 cm^{-1}; IR **11** (0.01M $CDCl_3$): 3443, 3381, 2982, 2933, 2866, 1701, 1505, 1166, 1062,

1031 cm^{-1}; ^{1}H NMR **10** (CDCl$_3$) δ 1.45 (s, 9 H), 1.55 (m, 1 H), 1.95 (m, 2 H), 2.50 (m, 3 H), 2.92 (m, 1 H), 3.18 (m, 1 H), 4.23 (m, 1 H), 4.90 (d broad, 1 H); ^{1}H NMR **11** (CDCl$_3$) 1.25 (m, 1 H), 1.40 (s, 9 H), 1.70 (m, 3 H), 2.43 (m, 1 H), 2.70 (m, 1 H), 2.90 (m, 2 H), 4.11 (m, 1 H), 6.53 (d broad, 1 H). MS (**10**) 217 (0.4), 177 (25.4), 160 (27.0), 133 (17.0), 116 (19.9), 100 (14.4), 82 (14.2), 70 (38.7), 57 (100), 43 (14.2), 41 (23.1); MS (**11**) 233 M$^+$ (0.3), 216 (0.6), 177 (60.8), 160 (54.4), 133 (26.1), 116 (31.3), 100 (16.7), 82 (19.0), 70 (34.8), 57 (100), 43 (19.5), 41 (26.6).

***N*-t-Butoxycarbonyl-3-aminothiacyclohexane *S,S*-Dioxide (12)** was prepared by treatment of **9** with an excess of oxidant following the procedure described for the sulfoxides **10, 11**. The crude sulfone was purified by flash chromatography (acetone). Yield 87%. (mp 134°C). IR (0.03M CDCl$_3$): 3421, 2983, 2938, 2871, 1708, 1504, 1313, 1165, 1138 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.32 (s, 9 H), 1.50 (m, 2 H), 1.90 (m, 2 H), 2.89 (m, 3 H), 3.22 (m, 1 H), 4.04 (m, 1 H), 5.55 (d broad, 1 H). MS 249 M$^+$ (0.6), 194 (10.8), 176 (13.1), 150 (39.1), 133 (12.5), 101 (6.2), 81 (30.6), 69 (74.4), 57 (100), 43 (58.9), 41 (67.1). Anal. Calcd. for C$_{10}$H$_{19}$NO$_4$S: C, 48.17, H, 7.68. Found: C, 48.40, H, 7.52.

3-Aminothiacyclohexane *S*-Oxide (2, 3). The two diastereomers were separatedly obtained by acid hydrolysis of **10** and **11**, respectively, as follows: the starting carbamate was dissolved in 3N HCl in ethyl acetate and stirred for 10 min, the solution was carefully neutralized with sodium bicarbonate, the solvent removed, and the solid mass extracted with CHCl$_3$ in a Soxhlet apparatus. The crude sulfoxides were purified by flash chromatography (methanol; yield 50%) but did not crystallize in our hands. IR **2** (film): 3436, 3317, 3265, 1653, 1597, 1445, 1416, 1026, 994 cm^{-1}; IR **3** (film): 3301, 2930, 2858, 1653, 1443, 1428, 1028 cm^{-1}. ^{1}H NMR **2** (CDCl$_3$) δ 1.35 (m, 1 H), 1.60 (m, 1 H), 1.70 (s broad, 2 H), 2.00 (m, 2 H), 2.35 (m, 2 H), 2.95 (m, 1 H), 3.15 (m, 1 H), 3.45 (m, 1 H); ^{1}H NMR **3** (CDCl$_3$) δ 1.26 (m, 1 H), 1.56 (m, 1 H), 1.83 (s broad, 2 H), 1.85 (m, 1 H), 2.13 (m, 1 H), 2.48 (m, 2 H), 2.98 (m, 1 H), 3.14 (m, 1 H), 3.23 (m, 1 H). MS (**2**) 133 M$^+$ (22.0), 116 (58.8), 105 (2.5), 99 (24.2), 91 (6.3), 82 (19.7), 70 (53.4), 57 (52.8), 43 (100), 42 (39.9); MS (**3**) 133 M$^+$ (8.7), 116 (24.7), 105 (10.0), 99 (12.3), 91 (10.5), 82 (15.5), 69 (32.0), 56 (34.2), 43 (100), 42 (35.2).

3-Aminothiacyclohexane *S,S*-Dioxide (4). Carbamate **12** was dissolved in a 10% potassium hydroxide/methanol 1:1 mixture and refluxed for 48 h. The solvent was then removed and the resulting solid mass extracted with CHCl$_3$ in a Soxhlet. The usual workup of the extracts yielded the crude sulfone which was purified by recrystallization from hexane/ethyl acetate (mp 83-84°C). IR (nujol): 3358, 1272, 1130 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.36 (m, 1 H), 1.82 (s broad, 2 H), 2.09 (m, 3 H), 2.81 (m, 1 H), 2.98 (m, 2 H), 3.23 (m, 1 H), 3.40 (m, 1 H). MS 149 M$^+$ (1.3), 121 (0.2), 106 (7.8), 84 (6.3), 69 (16.8), 57 (34.1), 43 (100), 42 (27.6).

***N,N*-Dimethyl-3-aminothiacyclohexane (13).** To 0.66 g (5.7 mmol) of **1** was slowly added 17.1 mmol of 88% formic acid and 17.1 mmol of 37% formaldehyde at 0°C. The reaction mixture was stirred at 80°C for 24 h and acidified with 20% hydrochloric acid at room temperature. The solution was extracted once with CH_2Cl_2 and the extract discarded; the aqueous layer was then carefully neutralized with sodium bicarbonate and extracted with CH_2Cl_2. Standard workup of the extracts yielded crude **13** that was purified as the oxalate by recrystallization from ethanol (oxalate mp 111-112°C). ^{1}H NMR (CDCl$_3$) δ 1.32 (m, 1 H), 1.70 (m, 1 H), 1.92 (m, 1 H), 2.14 (m, 1 H), 2.30 (s, 6 H), 2.60 (m, 5 H). MS 145 M$^+$ (29.2), 101 (8.6), 84 (63.1), 71 (100), 56 (23.0), 42 (17.5). Anal. Calcd. for C$_9$H$_{17}$NO$_4$S (oxalate): C, 45.94, H, 7.28. Found: C, 46.05, H, 6.98.

***N*-Phenyl-3-aminothiacyclohexane (5).** A solution of 4.24 g (37 mmol) of 3-oxothiacyclohexane, 4.08 g (44 mmol) of aniline and 0.04 g of anhydrous zinc chloride in 100 ml of benzene was refluxed in a Dean-Stark for 5 h. The solution was filtered and the solvent evaporated. The residue was dissolved in 100 ml of ethanol and 1.39 g of sodium borohydride were added at 0-5°C in small portions. The reaction mixture was stirred overnight at room temperature and treated with 50 ml of water. The solution was concentrated and extracted with CHCl$_3$. Work up of the extracts afforded 6.5 g of crude product which was purified by distillation in the Kugelrohr (bp. 120-140°C/0.1 mm Hg) or by flash chromatography (CHCl$_3$). IR (film): 3386, 2928, 1601, 1503, 749, 692 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.39 (m, 1 H), 1.72 (m, 2 H), 1.95 (m, 1 H), 2.32 (m, 1 H), 2.45 (m, 2 H), 2.86 (m, 1 H), 3.52 (m, 1 H), 3.84 (s broad, 1 H), 6.55-7.1 (m, 5 H).

***N*-Phenyl-3-aminothiacyclohexane *S*-oxide (6, 7).** To a solution of 68 mg (0.35 mmol) of **5** in 0.1 ml of trifluoracetic acid (TFA) was added 0.34 ml (0.35 mmol) of a solution of 0.12 g/ml of 30% hydrogen peroxide in trifluoracetic acid at 0°C. The mixture was stirred 1 h, carefully neutralized with saturated NaCO$_3$H solution and extracted with CD_2Cl_2. Work up of the extracts afforded a 2:1 mixture of the diastereomers (*cis* isomer as major product). Yield 57 mg (77%). The *trans* isomer precipitated from ethyl acetate (mp 172-173°C) and the *cis* isomer in the mother liquors was partially purified by flash chromatography (ethyl acetate/methanol 4.5:1); however, it was always contaminated with *ca.* 20%

of its diastereomer and was not crystalline in our hands. IR (nujol; mixture of diastereomers): 3347, 1601, 1497, 1009, 752, 696 cm^{-1}; ^1H NMR **6** ($CDCl_3$) δ 1.43 (m, 1 H), 2.00 (m, 1 H), 2.18 (m, 2 H), 2.43 (m, 1 H), 2.56 (m, 1 H), 2.98 (m, 1 H), 3.1 (s broad, 1 H), 3.39 (m, 1 H), 6.7-7.2 (m, 5 H); ^1H NMR **7** ($CDCl_3$) δ 1.68 (m, 1 H), 1.90 (m, 2 H), 2.45 (m, 1 H), 2.91 (m, 2 H), 3.03 (m, 2 H), 3.96 (m, 1 H), 6.6-7.2 (m, 5 H). Anal. Calcd. for $C_{11}H_{15}NOS$ (*trans*-isomer): C, 63.12, H, 7.22. Found: C, 63.02, H, 7.10.

***N*-Phenyl-3-aminothiacyclohexane *S,S*-dioxide (8).** To a solution of 67 mg (0.35 mmol) of thioether **5** in 0.2 ml of trifluoracetic acid was added 0.1 ml (0.88 mmol) of 30% hydrogen peroxide at 0°C. The mixture was stirred for 1 h, carefully neutralized with saturated $NaCO_3H$ solution and extracted with CD_2Cl_2. Work up of the extracts yielded 62 mg of sulfone **8** which was purified by flash chromatography (ethyl acetate) and recrystallized from methanol. Mp. 182 °C. IR (nujol): 3372, 1603, 1498, 1283, 1135, 744, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (m, 1 H), 2.05 (m, 2 H), 2.23 (m, 1 H), 2.87 (m, 1 H), 3.00 (m, 2 H), 3.46 (m, 1 H), 3.95 (s broad, 1 H), 4.09 (m, 1 H), 6.75-7.25 (m, 5 H). Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.64, H, 6.71. Found: C, 58.76, H, 6.81.

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5.- The model couplings $J_{2',3}$ (Hz) are as follows:

Groups	J_{2e3e}	J_{2a3a}
N/S	3.39	11.80
N/SO	3.34	11.65
N/SO_2	3.17	11.37
+N/S	3.93	11.51
+N/SO	3.87	11.35
$+N/SO_2$	3.70	11.08

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8.- The corresponding parameters for the $NHCO_2Bu^t$ and NHPh groups have not been found in the literature; those for the $NHCO_2Bu^t$ had been obtained from the low temperature spectrum of the mixture of *cis*- and *trans*-*N*-*t*-butoxycarbonyl-4-methylcyclohexylamine, taking the conformationaly homogeneous *trans* isomer as model for equatorial $NHCO_2Bu^t$, and the conformer with axial $NHCO_2Bu^t$ of the *cis* isomer as model for axial $NHCO_2Bu^t$, and subtracting the effect exerted by equatorial methyl (ref 7). The parameters (ppm) are as follows: equatorial $NHCO_2Bu^t$ C(1), +22.6, C(2,6), +5.2, C(3,5), -3.0, C(4), -2.2; axial $NHCO_2Bu^t$ C(1), +17.0, C(2,6), +2.1, C(3,5), -7.6, C(4), -1.8.In the case of the NHPh group the parameters were directly obtained from the low temperature spectrum of phenylcyclohexylamine and they are as follows (ppm): equatorial NHPh C(1), +23.0, C(2,6), +5.0, C(3,5), -2.7, C(4), -2.3; axial NHPh, C(1), +18.1, C(2,6),

+0.9, C(3,5), -7.5, C(4), -2.3.

9.- The large discrepancy between observed and calculated shifts for C(3) of the *cis*-sulfoxides **7** and **11** (*ca.* 11 ppm; Table II) has been observed in similar compounds (ppm): *cis*-3-hydroxythiacyclohexane *S*-oxide (**A**), calc. 54.0, obs. 65.5; 3-methyl derivative of **A** (**B**), calc. 64.7, obs. 70.0; acetyl derivative of **B**, calc. 63.1, obs. 75.0 (see ref. 2b).

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13.- The *gauche* (X/S), (X/SO) -*trans* sulfoxides-, (X/OS) -*cis* sulfoxides- and (X/O$_2$S) interactions are calculated to be 0.61, 0.69, 1.44 and 1.44 times, respectively, the (X/CH$_2$)*gauche* interaction. These estimates were arrived at based on several data: from 3-methylthiane (see ref. 15a) and methylthiocyclohexane (see ref. 15b), in which the respective (Me/S)*gauche* and (S/CH$_2$)*gauche* interactions (0.53 kcal/mol) are 0.61 times the (Me/CH$_2$)*gauche* interaction (0.87 kcal/mol); from methylsulfinylcyclohexane (see ref. 15b), in which the (SO/CH$_2$)*gauche* interaction (0.60 kcal/mol) is 0.69 times the (Me/CH$_2$)*gauche* interaction; and from methylsulfonylcyclohexane (see ref. 15b), in which the (SO$_2$/CH$_2$)*gauche* interaction (1.25 kcal/mol) is 1.44 times the (Me/CH$_2$)*gauche* interaction. We have taken the latter compound as model for both *cis*-sulfoxides and sulfones and methylsulfinylcyclohexane as model for *trans*-sulfoxides.

14.- The (X/CH$_2$)*gauche* interaction is considered as half of the A value of the group X; A values (kcal/mol): a) Me group, 1.74, Anet, F.A.L.; Bradley, C.H.; Buchanan, G.W. *J. Am. Chem. Soc.*, **1971**, *93*, 258; b) OH group, 0.60, Eliel, E.L.; Gilbert, E.C., *J. Am. Chem. Soc.*, **1969**, *91*, 5487; c) OAc group, 0.78, see ref. 7; d) OMe group, 0.58, Hofner, D.; Lesko, S.A.; Binsch, G. *Org. Magn. Reson.*, **1978**, *11*, 179; e) NH$_2$ group, 1.40, Booth, H. *J. Chem. Soc., Chem. Comm.*, **1973**, 945; Buchanan, G.W.; Weeb, V.L. *Tetrahedron lett.*, **1983**, *24*, 4519; f) NHPh group, 1.27, this work: $-\Delta G^0$ for cyclohexylphenylamine, 1.27 ± 0.09 kcal/mol; g) NHCO$_2$Bu^t group, 1.08, this work: $-\Delta G^0$ for *N*-*t*-butoxycarbonylcyclohexylamine, 1.08 ± 0.09 kcal/mol; $-\Delta G^0$ for the *cis*-4-methyl derivative of the latter, -0.74 ± 0.01 kcal/mol; h) NMe$_2$ group, 1.74, Manoharan, M. Ph.D. Dissertation, 1983, University of North Carolina at Chapel Hill; Booth, H; Jozefowicz, M.L. *J. Chem. Soc., Perkin Trans. II*, **1976**, 895.

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17.- Unfortunately, we were unable to purify compound **7** (see Experimental Section); this prevented a reliable analysis of the low-temperature ^{1}H NMR spectra at concentrations lower than 0.2 M.

18.- We have already seen in the *trans*-sulfoxides **2** and **6** that the possible $N^{\delta-}/S^{\delta+}$ should be negligible.

19.- Unfortunately, 3-phenylaminothiane *S,S*-dioxide (**8**) was very insoluble at low temperature and the signal to noise ratio of its spectra was too low to allow a reliable integration of the peaks.

20.- ^{13}C chemical shifts of a related compound, *N*-phenyl-2-methylthio-1-phenylethylamine (see ref. 1a), suggest that protonation of nitrogen is complete at TFA:sustrate molar ratios lower than two.