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# CONFORMATIONAL ANALYSIS OF 1-Y, 2-Z-CYCLOHEXANES ( Y = OH, OMe, F, Cl, Br and I; Z= SMe, SOMe and $SO_2Me$): STUDY OF THE Z/Y *GAUCHE* INTERACTIONS.

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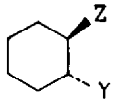
SUMMARY: The conformational study of the title compounds is reported. The configurational assignment of the epimeric sulfoxides was based on the relationship between the stereochemistry of the sulfinyl group and the chemical shifts of the neighboring nuclei. The values of the $(Z/Y)_{gauche}$ interactions have been estimated in different solvents from $G^0$ values measured in low temperature $^{13}C$-nmr spectra.

## INTRODUCTION

In previous publications we have reported the conformational properties of acyclic compounds bearing sulfur functions (in different oxidation states) and oxygen,[1] nitrogen[2] or halogen[3] functions on adjacent carbon atoms. In these papers, the conformational analysis of the substrates had to be based on qualitative considerations, since the energy values for *the gauche* interactions between the heteroatomic functions were unknown. The widespread occurrence of the fragment Z-C-C-heteroatom in natural and synthetic products of biological interest prompted us to extend our studies to cyclic models in order to obtain the magnitudes of the Z/heteroatom interactions. In this conection, we have reported the values of some $(Z/O)_{gauche}$ and $(Z/N)_{gauche}$ interactions, based on conformational studies of some 3-Z-oxanes (Z= SMe, SOMe and $SO_2Me$)[4] and 3-Y-thianes (Y = OH, OMe, OAc, $NH_2$ and $NMe_2$) and derivatives.[5,6] The number of possible *gauche* arrangements between heteroatomic functions in these substrates is restricted since one of them is always endocyclic. Therefore, the conclusions established must be accepted with caution.




| Z \ Y | OH | OMe | F | Cl | Br | I |
|---|---|---|---|---|---|---|
| SMe | 1 | 2 | 3 | 4 | 5 | 6 |
| SOMe | 7α,7β | 8α,8β | 9α,9β | 10α,10β | 11α,11β | |
| $SO_2Me$ | 12 | 13 | 14 | 15 | 16 | |

Scheme 1

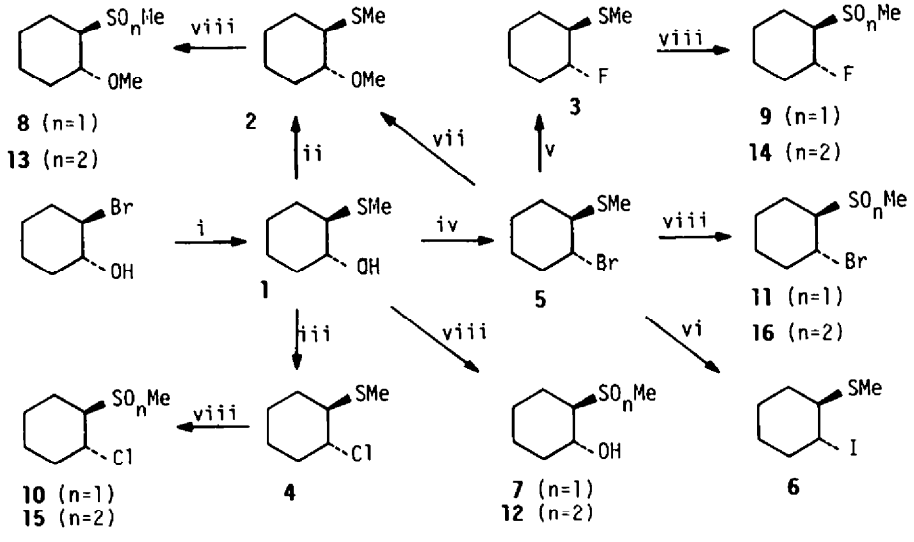
In the present study we report the stereochemical and conformational study of *trans*-1,2-disubstituted cyclohexanes shown in Scheme 1. Here, both heteroatomic functions are exocyclic and their relative spatial arrangements are less restricted than in the heterocyclic compounds mentioned above. This fact permits, in the case of the oxygenated substrates, to check the validity of the magnitude of the Z/O interactions previously established. Moreover, some of these compounds exhibit Z/halogen interactions, whose

magnitude can thus be determined. To the best of our knowledge, the only earlier paper related to this topic refers to 3,3,6,6-tetradeuterated derivatives of compounds 1, 2, 4 and 5[7] where the magnitude of the SMe/Y (Y = OMe, Cl, Br) interactions was estimated.

There is another question which confers additional interest on the spectroscopic study of these compounds. This question relates to the influence of the spatial arrangement of the sulfur substituents in sulfoxides and sulfones on the chemical shifts of the neighboring nuclei which has been established from substrates bearing the sulfur atom in an endocyclic position,[8,9] but scarcely used in stereochemical studies of carbocyclic or acyclic thioderivatives, due to their conformational mobility. The study of the $^{13}C$ and $^{1}H$-nmr spectra of the compounds in Scheme 1 allows us to determine the scope and the limitations of these effects in structural studies of non-heterocyclic substrates.

## SYNTHESIS and NMR-SPECTROSCOPY

Compounds 1-16 were prepared by standard methods, as shown in Scheme 2. The formation of compound 1, from cyclohexene bromhydrin (*trans*-2-bromocyclohexanol)[10] can be explained by anchimeric assistance of the hydroxy group. Similarly, the syntheses of 4 and 5 from 1 and those of 2, 3 and 6 from 5, all of them involving retention of the configuration at C-1, are based on the high degree of neigboring group participation of the SMe group.[11] As a result, the total yield in the sequence 1→5→2 (76%) is higher than that in the direct O-methylation 1→2 (62%). The low stability of iodothioether 6 (its spectroscopical study is based on samples generated *in situ* in the nmr tube) precluded the synthesis of the iodosulfoxides and iodosulfone.




i NaSMe/MeOH; ii NaH/MeI/$Et_2O$; iii HCl(g)/$CH_2Cl_2$; iv HBr(g)/$CH_2Cl_2$;
v AgF/MeCN; vi NaI/acetone; vii MeOH; viii $NaIO_4$ or MCPBA

Scheme 2

Sulfoxides (7-11) and sulfones (12-16) were prepared by oxidation of the corresponding thioethers. The sulfoxides were obtained as mixtures of diastereoisomers, epimeric at sulfur, whose chromatographic separation allowed us to isolate only 7β and all α epimers as diastereomerically pure compounds. The independent O-methylation of 7α and 7β yielded 8α and 8β respectively. The spectroscopic parameters of 9β, 10β and 11β were determined from α+β mixtures of sulfoxides enriched in the β epimers.

Table 1. Low temperature $^{13}C$-nmr chemical shifts (ppm) of compounds 1-16 in acetone-$d_6$.

| | | Diequatorial Conformation | | | | | | | Diaxial Conformation | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | T(K) | C(1) | C(2) | C(3) | C(4) | C(5) | C(6) | S-Me | C(1) | C(2) | C(3) | C(4) | C(5) | C(6) | S-Me |
| **1** | 183 | 73.5 | 52.5 | 32.2 | 26.6 | 25.1 | 36.0 | 13.1 | 67.7 | 49.3 | 25.2 | 21.6 | 20.1 | 26.7 | 15.6 |
| **2**[a] | 183 | 85.2 | 50.3 | 31.1 | 26.2 | 24.3 | 32.3 | 15.1 | 77.0 | 45.4 | 24.8 | 21.0[b] | 20.3[b] | 25.5 | 15.0 |
| **3** | 183 | 97.9 | 49.6 | 31.6 | 25.8 | 24.1 | 33.3 | 15.2 | 90.2 | 45.9 | [c] | 20.5 | [c] | [c] | 15.3 |
| | [d] | 175.3 | 16.9 | 6.8 | 1.4 | 11.6 | 18.5 | 3.6 | 173.2 | 21.8 | | 0.0 | | | 0.0 |
| **4** | 183 | 65.1 | 52.3 | 33.9 | 26.2 | 26.2 | 38.5 | 13.2 | 61.3 | 49.5 | 26.1 | 20.2 | 21.4 | 28.4 | 15.4 |
| **5** | 183 | 58.7 | 52.3 | 34.3 | 26.2 | 27.3 | 39.7 | 12.7 | 56.4 | 50.0 | 26.8 | 21.1 | 21.5 | 29.0 | 15.5 |
| **6** | 183 | 38.6 | 52.5 | 33.5 | 26.3 | 28.4 | 41.6 | 11.7 | 38.5 | 51.1 | 27.5 | 21.4 | 22.4 | 29.8 | 15.3 |
| **7α** | 183 | 67.9 | 64.9 | 19.9 | 24.9 | 24.6 | 34.1 | 36.4 | | | | | | | |
| **7β** | 183 | 70.4 | 64.2 | 22.2 | 25.2 | 24.5 | 32.8 | 36.3 | | | | | | | |
| **8α**[a] | 183 | 77.6 | 63.1 | 20.0 | 24.9 | 24.0 | 30.5 | 34.6 | | | | | | | |
| **8β**[a] | 183 | 78.6 | 61.9 | 21.8 | 25.5 | 24.3 | 30.8 | 31.9 | | | | | | | |
| **9α** | 183 | 90.2 | 62.2 | 19.0 | 24.1 | 23.6 | 32.6 | 33.9 | | | | | | | |
| | [d] | 174.5 | 15.3 | 6.2 | 0.0 | 11.5 | 17.9 | 0.0 | | | | | | | |
| **9β** | 183 | 88.6 | 60.5 | 25.8 | 24.8 | [c] | 32.5 | 36.1 | | | | | | | |
| | [d] | 173.5 | 16.4 | 6.5 | 0.0 | | 18.1 | 6.9 | | | | | | | |
| **10α** | 178 | 59.9 | 64.6 | 20.4 | 24.2 | 25.9 | 37.8 | 33.8 | | | | | | | |
| **10β** | 178 | 59.7 | 64.2 | 21.0 | 24.7 | 26.4 | 38.4 | 29.7 | 58.0 | 65.3 | 19.8 | 21.9 | 21.0 | [c] | 37.5 |
| **11α** | 183 | 53.1 | 64.8 | 21.3 | 24.4 | 27.1 | 39.0 | 34.1 | | | | | | | |
| **11β** | 178 | 51.4 | 64.1 | 21.8 | 24.8 | 27.1 | 39.5 | 29.2 | 51.9 | 65.8 | 20.6 | 21.9 | 21.6 | 30.3 | 37.5 |
| **12** | 183 | 70.1 | 66.2 | 22.5 | 24.8 | 24.5 | 36.0 | 44.0 | | | | | | | |
| **13**[a] | 178 | 79.7 | 65.0 | 22.9 | 25.0 | 24.0 | 30.0 | 44.1 | | | | | | | |
| **14** | 193 | 92.8 | 64.6 | 22.1 | 24.2 | 23.8 | 32.0 | 43.1 | | | | | | | |
| | [d] | 174.4 | 17.4 | 6.2 | 0.0 | 11.3 | 18.2 | 8.0 | | | | | | | |
| **15** | 183 | 59.1 | 66.9 | 25.8 | 24.4 | 25.8 | 37.7 | 44.0 | 55.9 | 62.2 | 19.4 | 19.7 | 20.8 | 39.6 | 39.6 |
| **16** | 183 | 50.3 | 67.2 | 26.5 | 24.7 | 27.0 | 39.2 | 43.4 | 49.1 | 62.8 | 20.0 | 20.4 | 21.0 | [c] | 39.6 |

[a] Values of δ-OMe; **2**: 56.2 (diequatorial) and 55.6 (diaxial); **8α**: 56.3; **8β**: 55.3; **13** : 56.0
[b] These assignments may have to be interchanged. [c] Hidden signals. [d] Values of coupling constants $J_{F,C}$

The $^{13}C$-nmr chemical shifts for compounds **1-16**, obtained in acetone-$d_6$ at temperatures below the coalescence are listed in Table 1.[12] In order to facilitate comparisons, the ring carbons have been identically numbered in all substrates, beginning with the carbon supporting the function Y. The assignment of the ring carbons were successfully made using the chemical shifts obtained for cyclohexane thioderivatives[13] as model and assuming that the effects of the Y substituents on the cyclohexane rings[14] are additive. Important deviations between experimental and calculated chemical shifts were observed for C-2 in all diequatorial conformations (Δδ~4-9 ppm, increasing with the atomic number of the heteroatom Y).

The $^{13}C$-nmr chemical shifts observed a room temperatures are listed in table 2. The assignments were easily effected based on the values in table 1. Evidently, there are some changes in chemical shifts whith temperature, even for substrates exhibiting monoconformational behavior.

Table 2. Room temperature $^{13}$C-nmr chemical shifts of compounds **1-16** in acetone-$d_6$.

| Comp. | C(1) | C(2) | C(3) | C(4) | C(5) | C(6) | SMe | OMe |
|---|---|---|---|---|---|---|---|---|
| **1** | 72.8 | 53.2 | 31.9 | 26.3 | 24.8 | 35.1 | 13.0 | |
| **2** | 83.6 | 50.1 | 30.4 | 25.3 | 23.9 | 31.2 | 15.1 | 56.6 |
| **3** | 96.1 | 49.9 | 31.1 | 25.2 | 23.7 | 32.4 | 14.9 | |
| [a] | 176.1 | 18.2 | 5.2 | 0.0 | 9.4 | 19.4 | 2.2 | |
| **4** | 64.1 | 52.3 | 31.2 | 24.1 | 24.4 | 35.0 | 14.6 | |
| **5** | 57.5 | 52.3 | 30.8 | 24.1 | 24.4 | 34.9 | 14.7 | |
| **6** | 38.5 | 53.5 | 31.1 | 23.2 | 24.3 | 34.6 | 14.6 | |
| **7α** | 69.4 | 66.2 | 22.1 | 24.1 | 24.5 | 35.4 | 36.4 | |
| **7β** | 71.9 | 66.5 | 24.4 | 25.5 | 24.6 | 35.7 | 37.1 | |
| **8α** | 78.8 | 65.1 | 21.5 | 25.2 | 24.5 | 31.5 | 37.2 | 56.4 |
| **8β** | 77.4 | 63.2 | 23.9 | 25.3 | 24.0 | 30.7 | 35.1 | 55.7 |
| **9α** | 90.7 | 64.0 | 20.6 | 24.4 | 23.8 | 32.9 | 36.2 | |
| [a] | 174.9 | 15.9 | 6.4 | 0.0 | 11.2 | 18.2 | 2.5 | |
| **9β** | 88.7 | 62.0 | 25.5 | 24.8 | 23.6 | 32.5 | 36.7 | |
| [a] | 174.7 | 18.4 | 5.6 | 0.0 | 13.5 | 16.8 | 5.3 | |
| **10α** | 59.8 | 66.2 | 21.2 | 24.4 | 25.9 | 37.9 | 35.6 | |
| **10β** | 58.7 | 65.8 | 22.4 | 24.1 | 24.3 | 36.1 | 34.0 | |
| **11α** | 52.7 | 66.3 | 21.9 | 24.4 | 26.8 | 38.8 | 35.8 | |
| **11β** | 51.1 | 66.5 | 22.9 | 24.0 | 24.9 | 36.3 | 34.4 | |
| **12** | 70.2 | 68.0 | 23.6 | 24.8 | 25.2 | 36.1 | 43.5 | |
| **13** | 80.0 | 66.4 | 23.4 | 25.3 | 24.5 | 30.7 | 44.4 | 56.4 |
| **14** | 92.1 | 65.4 | 23.6 | 24.3 | 23.9 | 32.2 | 43.2 | |
| [a] | 175.1 | 17.1 | 5.5 | 0.0 | 11.6 | 18.6 | 8.1 | |
| **15** | 58.2 | 67.8 | 24.8 | 24.0 | 24.8 | 36.7 | 43.5 | |
| **16** | 49.3 | 67.3 | 26.5 | 23.4 | 26.5 | 36.2 | 42.6 | |

[a] Values of coupling constants $J_{F,C}$

Table 3. Room and low temperature $^1$H-nmr values of compounds **1-16** in acetone-$d_6$.

| | Room Temp. | | | | Low Temp. | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Diequatorial conform. | | | | Diaxial conform.[a] | | |
| Comp. | δH(1) | δH(2) | $J_{1,2}$ | δSMe | δH(1) | δH(2) | $J_{1,2}$ | δSMe | δH(1) | δH(2) | δSMe |
| **1** | 3.35 | 2.34 | 9.9 | | 3.35 | 2.34 | 9.9 | | | | |
| **2** | 3.07 | 2.57 | 8.5 | 2.08 | 2.86[b] | | 10.1[b] | 2.08[b] | 3.27[b] | 2.77[b] | 2.03[b] |
| **3** | 4.39 | 2.69 | 8.9 | 2.18 | 4.40 | 2.67 | 10.2 | 2.20 | 4.87 | 3.04 | |
| **4** | 4.09 | 2.77 | 7.7 | 2.16 | 3.99 | 2.67 | 11.1 | 2.14 | 4.62 | 3.07 | 2.25 |
| **5** | 4.38 | 2.93 | 7.0 | 2.16 | 4.18 | 2.78 | 11.4 | 2.13 | 4.89 | 3.20 | 2.27 |
| **6** | 4.60 | 2.98 | 6.8 | 2.15 | 4.28 | 2.78 | 11.7 | 2.09 | 5.10 | 3.28 | 2.27 |
| **7α** | 3.70 | 2.44 | 9.9 | 2.56 | 3.63 | 2.41 | 11.0 | 2.61 | | | |
| **7β** | 3.90 | 2.68 | 9.9 | 2.66 | 3.74 | 2.88 | | 2.69 | | | |
| **8α** | 3.26 | 2.40 | 10.2 | 2.49 | 3.22 | 2.45 | | 2.56 | | | |
| **8β** | 3.43 | 2.72 | 9.0 | 2.53 | 3.31 | 2.92 | | 2.54 | | | |
| **9α** | 4.62 | 2.70 | 10.4 | 2.56 | 4.56 | 2.70 | 10.6 | 2.55 | | | |
| **9β** | | | | 2.65 | 4.94 | 3.02 | | 2.65 | | | |
| **10α** | 4.09 | 2.64 | 10.8 | 2.51 | 4.11 | 2.75 | 11.4 | 2.60 | | | |
| **10β** | 4.30 | 3.06 | 8.9 | 2.54 | 4.11 | 3.27 | | 2.52 | 4.84 | | 2.69 |
| **11α** | 4.25 | 2.78 | 10.8 | 2.51 | 4.23 | 2.86 | 11.8 | 2.59 | | | |
| **11β** | 4.49 | 3.14 | 7.8 | 2.54 | 4.25 | 3.40 | 11.6 | 2.51 | 5.04 | | 2.85 |
| **12** | 3.78 | 2.90 | 9.9 | 3.02 | 3.75 | 3.04 | | 3.16 | | | |
| **13** | 3.36 | 2.96 | 10.2 | 2.95 | | | | | | | |
| **14** | 4.74 | 3.30 | 10.5 | 2.95 | 4.72 | 3.43 | 10.3 | 3.04 | | | |
| **15** | 4.31 | 3.40 | 8.8 | 3.11 | 4.23 | 3.57 | | 3.28 | 5.18 | 3.76 | |
| **16** | 4.66 | 3.54 | 7.6 | 3.12 | 4.30 | 3.70 | | 3.32 | 5.35 | 3.81 | 3.32 |

[a] $J_{1,2}$ could not be determined in any case. [b] In $CS_2$

In table 3 are listed $^1$H-nmr data, in acetone-$d_6$, for compounds **1-16**, obtained at room and low temperature. The values of $J_{1,2}$ were obtained by first order analysis. Here also, the chemical shifts and coupling constants change slightly with temperature, even in those compounds which exhibit monoconformational behavior. In these cases, the observed changes must be due to the different population of the rotamers around the C-S bond.

## STEREOCHEMICAL AND CONFIGURATIONAL STUDIES

The configurational assignment of the sulfoxide epimers can be made taking into account, the $\gamma$-*gauche* effects of the sulfur substituents on C(1) and C(3). The magnitude of these effects, strongly dependent on configuration, was determined in cyclic substrates.[8] The oxidation of thioethers to sulfoxides leads to additional shielding of the carbons in ß-position with respect to the sulfur atom, which is greater (11-13 ppm) when there is an *anti* relationship between the lone electron pair at the sulfinylic sulfur and the pertinent carbon than in any other relative stereochemical position (4-6 ppm).[5]

Table 4. Low temperature values of $\Delta\delta$ [= $\delta_{SOMe}$(or $\delta_{SO_2Me}$) - $\delta_{SMe}$] for C(1), C(3) and Me(S) in compounds **7-16**.

| Y | Comp. | ΔδC(1) | ΔδC(3) | ΔδMe(S) | Comp. | ΔδC(1) | ΔδC(3) | ΔδMe(S) |
|---|---|---|---|---|---|---|---|---|
| OH | **7α (7ß)** | -5.6(-3.1) | -12.3(-10.0) | 23.3(23.2) | **12** | -3.4 | -9.7 | 30.9 |
| F | **9α (9ß)** | -7.7(-9.3) | -12.6 (-5.8) | 18.7(20.9) | **14** | -5.1 | -9.5 | 27.9 |
| OMe | **8α (8ß)** | -7.6(-6.6) | -11.1 (-9.3) | 19.5(16.8) | **13** | -5.5 | -8.2 | 29.0 |
| Cl | **10α(10ß)** | -5.2(-5.4) | -13.5(-12.9) | 20.6(16.5) | **15** | -6.0 | -8.1 | 30.8 |
| Br | **11α(11ß)** | -5.6(-7.3) | -13.0(-12.5) | 21.4(16.5) | **16** | -8.4 | -7.8 | 30.7 |

Table 4 shows the value of $\Delta\delta$ ($\delta_{sulfoxide}$ - $\delta_{thioether}$) for C(1) and C(3) in the diequatorial conformation of the sulfoxides. As can be seen, Δδ-C(3) is markedly greater than Δδ-C(1) in all compounds (except **9ß**). This indicates that the lone pair adopts mainly the 1,3-*parallel* arrangement with respect to Y (conformations A in Fig. 1) and therefore an *anti*

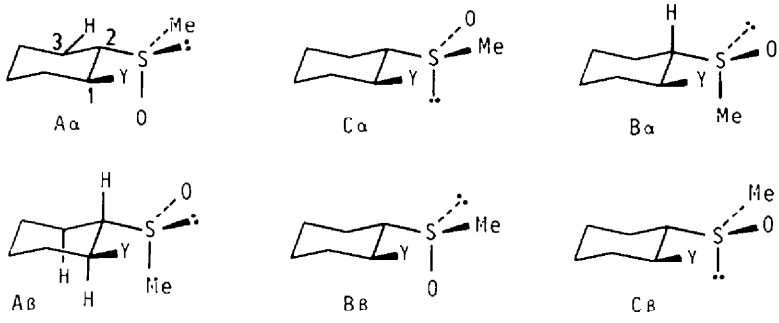



Fig. 1. Rotamers around the C-S bond for diequatorial conformations of sulfoxides **7-11**.

relationship in relation to C(3) (presumably because the other two possible conformations B and C are destabilized by $(Y/O)_{1,3\text{-}p}$ and $(Y/Me)_{1,3\text{-}p}$ interactions). In the epimeric pairs of sulfoxides **8**, **10** and **11** the α epimers show a δ-SMe value greater than that of the ß epimers,

suggesting that the upfield shifting steric compression effect on the sulfinyl methyl group is larger in the latter. Taking into account the geometry of the A conformation, depicted in figure 1 for each epimer, the configuration assigned to the β epimers must be that placing the methyl group in 1,3-*parallel* arrangement with respect to the axial hydrogens on C(1) and C(3) [the α epimers only exhibit one $(Me/H)_{1,3\text{-}parallel}$ interaction].

The difference between the values of δ-H(2) observed for α and β epimeric sulfoxides (table 3) is in agreement with this assignment. H(2) is more deshielded (0.5-0.6 ppm) in the β epimers than in the α ones. Taking into account the results obtained by Lett and Market,[9] the oxidation of thioethers to sulfoxides should induce a strong deshielding effect on H(2) only when its stereochemistry is similar to that of conformations Bα and Aβ (fig. 1). In any other arrangement (antiperiplanar to the oxygen or to the lone electron pair at sulfur) this proton should undergo a slight shielding effect. According to the $^{13}C$-nmr data discussed above, in the α epimers of sulfoxides **8**, **10** and **11**, the Aα rotamers must be predominant, whereas in β diastereoisomers the conformation favored is Aβ, and therefore the latter isomers must exhibit a greater deshielding effect for H(2).

In the case of fluorosulfoxides **9α** and **9β**, the values of $^5J_{F,H}$ of S-Me, which are strongly distance dependent,[15] may be used to confirm the configurational assignments established from the $^{13}C$-nmr parameters. Here, the relative values of Δδ-C(3) and Δδ-C(1) (table 4) suggested that Aα must be the favored conformation for **9α**, whereas for **9β**, the only compound in table 4 exhibiting a larger upfield shift value for Δδ-C(1) than for Δδ-C(3), the most populated rotamer must be Bβ (see above). The high value of $^5J_{F,H}$ of SMe for **9β** (6.9 Hz) suggest a close distance between the two coupled atoms, which is only possible when they adopt an 1,3-*parallel* arrangement as in Bβ. By the contrary, the value of the long range coupling constant for **9α** is scarce or none, suggesting a large distance between the coupled nuclei, which is in agreement with major participation of the Aα conformation (fig. 1). The fact that only epimer **9β** exhibits a high population of the rotamer with $(Me/Y)_{1,3\text{-}p}$ interaction, can be explained in terms of the smaller size and higher electronic density of the fluorine atom, which leads to a lower steric repulsion and a higher electrostatic attraction[16] in its interaction with the methyl group.

Since Δδ-SMe is identical for both hydroxysulfoxides **7α** and **7β**, (probably due to the effect of hydrogen bonding on the chemical shifts) the configurational assignment of these compounds cannot be established using the above approach. In this case, the relationship between the relative configuration of hydroxysulfoxides and their trend to form inter or intramolecular hydrogen bonds, may be used to make the assignment. In table 5 are shown the values of δ-H(1), δH(2), δ-OH and $J_{1,OH}$ at different concentrations in $CDCl_3$ at room temperature. The fact that the values of δ-OH and $J_{1,OH}$ observed for **7β** remain almost constants with dilution and the low value of this coupling constant, are characteristic of strong intramolecular hydrogen bonding.[17] In contrast, the decrease of δ-OH with dilution, observed for **7α**, and its higher value of $J_{1,OH}$[17] suggest the existence of intermolecular hydrogen bonds (which disappear with dilution) in this epimer. The same behavior has been found in other epimeric pairs of acyclic hydroxysulfoxides previously studied.[18] In those

compounds it was clearly demonstrated that intramolecular hydrogen bonding take place in those diastereoisomers that have different configurations at the hydroxyl carbon and sulfur atoms (R*S*), whereas the intermolecular association was characteristic of the epimers with the same relative configuration of both chiral centers (R*R*). The same rationale, applied to the cyclic compounds **7α** and **7β**, gives the configurational assignment shown in figure 1. The configurational correlation established by chemical methods between the hydroxysulfoxides, **7α** and **7β**, and their corresponding methoxy derivatives, **8α** and **8β**, reinforces the assignments made by applying, in each case, of one of the two mentioned criteria.

Table 5. Influence of dilution on the $^1$H-nmr parameters (δ in ppm and J in Hz) of **7α** and **7β**

| $10^2$.c (mol $l^{-1}$) | **7α** | | | | | **7β** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | δ-H(1) | δ-H(2) | δ-SOMe | δ-OH | $J_{1,OH}$ | δ-H(1) | δ-H(2) | δ-SOMe | δ-OH | $J_{1,OH}$ |
| 50 | 3.87 | 2.50 | 2.63 | 4.72 | 4.1 | 4.05 | 2.64 | 2.70 | 4.98 | 1.5 |
| 15 | 3.98 | 2.57 | 2.63 | 4.26 | 3.5 | 4.08 | 2.66 | 2.70 | 4.95 | 1.2 |
| 3 | 4.01 | 2.63 | 2.63 | 3.92 | 2.9 | 4.09 | 2.66 | 2.70 | 4.95 | 1.2 |
| 0.3 | 4.08 | 2.70 | 2.64 | 3.67 | 2.6 | 4.09 | 2.66 | 2.70 | 4.95 | 1.1 |
| 0.05 | 4.08 | 2.68 | 2.64 | 3.63 | 2.5 | 4.08 | 2.65 | 2.70 | 4.95 | 1.2 |

It is interesting to note that the favored conformation of **7α** is **Aα**, in which intramolecular hydrogen bonding is not possible. The predominance of this conformation may be explained in terms of the $n^2(Y) \rightarrow d^0(S)$ stabilizing donor-acceptor interaction proposed in previous studies.[4,19] This interaction may be responsible for the greater participation of the **Aα** conformation in all the α epimers, as compared with that of **Aβ** conformation in the **β** epimers, and hence for the higher value of Δδ-C(3) observed for the former (see Table 4).

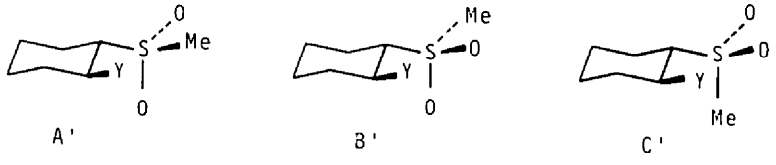



Fig. 2. Rotamers around the C-S bond for the diequatorial conformations of sulfones **12-16**.

The $^{13}$C-nmr data of sulfones provided useful information about the conformational equilibria around the C-S bond. The γ-$SO_2$ effect is always shielding, but its value is markedly higher (10 ppm) when the carbon nucleus under consideration [C(1) or C(3)] is in a *gauche* arrangement with respect to both sulfonyl oxygens. In any other possible arrangement this shielding is lower (3-5 ppm), as has been reported for cyclic compounds.[6] Taking into account this criterion and the data of table 4, one can deduce that conformation **A'** is more populous than **B'** (fig 2) in all sulfones except the bromosulfone **16**. As shown in table 4, the values of Δδ-C(1) increase and those of Δδ-C(3) decrease as Y changes in the series F, OMe, Cl, Br. This behavior is reasonable taking into account that the electrostatic repulsion ($Y^{\delta-}/O^{\delta-}$), which destabilizes **B'**, decrease in the sense of the above series and that, the $(Me/Y)_{1,3\text{-}p}$ interaction, present in **A'**, is larger when the van der Waals radius of Y

increases. Therefore, conformation A' should be most populated in fluorosulfone **14**. The high value of $^5J_{F,H}$ of S-Me observed in **14** (8.0 Hz), confirms that the two coupled atoms are very close in the major conformation (A').

Table 6. Conformational free energy of the compounds 1-16

| Comp. | Solv.[a] | T(K) | Signals measured[b] | K[c] | -ΔG°(kcal/mol) | |
|---|---|---|---|---|---|---|
| 1 | A | 183 | 3 | 29.07 ± 0.72 | 1.27 ± 0.01 | |
| | B | 183 | | [d] | >1.50 | |
| | C | 183 | 3 | 45.99 ± 1.64 | 1.40 ± 0.01 | |
| | D | 183 | 2 | 21.92 ± 0.59 | 1.13 ± 0.01 | |
| 2 | A | 183 | 7 | 3.59 ± 0.42 | 0.47 ± 0.04 | (0.43 ± 0.17)[e] |
| | B | 183 | 4 | 19.24 ± 1.60 | 1.08 ± 0.05 | |
| | C | 188 | 7 | 5.60 ± 1.36 | 0.62 ± 0.09 | |
| | D | 178 | 4 | 4.20 ± 0.15 | 0.51 ± 0.01 | |
| 3 | A | 183 | 4 | 9.00 ± 1.23 | 0.82 ± 0.04 | |
| | B | 188 | 2 | 50.08 ± 5.28 | 1.43 ± 0.04 | |
| | C | 188 | 1 | 27.0 | 1.24 | |
| | D | 188 | 2 | 21.47 ± 4.41 | 1.15 ± 0.08 | |
| 4 | A | 183 | 6 | 0.54 ± 0.06 | -0.22 ± 0.04 | (-0.03 ± 0.08)[e] |
| | B | 183 | 4 | 2.66 ± 0.09 | 0.36 ± 0.01 | |
| | C | 188 | 3 | 1.24 ± 0.05 | 0.08 ± 0.01 | |
| | D | 183 | 4 | 1.41 ± 0.05 | 0.13 ± 0.01 | |
| 5 | A | 183 | 7 | 0.19 ± 0.03 | -0.61 ± 0.06 | (-0.28 ± 0.09)[e] |
| | B | 183 | 7 | 1.22 ± 0.06 | 0.07 ± 0.02 | |
| | C | 188 | 6 | 0.54 ± 0.05 | -0.23 ± 0.03 | |
| | D | 183 | 7 | 0.57 ± 0.05 | -0.21 ± 0.03 | |
| 6 | A | 183 | 7 | 0.16 ± 0.01 | -0.68 ± 0.03 | |
| | B | 183 | 6 | 0.98 ± 0.13 | -0.01 ± 0.04 | |
| | D | 183 | 3 | 0.49 ± 0.02 | -0.26 ± 0.01 | |
| 7α | C,D | 183 | | [d] | >1.50 | |
| 7β | C,D | 183 | | [d] | >1.50 | |
| 8α | D | 183 | | [d] | >1.50 | |
| 8β | D | 183 | | [d] | >1.50 | |
| 9α | D | 183 | | [d] | >1.50 | |
| 9β | D | 183 | | [d] | >1.50 | |
| 10α | B,C,D[f] | 188 | | [d] | >1.50 | |
| 10β | B | 188 | 3 | 5.53 ± 0.38 | 0.64 ± 0.03 | |
| | C | 183 | 4 | 9.52 ± 0.60 | 0.83 ± 0.02 | |
| | D | 178 | 2 | 5.18 ± 0.05 | 0.58 ± 0.01 | |
| 11α | B,[g]C,D | 183 | | [d] | >1.50 | |
| 11β | B | 188 | 3 | 2.74 ± 0.05 | 0.38 ± 0.01 | |
| | C | 183 | 5 | 5.00 ± 0.63 | 0.59 ± 0.05 | |
| | D | 178 | 2 | 2.74 ± 0.10 | 0.36 ± 0.01 | |
| 12 | B,C,D | 178 | | [d] | >1.50 | |
| 13 | B,C,D | 178 | | [d] | >1.50 | |
| 14 | B,C,D | 193 | | [d] | >1.50 | |
| 15 | B | 188 | | [d] | >1.50 | |
| | C | 183 | 3 | 65.10 ± 18.5[h] | 1.52 ± 0.10 | |
| | D | 183 | 4 | 23.37 ± 3.00 | 1.15 ± 0.05 | |
| 16 | B | 183 | 4 | 11.72 ± 2.34 | 0.92 ± 0.08 | |
| | C | 183 | 4 | 2.42 ± 0.55 | 0.32 ± 0.08 | |
| | D | 183 | 3 | 1.00 ± 0.04 | 0.00 ± 0.02 | |

[a] Solvent A is $CS_2$; B, $CD_2Cl_2$; C, $CD_3OD$; D, acetone-$d_6$. [b] Number of signal pairs in the $^{13}C$-nmr spectrum used to evaluate K. [c] Defined as [diequatorial]:[diaxial]. [d] Diaxial conformation is not observed. [e] Data from reference 7. [f] Solvent D, T=178K. [g] Solvent B, T=188K. [h] Proportion of the axial conformation too low to obtain a more reliable value for K.

Finally, it should be noted that $\delta$-$^{13}$C values which may be deduced from Table 2 (room temperature) are much lower than those of Table 4 (low temperature). This should be the result of averaging rotation around the C-S bond with increasing temperature. Therefore, the conclusions drawn in this work from the study of cyclic sulfoxides may be applied to related acyclic substrates if, and only if, they are studied at temperatures close to 173K. Otherwise, the conformational analysis would be less satisfactory.

## CONFORMATIONAL STUDIES

Equilibrium constants and free energies for the conformational equilibria of compounds **1-16** in different solvents are given in table 6. They were obtained by integration of the two signals corresponding to each carbon nucleus in the $^{13}$C-nmr spectra recorded at temperatures below coalescence. The K value listed in table 6 is the arithmetic mean of the values obtained for each one of the pair of signals that could be used for each compound. The number of carbon studied[20] and the standard deviation respect to the arithmetic mean are also indicated in the table.

The reliability of this method used to calculate K is satisfactory for values of K<50 ($\Delta G^0$<-1.5 Kcal/mol). The low solubility of sulfoxides and sulfones in $CS_2$ has precluded the use of this solvent. Taking into account that the K value in acetone-$d_6$ is always smaller than in $CD_2Cl_2$ and $CD_3OD$, substrates in which the diaxial conformation could not be detected in the former solvent, were not studied in the two latter.

The values of $\Delta G^0$ in $CS_2$ for compound **2**, **4** and **5** had been reported below.[7] Only in the case of compound **2** is there good agreement between the data previously reported and those of table 6. In order to determine the reliability of our data, obtained by integration of the $^{13}$C-nmr signals at low temperature, we recorded the $^1$H-nmr spectra of compounds **4** and **5** at the same temperature in acetone-$d_6$. The integration of signals corresponding to H(1) and H(2), gave values of $G^0$ almost identical to those shown in table 6 ($\Delta G^0$(4)=-0.12 ± 0.01; $\Delta G^0$(5)=-0.22 ± 0.01). The disagreement between our data and those of Zefirov[7] may be due to the fact that the coupling constants $J_{1,2}$ (the basis of the Zefirov study) are slightly temperature dependent (vide supra), probably due to the influence of the temperature on the composition of the conformational equilibrium around the C-S bond. This fact, observed in some of our compounds which are monoconformational, as far as the cyclohexane moiety is concerned, would introduce small errors in the values of $\Delta G^0$ estimated by Zefirov.

Table 7. A values for the Y and Z groups of compounds **1-16**

| | A value(kcal/mol) | Ref. | | A value(kcal/mol) | Ref. |
|---|---|---|---|---|---|
| OH | 0.92 ± 0.05 | 21,22 | Br | 0.48 ± 0.03 | 21,22 |
| | (1.04 in $CD_3OD$) | 21 | I | 0.45 ± 0.03 | 21,22 |
| OMe | 0.57 ± 0.03 | 21,22 | SMe | 1.00 ± 0.05 | 13 |
| F | 0.26 ± 0.03 | 21,22 | SOMe | 1.20 ± 0.05 | 13 |
| Cl | 0.52 ± 0.03 | 21,22 | $SO_2Me$ | 2.50 ± 0.05 | 13 |

The A values ($-\Delta G^0$) for the Y and Z groups supported by compounds **1-16** are collected in table 7. For OMe, F, Cl, Br and I we have use the A values reported in reference 21, which in

agreement with those published by Hirsch.[22] In the case of OH, in which the agreement of both reports[21,22] is less than good, we have used the Hirsch's values.[22] As a results of this disagreement, the validity of the conclusion obtained for alcohols is lower. For the sulfur functions, we have used the values adduced by Eliel.[13] Although it has been postulated[21] that in the case of halogens the A value is not solvent dependent, we consider that it may be modified to some extent by the great ability of $CD_3OD$ to solvate all the groups presents in our compounds. Therefore, the data obtained using this solvent must be accepted with caution.

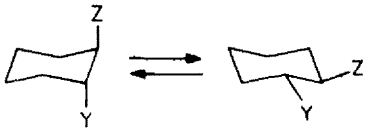
From the values of $\Delta G^0$(table 6) and A (table 7) it is possible to estimate the value of the $(Z/Y)_{gauche}$ interactions, using the equation shown in table 8. The term $\Delta G^0(Z/Y)$ must contain steric and electrostatic components. The latter should reflect the differences between dipolar interactions of both groups in *gauche* (diequatorial conformation) and *anti* (diaxial conformation) arrangements.

The data of table 8 show the strong influence of the solvent on the value of the $(SMe/Y)_{gauche}$ interactions. These data do not allowed to establish a good correlation between such influence and the polarity of the solvent. One of the factors that must contribute to the destabilization of the heteroatomic functions in *gauche* arrangement is the repulsion between the dipolar moments C→Y and C→S, which should be greater in sulfoxides and sulfones than in thioethers. Such repulsion ought to diminish with increasing dielectric constant of the solvent and thus produce a decrease in the $\Delta G^0$ value for the corresponding interaction. With very few exceptions, this behavior is observed when the data obtained in $CS_2$, acetone-$d_6$ and $CD_3OD$ are compared. However, the data in $CD_2Cl_2$ show anomalous behavior, since the $(SMe/Y)_{gauche}$ and the $(SO_2Me/Y)_{gauche}$ interactions are markedly lower than those observed in other, more polar solvents. Since the influence of $CD_2Cl_2$ on the A values of the groups involved in the interactions should be negligible, the equation shown in table 8 suggests existence of a specific stabilizing interaction between this solvent and the *gauche* arrangement of the groups in the diequatorial conformation of the cyclohexane ring.[23]

Comparison among the values obtained for the $(SMe/halogen)_{gauche}$ interactions, shows that they increase when the size of the halogen increases (steric effect). However, there is a large difference between the values for F and Cl, which suggest the presence, in the chlorothioether, of a destabilizing factor which does not exists in the fluoroderivative. The lone pair/lone pair repulsion between the occupied orbitals of chlorine and sulfur constitutes a good explanation for this additional destabilization which, because of the small size of the fluorine p-orbitals, should be absent in the case of fluorothioether 3. This effect between large heteroatoms has been previously formulated by Zefirov as the basis of the repulsive *gauche* effect.[7] On the other hand, it is also reasonable to assume the presence, in the fluorothioether, of an attractive *gauche* effect, related to that observed for the $(F/I)_{gauche}$ interaction,[7] which would stabilize the (F/SMe) *gauche* disposition and thus, would explain the small $\Delta G^0$ value observed for 3, which actually becomes negative in $CD_2Cl_2$. This effect, plus the repulsive *gauche* effect postulated for the (MeO/SMe) interaction[7,24] can explain the large observed differences (0.65-0.95 kcal/mol) between the (SMe/F) and (SMe/OMe) interactions. These differences are larger than what one would expect based on steric considerations alone.

The differences between hydroxy and methoxythioethers (1 and 2) may be easily explained on the basis of stabilizing intramolecular hydrogen bonding, possible only in the former when $CS_2$ and $CD_2Cl_2$ are used as solvents.

Table 8. Values of the $(Z/Y)_{gauche}$ interaction [ $G^0(Z/Y)$ in kcal/mol] obtained from Eq. [1]




$$\Delta G^0(exp) = \Delta G^0(Z/Y) - A_Y - A_Z \qquad \text{Equation [1]}$$

| Z | Y | $CS_2$ | Acetone-$d_6$ | $CD_3OD$ | $CD_2Cl_2$ |
|---|---|---|---|---|---|
| SMe | OH | 0.68 ± 0.16 | 0.82 ± 0.16 | 0.55 ± 0.16 | < 0.45 |
| | F | 0.44 ± 0.14 | 0.11 ± 0.14 | 0.02 ± 0.18 | -0.17 ± 0.11 |
| | OMe | 1.11 ± 0.14 | 1.06 ± 0.09 | 0.95 ± 0.21 | 0.49 ± 0.13 |
| | Cl | 1.75 ± 0.15 | 1.40 ± 0.10 | 1.44 ± 0.10 | 1.16 ± 0.10 |
| | Br | 2.09 ± 0.18 | 1.69 ± 0.12 | 1.71 ± 0.13 | 1.41 ± 0.12 |
| | I | 2.13 ± 0.12 | 1.74 ± 0.10 | | 1.46 ± 0.14 |
| SOMe(α) | OH | | < 0.65 | < 0.65 | |
| | F | | <-0.04 | | |
| | OMe | | < 0.27 | | |
| | Cl | | < 0.22 | < 0.22 | |
| | Br | | < 0.18 | < 0.18 | < 0.18 |
| SOMe(β) | OH | | < 0.65 | < 0.65 | |
| | F | | <-0.04 | | |
| | OMe | | < 0.27 | | |
| | Cl | | 1.14 ± 0.09 | 0.89 ± 0.11 | 1.08 ± 0.11 |
| | Br | | 1.32 ± 0.09 | 1.09 ± 0.14 | 1.31 ± 0.09 |
| $SO_2Me$ | OH | | < 1.95 | < 1.95 | < 1.95 |
| | F | | < 1.26 | < 1.26 | < 1.26 |
| | OMe | | < 1.57 | < 1.57 | < 1.57 |
| | Cl | | 1.87 ± 0.12 | 1.50 ± 0.18 | < 1.52 |
| | Br | | 2.98 ± 0.10 | 2.69 ± 0.17 | 2.03 ± 0.15 |

In those sulfoxides where the *gauche* interaction can be assessed (Y=Cl or Br), a relationship between the relative configuration at sulfur and the magnitude of the $(SOMe/Y)_{gauche}$ interaction is evident. In the other sulfoxides, this relationship, if extant, cannot be seen because the compounds in question are monoconformational in both SO configurations. A similar relationship has been previously found in acyclic compounds and explained in terms of the stabilizing $n^2 \rightarrow d^0$ donor-acceptor interactions between the occupied p-orbitals of the heteroatom and the unoccupied d-orbitals on sulfur, which are suitably oriented only in the case of the α epimers.[4,19] However, in none of these cases had the magnitude of such interactions been determined. From the data of table 8 it can be computed that the value is >0.92 kcal/mol for chlorosulfoxides and >1.14 kcal/mol for bromosulfoxides (both in acetone-$d_6$). (The values cannot be determined more accurately because the α epimers

are monoconformational). A lower value (0.3 kcal/mol) was found for this interaction in the case of ß-oxygenated sulfoxides (3-methylsulfinyloxanes[4]). This is in agreement with the fact that the interaction should be stronger when the energies of the orbitals involved ($p^2$ on Y and $d^0$ on sulfur) are more closely matched.

Comparison of the $\Delta G^0$ values of thioethers and sulfoxides shows that the (SOMe/Y) interaction is less destabilizing that the (SMe/Y). The two values become closer as the size of Y increases (In acetone-$d_6$, $\Delta G^0$ >0.79 kcal/mol for Y=OMe , while $\Delta G^0$ = 0.3 kcal/mol for Y = Cl and Br). This result agrees with the existence of a electrostatic attraction between Y and the electron deficient sulfinylic sulfur (postulated by Eliel in the case of ß-oxygenated sulfoxides[16]) that does not exist in thioethers. In addition, the repulsive *gauche* effect is lower in sulfoxides than in thioethers, as a consequence of the smaller size of the sulfinylic sulfur orbital containing the unshared electron pair.

Finally, the chloro and bromosulfones have an appreciable population of the diaxial conformation (table 6), presumably as a consequence of the high value of the $(SO_2Me/Y)_{gauche}$ interaction when Y = Cl and Br (table 8). When the heteroatom is O or F, the results obtained in other series[3,4] indicate that the ($SO_2Me$/Y) interaction is less destabilizing than (SMe/Y), despite the larger size of the $SO_2Me$ group compared to SMe. The electrostatic attraction between Y and the sulfonyl sulfur (the two atoms bear electronic charges of opposite sign) may explain this behavior. In those compounds in which Y = O or F, the methyl group, which may delocalize some of the positive charge on the sulfonylic sulfur,[16] adopts a 1,3-*parallel* arrangement in relation to the heteroatom. In chlorosulfone **15** the large size of chlorine makes this arrangement is less favorable. In this case, $\Delta G^0(SO_2Me/Cl)$ becomes greater than $\Delta G^0$(SMe/Cl). However this difference is small enough to suggest that electrostatic attraction almost compensates for steric destabilization. Finally, in the bromosulfone **16**, the methyl group cannot adopt a 1,3-*parallel* arrangement with respect to the bromine atom, since the distance between both groups would be lower than the sum of their Van der Waals radii. Thus, the ($SO_2Me$/Br) interaction is markedly larger than the (SMe/Br) one (see table 8).

We are presently studying cyclohexane derivatives containing an effective counterweight, to allow us to complete the evaluation of the Z/Y interactions.

## EXPERIMENTAL

*General.* Silica gel used in chromatography was MercK F-254 (TLC) or 60 (70-230 mesh) (flash chromatography). Melting points were determined on a Büchi 594392 type S apparatus in open capillary tubes and are uncorrected. Elemental microanalyses were performed by the Instituto de Química Orgánica (CSIC) in Madrid with a Perkin Elmer model 240 analyzer. IR spectra were obtained under the conditions specified for each compound on a Pye Unicam SP-1100 or Philips PU 9700 spectrometers. Mass spectra were recorded on a Hewlett Packard 5985 spectrometer with electron impact (70 eV) or chemical ionization (CI, methane as ionizing reagent) ionization modes. Mass data are reported in mass unit (m/z) and the values in brackets indicate the intensity relative to the base peak (as 100%). Proton and carbon NMR spectra were recorded on a Bruker WP-200-SY instrument and shifts are reported in ppm downfield from internal tetramethylsilane. Diastereomer ratios were established from the $^1$H-NMR spectra of the crude reaction mixtures by integration of well separated signals of each isomer (CHX or $CH_3S$). Data of ß-isomers of **9**, **10** and **11** were obtained from α+ß mixtures. Oxidation of thioethers **1-5** to sulfoxides or sulfones were carried out with sodium metaperiodate (Method A) or m-chloroperoxybenzoic acid (Method B) following the procedures previously described.[4,25]

*trans-2-Methylthiocyclohexanol* (1)

To a solution of 20 g (110 mmol) of *trans*-2-bromocyclohexanol in 60 ml of dry methanol 52.11 g (130 mmol) of a 18% methanolic solution of sodium methylsulfide were slowly added. The reaction mixture was stirred overnight at room temperature, quenched with 300 ml of water and extracted with methylene chloride. The extracts were dried and concentrated to dryness and the resulting material was distilled at reduced pressure (63%). Physical constants and spectroscopic data agreed with those previously reported.[10,26]

*trans-1-Methoxy-2-methylthiocyclohexane* (2)

A solution of 2.1 g (10 mmol) of 5 in 5 ml of dry methanol was stirred at room temperature for 2 h. The solvent was evaporated and the residue distilled at reduced pressure to afford 1.5 g (93%) of compound 2, bp 88-90°/2 mmHg. Spectroscopic data agreed with those previously described[7]. Compound 2 was also obtained from 1 (62% yield) by reaction with methyl iodide/sodium hydride in diethyl ether following Kondo's procedure.[27]

*trans-1-Fluoro-1-methylthiocyclohexane* (3)

To a solution of 2 g (9.61 mmol) of 5 in 5 ml of dry acetonitrile 1.3 g (10.2 mmol) of silver fluoride were added. The mixture was stirred at room temperature for 2 h and concentrated to dryness. The resulting material was extracted several times with hexane and the extracts were concentrated to afford 1.3 g (93%) of 3 as a colorless oil which was purified by bulb to bulb distillation. Distillation temperature 95-100°/18 mmHg. m/z 150 (4.1), 148 (74.2), 100 (55.6), 87 (100), 85 (56.3), 81 (79.4), 80 (75.7), 79 (38.1), 72 (52.8), 59 (62.1); δ ($CDCl_3$) 4.43 (ddt, 1H, 49.0, 4.3 and 9.1 Hz), 2.78 (m,1H), 2.33 (d,3H, 1Hz), 2.30-1.20 (m, 8H); $\nu_{max}$(film) 2965, 2880, 1455, 1370, 1035 and 960 $cm^{-1}$.

*trans-2-Methylthio-2-chlorocyclohexane* (4)

To a solution of 2 g (13 mmol) of 1 in 20 ml of methylene chloride, 3.26 g (26 mmol) of thionyl chloride was added dropwise. The resulting mixture was stirred for 30 min and then washed with 10 ml of cold water. The organic layer was dried and evaporated to dryness to yield 2.08 g (93%) of 4. Physical constants and spectroscopic data are in agreement with those described.[7,10]

*trans-2-Methylthio-2-bromocyclohexane* (5)

A stream of hydrogen bromide was bubbled through a solution of 4 g (26 mmol) of 1 in 50 ml of methylene chloride until the starting product disappeared (tlc). The hydrogen bromide was neutralized with solid sodium hydrogen carbonate. The reaction mixture was filtered, dried and evaporated to dryness affording 4.7 g (82%) of spectroscopically pure 5. Spectroscopic data agreed with those previously described.[7]

*trans-1-Iodo-2-methylthiocyclohexane* (6)

To an ice cooled solution of 30 mg (0.14 mmol) of 5 in 1 ml of acetone-$d_6$ 25 mg of sodium iodide were added. The mixture was stirred at 0° for 5 min and filtered. It decomposes rapidly on standing at room temperature. δ (acetone-$d_6$) 4.61 (dt, 1H, 3.7 and 7.0 Hz), 2.98 (dt, 1H, 3.7 and 6.4 Hz), 2.15 (s,3H), 2.40-1.30 (m,8H).

*trans-2-Methylsulfinylcyclohexanol* (7α *and* 7β)

It was obtained from 1. Method A: 91% yield, 7α/7β ratio 55/45. Method B: 75% yield, 7α/7β ratio 15/85. Chromatographic separation of both diastereoisomers was achieved using chloroform/methanol 10/1 as eluent. More polar isomer (7α): white solid, mp 98-99° (from toluene). m/z 162 (5.0), 145 (1.8), 99 (33.2), 81 (100); δ ($CDCl_3$) 4.72 (d,1H, 4.1 Hz), 3.87 (m,1H), 2.63 (s,3H), 2.50 (m,1H), 2.20-1.20 (m,8H); $\nu_{max}$(Nujol) 3280, 1130, 1070, 1010 and 965 $cm^{-1}$. Less polar diastereisomer (7β): white solid, mp 50-52° (from toluene-ethyl acetate). m/z 162 (5.0), 145 (5.4), 99 (35.5), 81 (100); δ($CDCl_3$) 4.95 (d,1H, 1.2 Hz), 4.07 (m, 1H), 2.71 (s,3H), 2.67 (m, 1H), 2.20-1.20 (m,8H); $\nu_{max}$(Nujol) 3360, 1130, 1080, 1020 and 960 $cm^{-1}$.

*trans-1-Methoxy-2-methylsulfinylcyclohexane* (**8α** *and* **8β**)

Oxidation of thioether **2** with sodium metaperiodate (method A) afforded an equimolecular mixture of **8α** and **8β** in quantitative yield. Separation of **8α** and **8β** was not possible. Diastereomerically pure **8α** and **8β** were obtained from **7α** and **7β** respectively as follows:
To a solution of 160 mg (0.98 mmol) of hydroxy compound, 250 mg (2.00 mmol) of dimethyl sulfate and 25 mg (0.07 mmol) of tetrabutylammonium iodide in 4 ml of methylene chloride 0.5 ml of an 50% aqueous solution of sodium hydroxide were added.The resulting two-phases system was vigorously stirred at room temperature for 4 h and then 1 ml of ammonium hydroxide solution (20%) was added. Stirring was extended for 30 min. The resulting mixture was diluted with 30 ml of methylene chloride and washed with water (2 x 10 ml). The organic layer was dried and evaporated to give the corresponding **8α** or **8β** as a colorless oil.
Diastereoisomer **8α**: 87% yield. m/z 113 (27.1), 81 (100), 45 (87.6); δ (acetone-$d_6$) 3.34 (s,3H), 3.26 (dt, 1H, 4.1 and 10.3 Hz), 2.49 (s,3H), 2.40 (ddd, 1H, 4.2, 10.2 and 11.8 Hz), 2.10-1.04 (m, 8H); $\nu_{max}$ (film) 2950, 2880, 2840, 1460, 1200, 1120, 1100 and 1040 $cm^{-1}$.
Diastereoisomer **8β**: 79% yield. m/z (CI) 177 (100), 145 (5.0), 113 (43.7); δ(acetone-$d_6$) 3.43 (dt, 1H, 4.5 and 9.3 Hz), 3.31 (s,3H), 2.73 (ddd, 1H, 4.0, 9.2 and 11.0 Hz), 2.53 (s,3H), 2.20-1.10 (m,8H); $\nu_{max}$ (film) 2940, 2860, 2830, 1450, 1190, 1115, 1095, 1035 and 930 $cm^{-1}$.

*trans-1-Fluoro-2-methylsulfinylcyclohexane* (**9α** *and* **9β**)

The fluoro-sulfoxide was obtained from **3** (method B) as a mixture of **9α and 9β** in a 60/40 ratio (quantitative yield). Flash column chromatography (eluent methylene chloride/methanol 10/1) allowed the isolation of diastereomerically pure **9α** (colorless oil). **9β** was contaminated with a 30% of **9α**. Diastereoisomer **9α**: m/z 166(0.8), 164 (10.4), 149 (6.8), 101 (7.1) 100 (3.7), 99 (13.3), 81 (100), 63 (7.8), 59 (20.9); δ($CDCl_3$) 4.64 (ddt, 1H, 48.3, 4.8 and 10.3 Hz), 2.64 (d, 3H, 0.8 Hz), 2.60 (m, 1H), 2.40-1.20 (m,8H); $\nu_{max}$(film) 2940, 2860, 1455, 1365, 1205, 1195, 1135, 1115, 1055-1020 and 950 $cm^{-1}$. Diastereoisomer **9β** (with a 30% of **9α**). m/z 166 (1.7), 164 (21.0), 101 (11.3), 81 (100), 63 (37.4), 59 (25.0); δ ($CDCl_3$) 4.97 (ddt, 1H, 48.6, 5.1 and 9.8 Hz), 2.71 (d, 3H, 1.5 Hz), 2.68 (m, 1H), 2.20-1.10 (m,8H); $\nu_{max}$(film) 2940, 2860, 1455, 1025 and 955 $cm^{-1}$.

*trans-1-Chloro-2-methylsulfinylcyclohexane* (**10α** *and* **10β**)

The isomeric mixture was obtained from **4** (method B) in 98% yield (α/β 61/39). Isomer **10α** was separated as a white solid by crystallization from hexane, mp 85-87°. Evaporation of the mother liquors and column chromatography (eluent methylene chloride/methanol 10/1) of the residue afforded a 60/40 mixture of **10β and 10α** (colorless oil). Diastereoisomer **10α**: m/z 182 (2.2), 180 (5.8), 117 (4.0), 81 (100), 79 (26.2), 64 (10.8), 63 (5.0); δ ($CDCl_3$) 4.09 (dt, 1H, 4.4 and 10.8 Hz), 2.58 (s,3H), 2.54 (m,1H), 2.15-1.30 (m,8H); $\nu_{max}$ (KBr) 2990, 2960, 2930, 2850, 1445, 1430, 1410, 1310, 1030, 980, 965 and 735 $cm^{-1}$. Diastereoisomer **10β** (with 40% of **10α**): m/z 182 (3.0), 180 (8.5), 117 (6.5), 81 (100), 79 (53.1), 64 (11.8), 63 (43.3); δ ($CDCl_3$) 4.10 (m,1H), 3.10 (m,1H), 2.58 (s,3H), 2.45-1.30 (m, 8H)

*trans-1-Bromo-2-methylsulfinylcyclohexane* (**11α** *and* **11β**)

Oxidation of thioether **5** (method B) afforded a 62/38 mixture of **11α and 11β** in 93% yield. Crystallization of the mixture from hexane afforded a white solid which was characterized as pure **11α**, mp 47-50°. Evaporation of mother liquors and crystallization of the residue from hexane lead to a mixture of **11β/11α** in a 37/63 ratio. Diastereoisomer **11α**: m/z 226 (1.5), 224 (1.6), 163 (4.6), 161 (4.9), 121 (3.0), 119 (3.6), 81 (100), 63 (4.6); δ ($CDCl_3$) 4.23 (dt, 1H, 4.4 and 10.9 Hz), 2.64 (dt, 1H, 4.1 and 10.8 Hz), 2.57 (s,3H), 2.20-1.30 (m, 8H); $\nu_{max}$(KBr) 3000, 2940, 2920, 2860, 1440, 1425, 1325, 1180, 1030 and 680 $cm^{-1}$. Diastereoisomer **11β** (with 37% of **11α**): m/z 226 (1.0), 224 (1.1), 163 (4.6), 161 (4.2), 121 (2.9), 119 (3.2), 81 (100), 63 (25.8); δ ($CDCl_3$) 4.35 (dt, 1H, 3.8 and 7.4 Hz), 3.20 (m, 1H), 2.56 (s, 3H), 2.48-1.35 (m, 8H); $\nu_{max}$(film) 2940, 2860, 1450, 1045 and 685 $cm^{-1}$.

*trans-2-Methylsulfonylcyclohexanol* (**12**)

Oxidation of thioether **1** yielded 60% (method A) or 52% (method B) of sulfone **12**. It was crystallized from light petroleum as a white solid, mp 95-96°. m/z 178 (3.5), 107 (22.2), 99 (26.6), 81 (100); δ ($CDCl_3$) 3.97 (m, 1H), 3.33 (d, 1H, 2.5 Hz), 3.02 (s, 3H), 2.87 (ddd, 1H, 3.9, 9.8 and 12.5 hz), 2.33-1,22 (m, 8H); $\nu_{max}$(Nujol) 3500, 1290, 1275, 1265, 1130, 1065, 940 and 760 $cm^{-1}$.

*trans-1-Methoxy-2-methylsulfonylcyclohexane* (13)

This compound was obtained from thioether 2 (method B) as a white solid, 65% yield, mp 46-47°. m/z 192 (2.9), 113 (15.0), 81 (100) 45 (48.5); δ ($CDCl_3$) 3.46 (m, 1H), 3.40 (s, 3H), 3.05 (s, 3H), 2.84 (ddd, 1H, 3.9, 10.0 and 12.6 Hz), 2.25-1.03 (m, 8H); $\nu_{max}$ (Nujol) 1370, 1330, 1300, 1270, 1190, 1130, 1110, 1100, 970 and 940 $cm^{-1}$.

*trans-1-Fluoro-2-methylsulfonylcyclohexane* (14)

Oxidation of thioether 3 yielded compound 14 (68%) which was purified by column chromatography (eluent methylene chloride/methanol 10/1). The colorless syrup so obtained solidified on standing, mp 47-49°. m/z 180 (0.4), 101 (8.5), 81 (100), 79 (33.1); δ ($CDCl_3$) 4.85 (ddt, 1H, 48.5, 5.0 and 10.5 Hz), 3.08 (m,1H), 3.05 (d, 3H, 2.0 Hz), 2.50-1.20 (m, 8H); $\nu_{max}$ (KBr) 3040, 3010, 2950, 2930, 1460, 1415, 1375, 1325, 1305, 1285, 1270, 1130, 1115, 1025, 945, 870 and 770 $cm^{-1}$.

*trans-1-Chloro-2-methylsulfonylcyclohexane* (15)

Oxidation of thioether 4 (method B) afforded 15 as a white solid in 70% yield. Crystallized from light petroleum, mp 34-36°. Found C 42.72, H 6.66, Cl 18.02, S 16.29. $C_7H_{13}ClO_2S$ requires C 42.54, H 6.97, Cl 18,44, S 16.58. m/z 161 (0.2), 117 (6.0), 81 (100) and 41 (11.3). δ ($CDCl_3$) 4.24 (ddd, 1H, 4.5, 9.5 and 10.6 Hz), 3.17 (s, 3H), 3.13 (ddd, 1H, 4.3, 9.5 and 11.5 Hz), 2.54-1.28(m, 8H); $\nu_{max}$(Nujol) 1305, 1280, 1140, 1100, 1100, 990, 940, 755 $cm^{-1}$.

*trans-1-Bromo-2-methylsulfonylcyclohexane* (16)

Thioether 5 was oxidized (method B) to yield 82% of 16 as a white solid which crystallized from light petroleum, mp. 47-48°. m/z 242 (0.2), 240 (0.3), 163 (7.9), 161 (8.7), 81 (100); δ ($CDCl_3$) 4.49 (ddd, 1H, 4.3, 8.0 and 9.4 Hz), 3.29 (ddd, 1H, 4.7, 8.0 and 9.4 Hz), 3.16 (s, 3H), 2.45-1.44 (m, 8H); $\nu_{max}$(Nujol) 1310, 1285, 1145 and 750 $cm^{-1}$.

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