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ANOMERIC AND STERIC EFFECTS OF BROMINE, CHLORINE AND METHOXY-GROUP IN CONFORMATIONAL ANALYSIS AND ANOMERIZATION OF HINDERED TETRAHYDROFURANS

Estera Touboul and Gilbert Dana*
Laboratoire de Stéréochimie Réactionnelle, Bât. F.

Odile Convert
Laboratoire de Chimie Organique Structurale, UA 455-CNRS

Université Pierre et Marie Curie, 4 Place Jussieu, 75252 PARIS CEDEX 05 France

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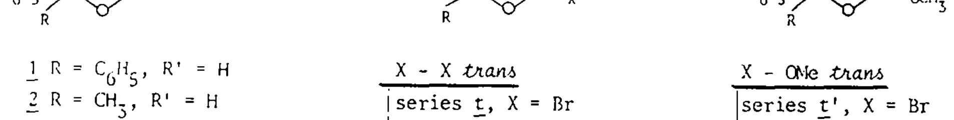
Abstract - The NMR spectra of a series of hindered tetrahydrofuran compounds, disubstituted in C5 and with two polar groups in C2 (Br, Cl or OMe in the anomeric position) and C3 (Br or Cl) have been examined. When the two polar groups are cis, the anomeric group is always in the axial orientation. If they are trans, three cases are observed. The molecule may be in a pure anomeric conformation, in a pure contra-anomeric conformation or is a mixture of the two. The anomerization reaction shows that the trans-isomers which are in the anomeric conformation appear more stable than the cis-ones (> 1.5 kcal/mole). In the reverse case, the cis-isomer is slightly more stable (< 0.5 kcal/mole). Despite the difference of bulkiness, the tendency of the halogen substituents Cl and Br to be axial in C2 is greater than for the MeO group.

The anomeric effect corresponds to the relative preference of a polar group X to be axial in the C2 position of tetrahydropyran or tetrahydrofuran (THF)[1]. This effect is related to an orbital overlap $n(O) \rightarrow \sigma^*(C-X)$ [2,3] leading to the picture of a "double bond - no bond" resonance (fig.1). This stabilizing effect is expected to increase with the X electronegativity i.e with a lower energy level of $\sigma^*(C-X)$ [4]. The experimental results are usually rather consistent with this rule [5,6] although the case of the heavy atoms is still in discussion [7,8].

In a previous paper, [9] we have compared the anomeric effect of bromine and methoxy group in some hindered THF. The present work generalizes this comparison to different groups (Br, Cl ou OCH_3) for a series of THF resulting from electrophilic addition of Br_2 or Cl_2 to the dihydrofurans 1 to 5.



1 R = C_6H_5, R' = H
2 R = CH_3, R' = H
3 R = C_6H_5, R' = CH_3
4 R = R' = CH_3 (*trans*)
5 R = R' = CH_3 (*cis*)

X - X *trans*
series t, X = Br
series r, X = Cl

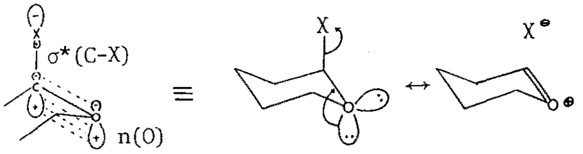
X - X *cis*
series c, X = Br
series i, X = Cl

X - OMe *trans*
series t', X = Br
series r', X = Cl

X - OMe *cis*
series c', X = Br
series i', X = Cl

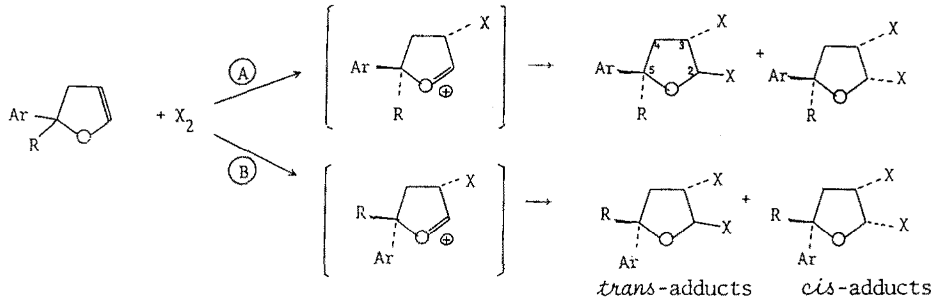
According to the bulkiness of the substituents, these compounds adopt one pure conformation or the two conformations, anomeric and contra-anomeric, in equilibrium. Besides, for the anomeric conformation, the pseudorotation parameter P is dependant on the steric hindrance and varies regularly around the pseudorotation circle between 170° and 240°.

Fig.1



Experimental results

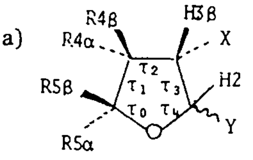
The *2,3-dibromo-* and *2,3-dichlorotetrahydrofuran compounds* are obtained by addition of Br_2 or Cl_2 to dihydrofurans at low temperature (-20° to -40°C), in the dark [9,10]. The stereochemistry of this addition has been discussed in similar series [10], in glycals [11] or linear ethers Ar(R)-O-CH=CH-CH_3, Z or E (addition of Cl_2, Br_2, ICl ; influence of the R or Ar groups...) [12]. With R = H (scheme I), the electrophilic approach is very selective when Ar is a bulky mesityl group (path A) [13]. In the present work (R = CH_3 or C_6H_5), four adducts are observed : two *trans*-adducts (t for Br_2 or r for Cl_2) and two *cis*-adducts (c for Br_2 and i for Cl_2), except for the dihydrofuran 1, for which paths A and B are not differentiated (fig.2 and scheme IIb).



Scheme I : Formation of the two anomeric pairs by addition of Br_2 or Cl_2 to dihydrofurans

The electrophilic addition is often followed by the *anomerization equilibrium* which occurs in a few minutes at room temperature for dibromo-compounds and in many days for the dichloro compounds. Consequently, the study was done at ≈-50°C in CS_2 (with C_6D_6 or C_6D_{12} as lock solvent for the NMR measurements) for dibromo compounds but at room temperature for the dichloro compounds (with eventually some drops of *tert*-butyl alcohol as a catalyst). Fig.2 shows an exemple of NMR spectra of these adducts (kinetic and thermodynamic products).

The *^1H NMR spectra of the dihalogeno-compounds* have been recorded at 250 or 500 MHz, (first order spectra). These isomers are not stable enough to be isolated from the mixture, but the NMR signals of each isomer are associated by inspection of J values and relative integration, by selective decoupling and (or) by 2D NMR (COSY spectra). As shown below, the coupling constant analysis allows a good determination of the structures. Table 1 reports the chemical shifts of dihalogeno-compounds as well as the experimental conditions of the a)



$$\tau_j = \tau_m \cos[P + (j-2)144]$$

b)

	R5α	R5β	R4α	R4β
10	Ph	Ph	H	H
20	Ph	Me	H	H
21	Me	Ph	H	H
30	Ph	Ph	Me	H
31	Ph	Ph	H	Me
40	Ph	Me	Me	H
41	Me	Ph	H	Me
50	Me	Ph	Me	H
51	Ph	Me	H	Me

Scheme II

a) Numbering of the endocyclic dihedral angles and their evaluation with the *pseudorotation phase* P and the *puckering angle* τ_m. N.B. The description of the corresponding enantiomeric form is obtained by adding 180° to P. All the signs of τ_j are then inverted.

b) Numbering of the THF compounds formed from dihydrofurans 1 to 5.

spectra and the compositions of kinetic and thermodynamic products measured by integration. Tables 3 and 4 give the coupling constants and the x, *y* values discussed below.

The preparation and the equilibration of the *methoxy-derivatives* are described in the Experimental Part and their NMR spectra are given in tables 2, 3 and 4.

All the products are racemic but in the discussion and schemes, the C3 carbon will be always of S configuration. The substituents are called α or β according to their position on the rear face (α) or on the front face (β). So, the proton on C3 is always called H3β (schemes I or II).

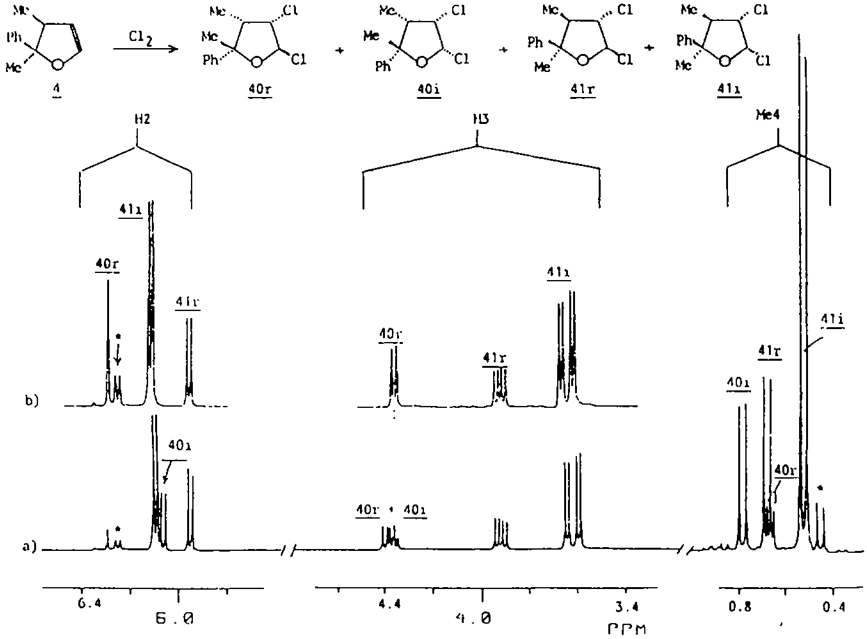
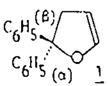
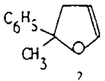
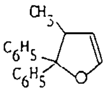
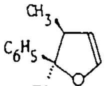
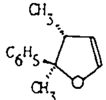


Fig. 2 : The NMR spectra of the chloro-adducts of 2α,3β-*dimethyl*-2β-*phenyl*-*dihydrofuran* 4 (250 MHz) (H4, Me5 and Ph are not shown). a) the kinetic product (-20°C, in CCl_4). b) the thermodynamic product (24h at room temperature).
The impurity (*) is a mono-chloro derivative, the 2α-*chloro*-4β,5α-*dimethyl*-5β-*phenyl*-*tetrahydrofuran*. (H2β eq., δ = 6.26 ppm, d, J = 4.5 and 0 Hz ; H3β ax., δ = 1.78 ppm, td, J = 4.5, 12.5 and 13 Hz ; Me4α eq., δ = 0.47 ppm, d ; δMe5β = 1.65 ppm, s).

Table 1 : Chemical shifts, conditions of spectra and isomeric % of the dichloro and dibromo-adducts to 2,3-dihydrofurans 1 to 5.

starting dihydrofurans	X2	n°	δH2	δH3β	δR4α	δR4β	δMe5	%^{a}	%^{b}	Conditions
 1	Br_2	10t	6.7	4.67	2.98	3.39		70	96	500 MHz, $CCl_4(CDCl_3)$
		10c	6.5	3.96	3.01	2.88		30	4	
	Cl_2	10r	6.17	4.32	2.75	3.08		13		500 MHz, $CCl_4(C_6D_6)$
		10i	5.98	3.93	2.824	2.775		87		
 2	Br_2	20t	6.74	4.60	2.68	3.09	1.70	24	28	250 MHz, -40°C $CS_2(C_6D_6)$
		21t	6.74	4.80	2.60	3.12	1.70	54	68	
		20c	6.49	4.14	---	---		4	0	
		21c	6.47	3.78	2.67	2.5	1.7	18	4	
	Cl_2	20r	6.12	4.31	2.39	2.65	1.46	5	15	500 MHz, $CCl_4(C_6D_6)$
		21r	6.13	4.30	2.21	2.77	1.56	20	80	
		20i	5.98	4.04	2.42	2.19	1.53	10	0	
		21i	5.96	3.78	2.30	2.38	1.51	65	<5	
 3	Br_2	30t	6.95	4.89	0.94	3.70		46	50	250 MHz, $CS_2(C_6D_6)$
		31t	6.30	4.25	3.14	0.95		32	18	
		30c	6.50	---	0.55	---		4	0	
		31c	6.70	3.90	3.40	0.77		18	32	
	Cl_2	30r	6.32	4.44	0.84	3.58		7	65	250 MHz, $CCl_4(C_6D_6)$
		31r	5.77	3.96	2.94	0.83		10	10	
		30i	5.94	4.21	0.92	3.08		58	0	
		31i	6.15	3.82	3.17	0.74		24	24	
 4	Br_2	40t	6.87	4.74	0.80	2.96	1.70	18	18	250 MHz, $CS_2(C_6D_6)$
		41t	6.42	4.24	2.48	0.84	1.66	26	25	
		40c	not observed					0	0	
		41c	6.60	3.62	2.64	0.60	1.72	56	57	
	Cl_2	40r	6.31	4.30	0.68	2.87	1.52	5	20	250 MHz, $CCl_4(C_6D_6)$ Fig.2
		41r	5.95	3.91	2.20	0.70	1.61	19	18	
		40i	6.07	4.35	0.78	2.15	1.27	15	0	
		41i	6.12	3.61	2.50	0.50	1.61	61	62	
 5	Br_2	50t	6.79	4.82	1.32	3.03	1.48	79	82	250 MHz, $CS_2(C_6D_6)$
		51t	6.47	4.5	2.44	1.08	1.18	8	8	
		50c	6.7	not observed				3	0	
		51c	6.6	3.92	2.75	1.15		10	10	
	Cl_2	50r	6.21	4.3	1.08	2.91	1.41	20		250 MHz, $CCl_4(C_6D_6)$
		51r	6.01	4.15	---	---		4		
		50c	5.92	4.0	1.26	2.35	1.42	69		
		51c	5.99	3.66	2.51	0.98	1.43	7		

a) initial values
b) at equilibrium
( ) solvent added for the lock

Table 2 :Chemical shifts, conditions of spectra and isomeric % at equilibrium of the bromo or chloro-methoxy-derivatives.

	δH2	δH3β	δR4α	δR4β	δMe5	δOMe	% eq.	Conditions
10t'	5.30	4.06	2.67	2.99		3.08	(75)	a, 500 MHz
10c'	4.73	3.77	2.73	3.00		3.08	(25)	a, 500 MHz
10r'	5.19	4.11	2.62	2.94		3.06	---	a, 250 MHz
10i'	4.65	3.73	2.86	2.63		3.04	---	a, 250 MHz
20t'	5.39	4.45	2.64	3.02	1.64	3.5	70	b, 80 MHz
20c'	4.70	3.86	2.55	2.15	1.12	3.09	30	a, 80 MHz
21t'	5.24	3.99	2.15	2.63	1.58	3.04	80	a, 80 MHz
21c'	5.12	4.09	2.50	2.65	1.71	3.35	20	b, 80 MHz
20r'	5.10	4.32	2.43	2.79	1.54	3.13	80	b, 200 MHz
20i'	4.69	3.88	2.48	2.11	1.10	3.10	20	a, 80 MHz
21r'	5.10	4.02	2.05	2.33	1.58	3.0	84	a, 80 MHz
21i'	5.05	4.03	2.40	2.68	1.63	3.45	16	b, 80 MHz
30t'	5.21	4.19	0.79	3.06		2.91	100	a, 80 MHz
30c'	4.44	3.98	1.0	2.90		3.21	0	a, 80 MHz
31t'	4.91	3.68	2.99	0.69		3.16	50	a, 80 MHz
31c'	5.06	3.81	3.19	0.84		3.12	50	c, 80 MHz
30r'	5.0	4.08	0.78	2.85		3.15	100	a, 80 MHz
30i'	4.60	4.05	0.95	2.95		3.25	0	a, 80 MHz
31r'	4.8	3.68	2.88	0.68		3.18	50	a, 80 MHz
31i'	4.69	3.16	2.81	0.66		3.26	50	a, 80 MHz
40t'	5.33	4.23	0.6	2.23	1.43	3.15	100	a, 80 MHz
40c'	4.71	4.23	0.83	1.95	1.20	3.25	0	a, 80 MHz
41t'	5.23	3.65	2.23	0.5	1.43	3.35	60	a, 80 MHz
41c'	4.85	3.55	2.54	0.48	1.50	3.28	40	a, 80 MHz
40r'	5.20	4.20	0.61	2.35	1.49	3.17	100	a, 80 MHz
40i'	4.76	4.20	0.77	2.0	1.60	3.25	0	a, 80 MHz
41r'	5.10	3.66	2.12	0.52	1.49	3.38	50	a, 80 MHz
41i'	4.85	3.50	2.50	0.50	2.05	3.30	50	a, 80 MHz
50t'	5.26	4.16	0.95	2.55	1.50	3.04	95	a, 80 MHz
50c'	4.58	3.85	1.20	2.15	1.31	3.20	5	a, 80 MHz
51t'	5.30	3.85	2.28	0.68	1.25	3.19	65	a, 80 MHz
51c'	4.65	3.53	2.70	0.83	1.04	3.20	35	a, 80 MHz
50r'	5.10	4.10	0.95	2.70	1.51	3.10	100	a, 250 MHz
50i'	4.70	3.88	1.20	2.23	1.39	3.24	0	a, 80 MHz
51r'	5.20	3.9	2.25	0.75	1.34	3.23	---	a, 250 MHz
51i'	4.68	4.30	2.63	0.85	1.08	3.18	---	a, 80 MHz

a) C_6D_6, b) CD_3COCD_3, c) $CDCl_3$

The conformation of the THF ring is described by using the pseudorotation concept [13, 14,15] with the definitions and the formulae of Altona (scheme IIa). Besides, the axial character of a substituent is evaluated by the difference $\tau_j - \tau_{j+1}$ of the two adjacent dihedral angles. If this difference is positive, the axial group is on the front face (β) and, *vice-versa* [13,16].

Conformational analysis has been done by using as models the molecules shown in scheme III and IV. Their dihedral angles have been measured by X-ray diffraction [9] for 30c', 31c', 30t', and 31t' or determined by NMR in solution [13] for 6, 7 and 8. In the *cis*-series, 6 and 31c' have been found very similar, but in 30c', an important decrease of the axial character of the anomeric group is observed ($\tau_3 - \tau_4 \simeq -28°$ instead of -80°)

Table 3 : Coupling constants in the *cis*-adducts c, i, c', i' (Hertz).

		$^3J_{HH}$			$^2J_{HH}$*
n°	Y	2β3β	3β4α	3β4β	4α4β
10c	Br	4.0	12.5	6.3	12.3
10c'	OMe	4.2	12.6	7.0	12.3
10i	Cl	4.3	12.5	6.4	12.3
10i'	OMe	4.2	12.2	7.0	11.8
20c	Br	3.6	12.2	7.0	
20c'	OMe	4.2	12.4	7.7	12.2
21c	Br	3.8	12.2	6.9	11.8
21c'	OMe	4.15	12.4	7.5	11.9
20i	Cl	4.2	12.2	7.0	12
20i'	OMe	4.2	12.0	7.6	12
21i	Cl	4.1	12.4	7.0	12.1
21i'	OMe	4.2	12.4	6.6	11.8
30c	Br	4.5	---		
30c'	OMe	5.35	---	6.25	
31c	Br	4.0	11.5	---	
31c'	OMe	3.75	11.25	---	
30i	Cl	5.3	---	6.4	
30i'	OMe	5.2	---	6.5	
31i	Cl	4.1	11.5	---	
31i'	OMe	3.75	11.0	---	
40c	Br		---		
40c'	OMe	4.8	---	7.25	
41c	Br	3.8	12.1	---	
41c'	OMe	4.25	12.2	---	
40i	Cl	4.8	---	7.4	
40i'	OMe	5.0	---	7.25	
41i	Cl	4.2	12	---	
41i'	OMe	4.25	11.75	---	
50c	Br	4.5	---		
50c'	OMe	4.7	---	7.4	
51c	Br	4.0	12	---	
51c'	OMe	4.3	12.2	---	
50i	Cl	4.6	---	7.5	
50i'	OMe	4.8	---	7.5	
51i	Cl	4.0	11.8	---	
51i'	OMe	4.5	11.5	---	

* When R4α or R4β is a methyl, it appears as a doublet with J = 6.8 to 7.5 Hz.

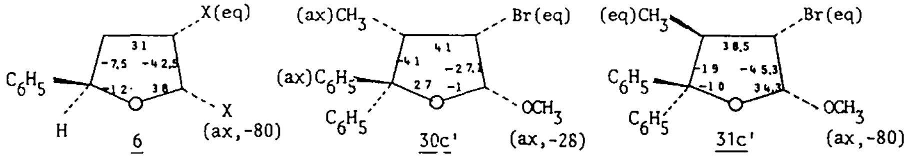
Table 4 : Coupling constants in the *trans*-adducts t, r, t', r', in Hz. The values x and *y* are the molecular ratios of the anomeric conformation (x) and of the *trans*-isomer at equilibrium (anomerization).

		$^3J_{HH}$			$^2J_{HH}$*		
n°	Y	2α3β	3β4α	3β4β	4α4β	x	*y*
10t	Br	0	1.3	5.9	14.6	0.97 ± 0.03	0.96
10t'	OMe	2.8	6.2	6.4	14.0	0.53 ± 0.04	0.75
10r	Cl	0.6	1.8	5.9	14.2	0.91 ± 0.02	---
10r'	OMe	2.2	4.9	6.5	14	0.62 ± 0.02	0.64
20t	Br	0	0.5	6.0	14.7	1	1
20t'	OMe	1.8	3.4	6.8	14.5	0.75 ± 0.01	0.70
21t	Br	0	0.5	6.0	14.7	1	0.94
21t'	OMe	2.0	4.3	7.0	14.5	0.70 ± 0.01	0.80
20r	Cl	0	0.8	5.7	14.3	1	1
20r'	OMe	1	2.8	6.5	14.3	0.83 ± 0.03 &	0.80
21r	Cl	0	0.6	5.9	14.4	1	0.95
21r'	OMe	1.5	3.5	6.5	14.1	0.75 ± 0.02 &	0.84
30t	Br	0	---	5.75		1	1
30t'	OMe	2.25	---	5.75		(0.67)	1
31t	Br	6.0	9.5	---		0	0.36
31t'	OMe	6.0	11	---		0	0.50
30r	Cl	0.8	---	5.6		(0.90)	1
30r'	OMe	2.25	---	5.75		(0.64)	1
31r	Cl	6.0	9.6	---		0	0.29
31r'	OMe	5.75	10.25	---		0	0.5
40t	Br	0	---	5.1		1	1
40t'	OMe	1.2	---	5.8		(0.84)	1
41t	Br	3.75	6.3	---		0.37 ± 0.01	0.30
41t'	OMe	6.25	11.5	---		0	0.60
40r	Cl	0	---	5.3		1	1
40r'	OMe	0	---	6.0		1	1
41r	Cl	4.6	7.8	---		0.17 ± 0.02	0.23
41r'	OMe	5.75	11.0	---		0	0.50
50t	Br	0	---	5.3		1	1
50t'	OMe	0	---	5.8		1	0.95
51t	Br	3.8	8.8	---		0.25 ± 0.16	0.44
51t'	OMe	4.4	10.7	---		0.19 ± 0.12	0.65
50r	Cl	0	---	5.25		1	---
50r'	OMe	0	---	5.7		1	1
51r	Cl	4.0	9.4	---		0.16 ± 0.16	0.36
51r'	OMe	4.2	10.1	---		0.19 ± 0.10	---

* When R4α or R4β is a methyl, it appears as a doublet with J = 6.5. to 7.2 Hz.

( ) Uncertainty due to a possible attractive interaction of C_6H_5 (5α) and Br (3α) (see texte).

& The same values are obtained at 25°, 60° and 90°C in Toluene-d8.



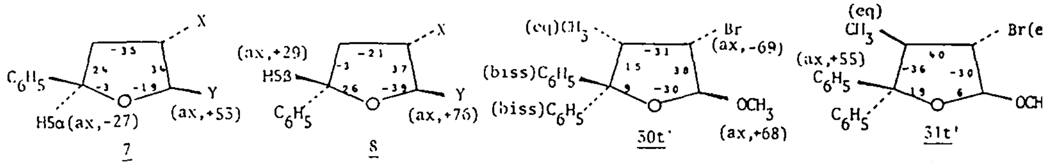
6
30c'
31c'

P = 45°, τ_m = 43° (JH2H3 = 3.6 to 4 Hz)

P = - 18°, τ_m = 43° (JH2H3 = 5.35 Hz)

P = 31°, τ_m = 45° (JH2H3 = 3.75 Hz)

Scheme III : Models for the conformational analysis of *cis* isomers.



7
8
30t'
31t'

P = 193°, τ_m = 36° conformation A

P = 238°, τ_m = 40° conformation A

P = 213°, τ_m = 38° conformation A

P = - 9°, τ_m = 41° conformation C

Scheme IV : Models for the conformational analysis of *trans* isomers.

This corresponds to a larger value for JH2H3 and is related to the 1-3 diaxial interac with the methyl substituent. In the *trans* series, the anomeric group is axial in molec 7, 8 and 30t' but equatorial in 31t' (contra-anomeric conformation, with a methyl on C *cis* to OMe).

Discussion

Conformation of the *cis* isomers (molecules c, i, c' and i').

Table 3 makes evident a relative homogeneity in the coupling constants for these lecules. The values JH3H4 *trans* ≃ 12 Hz means that all these isomers have H3β and H4α protons in axial position : the polar groups are equatorial on C3 and axial on C2, the anomeric position. Thus, the THF conformation is similar for these molecules and for t less hindered molecules 6 (X = Br or Cl, scheme III).

A significant variation of the JH2H3 coupling constant is found for 30c', 30i and 30i' (5.3 Hz instead of ≃ 4 Hz) but not for 30c (4.5 Hz). Despite of its bulkiness, th bromine atom keeps a character more axial than the chlorine or the methoxy group.

Conformation of the *trans*-isomers (molecules t, r, t' and r').

The behaviour of the *trans*-isomers is quite different. The inspection of table 4 reveals three different cases : these molecules may adopt a pure anomeric conformation (polar groups diaxial), a pure contra-anomeric conformation C (polar groups diequatori or may be found as a mixture of these two conformations.

1°/ Diaxial conformation

The molecules 20t, 20r, 21t, 21r show two small *trans*-diequatorial coupling const

JH2H3 ≃ 0 to 0.5 Hz

JH3H4 ≃ 0.5 to 1 Hz

These values are characteristic of two *trans*-diaxial X, Y groups. The molecules 30t, 40t... with R4α = CH_3 possess only one *trans* coupling constant (JH2H3 ≃ 0) and the polar groups X and Y are still diaxial.

The conformations of all these molecules are intermediate between those found for 7 (P = 193°, with a bulky group in R5β) and 8 (P = 238°, with a bulky group in R5α). The best situation for this intermediate case is obtained with two bulky groups (R5α = R5β = C_6H_5) and should correspond to a P value of 216°. In fact, for 30t', a value of 213° is found by X-ray diffraction [9].

According to the Altona's equations (scheme II), the axial character of R5α (negative values) or R5β (positive values), may be obtained by the expression :

$$\tau_0 - \tau_1 = (1.12 \cos P - 1.54 \sin P)\tau_m$$

On the representative curve (fig.3), the points M, N and L represent the axial character on C5 for the molecules 7, 8 and 30t'.

Simultaneously, the evaluation of the axial character of the anomeric group :

$$\tau_3 - \tau_4 = -(1.12 \cos P + 1.54 \sin P)\tau_m$$

is shown in fig.3 by the points N' (8), L' (30t') near the curve maximum and M' (7).

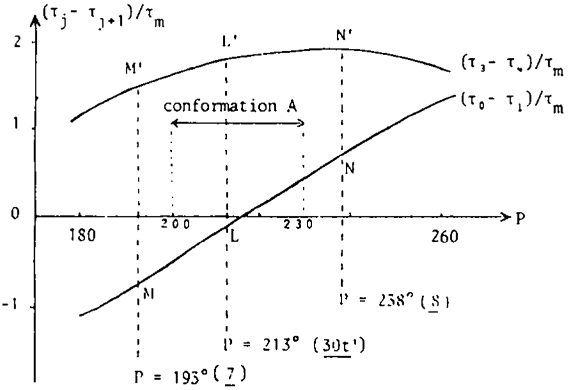


Fig. 3 : The axial character of the anomeric group and of the R5 axial substituent (R5α for negative values, R5β positive values) *versus* P.

So, P values around 210° - 220° are thought to be a good estimation for the diaxial conformation of the molecules with R5α = R5β = C_6H_5 and a methyl group R4α in equatorial position.

Finally, by assuming an intermediate situation for the molecules with R5α = C_6H_5 and R5β = CH_3 *or vice-versa*, the conformation of the molecules with JH2αH3β ≃ 0 Hz, is characterized by :

P ≃ 200° - 210° if R5α = CH_3 and R5β = C_6H_5
P ≃ 210° - 220° if R5α = R5β = C_6H_5
P ≃ 220° - 230° if R5α = C_6H_5 and R5β = CH_3

These conformations corresponding to 200° < P < 230° will be designated as the anomeric conformation (A, fig.3).

2°/ Diequatorial conformation

The molecules 31t, 31t', 31r... show two large coupling constants :

$$JH2\alpha H3\beta \simeq 5.75 \text{ to } 6.25 \text{ Hz}$$

$$JH3\beta H4\alpha \simeq 9.5 \text{ to } 11.5 \text{ Hz}$$

corresponding to X-Y *trans* diequatorial groups. The conformation of 31t' has been des bed by X-ray diffraction [9] ($P = -9°$, $\tau_m = 41°$, scheme IV). A calculation of the coup constants by using the Horton equation [17] and the X-ray dihedral angles :

$$J = (7.8 - \cos\phi + 5.6\cos 2\phi)\left|1-0.1\sum_{1}^{4}(X_i - 2.2)\right| \qquad (1)$$

gives a good evaluation of JH3H4 and JH2H3 ($\Delta J \leqslant 1$ Hz) and the conformation is assume be similar in solution and in the crystal structure. This conformation of 31t' (contr anomeric conformation) appears to be a good model for the molecules having only one nyl group R5β in axial position.

The existence of this unusual conformation is related to the presence of three typ of interactions in the anomeric conformation (fig.4). The analysis of the interaction is deduced from a previous NMR and MM2 study for the molecule 9 : in this molecule, tl phenyl group is, as for 41t', wedged between two methyl groups. In fact, without the methyl-5α, the molecule is found 100% A [13].

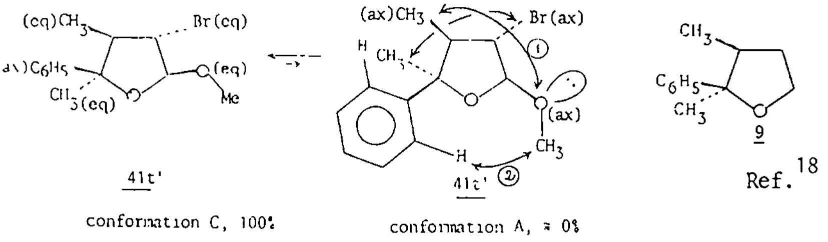


Fig.4 : Interactions in the molecule 41t'. In the conformation A, the methyl-5α is sl axial and its interaction with Br-3α is weak. In (A), the *endo*-anomeric stabi tion ought to be lost with ① and the *exo*-anomeric stabilization ought to be whith ② .

3°/ The other molecules show intermediate values for the coupling constants : exist as a mixture of A and C conformations (ratios x and 1-x). The values of x (tabl may be obtained by using the *trans* coupling constants JH2αH3β or JH3βH4α (equations 2

$$0.25x + J23(C)(1-x) = JH2\alpha H3\beta \qquad (2)$$

$$\text{and} \quad 0.75x + J34(C)(1-x) = JH3\beta H4\alpha \qquad (3)$$

Averaged values are used for the A conformation (0.25 and 0.75 Hz). For the C conform values are slighthy different according to the nature of X and Y :

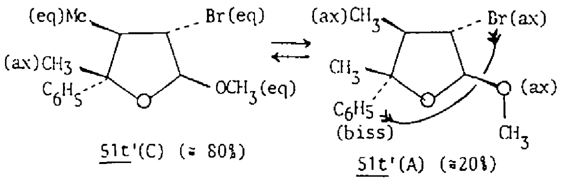
X	Y	J23(C)	J34(C)
Br	OMe	6.25 Hz	11.5 Hz
Cl	OMe	5.75 Hz	11.0 Hz
Br	Br	6.0 Hz	9.5 Hz
Cl	Cl	5.8 Hz	9.3 Hz

Some molecules as 30t', 30r',... present only one *trans* coupling constant (JH2H3) and the ratio x is evaluated by using the equation (2). For the other molecules, averaged values of x are reported in table 4 as well as the corresponding deviation.

The variations observed in the x values result from the balance of the different interactions in each molecule. In the molecule 30t', none of the fig.4 interactions is present (in the crystal structure, a phenyl group is found nearly eclipsing the C5-01 bond [9], but it is the phenyl-5α and not 5β).

For the molecules 51, the application of the equations (2) and (3) leads to a large discrepancy which is not clearly explained (fig.5).

From table 4, the *trans* dihalogenated compounds show a greater tendency to adopt the anomeric conformation than the bromo or chloro-ethers. Thus, the anomeric effect appears to be at least as important for the chlorine or the bromine as for the methoxy group.



51t'(C) (≈ 80%)

51t'(A) (≈20%)

Fig.5 : Conformational equilibrium of the molecule 51t'. The double-arrow is perhaps an attractive interaction [19] which disturbs the J values of the conformation C.

Epimerization at the anomeric center. Equilibration studies.

The equilibrium ratio of an anomeric pair results from a compromise between stabilizing or destabilizing, anomeric or steric effects.

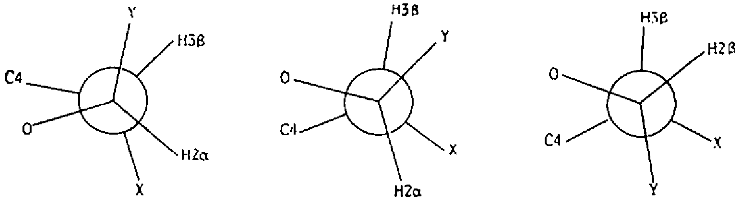
Table 1 shows the % of the isomers obtained in the kinetic product of chlorination or bromination of each dihydrofuran, and the % observed after equilibration at room temperature. (For the methoxy-derivatives see table 2). In this paper, we are interested in the values at equilibrium and so, the ratios y = t/t+c or t'/t'+c' have been evaluated for each anomeric pair, after equilibration.

As a general rule, a *trans* isomer which adopts the anomeric conformation (x ≃ 1, H2α singlet in the NMR spectrum) appears widely predominant at the equilibrium (y ≃ 1) and its anomeric *cis*-isomer is absent (fig.2, 40i → 40r). In the opposite case, if x = 0, the *cis*-isomer is the most stable (0.3 < y < 0.5) (fig.2, 41r ⇄ 41i). For the intermediate values of x, there is not a straitghforward correlation between x and y.

The polar and steric interactions of X and Y in a *trans*-isomer depend on the molecule conformation. They are almost fully alleviated in the anomeric conformation compared to the contra-anomeric one and even more compared to the *cis*-isomer (fig.6).

In fact, the two chemical and conformational equilibria will be fixed by the interactions of the substituents R4 and R5 in each case of fig.6. If the *trans*-isomer is not stabilized by the anomeric effect (conformation C), the *cis*-isomer becomes slightly more stable than the *trans*-isomer. Otherwise, in the conformation A, the *trans*-isomer is the most stable by at least 1.8 kcal/mole (fig.2, 40r).

At this stage, it is interesting to compare 31t with 31t' or 31r with 31r' (only X and



trans anomeric (A) *trans* contra-anomeric (C) *cis* anomeric

Fig.6 : Proximity and interactions of the X and Y groups in *trans* and *cis* isomers.

Y groups are different) :

The *trans* isomers are in the contra-anomeric conformation (x = 0) and the *cis*-isomer is stabilized by the anomeric effect. For Y = OCH_3 , the ratio y is observed to be 0.5 : *cis* and *trans* isomers have the same energy level. For Y = Br or Cl, the values of y decrease (0.36 and 0.29) : the *cis*-isomer is the most stable. All the interactions being roughly similar, we likewise found the Cl or Br anomeric effect more important than the MeO anomeric effect.

CONCLUSION

For the molecules 7 or 8, we had previously shown [13] that an increase of steric hindrance of the aromatic group leads to a deformation of the tetrahydrofuran ring (a compromise between the equatorial character of the aromatic group and the axial character of the anomeric group). In the present series, the steric interactions directly affect the anomeric group and we observe a different behaviour with an inversion of conformation, as in the cyclohexane series. Besides, there is, in the anomeric conformation, a deformation of the THF ring depending on the relative bulkiness of the two substituents R5α and R5β. This anomeric conformation varies over the pseudorotation circle from P = 170° (R5α = Mes, R5β = H) [13] to P = 240° (R5α = H, R5β = Ph) by increasing the hindrance of R5β compared to R5α (fig.7). This is an interesting illustration of the pseudorotation concept.

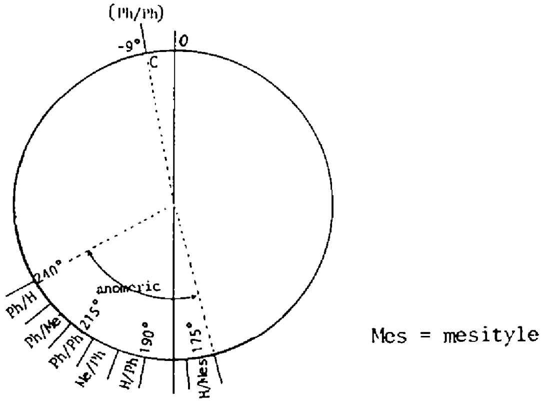


Fig.7 : Deformation of the THF ring by variation of the relative bulkiness R5α/R5β for the anomeric conformation of the *trans* isomers.
Corresponding variation of the P parameter.

Concerning the anomeric effect in the fragments O-C-Br, O-C-Cl or O-C-OMe, the anomeric form is found to be more stabilized with a bromine or a chlorine than with a methoxy group. This difference appears in the conformational equilibrium (x values) as well as in the anomeric equilibrium (*y* values).

Experimental section.

Synthesis of the 2,3-dihydrofuran starting materials.

The 2,3-dihydrofuran compounds were synthesized by previously published methods [20]. The acetylenic alcohols are obtained by Grignard synthesis [21]. As an example, we describe the preparation of the :

2,2-diphenyl-3-methyl-2,3-dihydrofuran, 3.

In a three-neck flask, equiped with a magnetic stirring bar, two pressure-equalizing dropping funnels and a thermometer, were placed 118 mmoles (4.5 g) $NaBH_4$ and 300 mmoles (21 g) 2-methyl-2-butene in 150 ml freshly distilled THF. The apparatus was kept under static pressure of nitrogen and cooled at -10°C. From the first funnel, 150 mmoles (21.3 g) of boron trifluoride etherate in 20 ml THF were added dropwise to the well-stirred reaction mixture and allowed to remain at 0°C for 3-4 hours. Then, the mixture was cooled at -10°C and from the second funnel, 100 mmoles (23.6 g) of 1,1-diphenyl-2-methyl-3-butyne-1-ol in 50 ml of THF were added. With this type of tertiary alcohol, there is no hydrogen evolved. After 0.5 hour at -10°C, the mixture is poured in 150 ml of cold N sodium hydroxyde. The oxydation is performed by dropwise addition under nitrogen of 90 ml of 15% hydrogen peroxyde (0-5°C). (In some other preparations, it is necessary to filter the mixture before pouring in NaOH to avoid the formation of the previously described 1,4-diol). After some hours at room temperature, the solution was saturated with NaCl and extracted with ether. The ether extract was washed and dried. By evaporation of the solvents and of the 3-methyl-2-butanol, we obtained 21.5 g (Yield 85%) of crystallised hemiacetal. (In other preparations, the hemiacetal does not crystallise but the reaction is pursued in the same way).

A mixture of 20 ml of pyridine and 40 ml of acetic anhydride was added to a solution of 18 g of the hemiacetal in 50 ml of ether. After 15 h at 3°C, the solvents were evaporated and the residue was heated at 200°C (0.5 hour) under 15 mm Hg. A flash distallation ($E_{0.1} \approx$ 118°C) gave 14 g of the dihydrofuran compound (90% purity measured by NMR). Purification is performed by thin layer chromatography. The electrophilic additions (Br_2 or Cl_2) are studied on a 50 mg sample (or 500 mg for the preparation of the methoxy-derivatives).

The *3-bromo* (or *chloro*) *2-methoxy-tetrahydrofuran derivatives* are obtained by diluting the crude solution of the halogenated products in methanol containing $NaHCO_3$ at 0°C. Purification of each stereoisomer is performed by thin layer chromatography (TLC) on 0.25 mm silica gel plates (Merck 60 FP - 254) and elution with light petroleum/ether (98/2 to 95/5). The *trans* isomers have sometimes the same R_f, but may be prepared pure by acidic anomerization of their *cis*-isomer (MeOH, TSOH, 70°C) [9].

The four methoxy derivatives are formed in various ratios, according to the composition of the starting mixture (kinetic or thermodynamic) of dichlorocompounds. The substitution occurs essentially with inversion at the anomeric center but with a small contribution of an SN_1 process. Sometimes, a slow decomposition in acidic medium prevents an easy determination of the equilibrium ratios.

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