Conformation Analysis of Spiranes by the Force-field Method. Part 1. Chirality and Diastereoisomerism of Spiro-compounds: Spiro[5.5]undecane and Derivatives

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In Cahn, Ingold, and Prelog's classification of chiral molecules, chirality of spiranes was analysed in terms of an unformulated assumption of planarity of molecular rings on the basis of rapid inversion. On this assumption (which remained unformulated and was never abandoned) the hydrocarbon skeleton is achiral, and chirality can be generated by appropriate substitution. Thus, the chirality of unsubstituted spiranes has been overlooked. A general condition for chirality of unsubstituted spiranes is given, and some examples of the manifestation of chirality of spiro[5.5]undecanes are discussed in detail. In particular, the diastereoisomerism of spiro[5.5]undecanes substituted at positions 1 and 5, and that of dispiro[5.2.5.2]hexadecane resulting from the chirality of the spiro atoms, are analysed on the basis of molecular mechanics calculations.

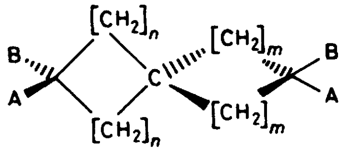
Chiral properties of tetrasubstituted spiro[5.5]undecane (**2a**) have long been recognized,[1] but the chirality of the spirane skeleton itself seems to have been overlooked.[2] † Cahn, Ingold and Prelog[1] classified the molecule (**2a**) as exhibiting an axis of chirality, on the basis of an unstated assumption of rapid inversion of the rings, leading to averaged planarity. This unformulated assumption has almost never been questioned, and its consequences are commonly accepted.[2] The implication is that substitution of the type (**1a**) is a condition for chirality; this is unfounded when the inversion of non-planar rings is frozen.

The consequences of chirality of the spiro atom were neglected by Mursakulov, Zefirov, Eliel *et al.*[3a,b] in their analysis of 1- and 5-substituted spiro[5.5]undecanes. In discussing steric relationships in these molecules, these authors treated them as 2-substituted 1,1-dialkylcyclohexanes, for which the number of *gauche* interactions between the substituents determined an axial-to-equatorial equilibrium.[3a] A molecular model of spiro[5.5]undecane (**2b**) reveals that such an approach is not justified, since (i) the magnitude of the long-range non-bonded interactions is similar to that of the *gauche* interactions, and (ii) the equatorial (and to a lesser extent the axial) substitutions at C(1) and C(5) are not equivalent, owing to the presence of two centres of chirality in spiro[5.5]undecanes monosubstituted at a position next to the spiro atom. Thus, the evaluation of the ratio of equatorial to axial substitution on the basis of n.m.r. spectra treated as those of two-component mixtures[3a,b] seems unfounded.

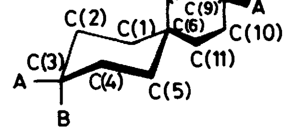
In this paper the chirality of (**2b**) and diastereoisomerism due to chirality of the spiro atom in its 1-Me (**3**), 1-OH (**4**), 1-OMe (**5**) derivatives and in dispiro[5.2.5.2]hexadecane (**7**) are discussed and analysed on the basis of molecular mechanics calculations. The method of calculation is described elsewhere.[4] The calculations were carried out using the MM2 program with a standard parametrization.[5]

Results and Discussion

As already stated, the chirality of spiranes was treated in an oversimplified way in Cahn, Ingold, and Prelog's classification[1] since the discussion was based on the unformulated assumption of rapid inversion of rings. Abandoning this assumption one can analyse spatial relationships in (**2b**) when inversion is frozen by an inspection of a Dreiding model, which reveals that the molecule exhibits a C_2 axis as the sole symmetry element, coinciding with the bisector of the C(1)C(6)C(11) angle. Therefore the unsubstituted molecule (**2b**) is chiral. Thus, like the spiro atom in vespirenes (**9**)[6] and N^+ in certain isomers of the tetramethylazoniaspiro[4.4]nonane (**10**)[7], C(6) in (**2**) is another interesting example of a centre of chirality of the type Caaaa formed by a carbon atom bearing four formally identical substituents. The 6*R* chirality of the molecule (**2b**) depicted can be determined on the basis of general rules given by Prelog and Helmchen.[8]



(1)



a: A≠B
b: A = B = H

(2)

An argument analogous to that just presented allows one to formulate a general condition of chirality of unsubstituted spiranes: a spirane molecule exhibits chirality if under experimental conditions the rings involved can be considered nonplanar. In this case the molecule has a centre of chirality. If the rings are mobile enough under experimental conditions, *i.e.* if they exhibit a rapid inversion, then unsubstituted spiranes behave as achiral, and chirality can be generated by appropriate substitution. The existence of several prochiral centres in the molecule (**2b**) leads on appropriate substitution, *e.g.* as in (**2a**), in the presence of the chiral centre to the occurrence of three diastereomeric pairs of enantiomers. Thus, contrary to Cahn, Ingold, and Prelog's classification,[1] when ring inversion is

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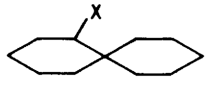
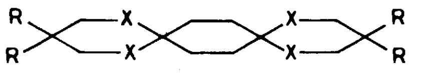
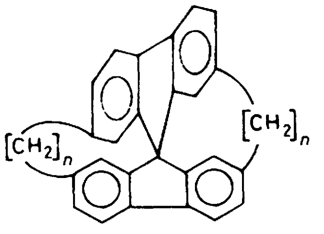
† Cahn and Prelog later recognized that the spiro atom is a centre of chirality in private letters, but they never discussed the conditions and implications of chirality (see ref. 73 in ref. 2*a*).



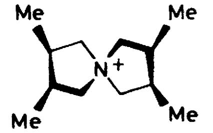
(**3**) X = Me
(**4**) X = OH
(**5**) X = OMe
(**6**) X = OAc



(**7**) X = CH$_2$, R = H
(**8**) X = O, R = Me



(**9**)



(**10**)

frozen the molecule (**2a**) does not possess an axis of chirality but exhibits three centres of chirality.

Similarly, as a result of the existence of the centre of chirality in the corresponding derivatives of (**2b**), equatorial (axial) substitutions on C(1) and C(5) are not equivalent and yield diastereoisomers. This consequence of chirality of the spiro atom, which has been overlooked by Mursakulov, Zefirov, Eliel *et al.*,[3a] will be discussed later in detail for methyl-, hydroxy-, and methoxy-substituted spiro[5.5]undecanes (**3**)—(**5**).

The chirality of the molecule (**2b**) is difficult to detect experimentally, since the usual c.d. and o.r.d. techniques cannot be applied. However, ^{13}C n.m.r. spectra should give different signals for C(1) and C(5), C(2) and C(4) *etc.* after freezing to *ca.* 200 K. Dallinga *et al.*[9] have observed such a differentiation, but limited and partly erroneous presentation of their results* renders their use difficult. Also these authors have not associated the differentiation observed with the chirality of spiro[5.5]undecane (**2b**).

The spiro junction of the rings can cause distortions of the tetrahedral arrangement around the spiro atom. For instance, the equatorial hydrogen atoms on C(1) and C(11) are closer to the axial hydrogen atoms on the other rings than those on C(5) and C(7). This should lead to differentiation of bond lengths and angles around the C(6) centre of chirality. To analyse distortions of this type and the diastereoisomerism caused by the presence of two chiral centres (at least one of them being the spiro atom), the steric energy of the molecules (**2b**), (**3**)—(**5**), and (**7**) was calculated.

The calculated distortions from an ideal arrangement of the atoms around the C(6) centre of chirality in the parent molecule are small. The most pronounced is that reflected by the difference between the angles C(1)C(6)C(7) and C(5)C(6)C(7) [and by symmetry between C(1)C(6)C(11) and C(5)C(6)C(11)], which is equal to 112.6 − 110.3 = 2.3°

Table 1. Calculated HOF values (kcal mol^{-1})

Compound	HOF			
(**2b**)	−46.29 (exp. −44.81 ± 0.75)*			
(**3**)	1-*eq*	−50.62	5-*eq*	−46.87
	1-*ax*	−50.9	5-*ax*	−50.08
(**4**)	1-*eq*	−85.76	5-*eq*	−84.07
		−85.36		−83.34
		−84.86		−82.92
	1-*ax*	−85.49	5-*ax*	−85.52
		−85.39		−85.43
		−84.51		−84.53
(**5**)	1-*eq*	−80.70	5-*eq*	−78.97
		−80.60		−78.92
	1-*ax*	−80.32	5-*ax*	−80.38
		−80.25		
(**6**)		−63.04		
		−63.22		

* Ref. 10.

Table 2. Calculated (with allowance for entropy of mixing) and experimental mixture contents

Compound	T/K	Mixture content (n_{ax}:n_{eq}) Calc.	Exp.[3a]
(**3**)	200	21:79	
	300	29:71	
(**4**)	200	41:59	
	300	45:55	63:37 (in CCl$_4$, room temp.)
(**5**)	200	31:69	18:82 (in CS$_2$, 168 K)
	300	40:60	55.4:44.6 (in CCl$_4$, room temp.)

As already noted, one of the most interesting consequences of the chirality of the spiro atom is the differentiation between 1- and 5- (and to a lesser extent between 2-and 4-) positions for the monosubstituted compounds. Therefore, calculations of heat of formation (HOF) were performed several times: twice for equatorial and axial substitution at position 1 (type a), and twice for the same substitution at position 5 (type b), and additionally three times for each OH and OMe substitution where three starting orientations were analysed. A monosubstituted spirane of type a is converted into type b by inversion of the second (unsubstituted) ring. The calculated HOF values for the molecules (**2b**), (**3**)—(**5**), and (**7**) are collected in Table 1, and axial to equatorial mixture contents calculated by involving entropy of mixing are given in Table 2.

The data collected in the tables reveal the following:

(1) The calculated HOF value for spiro[5.5]undecane (**2b**) reproduces the experimental result satisfactorily (−46.29 kcal mol^{-1} *vs.* −44.81 ± 0.75 kcal mol^{-1}).[10]

(2) Contrary to the usual situation, equatorial substitution in position 5 is less favoured than axial substitution in the same position. The effect is caused by long-range nonbonded repulsions, which are stronger for methyl substitution than for OH or OMe substitution in view of the smaller steric requirements of lone pairs.

(3) A second equatorial substitution, *e.g.* substitution in position 1, is slightly more stable than axial substitution in both 1- and 5-positions, which are very close in energy. Therefore, both conformers are present in the mixtures, the equatorial conformations prevailing for the molecule under consideration. This general result is in accordance with the enthalpic preference reported by Mursakulov, Zefirov, Eliel *et al.*[3a,b] for

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* In Table 2 of ref. 9, the atom no. 2 is marked no. 1 and the signal of protons 1 and 7 appears (by a misprint) as the last entry for the *cis*-9-methyldecalin system.

spiro[5.5]undecanes substituted by OH, OMe, and OAc in the vicinity of the spiro atom. On the other hand we were not able to confirm their observation on the entropic preference of the axial conformer and its prevalence at room temperature for **(5)** [and **(6)**] (see Table 2). This discrepancy cannot be resolved at present; further experimental studies of the molecules under investigation seem necessary since the n.m.r. spectra in ref. 3 were analysed as for two-component mixtures, and no accurate decoupling experiments were carried out.

(4) Owing to the buttressing effect, more conformations are allowed for the OH-substituted **(4)** than for the OMe-substituted **(5)** molecules.

(5) Like the tetraoxa analogue **(8)**,[11] dispiro[5.2.5.2]-hexadecane **(7)** exhibits diastereoisomerism due to chirality of the spiro atoms, and the two forms [extended (C_i) and compact (C_2)] are very close in energy ($\Delta H = 0.18$ kcal mol^{-1}), the 'extended form' being more stable.

Conclusions

Contrary to the Cahn–Ingold–Prelog classification,[1] the spirane skeleton **(2b)** is chiral if under experimental conditions the rings can be considered nonplanar. Therefore, when ring inversion is frozen, the spiro atom is chiral in spite of the fact that it bears four formally identical substituents. Diastereoisomerism and spatial relationships in the monosubstituted spiro[5.5]undecanes **(3)**—**(5)** and those of dispiro-[5.2.5.2]hexadecane **(7)** have been analysed on the basis of force-field calculations. One of the most interesting consequences of the chirality of the spiro atom is the differentiation of substitutions at positions 1 and 5 and the lower stability of equatorial substitution at position 1 than that of axial substitution. Considerations of models seem to invalidate the foundations of the analyses of monosubstituted spiranes **(3)**—**(6)** carried out by Mursakulov, Zefirov, Eliel *et al.*,[3] who treated the spiro compounds as 1,1,2-trisubstituted cyclohexanes.

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