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Conformational Analysis. Part XVII. A Simple Application of the Karplus Equation to Study the Preferred Conformations of the Ethyl Group in Some Alkylsubstituted 4-Ethyl-1,3-oxathiolanes

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The ^{1}H NMR spectra of 4-ethyl-1,3-oxathiolane and several alkylsubstituted derivatives were recorded and analysed using an iterative LAME program. From the Karplus equation, $J = J_0 \cos^2 \phi$, and the observed coupling constants (J_{46} and $J_{46'}$, where 6 and 6′ are the methylene protons of the ethyl group) the J_0 values were determined and used to estimate the relative amounts of the *gauche*(S), *gauche*(C5) and *trans*(H4) ethyl rotamers. In 5 methyl derivatives the *gauche*(C5) rotamer is practically nonexistent due to the "trans-annular" Me – Me interaction. In general the *gauche*(S) form is 1.7 ± 0.2 kJ mol^{-1} more stable than the *gauche* (C5) form and 3.0 ± 0.4 kJ mol^{-1} more stable than the *trans*(H4) rotamer.

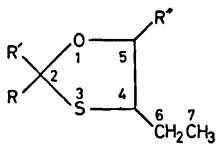
Despite the fact that the conformations of alkylsubstituted saturated heterocycles have been recently studied rather intensively [1] the conformational behaviour of alkyl groups has received much less attention. The ethyl rotation has been studied in the case of some alkylcyclohexanes,[2] 1,3-dioxanes,[3,4] 1,3-dioxolanes [3] and 1,3-dithianes.[5] In the heterocyclic compounds the ethyl group has always been at position 2.

In the present work we will describe some results dealing with the rotameric preferences of the ethyl group in 4-ethyl-1,3-oxathiolane and its alkyl derivatives.

RESULTS AND DISCUSSION

Analysis of the ^{1}H NMR spectra

Configurational assignments (Table 1) were based on the magnitudes of proton-proton coupling constants and chemical shifts for the ring protons which were compared with those of correspondingly substituted 4-methyl-1,3-oxathiolanes.[6–8]



	R	R′	R″
1	H	H	H
2	Me	H	H
3	Me	Me	H
4	Bu^t	Me	H
5	Me	Bu^t	H
6	H	H	Me
7	H	Me	Me
8	Me	Me	Me

The studied spectra fall into two groups of which the one forms an $ABCDEF_3$ system (*1* – *5*) and the other an M_3ABCDE_3 system (*6* – *8*).

The spectrum of 4-ethyl-1,3-oxathiolane (*1*) and that of *trans*-4-ethyl-5-methyl-1,3-oxathiolane (*6*) were completely analysed at 60 MHz and the former also at 300 MHz. The chemical shifts of H6 and H6′ for compounds *2* – *5* and *7* – *8* were taken from spectra of the above compounds due to the overlap of their signals with those of the alkyl groups at position 2.

The analyses were carried out using an iterative LAME program [9] on a DEC-10 computer.

Rotameric behaviour of the 4-ethyl group

The 300 MHz spectrum of 4-ethyl-1,3-oxathiolane (*1*) gives clearly distinct methylene proton signals for the ethyl group in good

Table 1. Chemical shifts (δ) of different protons in ppm from TMS for the studied compounds in CCl_4.

1,3-Oxathiolane	H(2)	H(4)	H(5)	H(5′)	H(6)	H(6′)	Me(7)	Me(5)	R(2)
1 4-Et- (300 MHz)	4.85 4.76	3.34	3.88	3.65	1.67	1.55	0.99		
4-Et- (60 MHz)	4.87 4.78	3.36	3.90	3.67	1.67	1.55	0.99		
2 *cis*-2-Me-4-Et-	5.11	3.35	3.98	3.73			0.95		1.54
3 2,2-Me_2-4-Et-		3.40	4.06	3.78			0.96		1.59,1.55
4 *r*-2-Bu^t-2-Me-*cis*-4-Et-		3.28	4.08	3.91					1.53,1.04[a]
5 *r*-2-Bu^t-2-Me-*trans*-4-Et-		3.31	4.24	3.59					1.55,1.02[a]
6 *trans*-5-Me-4-Et-	4.90 4.82	2.95	3.62		1.78	1.49	1.05	1.31	
7 *r*-2,*c*-5-Me_2-*t*-4-Et-	5.21	3.03	3.54				1.01	1.33	1.52
8 2,2,5-Me_3-*trans*-4-Et-		3.07	3.83				0.98	1.29	1.59

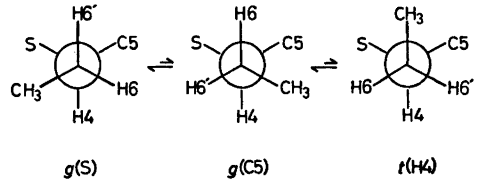
[a] δBu^t.

Table 2. Coupling constants (J/Hz) for the studied compounds.

1,3-Oxathiolane	J_{45}	$J_{45'}$	J_{46}	$J_{46'}$	$J_{55'}$	$J_{66'}$	J_{7Me}	J_{2R}
1 4-Et- (300 MHz) [a]	5.72	4.82	5.90	8.33	−9.03	−13.66	7.35	5.38
4-Et- (60 MHz) [b]	5.64	4.82	5.88	8.29	−8.96	−13.42	7.30	5.13
2 *cis*-2-Me-4-Et- [c]	5.35	2.18	5.93	8.08	−9.15		7.03	5.13
3 2,2-Me_2-4-Et- [c]	5.31	5.20	5.93	8.17	−9.14		7.16	
4 *r*-2-Bu^t-2-Me-*cis*-4-Et- [c]	5.27	3.13	6.14	8.66	−9.37		7.20	
5 *r*-2-Bu^t-2-Me-*trans*-4-Et- [c]	5.54	10.01	5.78	7.63	−9.21		7.45	
6 *trans*-5-Me-4-Et- [d]		7.28	4.13	9.50	6.02 [f]	−13.12	7.26	5.45
7 *r*-2,*c*-5-Me_2-*t*-4-Et- [e]		8.58	3.62	9.19	5.99 [f]		7.08	5.89
8 2,2,5-Me_3-*trans*-4-Et- [e]		8.94	3.52	9.51	6.01 [f]		7.29	

Standard deviation better than [a] 0.027, [b] 0.050, [c] 0.140, [d] 0.063 and [e] 0.059. [f] J_{5Me}.

agreement with the postulation that the anisochronism of these protons is enhanced by the restricted rotation of this group. The same situation prevails, of course, in the other compounds under study. We have pointed out earlier [7] that, *e.g.*, *cis*-2-methyl-4-ethyl-1,3-oxathiolane (*2*) exists predominantly in a C5 envelope (*cf.* the value of $J_{45'}$) where the ethyl group is axial. In this orientation the methyl-in-the-ring rotamer (*trans* in Scheme 1) is so crowded that it may be excluded on steric grounds. Compounds *1* and *3*–*5* include 31, 36, 11 and 93 % of the ring conformation where the ethyl group is equatorial as evident from the values of $J_{45'}$ (model values J_{ee} 2.2 and J_{aa} 10.6 Hz).[6,7] Hence even in compounds *1*, *3* and *4* the contribution of the *trans*(H4) rotamer (Scheme 1) is rather small as shown below.



Scheme 1.

From the two *gauche* rotamers, *gauche*(S) – the methyl end on the sulfur side – and *gauche*(C5) – the methyl end on the C5 side, both include one *trans* coupling [$J_{46'}(t)$ and $J_{46}(t)$, respectively] and one gauche coupling [$J_{46}(g)$ and $J_{46'}(g)$, respectively] whereas the *trans*(H4) form has two *gauche* type couplings.

To solve the relative amounts of the *gauche* rotamers one has to know the values of J_g and

J_t, separately. That is why we adopted the Karplus equation [10] in the form

$$J = J_0 \cos^2 \phi \quad (1)$$

where the magnitude of the J_0 value depends on the nature of the H – C – C – H fragment [11,12] and ϕ is the dihedral angle between the vicinal protons. In the case of the *gauche*(S) rotamers of 4-ethyl-1,3-oxathiolane and its alkyl derivatives it is reasonable to suppose that the ethyl group has an almost ideal trigonal projection symmetry. In other words, for these rotamers:

$$J_t = J_0 \cos^2 180° = J_0 \quad (2)$$

$$J_g = J_0 \cos^2 60° = 1/4 J_0 \quad (3)$$

Several iterative data fittings led, however, to the conclusion that for *gauche*(C5) $\phi_t \sim 185°$ and $\phi_g \sim 65°$ and for *trans*(H4) $\phi_{46'} \sim 70°$ and $\phi_{46} \sim 50°$ (*cf.* Scheme 1). Accordingly, the vicinal *trans* coupling constants are clearly larger than the vicinal *gauche* coupling constants.[12–14]

On the other hand, the methyl-sulfur interaction in the *gauche*(S) rotamer (Scheme 1) should be about half of the conformational energy of an axial methyl group at C5 in the 1,3-dithiane ring for which values from 3.8 [15] to 4.9 [1] kJ mol^{-1} have been reported. Correspondingly, the methyl-methyl interaction [1] in the *gauche*(C5) rotamer should be roughly 3.4 – 3.8 kJ mol^{-1} and hence the free energy difference between the two *gauche* forms should favour the *gauche*(S) rotamer by 1.0 – 1.9 kJ mol^{-1}. Therefore $J_{46'}$ must be larger than J_{46} (Scheme 1). The preceding postulate is close to 1.7 ± 0.2 kJ mol^{-1}, observed for compounds *1* – *5* (Table 3). It is reasonable to suggest that the *trans*(H4) rotamer must be significantly less favoured although this arrangement certainly does not exclude the presence of the *trans*(H4) rotamer in all cases.[12,16] In the light of the above discussion the *gauche*(S) form is at least 3 – 4 kJ mol^{-1} more stable than the *trans*(H4) rotamer. Hence compounds *6* – *8* cannot contain more than about 20 – 25 % of the *trans*(H4) rotamer. Consequently, we may write

$$J_{46'} = x_{g(S)} J_0 + x_{g(C5)} J_0 \cos^2 65° + x_{t(H4)} J_0 \cos^2 70° \quad (4)$$

$$J_{46} = x_{g(S)} 1/4 J_0 + x_{g(C5)} J_0 \cos^2 185° + x_{t(H4)} J_0 \cos^2 50° \quad (5)$$

Since the *cis*-2-Me-4-Et-derivative *2* exists exclusively in a 4-axial C5 envelope [7] it does not contain the *trans*(H4) rotamer at all. Hence

$$\begin{aligned} J_{46'} &= 0.821 x_{g(S)} J_0 + 0.179 J_0 = 8.08 \\ J_{46} &= -0.742 x_{g(S)} J_0 + 0.992 J_0 = 5.93 \end{aligned} \quad (6)$$

which results in $x_{g(S)} = 0.64$, $x_{g(C5)} = 0.36$ and $J_0 = 11.5$ Hz. From the latter the values of the

Table 3. J_0 values (Hz), the relative amounts of ring conformations and ethyl rotamers, the values of $J_{46'}$ and J_{46} corrected for *gauche*(C5) ⇌ *gauche*(S) (compounds *1* – *5*) and *trans*(H4) ⇌ *gauche*(S) equilibria (compounds *6* – *8*), the values of the rotameric equilibrium constants K = *gauche*(S)/*gauche*(C5) (compounds *1* – *5*) and K = *gauche*(S)/*trans*(H4) (compounds *6* – *8*), and the respective free energy differences for the studied 4-Et-1,3-oxathiolanes at 306 K.

Compound	J_0	x_{4e}	x_{4a}	$x_{t(H4)}$	$J_{46'}$	J_{46}	$x_{g(S)}$	$x_{g(C5)}$ or $x_{t(H4)}$	K[d,e]
1	12.1 [a,b]	0.31	0.69	0.05	8.69	5.95	0.66	0.34	1.9
2	11.5 [a,b]	–	1.00	–	8.08	5.93	0.64	0.36	1.8
3	12.1 [a,b]	0.36	0.64	0.06	8.60	5.99	0.65	0.35	1.9
4	12.1 [a,b]	0.11	0.89	0.02	8.81	6.16	0.67	0.33	2.0
5	12.1 [a,b]	0.93	0.07	0.17	8.91	5.94	0.68	0.32	2.1
6	11.5,12.1 [a,b]	0.76[c]	0.24[c]	0.15	9.74	3.56	0.79	0.21	3.8
7	11.5,12.1 [a,b]	0.95[c]	0.05[c]	0.26	9.21	3.50	0.73	0.27	2.7
8	12.1 [a,b]	1.00[c]	–	0.24	9.51	3.52	0.76	0.24	3.2

[a] For the *gauche*(S) rotamer $J_t = 12.1$ and $J_g = 3.0$ Hz, except *2* for which $J_t = 11.5$ and $J_g = 2.9$ Hz. [b] For the *gauche*(C5) rotamer $J_t = 11.4$ and $J_g = 2.05$ Hz in all cases. Correspondingly, for the *trans*(H4) rotamer $J_{46'} = 1.4$ and $J_{46} = 5.0$ Hz. [c] $x_{4e} = x_{4e5e}$ and $x_{4a} = x_{4a5a}$. [d] K = *gauche*(S)/*gauche*(C5) = 1.94 ± 0.15 and $-\Delta G^\ominus$/kJ mol^{-1} = 1.7 ± 0.2. [e] K = *gauche*(S)/*trans*(H4) = 3.2 ± 0.5 and $-\Delta G^\ominus$/kJ mol^{-1} = 3.0 ± 0.4.

different coupling constants are obtained (Scheme 1 and Tables 2 and 3).

Similarly, the 2,2,5-tri-Me-*trans*-4-Et-derivative *8* is exclusively in the 4e5e ring conformation [8] and hence due to the "trans-annular" methyl-methyl interaction does not include the *gauche*(C5) rotamer at all. Accordingly,

$$J_{46'} = 0.883x_{g(S)}J_0 + 0.117J_0$$
$$J_{46} = -0.163x_{g(S)}J_0 + 0.413J_0 \quad (7)$$

which results in $x_{g(S)} = 0.76$, $x_{g(C5)} = 0.24$ and $J_0 = 12.1$ Hz. From them the values of the different coupling constants are again obtained.

The small difference in the J_0 values for *2* and the other compounds -11.5 *vs.* $12.1-$ is easily understood since from compounds *1*–*5* only *2* has a biased ring conformation [7] and compounds *6*–*8* have an extra methyl substituent at C5.

From another study [8] we know, however, that the predominance of the diequatorial 4e5e conformation decreases when passing from *8* to *6*. Use of the equation

$$trans\text{-}4,5\text{: } J_{obs} = xJ_{4a5a} + (1-x)J_{4e5e} \quad (8)$$

where $J_{aa} = 8.9$ and $J_{ee} = 2.0$ Hz,[8] gives the mol fractions of the 4,5-diequatorial (x_e) and 4,5-diaxial (x_a) conformations of *6* and *7* (Table 3). In the diaxial ring conformations of *6* and *7* the amounts of the *gauche*(C5) and *gauche*(S) rotamers are roughly identical with those existing in compounds *1*–*5*. Using the results in Tables 2 and 3 and the postulate above the amounts of the *gauche*(S) and *trans*(H4) conformations in the 4e5e forms of *6* and *7* (Table 3) can be estimated. In all cases the free energy difference between the *gauche*(S) and *trans*(H4) rotamers of the 4e5e ring conformations is practically equal – *i.e.* 3.0 ± 0.4 kJ mol^{-1}.

The results for *2* and *8* were then employed to correct the rotamer equilibria of *1* and *3*–*5* for the contribution of the *trans*(H4) form. The corrected values of the $J_{46'}$ and J_{46} coupling constants were used to estimate the proportions of the *gauche* rotamers (Eqn. 6) and after one iterative cycle a good convergence was reached (Table 3).

Finally we would like to emphasize that our results clearly point out that a double-*gauche* interaction is not necessarily sufficient to exclude a rotameric contribution of this type.[12]

EXPERIMENTAL

4-Ethyl-1,3-oxathiolane and its alkyl derivatives were obtained as by-products in the preparation of some alkyl-substituted 1,3-oxathianes from mixtures of 1,3- and 1,2-mercaptoalcohols.[17,18]

The spectra were obtained for 15 % (v/v) solutions in CCl_4 on a Perkin-Elmer R-10 60 MHz NMR spectrometer at 306 K. For 4-ethyl-1,3-oxathiolane a 300 MHz spectrum was recorded at 293 K on a Varian HR-300 spectrometer at the State University of Gent, Belgium.

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