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Reference Data

Configurations and Conformations of Some Methyl-Substituted 2,4-Dioxabicyclo[3.3.1]Nonanes

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Three dimethyl- and one trimethyl-2,4-dioxabicyclo[3.3.1]nonanes were prepared and their configurations and conformations were determined by means of multinuclear high-field NMR spectroscopy. Even at 400 MHz the proton spectra were so degenerate that several 2D experiments and, also, deuterium NMR had to be used to make the spectral analysis possible. ^{13}C and ^{17}O NMR spectra are also reported. The information obtained shows that two of the dimethyl derivatives are in boat–chair conformations with 3α9*syn* and 3α6α configurations, whereas the third dimethyl and the trimethyl derivative exist in chair–chair conformations with 3*β*9*syn* and 3*β*9*syn*9*anti* configurations.

Methyl-substituted 2,4-dioxa[3.3.1]nonanes Multinuclear NMR Configurational and conformational analysis Preparation

INTRODUCTION

Bicyclo[3.3.1]nonane and its substituted and heteroatom-containing derivatives can adopt several different conformations (I–IV in Scheme 1),[1] the position of the conformational equilibrium being dependent on the heteroatom and the size and configuration of the substituents. The pure carbocycle prefers the chair–chair conformation (I). Compounds with 3β or 7β substitution prefer chair–chair conformations, whereas 3α- and/or 7α-substituted compounds favour boat–chair (II), boat–boat (III) or chair–boat (IV) conformations in order to avoid 3,7- and 3,9-interactions.[2,3]

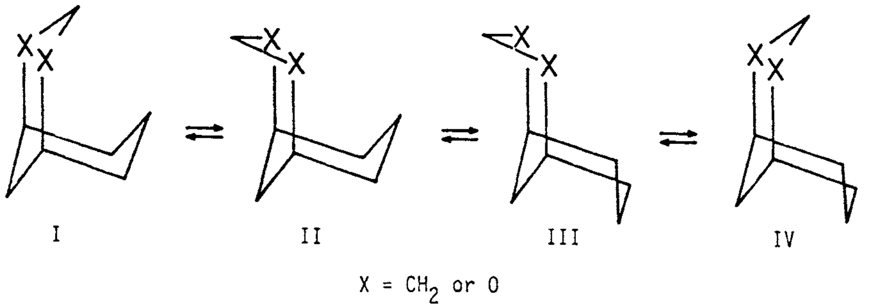
As a continuation of our study on the 3α- and 3β-methyl-2,4-dioxa[3.3.1]nonanes, in which the 3α-form exists in the boat–chair (II) and the 3β-form in the chair–sofa conformation,[1] we have investigated the configurations and conformations of two epimeric 3,9-dimethyl- and 3,9,9-trimethyl- and one 3,6-dimethyl-2,4-dioxabicyclo[3,3,1]-nonanes (1–4 in Scheme 2) by high-field ^1H,^2H, ^{13}C and ^{17}O NMR.

RESULTS AND DISCUSSION

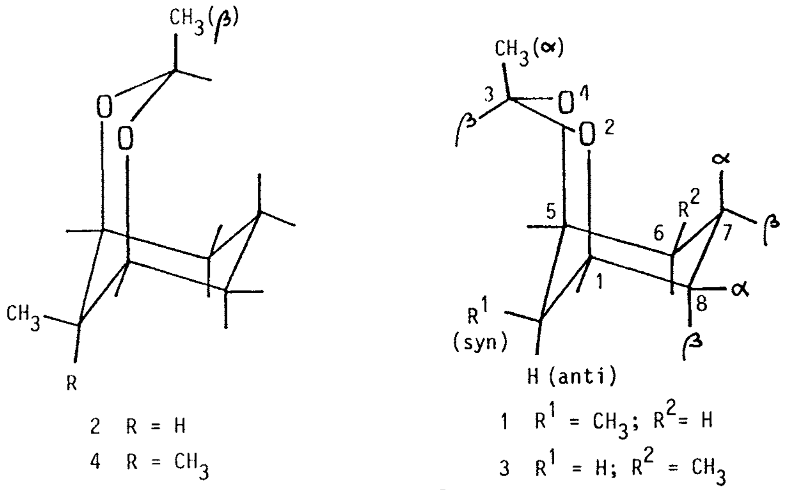
^{13}C NMR spectroscopy

The ^{13}C chemical shifts (Table 1) of C-3 for **1** and **2** parallel those of the 3-monomethyl derivatives,[1] and the ^{13}C chemical shift differences between **1** and **2** at C-7 and C-1 are comparable to those between 3α- and 3β-monomethyl derivatives. The deviations of the chemical shift differences at C-6(8) and C-9 between **1** and **2** from those of the 3-monomethyl derivatives are due to the bow-to-stern type interaction between the 3β-proton and the 9*syn*-methyl in **1**.

The ^{13}C chemical shifts of C-3 and C-9 of **4** differ very little from the corresponding



Scheme 1



Scheme 2

Table 1. ^{13}C **NMR chemical shifts in ppm**

	Carbon								
Compound	1	3	5	6	7	8	9	3-Me	Me
1	73.46	88.09	73.46	33.81	15.56	33.81	35.48	22.45	21.39[a]
2	72.33	91.97	72.33	30.29	20.60	30.29	33.69	22.91	16.50[a]
3	72.52	88.73	67.75	37.30	24.34	32.50	28.32	21.12	18.66[b]
4	76.31	91.97	76.31	25.37	19.02	25.37	33.08	23.79	22.64[a] 25.92[c]
3α-Me[d]	68.61	88.95	68.61	32.89	16.25	32.89	27.85	21.41	
3β-Me[d]	67.63	91.84	67.63	32.01	21.07	32.01	29.30	23.28	

[a] 9*syn*-Me.
[b] 6α-Me.
[c] 9*anti*-Me.
[d] See Ref. 1.

values for **2**. It is concluded[4,5] that **4** is a 3β-methyl epimer.

^1H NMR spectroscopy

The proton chemical shifts are shown in Table 2, but the vicinal coupling data (Table 3) of the protons at C-6 and C-8 are the most informative for the conformation of the carbocycle. The 1(5)-proton signal of **1** resonates as a broad doublet, showing signs of several small couplings. All the other coupling constants could be measured. The magnitudes of the 1,9*anti* (0.9 Hz) and 1,8β (0 Hz) couplings are reversed compared with those in the 3α-monomethyl derivative.[1] Since the coupling patterns were confirmed by decoupling experiments, the dihedral angle between the 1 and 9*anti* protons must be sensitive to the 9*syn*-methyl substitution. The *J* values (Table 3) show that the cyclohexane moiety is in a chair conformation. The conformation of the dioxane ring in **1** was defined by a 2D NOESY spectrum, which gives a clear NOE correlation between the 3β-proton and 9*syn*-methyl, in agreement with a boat–chair (II) system.

The proton chemical shifts of **2** could only be measured by natural abundance deuterium NMR. These values were then used as starting values for computer simulation/iteration, but our seven-spin simulation system was not sufficient to solve this eight-spin coupling pattern. Even decoupling experiments did not remove this dilemma. However, some coupling data (Table 3) could be obtained by the resolution enhancement technique. The 2D NOESY experiment yielded a clear NOE correlation between the 3α- and 7α-protons but no cross-peak could be detected for 3α–6α(8α) proton correlation. This and the coupling data show that **2** has the chair–chair conformation (I).

Similar problems were encountered in the proton spectrum of **4**. Deuterium NMR again yielded the chemical shifts, but only the 1,8α and 1,8β couplings (both 2.8 Hz) could be readily obtained. The 2D NOESY for **4** gave only a single cross-peak for the NOE correlation from the 3α-proton, between the 3α- and 7α-protons, and hence **4** also has the chair–chair conformation (I).

The spectrum of **3** in chloroform was degenerate but a well resolved spectrum was obtained in benzene. The coupling constants were consistent with a biased chair form for the cyclohexane ring. The C-3 configuration (3α) and the boat conformation of the dioxane moiety of the molecule were confirmed by 2D NOESY, which showed a clear NOE correlation between the 3β- and 9*syn*-protons.

^{17}O NMR spectroscopy

The ^{17}O chemical shifts are given in Table 4. It has been shown that β-effects are large and positive for 1,3-dioxadecalanes.[6] Here we are dealing with γ- and polysubstitution effects, but the data do not allow a detailed discussion. However, a comparison of the ^{17}O chemical shifts of **1** and **4** with those of the 3α- and 3β-monomethyl derivatives (Table 4), respectively, shows that the total effects due to the 9*syn*-Me or 9,9-Me_2 substitutions in these boat–chair of chair–chair forms are negligible.

Table 2. ^1H **NMR chemical shifts in ppm**

	Compound			
Proton	**1**	**2**	**3**[a]	**4**
1 (5)	4.09	3.64	4.31 (4.03)	3.56
3α	1.22	5.58	1.24	5.80
3β	5.40	1.10	5.41	1.48
8α (6α)	1.83	2.04	1.82 (0.98)	1.82
8β (6β)	1.37	1.69	1.39 (1.41)	1.79
7α	2.05	1.84	1.81	1.77
7β	1.39	1.68	1.40	1.58
9*anti*	1.32	1.14	1.32	0.64
9*syn*	1.32	1.47	2.64	1.50

[a] δ (5) and δ (6) in parentheses.

Table 3. Proton–proton coupling constants in Hz

Coupled protons	Compound			
	1	**2**	**3**	**4**
6,6	−13.4		6.6	
7,7	−13.4		−13.3	
9,9	7.3	6.8	−14.3	
1,9*anti*	0.9	1.6	0	
1,9*syn*			5.0	
5,6α	3.8	3.7	5.0	2.8
5,6β	0	3.7	1.5	2.8
6α,7α	5.0		4.8	
6α,7β	2.0		2.3	
6β,7α	13.4		13.3	
6β,7β	4.9		4.8	
8α,9*syn*			2.3	
1,7β	∼1		1.5	
1,5			1.5	

Table 4. ^{17}O NMR chemical shifts in ppm

Compound	O-2	O-4
1	60.0	60.0
2	54.7	54.7
3	52.0	65.1
4	69.6	69.6
3α-Me	60.5	60.5
3β-Me	69.1	69.1

Compound **2** (9*syn*-Me) shows a strong (−14.4 ppm) shielding effect in comparison with the 3β-monomethyl derivative. Comparison of the ^{17}O chemical shifts of **3** with those of the 3α-monomethyl derivative reflects the difference in the conformation of the cyclohexane moiety (biased chair vs sofa, respectively) by the diminished γ-effect (−8.5 ppm) at O-2 and in the low-field shift (+4.6 ppm) of O-4.

EXPERIMENTAL

Syntheses

2-Methyl cyclohexane-1,3-diol. A mixture of three isomers[7,8] was prepared by hydrogenating[7] 2-methylcyclohexane-1,3-dione[9] in the presence of Raney Ni catalyst at 120 °C and at 100 atm. The product gave two spots on TLC [silica *gel* G; $CHCl_3$–MeOH (5:1) and C_6H_6–EtOH (10:1)] and two peaks on GC (Carbowax 20M).

3,9-Dimethyl-2,4-dioxa[3.3.1]nonanes (1 and 2). A 2.6 g (0.02 mol) amount of the diol mixture described above was converted into 0.4 g of a 2:3 mixture of two isomeric dioxanonanes (**1** and **2**) with paraldehyde;[10] b.p. 88 °C/20 mmHg. Elemental analyses, % calc. (found): C 69.19 (69.37); H 10.32 (10.30); O 20.48 (20.25). The isomers were separated by preparative GC (110 °C, Fractonitril III). Unreacted diol was recovered.

4-Methyl cyclohexane-1,3-diol. The diol (11.2 g) was obtained by hydrogenating 4-methylcyclohexane-1,3-dione[11] (16 g) in 250 cm^3 of MeOH in the presence of Raney Ni catalyst at 120°C and at 100 atm; b.p. 120 °C/3 mmHg (solidified). The product showed two spots on TLC and three peaks on GC (see above).

3,6-Dimethyl-2,4-dioxa[3.3.1]nonane (3). A 6.5 g (0.05 mol) amount of the above diol was converted into the dioxane derivative[10] with paraldehyde; yield 1.8 g, b.p. 87 °C/20 mmHg. Part (3 g) of the unreacted diol was recovered. The major component (98%) of the product gave a single peak on six different GC columns. Elemental analyses, % calc. (found): C 69.19 (69.30); H 10.32 (10.15); O 20.48 (20.60).

2,2-Dimethyl cyclohexane-1,3-diol. This diol was obtained by hydrogenating 2,2-dimethylcyclohexane-1,3-dione (prepared by methylating 2-methylcyclohexane-1,3-dione[12]) as above;[13] b.p. 110–115 °C/1 mmHg (solidified). The product showed two spots on TLC and two peaks on GC (see above).

3,9,9-Trimethyl-2,4-dioxa[3.3.1]nonane (4). A 7.2 g (0.05 mol) amount of the above diol mixture was converted into the dioxane;[10] yield 0.7 g (5.5 g of the diol was recovered), b.p. 90–95 °C/6 mmHg. Elemental analyses, % calc. (found): C 70.55 (70.40); H 10.66 (10.79); O 18.80 (19.05).

NMR spectra

The NMR spectra were recorded on a JEOL GX-400 spectrometer operating at 399.78 MHz for ^{1}H, 100.53 MHz for ^{13}C, 61.37 MHz for ^{2}H and 54.21 for ^{17}O. All the spectra were recorded in 5 mm o.d. tubes using the solvent ($CDCl_3$) deuterium signal for field locking. The ^{2}D spectra were recorded in non-deuteriated solvents and without field lock. Internal TMS was the reference for proton, deuterium and carbon spectra. For ^{17}O spectra tap water was used as external reference. The 90° pulses were the following: 5.5 μs for ^{1}H, 14 μs for ^{2}H, 9 μs for ^{13}C and 22 μs for ^{17}O. The concentration for the ^{17}O samples was 2 M, and 5000 scans with a 0.1 s pulse delay and a 1.33 s acquisition time were accumulated. A 50 Hz exponential window was applied to the FT of the ^{17}O data.

The temperature in all measurements was kept at 303 ± 2 K. For 2D measurements JEOL standard pulse sequences were used. The digital resolution in the homonuclear COSY was 2.5 Hz on both axes. A sine-bell squared window was applied to the FFT of the homonuclear COSY. For the heteronuclear COSY 2.5 and 6 Hz digital resolutions were used for ^{1}H and ^{13}C, respectively. The FFT for shift correlated spectra was performed using sine-bell and normal exponential windows for ^{1}H and ^{13}C, respectively, To confirm the assignment of the ^{13}C and ^{1}H signals 2D COSY and 2D heteronuclear ^{1}H–^{13}C correlated spectra were recorded.

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