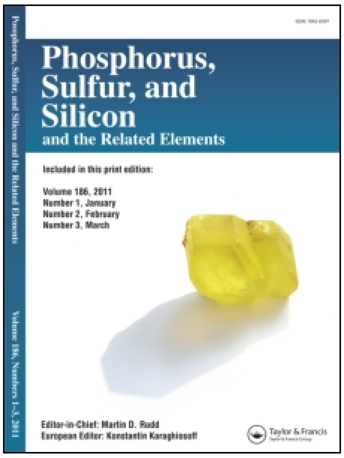


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

FUNCTIONALIZED SULFUR AS MONITOR OF CONFORMATIONAL ASPECTS OF STRUCTURE AND REACTIVITY

Jacques Metzger[a]
[a] University of Aix-Marseille, Marseille, France

To cite this Article Metzger, Jacques(1986) 'FUNCTIONALIZED SULFUR AS MONITOR OF CONFORMATIONAL ASPECTS OF STRUCTURE AND REACTIVITY', Phosphorus, Sulfur, and Silicon and the Related Elements, 27: 1, 233 — 242

To link to this Article: DOI: 10.1080/03086648608072774

URL: http://dx.doi.org/10.1080/03086648608072774

Phosphorus and Sulfur, 1986, Vol. 27, pp. 233–242
0308-664X/86/2702-0233/$15.00/0

FUNCTIONALIZED SULFUR AS MONITOR OF CONFORMATIONAL ASPECTS OF STRUCTURE AND REACTIVITY

JACQUES METZGER

University of Aix-Marseille, Marseille, France

Δ-4-thiazoline-2-thiones and imidazoline-2-thiones are suitable substrates for the study of steric interactions and particularly for the demonstration of preferential conformations of alkyl groups borne by these substrates (gear effect). The presence of the thiocarbonyl group induces a large space anisotropy allowing precise dynamic nmr studies at low temperature. By its reactivity this thiocarbonyl group can be used as a chemical probe to evaluate quantitatively the influence of preferential conformations on the reactivity of these molecules.

Relatively to their spatial structure, substituents may be divided into three classes:

–those with an axis of symmetry C_∞ as halogens, cyano,...

–those which are planar as aryl, formyl

–and those which are polyhedral as alkyl.

The mutual through-space interaction of these various groupings is called the steric effect.

On one hand the quantitative approach of reactivity (LFER) in the 1960s attempted to associate to each substituent a *unique* steric effect parameter by giving a description of its size. Thus several steric effect scales have been proposed, associating for example a unique steric parameter to an isopropyl group and thus giving it an average and globular description of its size. On the other hand, the development in the early 1970s of the DNMR and of the molecular mechanics calculations, allowed a much more detailed approach of steric effect. Thus it became clear that, concerning their steric interactions, the various groups of substituents did not call on the same intimate mechanisms for the strain minimization. For example when two spherical groups are in interaction the minimization of the strain can only result in an angular deformation (buttressing). On the other hand when the two interacting groups are polyhedral, the main way of strain minimization gets over the rotation of the groups although some stretching and twisting can also operate. In the early 1970s we introduced the term "gear effect" to describe the through-space interaction of tetrahedral groups. This pictorial analogy intends to support two aspects of the phenomenon (Fig 1):

1) the conformational interdependence of the groups, which means that the conformation of one group cannot be considered without taking that of its neighbors into account.

2) the transmission of conformational interaction through alkyl groups.

Both ideas will now be developed.

We are aware of the fact that using a term of the common language for the description of a microscopic phenomenon is not without danger, but we have always taken precautions for specifying that the interacting groups' rotation was not necessarily synchronous and disrotatory along the rotation pathway. Nevertheless

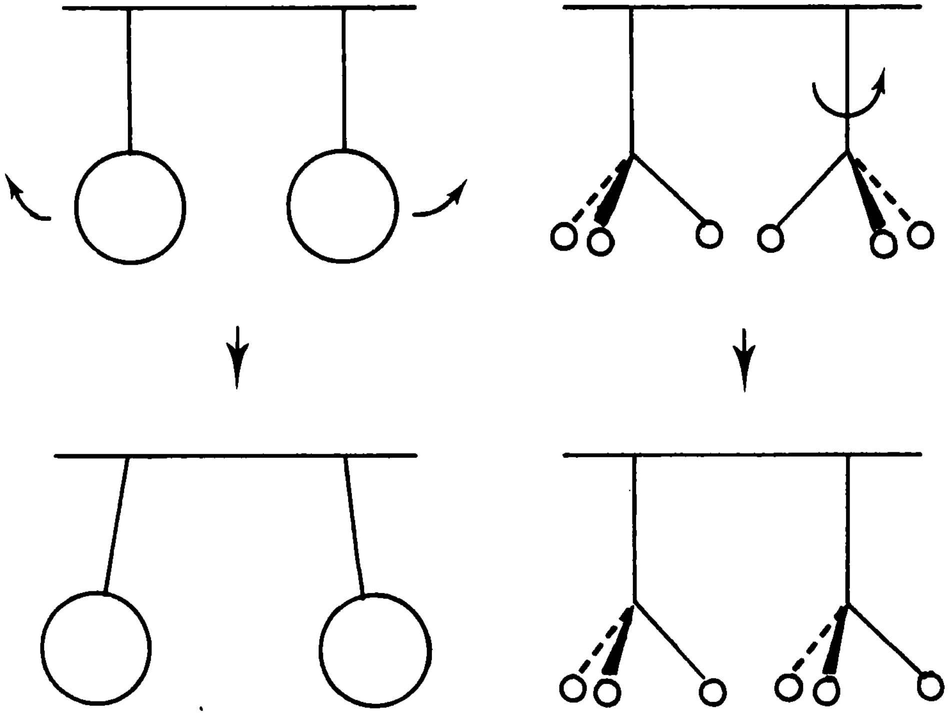


FIGURE 1

the term gear effect appeared to us as useful enough because it involves the idea of conformational transmission through interacting groups (like cogwheels) and it complements the English term of "buttressing effect" which, although related to through-space mutual interaction, does not include the conformational aspect of the interaction.

My talk shall be divided into two parts:

1) experimental evidence of the gear effect in the interaction of isopropyl groups.
2) application to the transmission of conformational information:
   - kinetics of alkylation
   - structure of an apparently symmetrical but geared molecule.

An *i*Pr group, bonded to an sp^2 carbon atom and surrounded at ortho and ortho-prime positions by two substituents X and Y, takes two conformations A and B, in which the methine hydrogen is situated in the molecular plane either in the direction of X group or in that of Y group (Figure 2). When the size of X is larger than that of Y, the equilibrium is shifted towards conformer B in order to minimize the interaction between the bulky group X and the two methyl groups. Thus it is possible to classify X groups according to their size when Y is kept constant. Here the *i*Pr group plays the role of a physical probe. Δ-4-Thiazoline-2-thiones are particularly suitable for this kind of study (Figure 3):

-their synthesis is easy and unequivocal,

-the thiocarbonyl group, located at the 2 position, is highly anisotropic which makes easy the low temperature NMR study

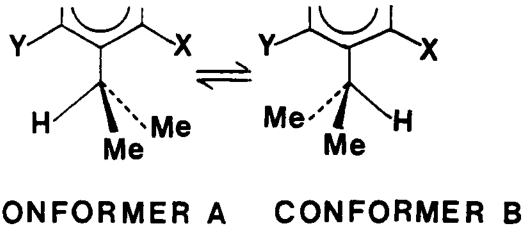


FIGURE 2

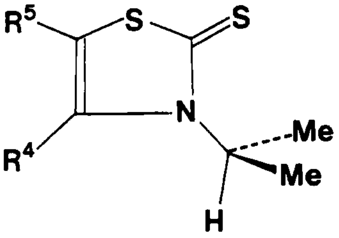


FIGURE 3

–X-rays studies show that *i*Pr group has its two methyls on both sides of the ring plane

–the thiocarbonyl group is a good nucleophile and can play the role of a chemical probe.

We have varied the substituent at the 4-position and observed the influence of that substituent on the conformational equilibrium of the *i*Pr group. This study was performed by low temperature proton NMR between −40° and +10°, in various solvents. We report the results in the case of acetone (Figure 4):

–When R_5 = H, the population of conformer A increases monotonically in the alkyl group series, clearly indicating an increase of the size of R_4. This result is quite expected: the bulkier R_4 group is, the more populated conformer A, in which both methyl groups are oriented toward the thiocarbonyl.

–When R_5 = Me, we introduce a perturbation at a position which does not allow a direct interaction between R_5 and *i*Pr group. Any modification of the R_3 population, resulting from the R_5 change from H to Me, must be relayed by the R_4 group.

Three situations are observed, apart from *t*Bu which represents a special case where conformer A is present at 100% before substitution:

1) when R_4 = H or Me, no variation of the *i*Pr population is observed: the apparent size of H-4 or Me-4 is not modified.

2) when R_4 = Et or *i*Bu, the percentage of conformer A increases, which means that the apparent size of Et or *i*Bu increases through the R_5 perturbation. This result could be explained by a buttressing effect of the Me at position 5, which induces the energy minimization by a twisting of the bond.

3) when R_4 = *i*Pr, an unexpected effect is observed: the 4-*i*Pr group is apparently smaller when it is perturbed by a Me at position 5, and its apparent size is even

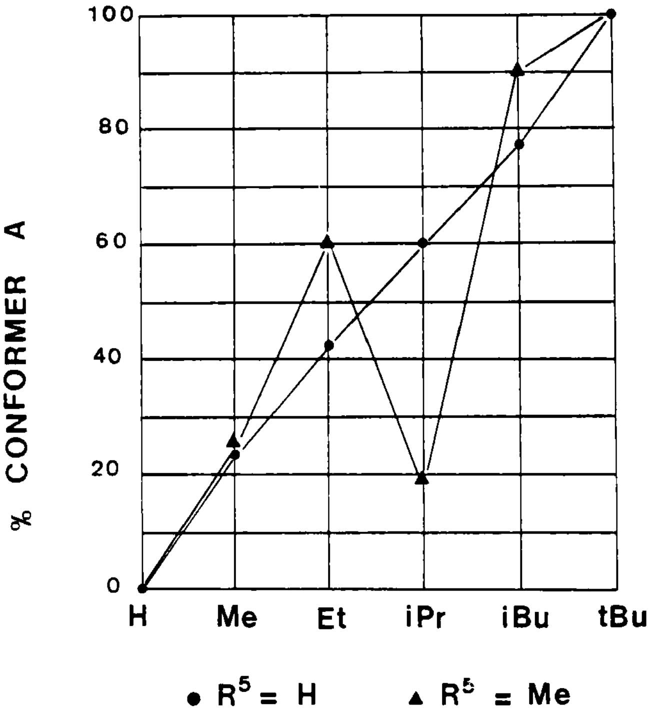


FIGURE 4

smaller than that of a Me. This is quite inconsistent with all the steric-effect scales and cannot be interpreted by a buttressing effect which would result in the opposite variation. This unexpected behavior, which we could verify in many other situations, was the first experimental evidence of the gear effect.

A most complete analysis of the compound with two *i*Pr groups at 3 and 4 positions was then necessary. Molecular mechanics calculations, taking only van der Waals interactions into account, allowed us to show that we had three conformers A_1, A_2 and B; B being the most stable (Figure 5).

Experimentally (A_1 + A_2), which differ only by the rotation of the 4-*i*Pr group, account for 19% and B for 81% (A_2 is very little populated). The measurement of rotation barriers shows clearly that the molecule passes from conformer A_1 to conformer B, by successive rotation of both *i*Pr groups via conformer A_2.

In the molecule of 3,4-di*i*Pr-5-methylthiazoline-2-thione, the conformations of the groups at 3- and 4-positions are 97% interdependent, that is to say geared, and it is impossible to treat the conformational state of one of these groups without considering its neighbors.

Concluding this first part, the existence of a new effect has been demonstrated: we call it the gear effect.

Let us now discuss the aspect of conformational transmission. The thiocarbonyl group at 2-position and the substituent at 5-position cannot interact directly for evident geometrical reasons. Nevertheless the thiocarbonyl group is informed of the

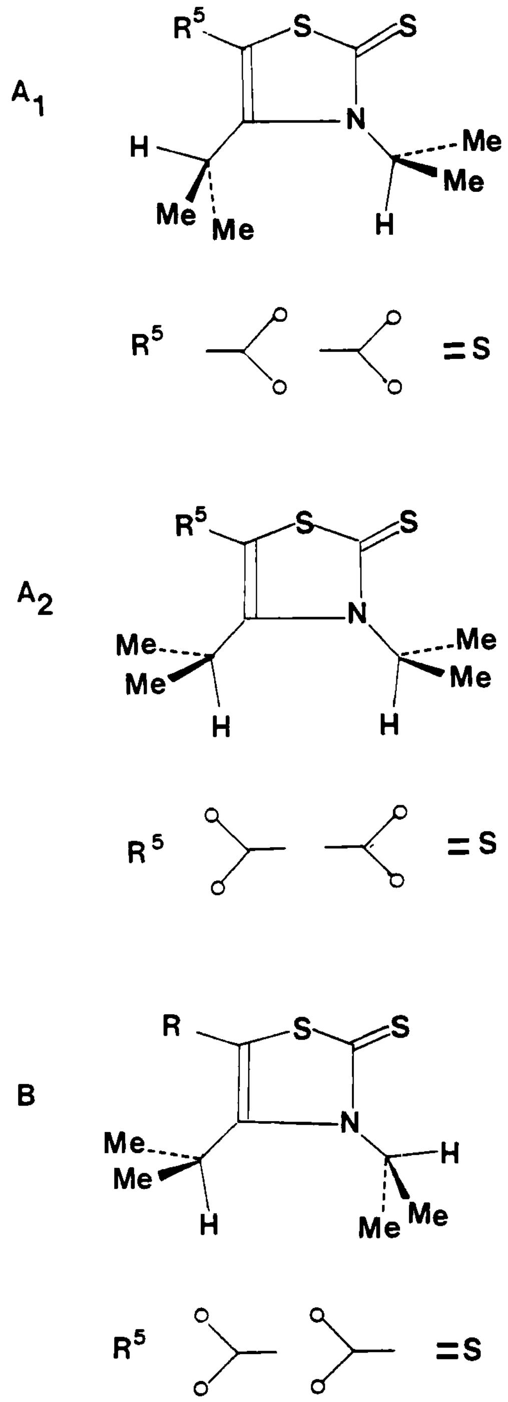

A1
R5
S
S
N
H
Me
Me
Me
Me
H
R5
=S
A2
R5
S
S
N
Me
Me
H
Me
Me
H
R5
=S
B
R
S
S
N
Me
Me
H
H
Me
Me
R5
=S

FIGURE 5

substitution at 5-position through the relay of alkyl groups at positions 4- and 3-. This is particularly well illustrated in Figure 6.

Here are collected the rate constants for the alkylation at sulfur atom of several trialkylthiazoline-2-thiones by methyl iodide in acetone at 25°C. We observe that the effect of the substitution by a Me group at position-5 results in two modes:

1) by a general accelerating effect, which is due to the general electron-donating effect of Me group.

2) by a non-monotonous variation which is directly related to the conformation of the 3-*i*Pr group.

The whole set of results can be interpreted in terms of a Winstein-Holness-Eliel approach, which expresses the variation of reactivity of the molecule with the conformational state of the 3-*i*Pr group (Figure 7).

The thiocarbonyl group is thus informed of the substitution at 5-position and this is an example of the influence of the conformational transmission on the reactivity.

We have just seen that the interaction of *two* *i*Pr groups, located between two substituents, results in interdependent conformations. Such a particular spatial arrangement leads one to consider the whole of the two *i*Pr groups as a supersubstituent, which presents the same spatial characteristics as the *i*Pr groups itself. This

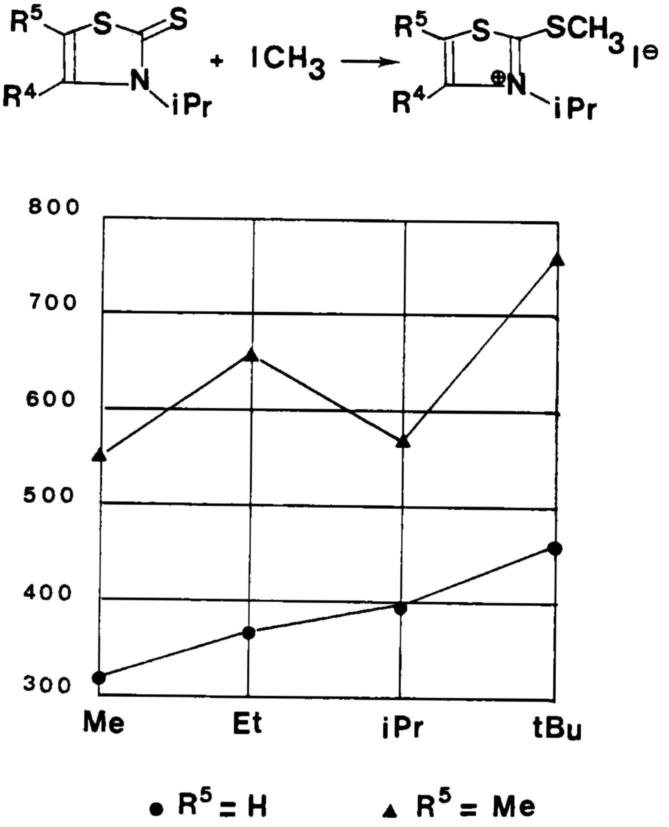


FIGURE 6

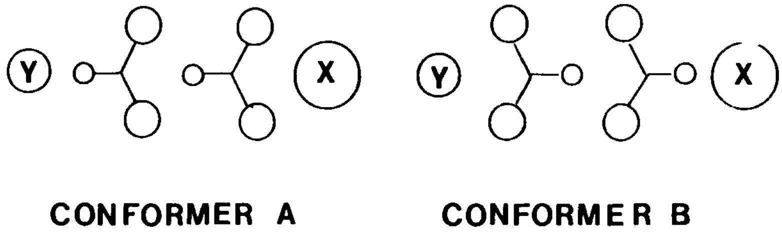


FIGURE 7

supersubstituent shows two faces: the one is very bulky and looks like a *t*Bu, whereas the other is less bulky and looks like a Me.

For the Y substituent, it behaves as if it would interact with a Me group in the A conformation and with a *t*Bu group in the B conformation. We shall now consider a molecule which allows us to illustrate this behavior. We must at first recall some elements of the conformational analysis of primary alkyl groups bonded to an sp^2 carbon atom. Where a primary alkyl group is bonded to a planar system with two substituents X and Y at positions ortho and ortho prime, its preferential conforma-

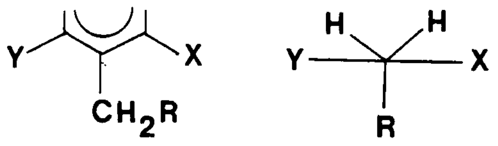


FIGURE 8

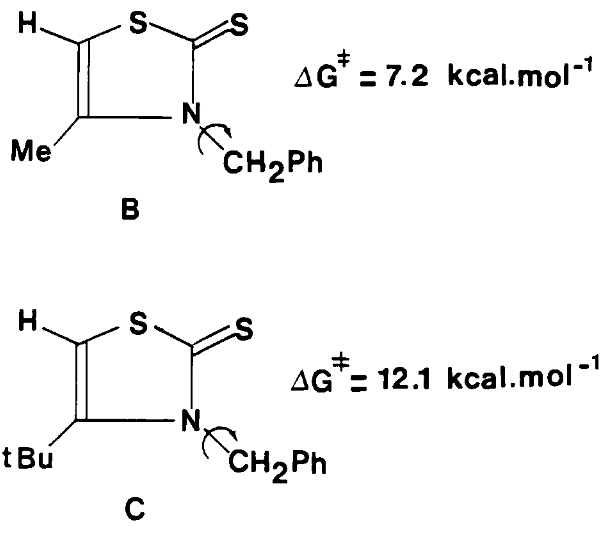


FIGURE 9

tion is such as to make both hydrogen atoms diastereotopic when X and Y are different (Figure 8). The transition state for the rotation is such that the R group passes facing the smallest X or Y group.

In the B and C molecules, the rotational barriers of the benzyl group around the carbon-nitrogen bond are respectively of 7.2 and 12.1 kcal. mole^{-1} (measured by low temperature DNMR) (Figure 9). These barriers are very different and reflect the difference in steric environment of benzyl in B and C: in C, benzyl is situated between a *t*Bu and a thiocarbonyl, whereas in B it is situated between a Me and a thiocarbonyl. In C rotational transition state corresponds to the passage of the phenyl group facing the thiocarbonyl, whereas, in B it faces the Me.

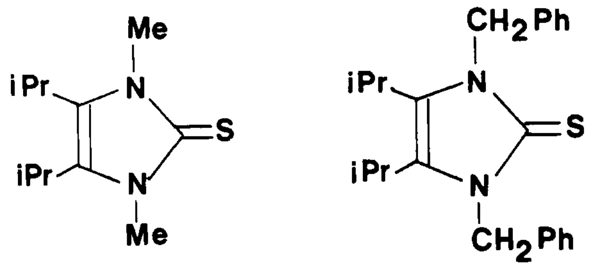
We have studied molecule D and shown that this molecule presents a conformational state which is geared at the level of the two *i*Pr groups (Figure 10). The set of molecules B, C and D allowed us to put forward molecule A for illustrating the importance of the role of geared conformations. Molecule A is apparently completely symmetrical if one considers the substituents as globular.

This impression is strengthened if one considers the proton NMR spectrum of compound A at ambient temperature: one observes a unique doublet (Me) and a unique septuplet (H) corresponding to both *i*Pr groups and a unique CH$_2$ signal (near 5.6 ppm) as well as a unique phenyl signal. By lowering the temperature, the signals of methylene and Me of the *i*Pr groups turn into a complex figure.

Considering the benzyl methylenes (Figure 11), one observes at −44°C an important broadening; at −68°C an AB spectrum clearly appears whereas a methylene (center), although very disturbed, keeps its singlet structure. At· −80°C there is a coalescence of this singlet and at −112°C appears a complex structure mode of four AB figures. The simulation of these spectra allows the assignment of a particular rate constant to each of the rotation processes.

In an apparently symmetrical molecule we have four couples of protons, each giving an AB spectrum. The successive locking of the various rotation processes results in the observed spectra.

The process having the highest barrier is the rotation of the isopropyl groups with $\Delta G^{\neq} = 11.5$ kcal. mole^{-1}. As soon as this process is slowed down, both benzyl



D A

FIGURE 10

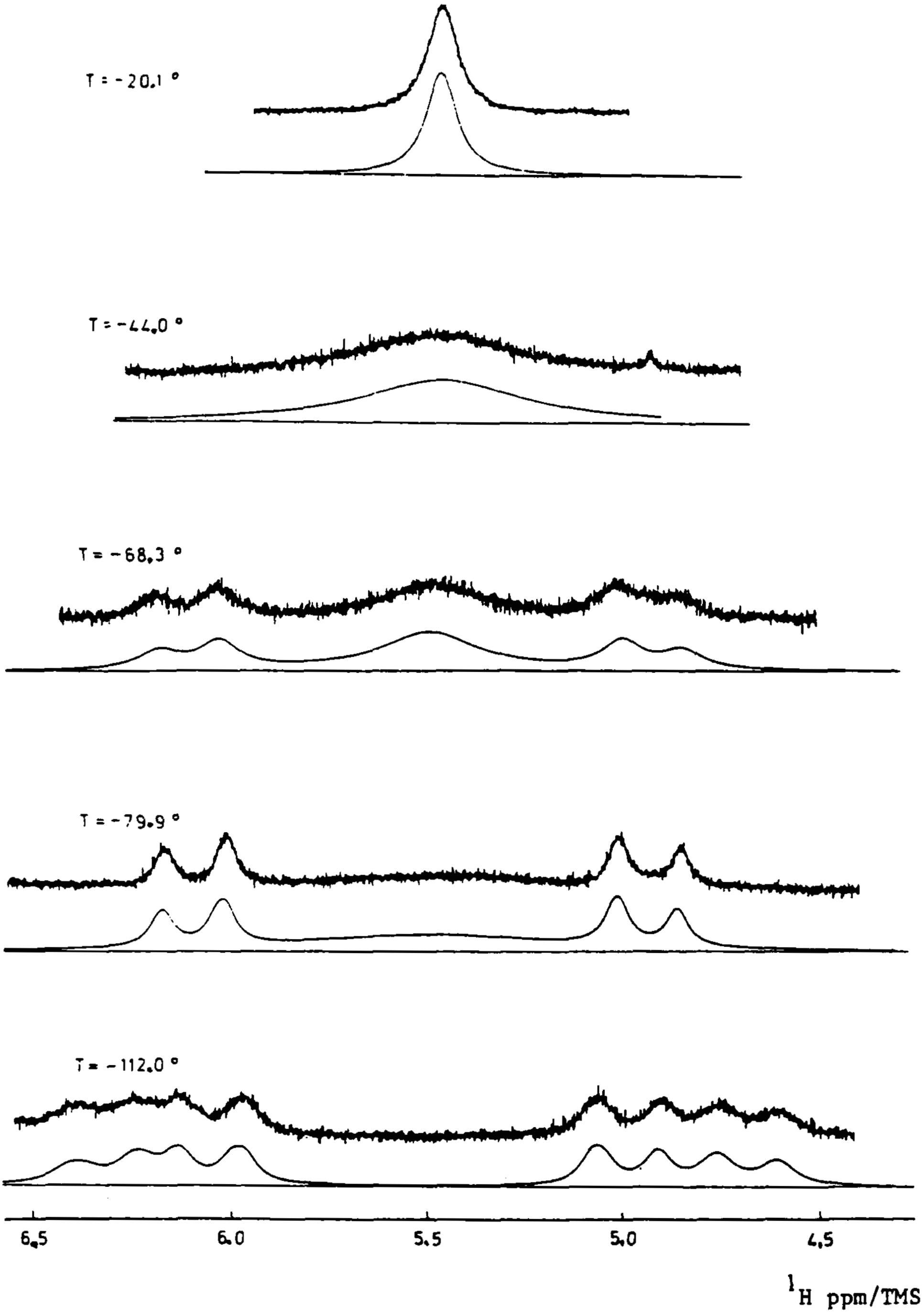


FIGURE 11

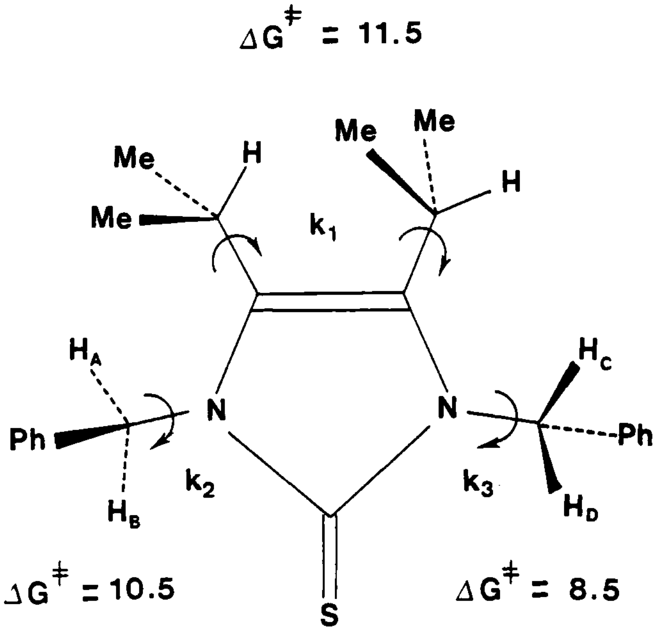


FIGURE 12

groups are no longer equivalent: the one located between the crowded face of *i*Pr and thiocarbonyl presents a barrier of 10.5 kcal. mole^{-1} whereas the other, situated between the less crowded face of *i*Pr and thiocarbonyl has a barrier of 8.5 kcal. mole^{-1} (Figure 12).

This means that, in an apparently symmetrical molecule, the existence of a geared conformation of the *i*Pr groups, induces such a steric anisotropy of the space, that a benzyl group rotates 200 times faster than the other one.

That is again an example of the conformational transmission.

BIBLIOGRAPHY

1. C. Roussel, M. Chanon and J. Metzger, *Tetrahedron Lett.*, 1861, (1971).
2. C. Roussel, M. Chanon and J. Metzger, *Tetrahedron Lett.*, 3843, (1972).
3. C. Roussel, M. Chanon and J. Metzger, *F.E.B.S. Lett.*, **29**, 253, (1973).
4. A. Liden, C. Roussel, M. Chanon, J. Metzger and J. Sandström, *Tetrahedron Lett.*, 3629, (1974).
5. C. Roussel, A. Liden, M. Chanon, J. Metzger and J. Sandström, *J. Amer. Chem. Soc.*, **98**, 2847, (1976).
6. A. Liden, C. Roussel, T. Liljefors, M. Chanon, R. E. Carter, J. Metzger and J. Sandström, *J. Amer. Chem. Soc.*, **98**, 2853, (1976).
7. B. Blaive, C. Roussel, J. Metzger and J. Sandström, *Can. J. Chem.*, **58**, 2212, (1980).
8. U. Berg and C. Roussel, *J. Amer. Chem. Soc.*, **102**, 7848, (1980).