Tetrahedron Vol. 43, No. 12, pp. 2761 to 2767, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

MULTINUCLEAR AND 2D NMR STRUCTURAL STUDY OF METHYL-SUBSTITUTED 1,3-DIOXADECALANES

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(*Received in UK* 22 *April* 1987)

Abstract - The configurations and conformations of 11 1,3-dioxadecalane derivatives were determined by multinuclear and 2D NMR spectroscopy. No conformational equilibria were found even in the 2,2-dimethyl substituted compound. In one case (9) only the <u>O-out</u> conformation prevails. The values of the methyl substituent effects on the ^{13}C NMR chemical shifts of 1,3-dioxane were found useful in the present case, too. The ^{17}O NMR chemical shifts were also helpful in both conformational and configurational assignments.

The decalane ring system offers an interesting and well documented stereochemical model.[1] However, for 1,3-dioxadecalanes, their heterocyclic analogs, only some ^{1}H NMR studies has been reported earlier.[2-5] Hence the present paper deals with the conformations and configurations of eleven 1,3-dioxadecalanes (1-11) in the light of their ^{1}H and ^{13}C NMR spectra together with different 2D experiments. The validity of shift increment calculations using substituent effects derived for 1,3-dioxanes[6] will also be tested. The ^{17}O NMR spectra are also utilized in configurational and/or conformational assignments.

RESULTS AND DISCUSSION

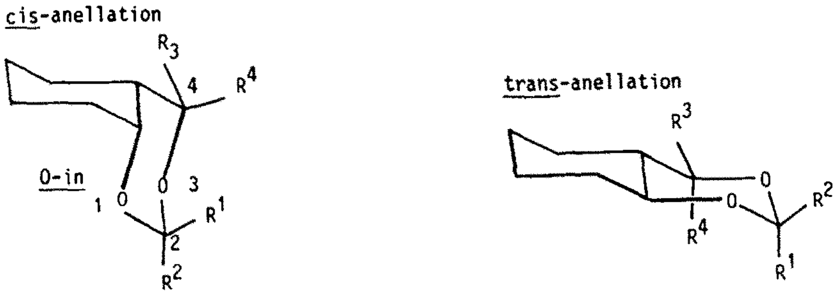
Configurational and conformational assignments.

The spectral data are collected in Tables 1-4. The anellations, <u>ie</u> the <u>cis</u> or <u>trans</u> fusions, are relatively easy to reveal by analyzing the ABX-type spectra due to the protons at C-4 and C-5 or the ABKX-type spectra due to the protons at C-5, C-6, and C-10. Luckily, the latter are practically of first order since the 10ax and 10eq protons are always well separated (Table 1). This was confirmed by measuring the 2D carbon proton shift correlations after assigning the carbon signals with 2D INADEQUATE.[7]

The values of the indirect H,H-coupling constants listed in Table 2 do not indicate any conformational equilibria. According to the values of the vicinal coupling constants (Table 2) compounds 1, 3, 5, and 7 prefer greatly the <u>O-in</u>

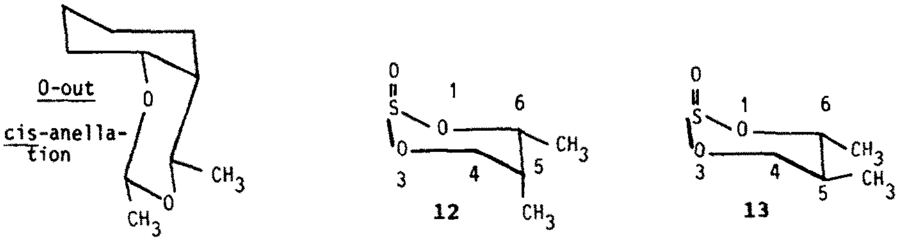
conformation (Scheme). The coupling data also indicate that **7** has an equatorial methyl at position 4. Even **8** with an axial methyl at C-4 seems to attain an anancomeric O-in conformation where the dioxane chair is slightly deformed due to the 4ax-methyl substitution. This deformation can be seen in the 4,5-coupling, too (J = 0 Hz). On the other hand **9** is obviously in the O-out conformation with an equatorial 4-methyl.

SCHEME



	R^1	R^2	R^3	R^4
1	H	H	H	H
3	H	CH_3	H	H
5	CH_3	CH_3	H	H
7	H	CH_3	CH_3	H
8	H	CH_3	H	CH_3

	R^1	R^2	R^3	R^4
2	H	H	H	H
4	H	CH_3	H	H
6	CH_3	CH_3	H	H
10	H	CH_3	CH_3	H
11	H	CH_3	H	CH_3



9 **12** **13**

Table 1. ^1H NMR chemical shifts (in ppm) of the compounds studied.[a]

	2a	2e	4a	4e	5	6	7a	7e	8a	8e	9a	9e	10a	10e
1	4.70	5.05	3.80	3.75	1.36	3.83	2.03	1.45	1.25	1.77	1.45	1.45	1.52	1.88
2	4.73	5.05	3.30	3.91	1.65	3.19	0.87	1.45	1.27	1.68	1.31	1.80	1.38	1.90
3	4.69	$\underline{1.31}$	3.82	3.73	1.23	3.85	1.98	1.41	1.21	1.77	1.51	1.42	1.41	1.83
4	4.72	$\underline{1.30}$	3.33	3.88	1.55	3.21	0.85	1.45	1.24	1.66	1.28	1.79	1.35	1.88
5	$\underline{1.43}$	$\underline{1.39}$	4.06	3.48	1.36	4.09	2.04	1.45	1.33	1.73	1.55	1.43	1.40	1.77
6	$\underline{1.38}$	$\underline{1.45}$	3.56	3.63	1.48	3.48	0.89	1.52	1.25	1.67	1.30	1.78	1.29	1.78
7	4.78	$\underline{1.34}$	3.80	$\underline{1.14}$	1.20	3.81	1.60	1.78	1.50	1.25	1.45	1.45	1.45	1.90
8	5.03	$\underline{1.33}$	$\underline{1.29}$	3.82	1.15	4.06	2.03	1.45	0.87	1.68	1.45	1.45	1.55	1.80
9	5.12	$\underline{1.28}$	4.01	$\underline{1.22}$	1.91	3.93	1.35	1.76	1.13	1.38	1.25	1.80	2.10	1.67
10	4.81	$\underline{1.35}$	3.41	$\underline{1.19}$	1.18	3.23	1.30	1.75	1.25	1.70	1.20	1.80	1.40	1.80
11	5.07	$\underline{1.28}$	$\underline{1.26}$	4.08	1.85	3.54	0.93	1.45	1.25	1.69	1.30	1.78	1.35	1.94

[a] The methyl chemical shifts have been underlined.

Table 2. The values of the H,H-coupling constants in the dioxane moiety.

No	Coupling constants/Hz							
	2,2	4,4	4a,5	4e,5	5,6	6,10a	6,10e	long-range
1	-6.1	-11.2	2.8	1.2	3.0	3.0	3.0	
2	-6.2	-11.0	11.0	4.4	10.7	10.2	4.4	0.4 (2e4e)
3	5.0[a]	-11.4	2.9	1.3	2.9	2.9	2.9	
4	5.0[a]	-11.0	11.0	4.4	10.8	9.8	4.0	
5	---	-11.6	2.9	1.1	2.6	2.6	2.6	0.5 (MeMe)
6	---	-11.1	11.1	4.7	10.2	10.2	3.8	0.7 (MeMe)
7	5.1[a]	6.6[a]	2.5	---	2.8	2.8	2.8	
8	5.0[a]	7.0[a]	---	0.0	3.1	3.1	3.1	
9	5.0[a]	6.2[a]	10.6	---	5.1	12.2	5.1	
10	5.2[a]	6.1[a]	9.6	---	10.8	9.8	4.1	
11	5.0[a]	6.9[a]	---	5.8	10.4	10.4	4.1	

[a] $\underline{H}$,C$\underline{H}_3$-couplings.

The *trans* derivatives have naturally less conformational freedom since the rotation about the anellation bond is hindered. The H,H-couplings show, however, that the 4-methyl group is equatorial in **10** and axial in **11**.

However, the configuration at C-2 cannot be determined directly by the H,H-couplings. Anteunis *et al.* stated that the *O-in* conformation is more stable than the *O-out*.[2] They also said that 2-substitution can be used as a conformation holding group since the 2-equatorial substitution is greatly favoured over the 2-axial one as in 1,3-dioxanes.[6] The above effects can be, however, counteracting and furthermore also the 4 position can be substituted. Therefore one cannot determine the configurations on the basis of the the H,H-coupling constants only, not even for the *cis* isomers. The *trans* isomers are more difficult since the 2-substitution can only push the dioxane moiety toward a boat conformation and its effect need not to be seen in the values of the coupling constants at all. The remaining means to ascertain the configurations is to utilize the NOE effects between the protons at C-2, C-4, and C-6.

First the normal 2D COSY spectra and then the 2D NOE correlations were measured. The former were necessary to enable correct interpretations of the latter because of traces of coupling correlations.

The protons at C-2. C-4, and C-6 were well separated from each other which made the interpretation of 2D NOESY straightforward. Compounds **3**, **7**, and **8** gave clear NOE correlations between 2- and 6-protons and hence the C-2 methyl group is equatorial in all of them . However, in **9** there was no NOE between the respective protons as could be expected since according to the values of its H,H-coupling constants it exists in the *O-out* conformation. The latter also show that the C-4 methyl group must be equatorial. Furthermore there was a clear NOE correlation between the 2- and 4ax-protons which is only possible when the C-2 methyl group is also equatorial. The *trans* derivatives were studied in the same manner. Compounds **4** and **10** gave clear NOE correlations between H-2, H-4, and H-6. On the other hand **11** gave a correlation between its 2- and 6-protons and the C-4 methyl group. Hence **4**, **10**, and **11** all have an equatorial methyl group at C-2. 2D NOESY was also utilized for assigning the methyl signals of **5** and **6**.

^{13}C spectra.

The ^{13}C chemical shifts are collected in Table 3. The signals were assigned using two-dimensional carbon,carbon double quantum coherence INADEQUATE.[7] Unfortunately, the experimental limitations forced us to use so low digital resolution (8 Hz) that exact values of the direct ^{13}C-^{13}C-coupling constants cannot be reported but they are around 35 Hz between the ring carbons and around 50 Hz between the ring and methyl carbons. The experimental chemical shifts are in good agreement with the estimated ones (Table 3). The estimates were based on substituent effects obtained from an earlier work[6] on methyl-substituted 1,3-dioxanes.

However, the 1,3-dioxane ring itself could not be taken as the parent compound since the cyclohexane moiety causes also other shielding/deshielding effects than a simple 5,6-dimethyl substitution does. This is demonstrated in Table 3 by compounds **1**, **2**, and **9** where the calculation of the chemical shifts must be based on the assumption that the carbocycle can be treated as a dimethyl substitution. In this way the values estimated for the chemical shifts of C-2 in **1** and **2** are in close agreement with the observed values. This can be expected since only the δ-substituent effects, which in general are small, cannot be properly approximated. The chemical shifts calculated for C-4, C-5, and C-6 of **1** and **2** deviate already much more from the observed values because of the β- and γ-type effects initiated by the carbocycle but that cannot be properly estimated.

Table 3. ^{13}C NMR chemical shifts (in ppm) of 1,3-dioxadecalanes **1-11**.[a]

No	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	2e-Me	2a-Me	4e-Me	4a-Me
1	93.93	71.73	35.94	74.28	24.36	25.23	19.88	31.38				
	(94.14	73.48	33.69	75.18)								
2	93.61	71.09	41.36	81.00	25.76	24.65	24.18	31.09				
	(93.53	72.58	36.64	79.02)								
3	98.79	71.46	34.97	73.83	24.33	25.27	19.82	31.40	20.91			
	(98.99	71.58	35.02	74.13)								
4	98.74	71.40	40.41	80.72	25.62	24.70	24.21	31.16	20.67			
	(98.67	70.94	40.44	80.85)								
5	97.85	65.10	35.02	66.23	23.91	25.25	19.60	31.37	29.61	18.60		
	(98.10	65.11	35.22	66.55)								
6	98.27	64.96	41.05	73.45	25.82	24.93	24.46	31.77	29.76	19.02		
	(97.78	64.74	40.64	73.27)								
7	98.78	75.52	39.12	75.33	19.41	25.24	20.51	31.74	21.19		17.83	
	(98.84	74.53	39.22	75.38)								
8	91.32	73.93	38.66	69.21	26.55	25.78	20.22	31.47	21.36			16.74
	(91.29	73.22	38.31	68.81)								
9	91.55	70.21	40.88	74.00	26.49	20.97	25.12	25.28	21.51		19.33	
	(90.89	72.54	38.86	72.59)								
10	98.77	76.84	47.17	80.37	25.55	25.31	24.52	31.59	21.12		18.49	
	(98.24	76.47	47.30	79.94)								
11	91.19	71.88	43.65	74.22	26.68	25.73	24.64	32.20	21.42			13.14
	(90.97	71.10	43.58	74.52)								

[a] Calculated values in parentheses.

However, in all cases the relative magnitudes of the calculated chemical shifts are on line with those of the observed values thus confirming the configurations and conformations of 1 and 2.

The chemical shifts of C-9 form another nice configurational indicator since C-9 of 1 resonates at a 4.3 ppm higher field than that of 2 as can be expected because of the more shielding character of the (γ_{axial} + γ_{gauche})-effect in the latter than that of the γ_{anti}-effect in the former.[6] As to the chemical shifts of C-9 a similar shielding difference prevails for all isomer pairs (4.4 ppm for 3 vs **4**, 4.9 ppm for 5 vs **6**, 4.0 ppm for **10** vs 7, and 4.5 ppm for **8** vs **11**). A further indication for the configurational difference between **10** and **7** is the observation that C-7 resonates at a 6.1 ppm higher field in the latter. This is now due to the difference in the γ_{anti}- (**10**) and γ_{gauche}-effects (**7**) introduced by the C-4 methyl groups.[6]

The only compound with the O-out-conformation is **9**. In this case the deviations between the calculated (using the 5eq,6ax-diMe-substituted 1,3-dioxane as the model compound) and observed ^{13}C chemical shifts ranging from -0.7 (C-2) to +2.3 ppm (C-4) are comparable to those found for 1 and 2 above. The best indicator for the O-out conformation of **9** is, however, C-8, which is ca 4.3 ppm shielded in comparison with the situation, eg, in **7** in agreement with the axial character of C-4 in respect of C-8 in **9**.

For the other compounds the calculations were carried out by using the chemical shifts of the unsubstituted cis (1) and trans (2) derivatives as the parent values. The carbocycle was treated as a 4,5-dimethyl substitution when deciding which polysubstitution effects should be taken into account. The chemical shifts calculated in this manner for the chemical shifts of the dioxane ring carbon atoms deviate usually less than 0.5 ppm from the observed values. However, there are three exceptions: for C-4 of **7**, **8**, and **11** the δ(obs. - calc.) values are 1.0, 0.7, and 0.8 ppm, respectively. Obviously in all these cases there exist some small but definite extra deshielding increment most probably due to some interaction between the C-4 methyl and C-8.

The ^{13}C NMR chemical shifts of the methyl substituents are also closely related to the values which could be predicted in comparison with 1,3-dioxanes.[8]

^{17}O NMR spectra

The ^{17}O chemical shift of the parent compounds 1 and 2 support nicely their configurations and conformations. The shifts differences between 1 and 2 and between O(1) and O(3) in them are closely related to those of r-2-oxo,trans-4,cis-5-dimethyl- (**12**) and r-2-oxo,trans-4,trans-5-dimethyl-1,3,2-dioxathianes (**13**)[9] (Table 4; remembering the opposite numberings) indicating clearly cis (**1**) and trans (**2**) decalane type structures.

In compounds **3**-**6** almost the same deshielding effect (14-19 ppm) can be seen on both O(1) and O(3). Hence the β_{2eq}-effect has a dominating role whereas the second methyl substituent at C-2 has no significant effect [0.9 -(-1.6) ppm] or the β_{2ax}-effect and the geminal effect cancel each other (Table 4). The β-effects at O(1) may be slightly enhanced as can be understood in the light of the more biased nature of the trans isomers.

The effect of the equatorial C-4 methyl substitution can be seen by comparing the ^{17}O chemical shifts of **7** and **10** with those of **3** and **4**, respectively. The δ_{eq}-effect is very small as could be expected[9] whereas the β_{4eq}-effect is even larger than in 2-oxo-1,3,2-dioxathianes.[9] The substituent effects derived for the latter compounds were actually utilized for a proper assignment of the ^{17}O chemical shifts of **7** where O(1) is upfield from O(3).

Table 4. ^{17}O NMR chemical shifts (in ppm) of **1**-**13**.

No	O(1)	O(3)	No	O(1)	O(3)	No	O(1)	O(3)
1	45.8	24.1	**6**	84.0	57.6	**11**	75.9	75.9
2	64.6	45.8	**7**	66.7	60.0	**12**[a]	138.4	112.8
3	62.4	39.3	**8**	56.4	56.4	**13**[a]	152.9	131.3
4	83.1	57.7	**9**	76.2	78.1			
5	61.1	37.7	**10**	85.0	85.0			

[a] The numbering here has been reversed to help comparison.

The δ_{4ax}- and β_{4ax}-effects can be derived by comparing the ^{17}O chemical shifts of **8** and **11** with those of **3** and **4**, respectively. In both sets of compounds the δ_{4ax}- (ca -7 ppm) and β_{4ax}-effects (ca 18 ppm) are practically equal (Table 4) which shows that there are no significant polysubstitution effects.

Finally the ^{17}O chemical shifts of **9** show clearly that this compound must be in a different conformation, ie in the O-out form since by comparing the chemical shifts of both **7** and **9** with those of **1** it can be seen that the total deshielding effects in **9** are 10-18 ppm larger which can be explained by a difference in the parent structure only.

EXPERIMENTAL

The compounds were prepared conventionally from a carbonyl compound and a suitable diol as described earlier.[3,5,10] Five isomeric 2,4-dimethyl substituted derivatives could be separated from a product obtained by starting from a mixture of the corresponding cis and trans diols. They were separated on a Carlo Erba Fractovap Mod P preparative gas chromatograph using an Apiezon column at 130°C. Isomer **7** came out in 9.3 minutes, isomers **8** and **10** in 13 and 15 minutes (they could not, however, be separated), isomer **9** in 24 and isomer **11** in 29 minutes.

The NMR spectra were recorded on a JEOL JNM GX-400 spectrometer operating at 399.78 MHz for ^{1}H, 100.53 MHz for ^{13}C and 54.21 MHz for ^{17}O, respectively. All the spectra were taken in 5mm o.d. tubes in $CDCl_3$. The solvent deuterium signal was used for field locking. Internal TMS was the reference for ^{1}H and ^{13}C and external tap water for ^{17}O chemical shifts. The 90 degree pulses were the following: 5.5 µs for ^{1}H, 9 µs for ^{13}C and 22 µs for ^{17}O. We accumulated 8 scans for ^{1}H, 300 scans for ^{13}C and 4000 for ^{17}O (pulse delay 0.1 s, acquisition time 0.133 s). A 50 Hz exponential window was applied for FT of ^{17}O data.

The temperature was kept constant at 303 K during all the measurements. The concentration for ^{17}O and 2D-INADEQUATE measurements was 2 M. For 2D experiments we used known pulse sequences.[7] The digital resolution in COSY and NOESY was 2.5 Hz on both axis and in heteronuclear shift correlation 2.5 Hz for proton and 6Hz for carbon. The 2D-INADEQUATE matrix size was 4096 x 128.

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