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Studies on the γ-Effect. Part 2.† The Constancy of the γ-Effect Caused by Methyl, Ethyl, Benzyl or Phenyl Substitution in Dihydrobenzoxazines

Kari Neuvonen[a, b, *] and Kalevi Pihlaja[a, *]

[a] Department of Chemistry and [b] Department of Chemistry in Biomedicine, University of Turku, SF-20500 Turku, Finland

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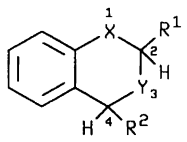
The magnitude of the γ-effect on the ^{13}C chemical shifts of C-4 and C-2 has been studied as the function of substitution (Me, Et, Bzl, Ph or *p*-$NO_2C_6H_4$) at C-2 and C-4, respectively, for several *N*-unsubstituted and *N*-methyl-substituted 3,4-dihydro-2*H*-1,3-benzoxazines and *N*-unsubstituted 1,2-dihydro-4*H*-3,1-benzoxazines. The magnitude of the γ^4_{ax}-2 effect (the effect caused by an axial 4-methyl at C-2) was found to be practically independent of the nature of the substitution causing it, a discovery which may increase the diagnostic value of the γ-effect. The results are discussed with reference to the alternative mechanisms presented by Grant and Cheney and by Beierbeck and Saunders.

γ-Substituents are useful structural indicators in ^{13}C NMR spectral studies. The two most prominent attempts to explain the mechanism of γ_{ax}- and γ_{gauche}-effects are still the steric polarization theory by Grant and Cheney[1] and the theory of Beierbeck and Saunders.[2] According to the latter the upfield shift is not due to non-bonded interactions with the γ-group but is due to the removal of the hydrogen on the β-substituent. The postulation of Beierbeck and Saunders is consistent, for example, with the fact that electronegative atoms exert a γ_{gauche}-effect to the same extent as a methyl group.[3]

However, there is relatively little information about the γ-effects caused by alkyl groups other than methyl, or by aryl groups. The exact understanding of the γ-effects caused by different substitutions is interesting not only mechanistically, but also diagnostically in structure determination with ^{13}C NMR spectroscopy. 3,4-Dihydro-2*H*-1,3-benzoxazines[4] and 1,2-dihydro-4*H*-3,1-benzoxazines[5] offered suitable model compounds for such a study.

Results

The ^{13}C NMR spectral shifts of 3,4-dihydro-2*H*-1,3-benzoxazines **1**–**11** (X = O, Y = NH) and their *N*-methyl derivatives **12**–**28** (X = O, Y = NCH_3) are given in Tables 1 and 2, respectively, and those of 1,2-dihydro-4*H*-3,1-benzoxazines **29**–**38** (X = NH, Y = O) in Table 3. Although, in principle, the *N*-unsubstituted derivatives appear as mixtures of ring- and chain-tautomers in solution, only for compounds **3**, **4**, **9**, **10**, **11**, **31** and **32** could the presence of chain-tautomers be detected. Only the ring forms are discussed in this work. However, the percentages and ^{13}C chemical shifts of the chain-tautomers are also included in Tables 1 and 3 to characterize the respective compounds more completely.



R¹	R²	X = O Y = NH	X = O Y = NCH_3	X = NH Y = O
H	H	1	12	29
Me	H	2	13	30
Et	H		14	
Ph	H	3		31
p-$NO_2C_6H_4$	H	4	15	32
H	Me	5	16	33
H	Et		17	
H	Bzl		18	
H	Ph	6	19	34
Me	Me	7	20	35
Me	Et		21	
Me	Bzl		22	
Me	Ph	8	23	36
Et	Me		24	
Et	Et		25	
Ph	Me	9		37
p-$NO_2C_6H_4$	Me	10	26	38
p-$NO_2C_6H_4$	Et		27	
p-$NO_2C_6H_4$	Bzl		28	
p-$NO_2C_6H_4$	Ph	11		

Evaluation of conformational equilibria. 2- (**1**–**4**, **12**–**15**, **29**–**32**), *cis*-2,4- (**7***cis*–**11***cis*, **20***cis*–**28***cis*, **34***cis*–**38***cis*) and *trans*-2,4-substituted derivatives (**7***trans*–**11***trans*, **20***trans*–**28***trans*, **34***trans*–**38***trans*) were taken to be

* To whom correspondence should be addressed.
† For Part 1, see Ref. 6. This paper is also Part 4 in the series: Studies on the Benzoxazine Series, see Ref. 6.

Table 1. ^{13}C NMR chemical shifts for 3,4-dihydro-2*H*-1,3-benzoxazines (X = O, Y = NH) in $CDCl_3$ solution (ppm from Me_4Si).

	R^1	R^2	C-2	C-4	Me^1	Me^2	% of chain tautomer	% of isomers
1[a]	H	H	78.07	44.01				
2[a]	Me	H	83.90	44.18	21.45			
3	Ph	H	87.06	44.05			84[b]	
4[a]	*p*-$NO_2C_6H_4$	H	85.82	43.67			52[b]	
5[a]	H	Me	75.64	47.75		21.87		
6	H	Ph	75.32	56.59				
7cis[a]	Me	Me	83.39	48.98	21.65	20.76		61
7trans[a]	Me	Me	78.67	47.24	21.39	23.85		39
8cis	Me	Ph	83.42	59.14	21.39			52
8trans	Me	Ph	79.04	55.39	21.25			48
9cis	Ph	Me	86.96	49.44		20.73	80[b]	53
9trans	Ph	Me	82.67	46.96		23.36		47
10cis[a]	*p*-$NO_2C_6H_4$	Me	85.69	49.62		20.72	38[b]	55
10trans[a]	*p*-$NO_2C_6H_4$	Me	81.85	46.70		23.08		45
11cis	*p*-$NO_2C_6H_4$	Ph	85.76	59.62			30[b]	43
11trans	*p*-$NO_2C_6H_4$	Ph	81.79	55.39				57

[a] The ^{13}C chemical shifts in question from Ref. 4. [b] For the chain tautomer: compound **3**, 161.78 (C=N), 64.19 (CH_2N); compound **4**, 159.88 (C=N), 64.26 (CH_2N); compound **9**, 160.40 (C=N), 71.15 (CH_2N), 24.99 (Me); compound **10**, 158.42 (C=N), 71.60 (CH_2N), 24.64 (Me); compound **11** 160.00 (C=N), 78.78 (CH_2N).

conformationally homogeneous in accordance with the earlier results.[4,5] The 4-substituted derivatives (**5**, **6**, **16–19**, **33** and **34**), however, represent conformational mixtures in which the equilibrium 4eq′ ⇌ 4ax′ occurs. In the case of 4-methyl substitutions, **5**, **16** and **33**, the evaluation of the conformer populations can be carried out by detailed substituent effect computations,[4,5] which, however, require more model compounds than are available for other than methyl substitutions. Therefore, in the case of the *N*-substituted compounds **17**, **18** and **19**, the corresponding equilibria were taken to be equal to that of **16** (4eq′/4ax′ = 8/92).[4] In fact, the nearly constant *N*-methyl chemical shifts of **17**, **18** and **19** lend support to the postulation that their conformational equilibria must

Table 2. ^{13}C NMR chemical shifts for *N*-methyl-substituted 3,4-dihydro-2*H*-1,3-benzoxazines (X = O, Y = NCH_3) in $CDCl_3$ solution (ppm from Me_4Si).

	R^1	R^2	C-2	C-4	R^1	NCH_3	R^2
12[a]	H	H	83.65	52.02		39.59	
13[a]	Me	H	87.62	52.62	18.98	35.62	
14	Et	H	92.61	52.32	25.68, 9.54	35.88	
15[a]	*p*-$NO_2C_6H_4$	H	90.14	51.03		37.26	
16[a]	H	Me	79.31	54.82		39.59	23.07
17	H	Et	79.21	61.33		40.83	30.46, 11.13
18[b]	H	Bzl	79.06	60.94		40.95	43.93 (CH_2)
19	H	Ph	79.58	63.88		40.55	
20cis[a]	Me	Me	88.85	56.08	19.17	27.04	17.70
20trans[a]	Me	Me	81.87	57.30	18.80	34.35	23.84
21cis	Me	Et	89.44	61.57	19.25	27.28	23.62, 10.40
21trans	Me	Et	81.90	63.94	18.81	34.66	30.72, 11.18
22cis[b]	Me	Bzl	89.26	60.74	19.30	29.31	38.06 (CH_2)
22trans[b]	Me	Bzl	82.04	63.85	18.74	34.47	44.15 (CH_2)
23cis	Me	Ph	88.85	68.86	20.10	35.55	
23trans	Me	Ph	82.02	65.37	18.44	34.52	
24cis	Et	Me	94.03	55.92	25.93, 9.71	26.91	17.59
24trans	Et	Me	87.09	57.19	25.42, 9.71	34.49	23.78
25cis	Et	Et	94.55	61.52	25.90, 9.52	27.54	23.61, 10.49
25trans	Et	Et	86.94	63.82	25.17, 9.52	34.64	30.58, 11.01
26cis[a]	*p*-$NO_2C_6H_4$	Me	91.11	56.08		28.28	17.67
26trans[a]	*p*-$NO_2C_6H_4$	Me	85.02	56.39		34.89	23.53
27cis	*p*-$NO_2C_6H_4$	Et	91.44	61.69		29.21	23.73, 10.32
27trans	*p*-$NO_2C_6H_4$	Et	84.71	63.23		35.27	30.58, 11.16
28cis[b]	*p*-$NO_2C_6H_4$	Bzl	91.26	60.66		30.97	37.83 (CH_2)
28trans[b]	*p*-$NO_2C_6H_4$	Bzl	84.79	63.04		35.23	44.00 (CH_2)

[a] The ^{13}C chemical shifts in question from Ref. 4. [b] The ^{13}C chemical shifts in question from Ref. 9.

Table 3. ^{13}C NMR chemical shifts for 1,2-dihydro-4*H*-3,1-benzoxazines (X = NH, Y = O) in $CDCl_3$ solution (ppm from Me_4Si).

	R^1	R^2	C-2	C-4	Me^1	Me^2	% of chain tautomer	% of isomers
29[a]	H	H	75.65	67.27				
30[a]	Me	H	80.85	67.57	21.06			
31	Ph	H	85.13	67.57			10[b]	
32	*p*-$NO_2C_6H_4$	H	83.78	67.12			5[b]	
33[a]	H	Me	73.35	71.98		21.28		
34	H	Ph	72.80	78.48				
35*cis*[a]	Me	Me	80.30	72.85	21.22	20.85		76
35*trans*[a]	Me	Me	73.52	70.55	21.22	22.90		24
36*cis*	Me	Ph	80.56	80.81	21.22			61
36*trans*	Me	Ph	73.89	76.38	20.96			39
37*cis*	Ph	Me	84.99	73.49		20.93		68
37*trans*	Ph	Me	78.81	70.43		22.59		32
38*cis*[a]	*p*-$NO_2C_6H_4$	Me	83.84	73.68		20.99		65
38*trans*[a]	*p*-$NO_2C_6H_4$	Me	78.29	70.11		22.31		35

[a] The ^{13}C chemical shifts in question from Ref. 5. [b] For chain tautomer: compound **31**, 159.77 (C=N), 63.74 (CH_2N); compound **32**, 157.08 (C=N), 63.08 (CH_2N).

be very much the same. On the other hand, Et, Bzl and Ph substitution exerts about the same deshielding effect on the *N*-methyl groups—therefore they are somewhat downfield from that of **16**.

However, the case of the *N*-unsubstituted derivatives **5**, **6**, **33** and **34** is more complicated, because of the obvious alterations in the 4eq′/4ax′ ratios. In the case of 4-methyl substitution the values estimated earlier could be used (**5**,[4] 4eq′/4ax′ = 54/46; **33**,[5] 4eq′/4ax′ = 75/25). The contributions of the *cis* and *trans* forms of some 2,4-disubstituted compounds are governed by the conformational status of the 4-substitution.[4,5] Equilibration can occur via open-chain forms (see below). Therefore the values for the 4eq′/4ax′ ratios of the 4-phenyl derivatives **6** and **34** were derived from the *cis*/*trans* ratios of the corresponding 2,4-disubstituted derivatives. Similarly, the isomer populations of compounds **8** and **11** (52% and 43%, respectively) give an estimate 47. 5% for the population of the

Table 4. Substituent effects (in ppm) at C-2.

	Substitution pattern			Substituent effect in ppm			
Set	2-Mono-substitution	4-Mono-substitution	2,4-Di-substitution	2eq[a]	4eq′[b]	4ax′[c]	2eq4ax′[d]
3,4-Dihydro-2*H*-1,3-benzoxazines (X = O, Y = NH)							
1	Me	Me	2-Me, 4-Me	5.83	−0.51	−4.68	−0.55
2	Me	Ph	2-Me, 4-Ph	5.83	−0.48	−4.80	−0.06
3	Ph	Me	2-Ph, 4-Me	8.99	−0.10	−5.17	0.78
4	*p*-$NO_2C_6H_4$	Me	2-*p*-$NO_2C_6H_4$, 4-Me	7.75	−0.13	−5.13	1.16
5	*p*-$NO_2C_6H_4$	Ph	2-*p*-$NO_2C_6H_4$, 4-Ph	7.75	−0.06	−5.18	1.,15
3,4-Dihydro-2*H*-1,3-benzoxazines (X = O, Y = NCH_3)							
6	Me	Me	2-Me, 4-Me	3.97	1.23	−4.82	−0.93
7	Me	Et	2-Me, 4-Et	3.97	1.82	−4.98	−0.74
8	Me	Bzl	2-Me, 4-Bzl	3.97	1.64	−5.13	−0.45
9	Me	Ph	2-Me, 4-Ph	3.97	1.23	−4.53	−1.07
10	Et	Me	2-Et, 4-Me	8.96	1.42	−4.84	−0.68
11	Et	Et	2-Et, 4-Et	8.96	1.94	−4.99	−0.68
12	*p*-$NO_2C_6H_4$	Me	2-*p*-$NO_2C_6H_4$, 4-Me	6.49	0.97	−4.80	−0.32
13	*p*-$NO_2C_6H_4$	Et	2-*p*-$NO_2C_6H_4$, 4-Et	6.49	1.30	−4.94	−0.49
14	*p*-$NO_2C_6H_4$	Bzl	2-*p*-$NO_2C_6H_4$, 4-Bzl	6.49	1.12	−5.09	−0.26
1,2-Dihydro-4*H*-3,1-benzoxazines (X = NH, Y = O)							
15	Me	Me	2-Me, 4-Me	5.20	−0.55	−7.55	0.22
16	Me	Ph	2-Me, 4-Ph	5.20	−0.29	−6.85	−0.11
17	Ph	Me	2-Ph, 4-Me	9.48	−0.14	−8.78	2.46
18	*p*-$NO_2C_6H_4$	Me	2-*p*-$NO_2C_6H_4$, 4-Me	8.13	0.06	−9.38	3.89

Each set includes the corresponding 2-mono-, 4-mono- and 2,4-disubstituted compounds. [a] α_{eq}. [b] $\gamma^4_{eq} - 2$. [c] $\gamma^4_{ax'} - 2$. [d] $\alpha_{eq}\gamma_{ax'}$.

4eq′ conformation of **6**. For 1,2-dihydro-4*H*-3,1-benzoxazines, owing to the limited selection of compounds, the equilibrium proportions of **36***cis* and **36***trans* must be used to approximate the 4eq′ ⇌ 4ax′ equilibrium of **34**, giving a 61 % population for the 4eq′ conformation.

It must be emphasized here that, even if some of the above approximations were selected to give the most consistent total picture, reasonable alterations do not change the final outcome of our paper and the conclusions made.

Calculation of the substituent effects. The substituent-effect calculations (Tables 4 and 5) are based on the ^{13}C chemical shifts of the sets including the corresponding 2-, 4-, *cis*-2,4- and *trans*-2,4-substituted derivatives. In the calculations the effect of 2eq,4eq′-disubstitution at C-2 or C-4 was neglected. The following example in the case of compounds **2**, **6**, **8***cis* and **8***trans* (set 2) illustrates the procedure used.

At C-2

$$2eq = 5.83 \text{ ppm} \quad (1)$$

$$0.475 \times 4eq' + 0.525 \times 4ax' = -2.75 \text{ ppm} \quad (2)$$

$$2eq + 4eq' = 5.35 \text{ ppm} \quad (3)$$

$$2eq + 4ax' + 2eq4ax' = 0.97 \text{ ppm} \quad (4)$$

Here 2eq, 4eq′, 4ax′ and 2eq4ax′ correspond to the increments responsible for the total substituent effect at C-2 (in comparison with the corresponding parent compound). Solving eqns. (1)–(4) gives 2eq′ = 5.83 ppm, 4eq′ = −0.48 ppm, 4ax′ = −4.80 ppm and the disubstitution effect due to the 2eq4ax′ substitution is practically zero.

Analogously at C-4

$$2eq = 0.17 \text{ ppm} \quad (5)$$

$$0.475 \times 4eq' + 0.525 \times 4ax' = 12.58 \text{ ppm} \quad (6)$$

$$2eq + 4eq' = 15.13 \text{ ppm} \quad (7)$$

$$2eq + 4ax' + 2eq4ax' = 11.38 \text{ ppm} \quad (8)$$

Solving eqns. (5)–(8) gives 2eq = 0.17 ppm, 4eq′ = 14.96 ppm, 4ax′ = 10.43 ppm and 2eq4ax′ = 0.78 ppm.

For the 3,4-dihydro-2*H*-1,3-benzoxazine series (X = O, Y = NH), both the $\gamma^2_{eq} - 4$ effects (i.e., the effects of an equatorial substituent at C-2 on the ^{13}C chemical shift of C-4) and their variation (three independent occurrences) were small. Similarly the scatter and the $\gamma^4_{eq'} - 2$ effects themselves (five occurrences) were small. The marked upfield $\gamma^4_{ax'} - 2$ effect (five occurrences) was practically constant (the average value, -4.9 ± 0.4 ppm or, by omitting the 4-phenyl substitution, -4.95 ± 0.2 ppm). As to the corresponding *N*-methyl derivatives (X = O, Y = NCH_3) the $\gamma^2_{eq} - 4$ effects (three occurrences) were small and either downfield or upfield (2-*p*-nitro substitution behaves exceptionally for both series, cf. Table 4).

Table 5. Substituent effects (SE) in ppm at C-4.

	Substitution pattern			Substituent effect in ppm			
Set	2-Mono-substitution	4-Mono-substitution	2,4-Di-substitution	2eq[a]	4eq′[b]	4ax′[c]	2eq4ax′[d]
3,4-Dihydro-2*H*-1,3-benzoxazines (X = O, Y = NH)							
1	Me	Me	2-Me, 4-Me	0.17	4.80	2.50	0.55
2	Me	Ph	2-Me, 4-Ph	0.17	14.96	10.43	0.78
3	Ph	Me	2-Ph, 4-Me	0.04	5.39	1.80	1.11
4	*p*-$NO_2C_6H_4$	Me	2-*p*-$NO_2C_6H_4$, 4-Me	−0.34	5.95	1.15	1.88
5	*p*-$NO_2C_6H_4$	Ph	2-*p*-$NO_2C_6H_4$, 4-Ph	−0.34	15.95	9.53	2.19
3,4-Dihydro-2*H*-1,3-benzoxazines (X = O, Y = NCH_3)							
6	Me	Me	2-Me, 4-Me	0.60	3.46	2.74	1.94
7	Me	Et	2-Me, 4-Et	0.60	8.95	9.34	1.98
8	Me	Bzl	2-Me, 4-Bzl	0.60	8.12	8.99	2.24
9	Me	Ph	2-Me, 4-Ph	0.60	16.24	11.48	1.27
10	Et	Me	2-Et, 4-Me	0.30	3.60	2.73	2.14
11	Et	Et	2-Et, 4-Et	0.30	9.20	9.32	2.18
12	*p*-$NO_2C_6H_4$	Me	2-*p*-$NO_2C_6H_4$, 4-Me	−0.99	5.05	2.60	2.76
13	*p*-$NO_2C_6H_4$	Et	2-*p*-$NO_2C_6H_4$, 4-Et	−0.99	10.66	9.19	3.01
14	*p*-$NO_2C_6H_4$	Bzl	2-*p*-$NO_2C_6H_4$, 4-Bzl	−0.99	9.63	8.86	3.15
1,2-Dihydro-4*H*-3,1-benzoxazines (X = NH, Y = O)							
15	Me	Me	2-Me, 4-Me	0.30	5.28	3.00	−0.02
16	Me	Ph	2-Me, 4-Ph	0.30	13.24	8.04	0.78
17	Ph	Me	2-Ph, 4-Me	0.30	5.92	1.08	1.78
18	*p*-$NO_2C_6H_4$	Me	2-*p*-$NO_2C_6H_4$, 4-Me	−0.15	6.56	−0.84	3.83

Each set includes the corresponding 2-mono-, 4-mono- and 2,4-disubstituted compounds. [a] $\gamma^2_{eq} - 4$. [b] α_{eq}. [c] α_{ax}. [d] $\gamma_{eq}\alpha_{ax'}$.

The $\gamma^4_{eq'}-2$ effects (nine occurrences) were significantly larger than the above effects and all downfield. The $\gamma^4_{ax'}-2$ effects (nine occurrences) again caused significant high-field shifts and did not vary essentially. The behaviour of the *N*-unsubstituted 1,2-dihydro-4*H*-3,1-benzoxazines was essentially similar to that of the corresponding 3,4-dihydro-2*H*-1,3-benzoxazines with the exception of the somewhat varied $\gamma^4_{ax'}-2$ effects.

Discussion

General and N-*methyl derivatives.* The interpretation of an experimental γ-effect is complicated by (i) the nature of the γ-substitution in question and (ii) the potential conformational alteration caused by the change of substitution. The goal of this work was to study the γ-effect as the function of substitution. For this purpose 3-methyl-3,4-dihydro-2*H*-1,3-benzoxazines were considered useful models, because of their special structural (conformational) properties (cf. Fig. 1): (i) a strong preponderance of the *N*-axial and 4-pseudoaxial orientations and (ii) the non-appearance of the 2-axial orientations.[4]

As mentioned above, the $\gamma^4_{ax'}-2$ effect (Table 4) for this series is practically independent of the substitution causing it. This behaviour strongly supports the theory of Beierbeck and Saunders.[2]

The alternative steric polarization theory[1] is based on the steric influence of the proximate hydrogens being dependent on their mutual distance and on the angle between their axis and the perturbed C–H bond. The fact that different substitutions (Me, Et, Bzl or Ph) caused nearly identical $\gamma_{ax'}$-effects can be taken as an argument against this theory about the origin of γ-effects.

In principle all substituents studied are subject to potential hydrogen–hydrogen interactions (Fig. 1) and hence able to cause steric perturbation. The most probable spatial orientation of the 4-ethyl group is the one where the methyl end is *anti* to the benzo ring (the 4-benzyl group behaves analogously). As to the 4-phenyl derivatives there are severe steric interactions between its *ortho*-hydrogens and the hydrogens of the dihydrobenzoxazine moiety. In other words, an interaction with H-2 is unavoidable. According to the steric polarization theory, one would expect some alteration in the magnitude of the γ-effect at least in the case of phenyl substitution. This is, however, not in accord with our experimental findings.

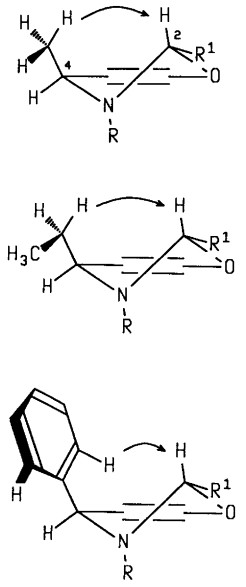


Fig. 1. Steric hydrogen–hydrogen interactions in 4-substituted 3,4-dihydro-2*H*-1,3-benzoxazines.

Putting the mechanistic aspects aside, our results suggest that the γ_{ax}-effect does not vary with variation in the substitution (Me, Et, Bzl and Ph), a fact that increases its diagnostic value. However, the values for the γ-effects (Table 4) prevailing for 4-methyl (sets 6, 10 and 12), 4-ethyl (sets 7, 11 and 13) and 4-benzyl (sets 8 and 14) derivatives correlate ($r=0.93$)—even if their range is narrow—to Taft's steric substituent constants (E_s).[7] In other words the total γ-effect is a sum of two factors—a Beierbeck–Saunders type constant (4-Me, −4.82 ppm) and another minor factor which depends on the steric nature of the substitution (range 4-Ph, 0.29 to 4-Bzl, −0.29 ppm).

N-*Unsubstituted derivatives.* *N*-unsubstituted 3,4-dihydro-2*H*-1,3-benzoxazines (X = O, Y = NH) and the corresponding 1,2-dihydro-4*H*-3,1-benzoxazines (X = NH, Y = O) are suitable models to study the dependence of the γ_{ax}-effect about conformational alterations caused by the change of substitution. These compounds are conformationally more labile than 3-methyl-3,4-dihydro-2*H*-1,3-benzoxazines.[4,5] The 4-substituted derivatives **5**, **6**, **33** and **34** are mixtures of the 4eq′- and 4ax′-forms as discussed above. The behaviour of the $\gamma^4_{ax'}-2$ effects for 3,4-dihydro-2*H*-1,3-benzoxazines (-5.0 ± 0.3 ppm, sets 1–5) supports the constancy of the γ_{ax}-effect.

The variation of the γ_{ax}-effect in the case of 1,2-dihydro-4*H*-3,1-benzoxazines (from −6.8 to −9.4 ppm, sets 15–18) suggests that the neglect of the 2eq4eq′ effect is not justified or more probably that the 2,4-disubstituted derivatives in question are not conformationally homogeneous. Therefore this behaviour does not detract from the constancy of the $\gamma_{ax'}$-effect. The isomer proportions of compounds **37** and **38** deviate from the value calculated for the 4-methyl equilibrium in compound **33**. This supports the above explanation. Thus the two very negative values for the $\gamma^4_{ax'}-2$ effect (sets 17 and 18, Table 4) probably cannot properly be separated into the effects involved.

Conformational properties. 4-Methyl-3,4-dihydro-2*H*-1,3-benzoxazine **5** is a 54:46 conformational mixture of the 4eq′ and 4ax′ half-chair forms.[4] It is interesting to note that in three cases, isomer pairs **8**, **9** and **10** (Table 1), out of the total five the proportions of the isomeric 2,4-disubstituted derivatives are very close to the above ratio. They can be treated as equilibrium mixtures, since the

equilibration occurs via the ring–chain tautomeric process.[8] Furthermore, in these three cases the equilibria are governed mainly by the relative stabilities of the 4-methyl substitutions.[4] In contrast, the isomer distributions of 2,4-dimethyl and 2-*p*-nitrophenyl-4-phenyl derivatives, isomer pairs **7** and **11**, respectively, diverge somewhat, probably as a result of different buttressing effects.[4]

As to the analogous 1,2-dihydro-4*H*-3,1-benzoxazines, the 4-methyl derivative **33** is a 75:25 mixture of the 4eq′ and 4ax′ half-chair forms (Table 3).[5] In this family of compounds the isomer proportions are close to this value only in the case of the 2,4-dimethyl derivative **35**.

Conclusions

In conclusion, the γ_{ax}-effect is practically independent of the nature of the substitution causing it as soon as one can eliminate the (possible) influence of conformational factors.

Experimental

All 3,4-dihydro-2*H*-1,3-benzoxazines (X = O, Y = NH or NCH_3)[4] and 1,2-dihydro-4*H*-3,1-benzoxazines (X = NH, Y = O)[5] were prepared by the procedures described earlier.

Compounds were characterized by their ^{1}H NMR spectra and by elemental analyses (C, H, N: ±0.4%) and/or high resolution mass spectra recorded on a VG Analytical MM 7070E mass spectrometer. Noise-decoupled ^{13}C NMR spectra were recorded for 1.0 M solutions in $CDCl_3$ (used as a field/frequency lock signal) at ambient temperature on a JEOL FX-60 spectrometer operating at 15.03 MHz or on a JEOL GX-400 spectrometer operating at 100.54 MHz. For structure determinations, if necessary, proton coupled ^{13}C NMR spectra with NOE were also recorded.

^{1}H NMR spectra were recorded on either a JEOL FX-60 spectrometer operating at 60 MHz or on a JEOL GX-400 spectrometer operating at 400 MHz. The proportions of the open-chain vs. ring forms and the isomer distributions of the 2,4-disubstituted derivatives were based on the integrals of the appropriate proton signals (H-2 for the ring form and the corresponding proton for the open-chain form, H-2/H-4 protons or C-2/C-4 methyl protons for the *cis*- and *trans*-isomers).

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