

Spectroscopic Investigations on Derivatives of Tetrahydrofuran. I. Correlation of Semiempirical Parameters with Chemical Shifts of 2-Alkoxy-3-substituted Tetrahydrofurans

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NMR spectra of sixteen *trans*-2-alkoxy-3-substituted tetrahydrofurans have been measured. Correlations with Taft's σ^* and E_s constants of α -substituents and van der Waals' radii and electronegativities of β -substituents, for C-2 hydrogen, have been found.

In connection with the investigation of reactivity of halogenated tetrahydrofurans [1–4] a series of *trans*-2-alkoxy-3-substituted tetrahydrofurans was synthesized (compounds I–XVI, see Table 1). 2-Alkoxy-3-chlorotetrahydrofurans were synthesized either by alcoholysis or by the action of corresponding alkoxides on 2,3-dichlorotetrahydrofuran [5, 6]. 2-Alkoxy-3-bromotetrahydrofurans were prepared in similar way from 2,3-dibromotetrahydrofuran. Lemieux's method [7, 8] was adapted for making 2-alkoxy-3-iodotetrahydrofurans.

Applying NMR technique an attempt was made to determine the effect of the bulkiness of the C-2 and C-3 substituents in *trans*-2-alkoxy-3-substituted tetrahydrofurans upon the conformation of the cyclic part of the molecule. Our attention was focused on the NMR signal of the hydrogen on C-2 which is shifted downfield, the shift being caused by the neighbouring atoms of oxygen. As a result, the signal of the C-2 hydrogen appears in the spectra of I–XVI as a well pronounced singlet. The interaction between the atoms of hydrogen on C-2 and C-3 is negligible and the dihedral angle of these two atoms is, according to Karplus' equation [9], approximately 90°. Thus the bulkiness of the substituents has practically no effect upon the conformation of the system involving carbons C-2, C-3.

The chemical shift of the C-2 hydrogen signal does not depend on concentration but on the solvent. Such a shift was observed for C-2 hydrogen in 2-methoxy-3-chlorotetrahydrofuran (I) when as solvents CCl₄, CDCl₃, DMSO-*d*₆, benzene, pyridine or methanol were used. The observed chemical shift was found to decrease proportionally to the increasing polarity of the solvent. However, correlation with dielectric constants of the solvents was not found.

On the other hand, we found a significant correlation of the chemical shift of C-2 hydrogen in 2-alkoxy-3-chloro- and 2-alkoxy-3-bromotetrahydrofurans with Taft's σ^* constants for methyl, ethyl, isopropyl and *tert*-butyl groups (Fig. 1). As the σ^* values of alkoxy groups for all the substituents were not at hand the values of alkyls

Table 1

Chemical shifts (τ p.p.m.) of 2-(R-oxy)-3-X-tetrahydrofuran derivatives

No.	Compound		Ring protons			Alkoxy protons			
	R	X	$\overline{C-2}$	$\overline{C-3} + \overline{C-5}$	$\overline{C-4}$	$\text{CH}_2\text{-O}$	$\text{CH}_2\text{-C}$	$\text{CH}_3\text{-O}$	$\text{CH}_3\text{-C}$
<i>I</i>	Me	Cl	5.12	5.84–6.10	7.30–8.14	—	—	6.72	—
<i>II</i>	Et	Cl	5.02	5.81–6.11	7.29–8.15	6.32–6.71	—	—	8.85
<i>III</i>	<i>n</i> -Pr	Cl	5.03	5.84–6.11	7.30–8.16	6.37–6.77	8.34–8.60	—	9.12
<i>IV</i>	<i>i</i> -Pr	Cl	4.92	5.89–6.26 ^a	7.27–8.17	—	—	—	8.88
<i>V</i>	<i>n</i> -Bu	Cl	5.04	5.85–6.12	7.31–8.16	6.37–6.71	8.41–8.87	—	9.11
<i>VI</i>	<i>t</i> -Bu	Cl	4.77	5.92–6.10	7.70–8.16	—	—	—	8.79
<i>VII</i>	<i>i</i> -Am	Cl	5.05	5.85–6.11	7.31–8.16	6.42–6.80	8.25–8.90	—	9.11
<i>VIII</i>	<i>n</i> -Hexyl	Cl	5.05	5.85–6.11	7.31–8.16	6.25–6.70	8.42–8.86	—	9.13
<i>IX</i>	Me	Br	4.99	5.86–6.11	7.22–8.06	—	—	6.73	—
<i>X</i>	Et	Br	4.89	5.85–6.11	7.20–8.05	6.34–6.72	—	—	8.86
<i>XI</i>	<i>i</i> -Pr	Br	4.80	5.90–6.26 ^a	7.20–8.13	—	—	—	8.88
<i>XII</i>	<i>t</i> -Bu	Br	4.65	5.94–6.11	7.20–8.13	—	—	—	8.79
<i>XIII</i>	Me	I	4.77	5.81–6.12	7.30–7.88	—	—	6.74	—
<i>XIV</i>	<i>t</i> -Bu	I	4.47	5.92–6.14	7.39–7.96	—	—	—	8.81
<i>XV</i>	Me	OH	5.32	5.86–6.18	7.77–8.26	—	—	6.73	—
<i>XVI</i>	<i>t</i> -Bu	OH	4.94	6.00–6.20	7.95–8.30	—	—	—	8.81

^a) This multiplet overlaps the signal of methine proton of isopropyl group.

were used instead. We assume that this replacement was justified as the correlation was found for substituents of the same kind. In the case of 2-alkoxy-3-chlorotetrahydrofurans the values for *n*-propyl and *n*-butyl were also included, although it can be seen (Fig. 1) that these two values do not fit quite into the correlation plotting.

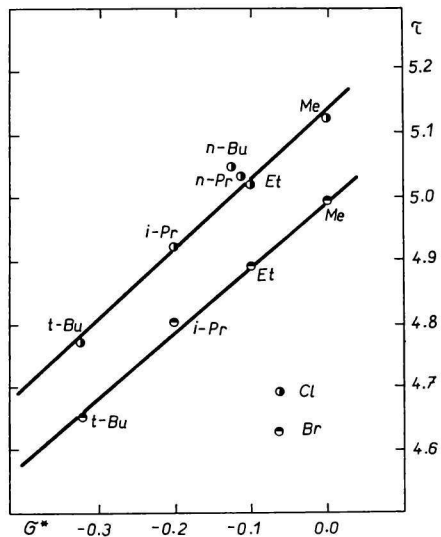


Fig. 1. Correlation of the chemical shifts of C-2 hydrogen with Taft's σ^* constants.

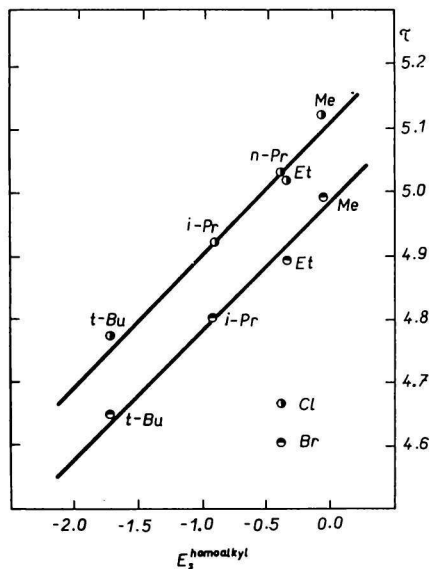


Fig. 2. Correlation of the chemical shifts of C-2 hydrogen with Taft's E_s constants.

We tried also to determine if there is a correlation of the chemical shift of the C-2 hydrogen with Taft's E_s constants [10]. As the needed constants were not available we formulated an assumption according to which the steric effect of an alkoxy would be roughly the same as the one of a homologous alkyl. Thus, for instance, E_s for isopropoxy group was replaced with E_s for isobutyl, etc. We obtained good correlation with the correlation coefficient 0.9927 (Fig. 2). The replacement of alkoxy with alkyl was not satisfactory (correlation coefficient 0.9501).

The chemical shift of C-2 hydrogen is affected by the substituents on C-3. This can be inferred from the fact that there is a good correlation of the chemical shift of the C-2 hydrogen with van der Waals' radii of the C-3 substituents in 2-methoxy- and 2-*tert*-butoxy-3-substituted tetrahydrofurans (Fig. 3; correlation coefficient 0.9885). For this correlation, apart from 3-halogeno derivatives (Cl, Br, I), also 3-hydroxy-substituted tetrahydrofurans [11, 12] were utilized. Van der Waals' radius of OH group ($r_{\text{W}}\text{OH}$) was calculated from the values for oxygen ($r_{\text{W}}\text{O}$) and hydrogen ($r_{\text{W}}\text{H}$) and from the value of the radius of single O—H bond ($r_{\text{s}}\text{OH}$) according to the equation

$$r_{\text{W}}\text{OH} = \frac{1}{3} (2r_{\text{W}}\text{O} + r_{\text{s}}\text{OH} + r_{\text{W}}\text{H}).$$

In *trans*-2,3-disubstituted tetrahydrofurans the C-2 hydrogen is very near the C-3 substituent. The bulkier the substituent the greater the distortion of the electron cloud around C-2 hydrogen and, consequently, the larger is the paramagnetic shift of the corresponding NMR signal. Similar effects were described for *trans*-2,5-dialkyl-tetrahydrofuran [13].

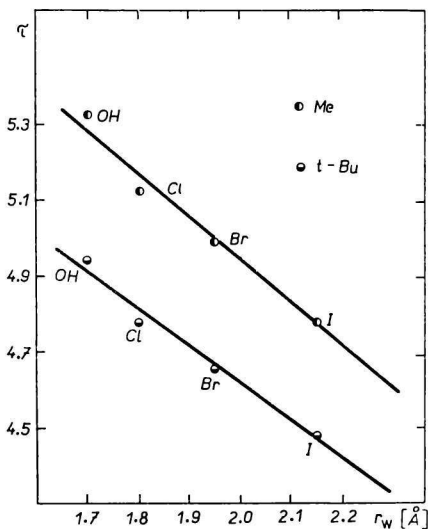


Fig. 3. Correlation of the chemical shifts of C-2 hydrogen with van der Waals' radii of C-3 substituents.

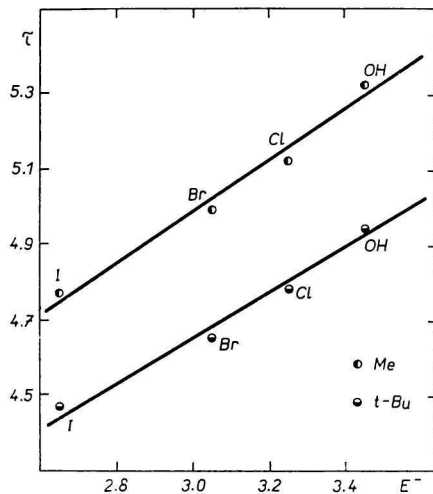


Fig. 4. Correlation of the chemical shifts of C-2 hydrogen with the electronegativities [14] of C-3 substituents.

It is interesting that in the case of 2-methoxy- and 2-*tert*-butoxy-3-substituted tetrahydrofurans there is a good correlation between chemical shifts and the electronegativities of 3-substituents (correlation coefficients 0.9888 and 0.9901; Fig. 4). Either strong inductive effect of the electronegative C-3 substituents or the dependence of the electronegativity on van der Waals' radii of the corresponding substituents (correlation coefficient 0.9969) account for this phenomenon.

Experimental

The purity of the compounds under investigation was tested by gas chromatography using Chrom II (Laboratorní přístroje, Praha) gas chromatograph on a column packed with 20% poly(ethyleneglycoladipate) on Rysorb BLX-400 at 120–140°C. When purification by distillation was not satisfactory, pure compounds were obtained by preparative gas chromatography using Fractovap Preparative Gas Chromatograph (Carlo Erba, Milano) on 15% Squalan on Chromosorb 3060 at 105°C. The compounds were identified by determining their Kováts indices, density, refractive index and IR spectra (UR-10 spectrometer Zeiss, KBr cells, liquid film). The yields as well as the physical constants of the compounds I–XVI are summarized in Table 2.

Table 2

Yields and physical properties of synthesized tetrahydrofurans

Compound	Yield [%]	B.p./Torr	n_D^{20}	d_4^{20}	Ref.
<i>I</i>	18	48/13	1.4419	1.1652	[5]
<i>II</i>	47	58/10	1.4430	1.1061	[2]
<i>III</i>	52	66–68/12	1.4350	1.0436	[2]
<i>IV</i>	34	57.5/13	1.4400	1.0752	[2]
<i>V</i>	79	88–90/20	1.4429	1.0588	[2]
<i>IV</i>	24	59/12	1.4450	1.0695	[19]
<i>VII</i>	65	95–97/20	1.4432	1.0360	this paper
<i>VIII</i>	75	115–118/25	1.4438	1.0257	this paper
<i>IX</i>	51	65–68/15	1.4732	1.4914	this paper
<i>X</i>	62	76–78/15	1.4692	1.3990	[5]
<i>XI</i>	60	75/15	1.4665	1.3379	this paper
<i>XII</i>	32	86–88/15	1.4723	1.3381	this paper
<i>XIII</i>	31	89–90/18	1.5212	1.7651	this paper
<i>XIV</i>	13	114–116/14	1.5046	1.5569	this paper
<i>XV</i>	52	86–89/25	1.4419	1.1070	[11]
<i>XVI</i>	61	68–72/2	1.4425	1.0225	[11]

Table 3

Chemical shifts of C-2 hydrogens and Taft's constants [10]

R	τ C-2		σ^* alkyl	E_s^{alkyl}	$E_s^{\text{homoalkyl}}$
	Cl	Br			
Me	5.12	4.99	0.00	0.00	–0.07
Et	5.02	4.89	–0.10	–0.07	–0.36
<i>n</i> -Pr	5.03	—	–0.115	–0.36	–0.39
<i>i</i> -Pr	4.92	4.80	–0.20	–0.47	–0.93
<i>n</i> -Bu	5.04	—	–0.13	–0.39	—
<i>t</i> -Bu	4.77	4.65	–0.32	–1.54	–1.74

Table 4

Chemical shifts of C-2 hydrogens, van der Waals' radii [20] and electronegativities [14] of C-3 substitutes

R	τ C-2		r_w [Å]	E^-
	Me	<i>t</i> -Bu		
OH	5.32	4.94	1.70*	3.45
Cl	5.12	4.77	1.80	3.25
Br	4.99	4.65	1.95	3.05
I	4.77	4.47	2.15	2.65

* Calculated value.

NMR spectra were taken on Tesla BS 478 A (80 MHz) spectrometer in carbon tetrachloride, concentration of the solutions 10–15%, internal standard HMDS ($\tau = 9.95$).

2-Alkoxy-3-chlorotetrahydrofurans

The compounds were prepared from 2,3-dichlorotetrahydrofuran [3] and the corresponding sodium alkoxide [5, 6].

2-Iso-amylloxy-3-chlorotetrahydrofuran

For $C_9H_{17}O_2Cl$ (192.69) calculated: 56.10% C, 8.89% H, 18.40% Cl; found: 55.86% C, 8.92% H, 18.57% Cl.

2-Hexyloxy-3-chlorotetrahydrofuran

For $C_{10}H_{19}O_2Cl$ (206.72) calculated: 58.10% C, 9.26% H, 17.15% Cl; found: 58.12% C, 9.29% H, 18.18% Cl.

2-Alkoxy-3-bromotetrahydrofurans

The compounds were prepared by alcoholysis of 2,3-dibromotetrahydrofuran [4] which was made from 2-chlorotetrahydrofuran in the following manner: To a solution of 44 ml (0.5 mole) 2-chlorotetrahydrofuran (b.p. 38–40°C/18 Torr, n_D^{20} 1.4625) in 50 ml of carbon tetrachloride 20 ml (0.4 mole) of bromine was added dropwise while the temperature was kept at 4°C. The rate of addition of bromine was controlled so that the solution was allowed to decolourise before the following amount of bromine was introduced. 2,3-Dibromotetrahydrofuran thus formed was, without isolation, treated with an excess of corresponding alcohol, the reaction mixture neutralized with anhydrous sodium bicarbonate, filtered and the filtrate vacuum distilled.

2-Methoxy-3-bromotetrahydrofuran

For $C_5H_9O_2Br$ (181.04) calculated: 33.17% C, 5.01% H; found: 32.53% C, 5.01% H.

2-Iso-propoxy-3-bromotetrahydrofuran

For $C_7H_{13}O_2Br$ (209.10) calculated: 40.21% C, 6.27% H, 38.22% Br; found: 39.04% C, 6.31% H, 39.00% Br.

2-t-Butoxy-3-bromotetrahydrofuran

For $C_8H_{15}O_2Br$ (223.12) calculated: 43.06% C, 6.78% H, 35.82% Br; found: 43.13% C, 6.63% H, 35.81% Br.

2-Alkoxy-3-iodotetrahydrofurans

The compounds were synthesized from 2,3-dihydrofuran [15–18] as follows: A mixture of 2,3-dihydrofuran (8.4 g, 0.12 mole) and silver acetate (26.1 g, 0.15 mole) in absolute alcohol (750 ml) was cooled to 0°C and, under stirring, iodine (39.6 g, 0.15 mole) was added within a period of 5 minutes. Stirring was continued for further 10 minutes and the reaction mixture was concentrated under reduced pressure. The sirupy residue was taken up in chloroform and the solution washed successively with solution of sodium carbonate and sodium thiosulfate. The colourless solution was dried with anhydrous sodium sulfate and fractionally distilled.

2-Methoxy-3-iodotetrahydrofuran

For $C_5H_9O_2I$ (228.04) calculated: 26.34% C, 3.98% H, 55.65% I; found: 26.33% C, 4.11% H, 55.25% I.

2-Alkoxy-3-hydroxytetrahydrofurans were synthesized from 2,3-dihydrofuran as described by Sweet and Brown [11].

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