THE GEAR EFFECT. III. A SIMPLE MODEL FOR STERIC INDUCED MODIFICATION OF *SYN–ANTI* EQUILIBRIUM IN NUCLEOTIDES

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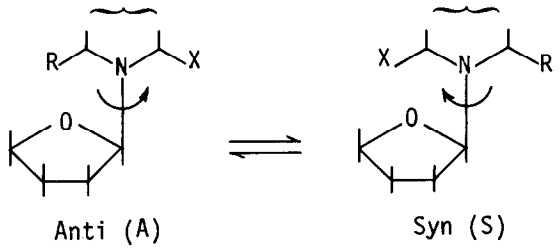
1. Introduction

The study of *syn–anti* isomerism (S/A) (eq. 1) in nucleosides and nucleotides is of current interest in biochemistry [1–4]. Recently results on substituent effects on the S/A ratio in several bases have been reported and serious controversies arise on the true role of the substituent in the conformational change [5].



(Eq. 1.)

These studies are difficult in biological systems in which several effects affect the S/A ratio (steric effect, hydrogen bonding...) and often, more simple organic models are useful to underline a particular behaviour [6].

In a general study of intramolecular steric affect, we have already shown [7] in very simple models that the long range conformational change is usually induced by the means of interlocking groups (fig. 1).

Fig. 1.

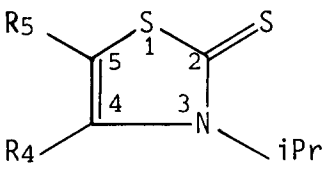
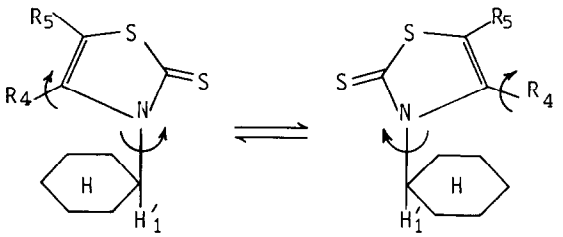


Fig. 2.

We used for this purpose 3-isopropyl-4-alkyl-4-thiazoline-2-thione and 3-isopropyl,4,5-alkyl 4-thiazoline 2-thione (fig. 2). We have named this substituent induced conformational change the "*gear effect*". Our aim is to show that these conformational changes in models similar to nucleosides may be induced by the same *gear effect*.

2. Model and method



(Eq. 2.)

We have thus studied the 3-cyclohexyl-4-alkyl-thiazoline-2-thione for three main reasons (eq. 2). First the substrates are obtained without ambiguity in high purity [8], second the change in S/A ratio is induced purely by steric effect and third the easy and

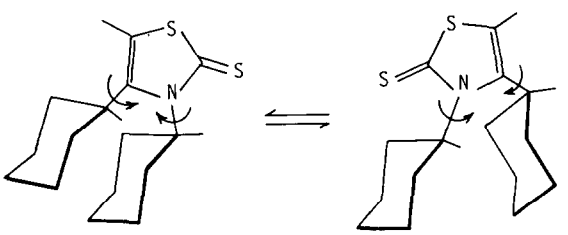
unequivocal conformation attribution can be done by low temperature HNMR because of the important anisotropy of the thiocarbonyl group [7] and the exceptional high rotational barrier around the C–N bond. In the studied system these barriers vary between 13 and 16 Kcal/mole [9].

The relative percentages are determined by averaged integrations, and the obtained precision is of the order of ±3%.

3. Results and discussion

The results given in table 1 show unequivocally that the S/A ratio is dramatically changed by substitution in the ortho position (R_4) of the C–N bond (compounds *1, 2, 3, 4, 5*), and that an increase in the effective size [10] of the R_4 alkyl group induces an increase of the S/A ratio (compounds *1, 2, 3, 4*). This same effect was found [7] when R_3 was an isopropyl group instead of a cyclohexyl one. Furthermore it was shown that the two groups R_3 and R_4 were in a geared conformation.

This same interdependency is observed in the present system (eq. 3).



(Eq. 3.)

This gear effect is even more clearly illustrated when $R_5 \neq H$ (compounds *6, 7, 8*), since substitution on R_5 induces conformational changes on R_3 through R_4. This implies that the prediction on occurring changes are no longer possible by simple consideration of the steric size of the ortho group (R_4) (tBu > iPr > Et > Me) and that all interacting groups should be considered together since the effective size of the ortho group becomes very much dependent on long range substitution. For instance the ortho effect is more important with R_4 = Et than R_4 = iPr when R_5 = Me, and in this case the apparent size order of the ortho group is Et > Me ≃ iPr.

In conclusion, this simply demonstrates that long range conformational transmission on simple organic models could be directly applied in biological systems. In the case of 5,6-distributed uridine and cytidine nucleosides the *gear effect* should be even more evident since steric effects are more marked in 6 membered rings [11].

Acknowledgement

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References

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Table 1

Compounds	R_4	R_5	*Syn*	*Anti*	S/A	H'_1 Chemical shifts S	A
1	Me	H	32%	68%	0.47	4.25	5.58
2	Et	H	38%	62%	0.61	4.26	5.65
3	iPr	H	59%	41%	1.44	4.25	5.75
4	tBu	H	100%	0%	>10	4.28	–
5		H	50%	50%	1.0	4.20	5.75
6	Me	Me	35%	65%	0.54	4.26	6.12
7	Et	Me	61%	39%	1.56	4.18	5.70
8	iPr	Me	32%	68%	0.47	4.20	5.80

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