^{13}C NMR Chemical Shifts – a Conformational Probe for 1-Alkoxyalkyl Esters
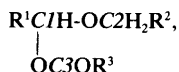
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Eighteen 1-alkoxyalkyl formates, acetates and propionates,

$$R^1C1H\text{-}OC2H_2R^2,$$
$$|$$
$$OC3OR^3$$

have been analysed by ^{13}C NMR spectroscopy.
When the chain length of R^1, R^2 or R^3 increases, the ^{13}C NMR resonances of C1, C2 and C3, respectively, shift to lower field. In addition to the primary substituent effects there are a few but minor interactive influences which, however, are clearly significant. All of these effects can be used to predict the most favoured conformation of the 1-alkoxyalkyl esters.

In connection with studies on proton catalysed hydrolysis of acylals several 1-alkoxyalkyl esters were prepared. The ^{13}C NMR chemical shifts of the compounds were subjected to multilinear regression analysis, the results of which turned out to be very helpful in assigning the most favoured conformation of the 1-alkoxyalkyl esters.

Experimental

Syntheses. α-Chloroethers were prepared by passing dry hydrogen chloride into the aldehyde (R^1CHO) – alcohol (R^2CH$_2$OH) mixtures[1] at 0 to 5 °C. The progress of the reactions was monitored by ^{1}H NMR spectroscopy. The products (yields 72–84 %) were used further without distillation. CH$_3$OCH$_2$Cl and C$_2$H$_5$OCH$_2$Cl were commercially available.

1-Alkoxyalkyl propionates and acetates (Table 1) were prepared according to the procedure of Hurd and Green[2] from α-chloroethers and sodium salts of the appropriate carboxylic acids. The yields varied from 70 to 95 %.

The formates (Table 1) were synthesised in a slightly different way. To 0.6 mol of dried, pulverized sodium formate, which was warmed to 40 °C and protected against moisture, 0.15 mol of dry α-chloroether was added from a dropping funnel. When the evolution of heat ceased, the synthesis was completed in the usual way[2] (yields 40–60 %).
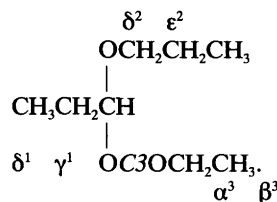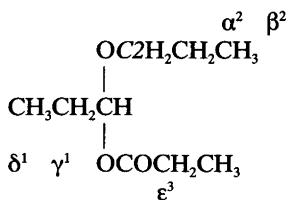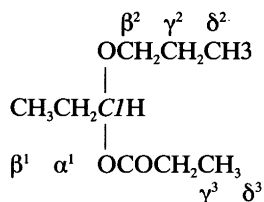
Product analyses. The products were identified and their purities checked by GC and ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer in CCl$_4$ (total concentration 15 %) using 1 % TMS as internal standard and the ^{13}C NMR spectra on a JEOL FX 60 FT spectrometer as total concentration 10 % (v/v) in CDCl$_3$ with 3 % TMS as internal standard. The boiling points and ^{1}H and ^{13}C NMR chemical shift data are shown in Tables 1 and 2.

Results and discussion

The different effects on the ^{13}C NMR chemical shifts of C1, C2 and C3, respectively were given the following notations:

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$$\overset{\beta^2\ \gamma^2\ \delta^2}{OCH_2CH_2CH3}$$
$$|$$
$$CH_3CH_2ClH$$
$$|$$
$$\overset{\beta^1\ \alpha^1}{\ }OCOCH_2CH_3$$
$$\gamma^3\ \delta^3$$

$$\overset{\alpha^2\ \beta^2}{OC2H_2CH_2CH_3}$$
$$|$$
$$CH_3CH_2CH$$
$$|$$
$$\overset{\delta^1\ \gamma^1}{\ }OCOCH_2CH_3$$
$$\varepsilon^3$$

$$\overset{\delta^2\ \varepsilon^2}{OCH_2CH_2CH_3}$$
$$|$$
$$CH_3CH_2CH$$
$$|$$
$$\overset{\delta^1\ \gamma^1}{\ }OC3OCH_2CH_3.$$
$$\alpha^3\ \beta^3$$

The values of the different substituent effects were solved with a multilinear regression analysis from the equation:[3,4]

$$\sigma C(x) = \sigma C_p(x) + \Sigma SE(x),$$

where $\sigma C(x)$ is the chemical shift of the x'th carbon atom ($x = 1, 2$ or 3), $\sigma C_p(x)$ that of the same carbon atom in the parent compound (no 1) and $\Sigma SE(x)$ the sum of the substituent effects influencing it.

For instance, $\Sigma SE(1)$ in the various compounds (1–18) consists of the following substituent effects:

No. $\Sigma SE(1)$
1   parent compound
2   -1.26 γ^2
3   7.26 α^1
4   $6.06\alpha^1 + \gamma^2$
5   9.29 $\alpha^1 + \gamma^2 + \beta^1$
6   0.12 γ^3
7   -1.03 $\gamma^2 + \gamma^3 + \gamma^2\gamma^3$
8   7.21 $\alpha^1 + \gamma^3 + \alpha^1\gamma^3$
9   5.95 $\alpha^1 + \gamma^2 + \gamma^3 + \gamma^2\gamma^3 + \alpha^1\gamma^3 + \alpha^1\gamma^2\gamma^3$
10 6.18 $\alpha^1 + \gamma^2 + \gamma^3 + \gamma^2\gamma^3 + \alpha^1\gamma^3 + \alpha^1\gamma^2\gamma^3 + \delta^2$
11 10.47 $\alpha^1 + \beta^1 + \gamma^3 + \alpha^1\gamma^3$

Table 1. The boiling points and ^{1}H NMR chemical shifts (δ/ppm) of the prepared acylals $R^1CH{-}OCH_2R^2$ | $OCOR^3$

	R^1	R^2	R^3	b.p. (°C/kPa)	$-OCOH$	$R^1{-}CH{-}$ / $-OCH{-}$	$-OCH_2CH_3$ / $-OCH_3$	$-OCOCH_2CH_3$ / $-OCOCH_3$	$-OCH_2CH_3$	$CH_3CH_2CH{-}O{-}$ / $CH_3CH{-}O{-}$	$CH_3CH_2CH{-}O{-}$	$-OCOCH_2CH_3$
						b	b		b			
1	H	H	H	103–105 /101	7.95	5.19	3.41					
2	H	CH₃	H	117–118 /101	7.98	5.25	3.65		1.18			
3	CH₃	H	H	37.8–37.2/8.67ᵃ	7.88	5.78	3.33			1.37		
4	CH₃	CH₃	H	41.0–42.0/9.33ᵃ	7.92	5.90	3.55		1.18	1.37		
5	C₂H₅	CH₃	H	68–70 /8.67	8.00	5.77	3.37		1.17	1.63	0.97	
6	H	H	CH₃	118–119 101		5.07	3.35	2.02				
7	H	CH₃	CH₃	57.4–57.7/6.67ᵃ		5.13	3.60	2.03	1.18			
8	CH₃	H	CH₃	116–117 /101		5.67	3.30	2.00		1.27		
9	CH₃	CH₃	CH₃	60.4–60.6/6.27ᵃ		5.77	3.60	1.98	1.15	1.25		
0	CH₃	C₂H₅	CH₃	58.4–59.4/3.60ᵃ		5.77	3.43	2.00	1.50ᶜ, 0.92ᵈ	1.32		
1	C₂H₅	H	CH₃	52.5–53.5/6.40ᵃ		5.53	3.32	2.02		1.58	0.90	
2	C₂H₅	CH₃	CH₃	68.5–69.0/6.67ᵃ		5.63	3.55	2.00	1.17	1.60	0.90	
3	H	H	C₂H₅	67–68 /8.00		5.10	3.35	2.30				1.13
4	H .	CH₃	C₂H₅	54–57 /2.67		5.17	3.60	2.30	1.18			1.12
5	CH₃	H	C₂H₅	66–68 /8.00		5.70	3.28	2.30		1.33		1.13
6	CH₃	CH₃	C₂H₅	58.8–60.0/6.95ᵃ		5.77	3.50	2.27	1.17	1.33		1.10
7	C₂H₅	H	C₂H₅	76–78 /6.67		5.53	3.30	2.28		1.55	0.88	1.12
8	C₂H₅	CH₃	C₂H₅	82–84 /8.00		5.63	3.53	2.30	1.17	1.57	0.90	1.13

Distilled with the PERKIN ELMER 251 Auto annular still.
The methylene proton shifts are given as averages only.
$-OCH_2CH_2CH_3$.
$-OCH_2CH_2CH_3$.

Table 2. The ^{13}C NMR chemical shifts (δ/ppm) of the products $R^1CH-OCH_2R^2$ with $OCOR^3$

	R^1	R^2	R^3	$-OCOR^3$	R^1CH-	$-OCH_2-$	$CH_3CH_2CH-OR^2$ / CH_3CH-OR^2	$-OCOCH_2CH_3$ / $-OCOCH_3$	$-OCH_2CH_3$	$CH_3CH_2CH-OR^2$	$-OCOCH_2C$
1	H	H	H	160.709	90.250	57.765					
2	H	CH_3	H	160.763	88.992	66.229			14.984		
3	CH_3	H	H	160.763	97.512	56.449	20.475				
4	CH_3	CH_3	H	160.763	96.313	64.856	20.875		14.927		
5	C_2H_5	CH_3	H	160.969	99.540	65.103	27.678		14.943	8.168	
6	H	H	CH_3	170.616	90.375	57.632		20.986			
7	H	CH_3	CH_3	170.665	89.221	66.001		21.046	15.098		
8	CH_3	H	CH_3	170.829	97.457	56.335	20.589	21.218			
9	CH_3	CH_3	CH_3	170.775	96.198	64.628	20.875	21.218	14.984		
10	CH_3	C_2H_5	CH_3	170.827	96.427	70.862	20.761	21.275	10.466[a], 22.819[b]		
11	C_2H_5	H	CH_3	171.003	100.715	56.621	27.452	21.105	21.105	8.121	
12	C_2H_5	CH_3	CH_3	171.003	99.516	64.914	27.738	21.218	15.041	8.238	
13	H	H	C_2H_5	174.130	90.246	57.566		27.613			8.966
14	H	CH_3	C_2H_5	174.057	89.076	65.948		27.678	15.138		8.966
15	CH_3	H	C_2H_5	174.206	97.228	56.278	20.587	27.795			9.035
16	CH_3	CH_3	C_2H_5	174.325	96.025	64.628	20.875	27.852	15.041		9.035
17	C_2H_5	H	C_2H_5	174.490	100.546	56.621	27.509	27.795		8.178	9.150
18	C_2H_5	CH_3	C_2H_5	174.546	99.342	64.908	27.808	27.808	15.073	8.316	9.128

[a] $-OCH_2CH_2CH_3$.
[b] $-OCH_2CH_2CH_3$.

No.	$\Sigma SE(1)$	
12	9.27	$\alpha^1 + \beta^1 + \gamma^2 + \gamma^3 + \gamma^2\gamma^3 + \alpha^1\gamma^3 + \alpha^1\gamma^2\gamma^3$
13	0.00	$\gamma^3 + \delta^3$
14	-1.17	$\gamma^2 + \gamma^3 + \delta^3 + \gamma^2\gamma^3$
15	6.98	$\alpha^1 + \gamma^3 + \sigma^3 + \alpha^1\gamma^3 + \alpha^1\delta^3$
16	5.78	$\alpha^1 + \gamma^2 + \gamma^3 + \delta^3 + \gamma^2\gamma^3 + \alpha^1\gamma^3 + \alpha^1\delta^3 + \alpha^1\gamma^2\gamma^3$
17	10.30	$|\alpha^1 + \beta^1 + \gamma^3 + \delta^3 + \alpha^1\gamma^3 + \alpha^1\delta^3$
18	9.09	$\alpha^1 + \gamma^2 + \alpha^1\gamma^2 + \gamma^3 + \gamma^2\gamma^3 + \alpha^1\gamma^3 + \alpha^1\gamma^2\gamma^3 + \beta^1 + \delta^3 + \alpha^1\delta^3.$

The effects (Table 3) are considered significant if they are larger than twice their standard deviations. All substituent effects are present at least twice except two, of those in compound 10, which is the only derivative with $R^2 = C_2H_5$.

1-Alkoxyalkyl esters have two structural features, which to some extent predetermine their spatial structure. First of all, the ester end has probably the s-cis conformation (Fig. 1).[5] Secondly, the O-C-O fragment tends to attain the gauche conformation to minimize the anomeric effect.[6]

The magnitudes of the α-effects are quite normal and the ratio of α^1 and α^2 is practically equal to the ratio of the respective effects at C2 and C4 of 1,3-dioxanes.[7]
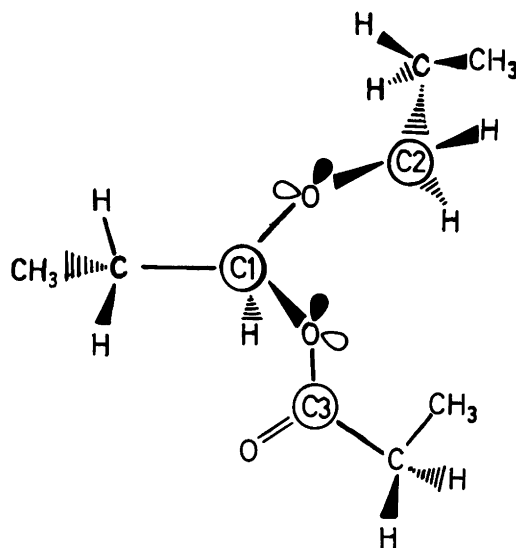

Fig. 1. The most probable conformation of the 1-alkoxyalkyl esters studied.

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Table 3. The solved effects at C1, C2 and C3 of
$R^1C1H-OC2H_2R^2$
|
$OC3OR^3$

Carbon no.	Effect	Parameter value/ppm	No. of occurrences
C1[a]	α^1	7.27±0.02	12
	β^1	3.29±0.02	5
	γ^2	−1.25±0.02	10
	δ^2	0.21±0.03	1
	$\alpha^1\,\gamma^3$	−0.21±0.03	9
	δ^3	−0.13±0.02	6
	γ^3	0.12±0.02	13
	$\gamma^2\,\gamma^3$	0.09±0.03	7
	$\alpha^1\,\gamma^2\,\gamma^3$	−0.06±0.03	5
	$\alpha^1\,\delta^3$	−0.06±0.03	4
C2[b]	α^2	8.42±0.02	10
	β^2	6.24±0.04	1
	γ^1	−1.33±0.02	12
	δ^1	0.29±0.02	5
	ε^3	−0.13±0.02	13
	$\alpha^2\,\varepsilon^3$	−0.09±0.03	7
C3[c]	α^3	9.94±0.02	13
	β^3	3.44±0.02	6
	δ^1	0.21±0.02	5
	$\alpha^3\,\gamma^1$	0.11±0.03	9
	$\beta^3\,\gamma^1\,\varepsilon^2$	0.09±0.03	2
	γ^1	0.05±0.02	12

[a]Av. diff., ±0.01 ppm; range 11.56 ppm; rms 0.024 ppm.
[b]Av. diff., ±0.02 ppm; range 14.59 ppm; rms 0.036 ppm.
[c]Av. diff., ±0.02 ppm; range 13.79 ppm; rms 0.032 ppm.

The β-effects are structurally most informative. It has been pointed out recently that β_e is clearly larger than β_a in cyclic compounds.[7,8,9] Accordingly the methyl groups causing the β^1 and β^3 ef- fects (Table 3) have an orientation which resem- bles that of β-axial groups, *e.g.* in 1,3-dioxanes and oxanes.[9,10] Correspondingly, the methyl group which is responsible for the β^2 effect attains principally an equatorial position (see Fig. 1).

Both γ-effects ($\gamma^1$and γ^3) which are only slightly negative support strongly the predominant γ-*anti* orientation of the respective methyl groups[6,8] in good agreement with the above discussion on the β-effects.

All the other effects are very small but signifi- cant. Together with the primary effects they al- low a very accurate evaluation of the ^{13}C NMR chemical shifts of C1, C2 and C3 in the title com- pounds. This is in line with the deduced structure since in general ^{13}C NMR chemical shift correla- tions work best when the basic conformation of the studied compounds does not change much with increasing substitution.[7]

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