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CAN THE SIGN OF CROSS-RING COUPLINGS (^4J) BECOME A TOOL FOR THE ASSIGNMENT OF STEREOCHEMISTRY IN FOUR-MEMBERED RINGS ?

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Although a large number of experimental values of couplings through four σ bonds are known (1), relatively few data for cyclobutane rings have been published (2,3); and if one considers their sign, only scanty examples are available (4-9,14-16). We have studied two series of vic--dihalo-2,3-oxazabicyclo[3.2.0]-hept-3-enes,where all the chloro- and most of the bromo stereisomers were available, together with some other similar derivatives (I-XI)(17).
Since the assignment of cis and trans orientation of protons on four-membered rings, on the basis of vicinal coupling constants only, cannot be safely made, as pointed out by Williams (2a),we focused our attention on four-bond couplings and their relation with stereochemistry. The complete analysis (18) of the spectra in different solvents was performed by using the LAOCN3 computer program (23);the sign of all coupling constants were determined by "tickling" experiments (18) and again deduced from the analysis (all spectra are 2nd order). The results reported in Tab. 1 show that the cross-couplings (^4J) are positive, when the two interacting protons are cis; negative, when they are trans. All the other data found in the literature[***] for four membered ring compounds are listed in Tab.1 and 2, and are consistent with this general pattern.

The stereochemistry of compounds I-IX has been proved by both chemical (17) and spectroscopic (18) evidence. The anti configuration of X has been deduced by conversion into VI on HCl treatment; so the syn structure follows for XI: the complete analysis of its spectrum was carried out, and all couplings were found to be positive, but the assignment of ^3J and ^4J (both small) is so far ambiguous. For the same reason, the values of J_{13} and J_{24} in IX, being too similar, cannot be unambiguously attributed. But this indeed will not affect the following considerations. No change in coupling constant values was observed in a range of temperatures between +150° and -80°; and this means that the conformation of the ring does not change under these conditions, or that interconversion is still fast enough on the NMR

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[***]All the signs, except in XXVIII, are deduced from the analysis.

Table 1

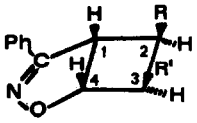
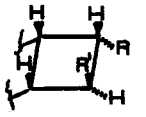
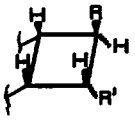
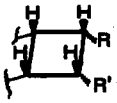
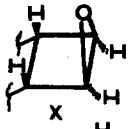
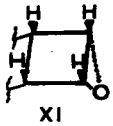
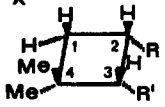
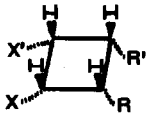
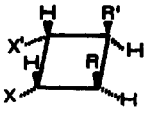
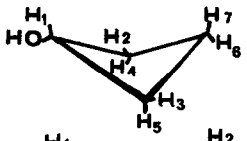
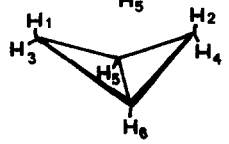
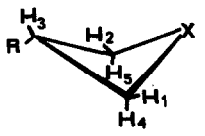
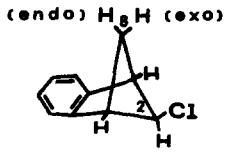
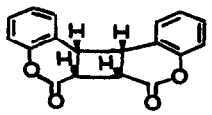
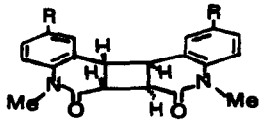
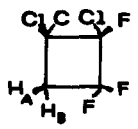
			$^4J_{1,3}$ trans	$^4J_{2,4}$ trans	$^4J_{1,3}$ cis	$^4J_{2,4}$ cis	
	I	R = R'= Cl	-1.66	-0.68			
	II	R = R'= Br	-1.77	-0.73			
	III	R = R'= COOMe	-1.44	-0.94			
	IV	R = R'= Cl	-1.49			+1.23	
	V	R = R'= Br	-1.38			+1.21	
	VI	R=Cl, R'=OH	-1.55			+1.42	
	VII	R = R'= Cl		-0.91	+2.42		
	VIII	R = R'= Br		-0.61	+2.48		
	IX	R = R'= Cl			+2.98	+2.13	
	X		-0.57	-0.73			
	XI		all J are positive				
	XII	R = R'= COOMe	-0.82		+2.23		(4)
	XIII	R = R'= COOH	-0.4		+2.31		(4)
	XIV	X = X'= Cl R = R'= COOH			+1.3	+1.3	(5)
	XV	X = X'= Cl R = R'= COOMe			+1.4	+1.4	(5)
	XVI	X = X'= Br R = R'= COOMe			+1.2	+1.2	(5)
	XVII	X = X'= Cl R–R' = CO–O–CO			+1.5	+1.5	(5)
	XVIII	X = R = COONa X'= R'= o-PhONa			+0.6	+0.6	(6)
	XIX	X = X'= Cl R = R'= COOH	-1.4	-1.4			(5)
	XX	X = X'= Cl R = R'= CH_2OH	-1.5	-1.5			(7)
	XXI	X = R = COONa X'= R'= o-PhONa	-1.1	-1.1			(6)

Table 2

			$^4J_{cis}$	$^4J_{trans}$	
	XXII		+5.16 (J_{23}) +0.01 (J_{17}) -0.01 (J_{45})	-0.93 (J_{25}= J_{43}) -1.07 (J_{16})	(8)
	XXIII		+5.9 (J_{34}) +1.1 (J_{12})	0.4 or 0.6 (#) (J_{32}= J_{41})	(9)
	XXIV	X = S R = Cl	+3.11 (J_{12}) -0.48 (J_{45})	-0.75 (J_{15}) -0.75 (J_{24})	(10)
	XXV	X = S R = H	+1.20	-0.20	(11)
	XXVI	X = O R = H	+0.20	+0.14	(11)
	XXVII	X = CO R = H	+4.2 +4.6	-2.99 -2.8	(12) (13)
	XXVIII		+7.4 (J_{28endo})	-0.25 (J_{28exo})	(14)
	XXIX		+1.47		(15)
	XXX XXXI XXXII	R = H R = Me R = Cl		-1.35 -0.94 -0.94	(15) (15) (15)
	XXXIII		+7.40 ($J_{H_A,F}$)	-2.92 ($J_{H_B,F}$)	(16)

(#) These signs, deduced from AA'B_2RR' analysis, are presumed to be positive, but the Authors don't discuss this point.

scale. A distortion of no more than 20° is, on other hand, expected, especially in the most hindered IV-IX isomers. A larger distortion can be excluded from examination of models and on the basis of the values of $^4J_{cis}$, which show a maximum of 2.98 Hz, in comparison with 7.4 Hz in XXVIII and with similar values in bicyclo[3.1.1]heptanes and bicyclo[2.1.1]hexanes (1a).

Our results are qualitatively in agreement with the theoretical prediction of Barfield (1a,19). The agreement lies solely in that $^4J_{cis}$ are higher than $^4J_{trans}$, and the arrangement of cis proton is more close than the trans to the "sig-sag" path, for which a maximum positive coupling is theoretically expected. The four bonds in the cis configuration are not coplanar, and the ϕ and ϕ' angles are well below 180°, even with a distortion of the cyclobutane ring. On the other hand the trans interactions are more negative than theoretically expected. Of course agreement with theory in these couplings would have been surprising, because Barfield's angular calculation are based only on the indirect "through bond" contribution to coupling, in the absence of any quantitative information about the direct "through space" contribution. Thus in these small rings, many factors can be important, such as the number of coupling paths which link the coupled protons, the relative orientation of substituents, as well as the probable increasing contribution of a direct mechanism, even in molecules not highly strained.

The values of long-range couplings in compounds I-XI are in line with the results obtained by other Authors (4-9, 14-16). The only discrepancies in sign are : J_{17}= -0.61 in XXII (8), $^4J_{trans}$= +0.14 in XXVI (11), J_{45}= -0.48 in XXIV (10). Concerning the first and the second case, we must point out that couplings with such a low absolute value, obtained only by the iterative procedure of analysis, have no significance. Moreover J= +0.14 is an average value for the trans coupling in oxetane (XXVI), which is considered as rapidly flipping. In this molecule two completely different values have been published (20): -0.4 and +0.7 Hz. It appears that the determination of such small couplings in the complex spectrum of oxetane requires a more accurate analysis. The third case seems a little more significant, and this negative coupling should be considered as an exception to the positive values of cis interactions; but we must take into account that, even in this case, the sign is not obtained directly by a double resonance experiment. On the other hand the influence of the heteroatom seems not to be relevant, since the other couplings in XXIV-XXVI and in cyclobutanone (XXVII) are in agreement with the general trend of positive cis and negative trans interactions[M].

[M] From the analysis of the proton spectrum of cyclobutane in a nematic solvent (21) the values of cross-ring couplings have been deduced as: $^4J_{cis}$ = +2.5 and $^4J_{trans}$ = +0.5 Hz with an accuracy of ± 0.7 Hz. With such an error the sign of $^4J_{trans}$ lacks any significance, whilst that of $^4J_{cis}$ can be accepted as positive.

The four stereoisomers of the chloro series I, IV, VII and IX are particularly interesting, because we can observe the variation of cross-coupling constants with the stereochemistry in the same fragments on cyclobutane ring. The data for the bromo series, even if not complete because the fourth isomer was not available, confirm these results. No coherent variation was observed from chloro to bromo derivatives, whereas $^4J_{13}$ were always found to be higher (absolute value) than $^4J_{24}$. This could be attributed to the isoxazole oxygen substituent effect (compare also compounds XII, XIII with XIV, XV, XIX); but if one takes the signs into account, an opposite trend is observed for J_{cis} and J_{trans}, which is difficult to explain only with this observation. Other factors, for instance the orientation of substituents, must be considered in small rings, where groups are quite near to each other.

Nevertheless the sign of four bond couplings in cyclobutanes seems highly stereospecific, much more sensitive to the cis-trans orientation of the two interacting protons, than to the effect of substituents, or to the distortion of the ring, if one excludes the highly strained bicyclic molecules. In that case however the anomalous values of cis four-bond couplings is presumably positive (14,22), suggesting again that the sign of cross-couplings is strictly correlated with the orientation of protons. The same trend is thus observed in cyclobutanone XXVII, in thietane XXV, and for H-F interaction in XXXIII.

We conclude that the four-bond couplings seem much more suitable for studying the stereochemistry of cyclobutanes, than the usual vicinal couplings, which show strong variations with small distortions, and ambiguity between the cis and trans values. This is why we would suggest their use, except when their absolute value is below 0.5 Hz, in that case the sign has no significance; and we emphasize once more that the use of small couplings for structural purpose always needs the knowledge of their sign.

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