Stereochemical Aspects of Proton Chemical Shifts

VII.† The γ Effects of Hydroxyl, Methoxyl and Methyl Substituents

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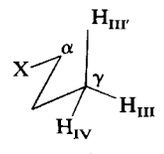
The ^{1}H NMR chemical shifts of some hydroxy, methoxy or methyl substituted *trans*-decalins, *trans*-1, 3-dioxadecalins and cyclohexanes are reported. It is concluded that the replacement in a g^+g^+ H—C—C—C—H fragment of one hydrogen by hydroxy, methoxy or methyl results in a modest (0.1 ppm) upfield shift of the other hydrogen atom. Experimental limitations to the transferability of shift increments from one molecular environment to another are demonstrated. The syntheses of 1α,5β-dimethoxy- and 1β,5α-dimethoxy-*trans*-decalin are given.

The changes in chemical shift of the γ protons on the replacement, in a three carbon unit C-α—C-β—C-γ, of an α-hydrogen atom by some other group X (OH, OMe, Me) are discussed in this paper. There are five distinct stereochemical relationships between X and the γ protons in the *anti* (1) and *gauche* (2) conformations of 1-X-propane. These are named as I, II, III, III′ and IV according to the nomenclature of Dunitz and Prelog.[2] The type III conformation has a *gauche*, *anti* torsion angle sequence. We use III and III′ when the group X is part of a *Gauche* and an *anti* four atom unit X—C—C—C′, respectively.



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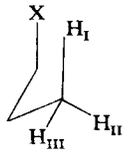

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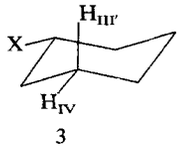
Because of rapid conformational averaging it is not possible to measure these γ-effects in 1-X-propanes directly. One can resort, however, to model compounds in which the conformational relationships are rigidly maintained. Incorporation of the propane unit into a cyclohexane ring allows the evaluation of the I, III (4) and III′, IV (3) effects. Effect II, however, cannot be determined.



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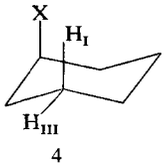

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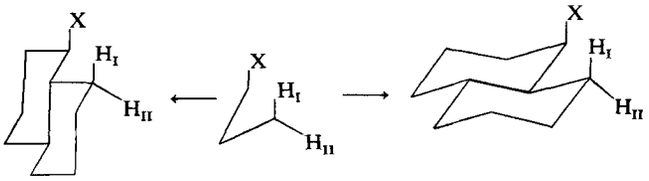
Effects III′ and IV are unimportant, being less than 0.1 ppm. I is an important downfield effect and effect III results in a sizeable upfield shift.[3,4]

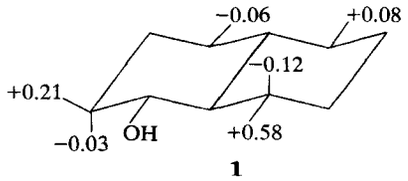
To our knowledge no systematic study of effect II has been undertaken. Gorrichon[5] has presented indirect evidence showing that, for X = methyl, it would be a fairly substantial upfield shift (−0.13 ppm). We have used the rigid *trans*-decalin skeleton to examine effect II; X can be in the 1-axial, as well as in the 1-equatorial, position (Scheme 1). The shift effects, in



Scheme 1. Effect II in *trans*-decalins.

ppm, of equatorial hydroxyl and methoxyl are shown in formulae **1** and **2**. For hydroxyl we observe an upfield effect II (−0.12 ppm) which is smaller than effect III[3] (−0.30), also upfield. The downfield effect I in **1** is somewhat larger (0.58 ppm) than in cyclohexane[3] (0.48 ppm). The data presented for **2** extend the above statements to the methoxyl substituent.

Unfortunately, the ^{1}H NMR spectra of axially substituted 1-hydroxy- and 1-methoxy-*trans*-decalin could not be unravelled. Symmetrical derivatives, e.g.



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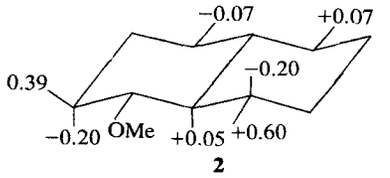

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† For Part VI, see Ref. 1.

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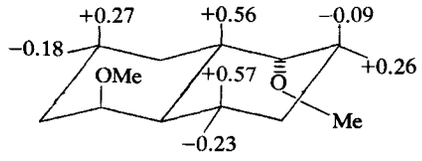

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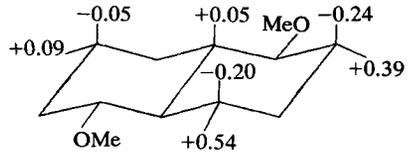

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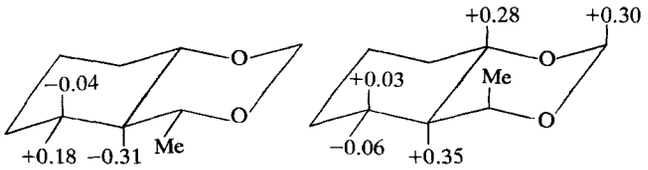
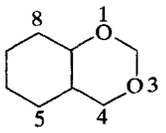
3, will obviously show a less complicated spectrum but unfortunately, of course, the changes in chemical shift reflect the conjugated effects of *two* substituents.

It is satisfying that effects I and II obtained from the axially substituted **3** and the equatorially substituted **4** are in excellent agreement with each other, and also with the data from the monosubstituted **2**. The diols corresponding to **3** and **4** are insoluble in carbon tetrachloride and a CW NMR spectrum could not be obtained.

To evaluate the methyl substituent effect we examined the dioxadecalins **5** and **6**, since we expect that even symmetrical methyldecalins will give spectra which are too complicated.

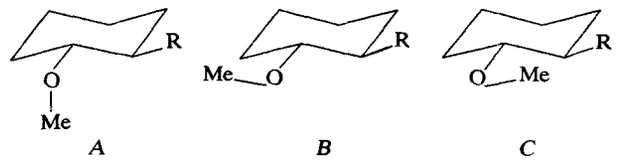


5 **6**



Effect I in **5** (+0.18 ppm) is somewhat less than that found in cyclohexane (+0.25 ppm), whereas effect I for hydroxy- and methoxy-decalins is slightly larger than that for cyclohexane. Effect II is upfield but is very small. Compound **6** is in serious disagreement with our expectations. The hydrogen atoms 2a and 9 show[6] the deshielding effect I fully (about +0.30 ppm) but H-5a has moved downfield by only +0.03 ppm! Here we are confronted with a clear cut deviation from our simple model of similar geometric changes being associated with similar shift effects. Effect II, on the other hand, is identical in **5** and **6**.

There are additional points which deserve brief comment. The hydroxyl and methoxyl rotamer populations may be different in cyclohexane and in decalin. However, the effect of the hydroxyl group on the shift of the vicinal hydrogen atoms H-2e, H-2a (β effects) in the decalin **1** and in cyclohexane[3] are nearly identical, suggesting that the hydroxyl group rotates quite freely. On the other hand, the methoxyl β effects in **2** and in cyclohexane do not compare well; the upfield shift of H-2a and the downfield shift of H-2e are more pronounced in **2**, and H-9, also an axial β proton, is



A *B* *C*

Figure 1. The rotamers of an equatorial methoxyl group.

displaced slightly downfield. Consider the methoxyl rotamers *A*, *B* and *C* (Fig. 1). In cyclohexane, $B \equiv C$. The sterically strained *C* rotamer will not be a significant conformation of **2**. The single *B* rotamer in **2** will be more populated than each of the two *B* forms in cyclohexane (this is true whatever the relative free energy content of *A* and *B*; however the change in population will be more important when the *B* conformation is the more stable, as is probably the case). As a consequence H-2e in **2** is more subject to the deshielding effect I than each of the two β equatorial protons in cyclohexane. In addition, the increased upfield shift of H-2a in **2** can be viewed as a manifestation of the now known effect II. Even the slight downfield displacement of H-9a, in comparison to cyclohexane, can be explained in a straightforward manner by the small increase in the *A* rotamer population. In the above reasoning we have neglected effects III′ and IV of the methoxyl group.

In cyclohexane, both axial and equatorial hydroxyl or methoxyl groups have a small upfield effect on the δ ring protons, especially on the equatorial proton. [In Ref. 3 a small downfield effect on H-4e is proposed for equatorial hydroxyl. Later work has in fact shown the reverse to be true (D. Danneels, Ph.D. Thesis, State University at Gent, Belgium, 1975).] In contrast, the hydroxyl group seems to have a *down*field effect on the δ hydrogen atoms of a 3-equatorial methyl group. Data collected from the literature and supporting the above statement are displayed in Fig. 2. This observation was put to use for the assignment of H-4e and H-5e in **1** and **2**. The resonance of H-4e in **4** is exactly reproduced by addition of the γ and δ effects observed in **2**.

We have tacitly assumed that shift effects in a 1-X-propane unit are determined only by geometrical factors. What however is, in fact, the influence of

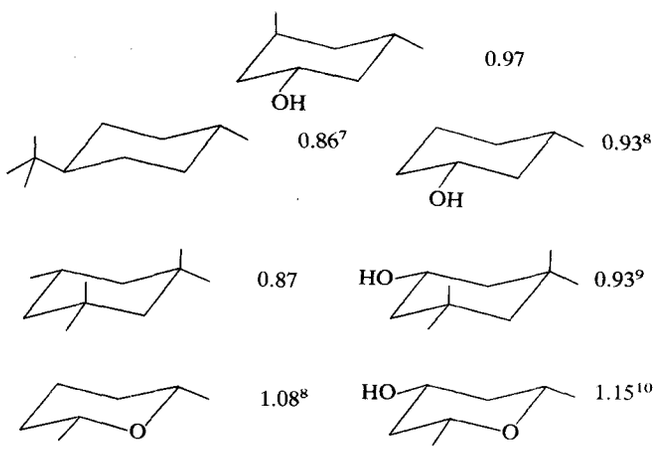
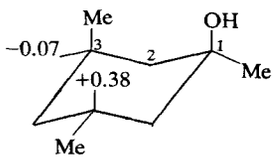


Figure 2. Methyl group chemical shifts in some methyl- and methyl,hydroxyl substituted hexacyclic compounds. (Superscripts are Reference numbers.)

additional substituents? One might for example imagine the upfield effects II and III and the downfield effect I to be entwined through sterically induced electronic distortion of the C—H_I bond. If H_I is replaced by a methyl group will the remaining hydrogens still be found at high field? Comparison of *trans*-1,3,5-trimethylcyclohexane[4] and *trans*-1,3,5-trimethylcyclohexan-1-ol (**7**) shows that effect III on H-3 is much reduced (−0.07 ppm), whereas the downfield effect I on the axial H-5 has the expected value (+0.38 ppm). There are some caveats and punctilios here. The hydroxyl group in H—O—C(—Me)—CH_3 (tertiary OH) and in a simple cyclohexanol (secondary OH) may have different shift effects.[1] Also, the inverted chair form, where H-3 suffers a downfield effect I, must contribute somewhat to the properties of **7**. Yet, the conclusion



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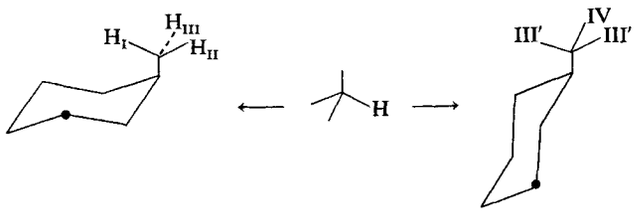
seems warranted that replacement of H_I by methyl has largely annihilated the upfield effect III. Additional substituents should be treated with caution when stereochemical information is sought. The following example should be considered. The axial and equatorial conformer of methylcyclohexane can be formally derived from isobutane by the addition of a three carbon chain (Scheme 2).



Scheme 2. Shift effects contributing to the axial and equatorial methyl resonance.

The propanic shift effects of the newly introduced carbon atoms (one of them is dotted in Scheme 2) are (a) equatorial methyl, small; (b) axial methyl, (i) downfield effect I (ii) upfield effect III which compensates effect I[3] and (iii) upfield effect II. An axial methyl would therefore be expected to absorb upfield from an equatorial group, but experimentally the opposite is the case where δMe ax > δMe eq > δMe in isobutane. (This sequence is based on shift data collected in Refs 11 and 4). The discrepancy could be due to the axial methyl being subjected to two *gauche* C—C—C—C interactions. It would be interesting to know the chemical shifts of the methyl groups in *anti*- and *gauche*-butane.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian HR-300 MHz spectrometer, operating in the CW mode, for 5 vol. % solutions (CCl_4) at 18 °C, with internal TMS as reference. The compounds were purified by preparative gas chromatography. The samples were not degassed. The spectra were assigned by double resonance and, in some cases, checked by calculation (SIMEQ 16/II). Coupling constants are in Hz.

trans-Decalin: δ: 1e(1.55) 1a(0.93) 2e(1.68) 2a(1.23) 9(0.87) See also Ref. 12.

2 δ: 1a(2.60) 2e(2.07) 2a(1.02) 8e(2.15) 8a(0.73) 4e(1.48) 5e(1.62) 9(0.92±0.02) 6e(1.68) 3e,7e(1.73) 7a(~1.21) 6a,3a(1.19) 4a,5a,10(0.92±0.02). J(1a, 2e) = 4.2; J(1a, 9) = 9.2; J(2e, 2a) = −11.7; J(2e, 3e) ~ J(2e, 3a) ~ 3.2.

1 δ: 1a(3.06) 2e(1.89) 2a(1.20) 8e(2.13) 8a(0.81) 4e(1.49) 5e(1.63) 9(~0.81) 10,4a,5a(~0.95) 6e, 7e(1.68; 1.70), 6a,7a(1.22, 1.24). J(1a, 2e) = 4.2; J(1a, 9) = 9.0; J(1a, 2a) ≈ 10.

4 δ: 1a(2.65) 2e(2.07) · 2a(0.99) 3e(1.77) 3a(1.18) 4e(2.09) 4a(0.73) 9(0.92) OMe(3.24). J(1a, 2e) = 4; J(1a, 2a) = 10.5; J(2e, 2a) = 11.7; J(2e, 3e) = J(2a, 3e) = 3.2; J(1a, 9) = 9.5; J(4a, 10) = 11.7.

3 δ: 1e(3.09) 2e(1.94) 2a(1.14) 4e(1.32) 4a(1.50) 9(1.43) 3e, 3a(1.50) OMe(3.22).

trans-1,3-*Dioxadecalin*: δ: 4e(3.81) 4a(3.18) 5e(1.45) 5a(0.85) 6e(1.68) 6a(1.32) 7e(1.81) 7a(1.32) 8e(1.85) 8a(1.32) 9(3.09) 10(1.49) 2e(4.88) 2a(4.58).

5 δ: 2e(4.88) 2a(4.63) 4a(3.23) 5e(1.63) 5a(0.81) 6e(1.68) 6a(1.28) 7e(1.78) 7a(1.28) 8e(1.93) 8a(1.32) 9(3.05) 10(1.18).

6 δ: 2e(4.61) 2a(4.88) 4e(3.95) 5e(1.39) 5a(0.88) 6e(1.68) 6a(1.27) 7e(1.77) 7a(1.27) 8e(1.87) 8a(1.27) 9(3.37) 10(1.84).

7 δ: 2e(1.42) 2a(1.43) 3e(1.95) 4e(1.44) 4a(1.07) 5a(1.99) 6e(1.57) 6a(0.96) 1-Me(1.14) 3-Me(1.14) 5-Me(0.88). J(3e, 4a) = 5.0; J(4e, 4a) = −13.2; J(4a, 5a) = 11.2; J(5a, 6a) = 11.0; J(6e, 6a) = −13.2; J(*H*-3, 3-Me = 7.4; J(J-5, 5-Me) = 6.8.

The compounds studied were prepared according to literature procedures or were available from earlier work; **3** and **4** are new compounds.

1α,5β-Dimethoxy-*trans*-decalin (3)

1α,5β-Decalindiol was prepared by the stereospecific reduction of 1,5-*trans*-decalindione with dicyclohexylborane.[15] A diglyme solution of dicyclohexylborane was prepared from 16.4 g (0.2 mole) cyclohexene, 2.85 g (0.075 g) sodium borohydride and 12 ml boron trifluoride etherate.[15] To this solution 3 g (0.018 mole) of *trans*-1,5-decalindione were added gradually. The mixture was stirred for 24 h. Under stirring and cooling, 8 ml water, 22 ml 3N sodium hydroxide and then 22 ml perhydrol (30%) were added. The aqueous layer was saturated with potassium carbonate, the diglyme layer was separated and the aqueous layer extracted twice with chloroform. Evaporation of the combined organic layers and recrystallization from isopropyl alcohol afforded 200 mg (6%) of the pure 1α,5β-*trans*-decalindiol, m.p. 178 °C (Kofler hot stage apparatus). Treatment with diazomethane[14] gave **3**,

isolated as a liquid by gas chromatography. $C_{12}H_{22}O_2$. % C (72.98), % H (10.98), % O (16.12) Calc. see **4**. IR absorptions, cm^{-1}: 800, 814, 825, 870, 920, 1010, 1044, 1055, 1086, 1097, 1155, 1275.

1β,5α-Dimethoxy-*trans*-decalin (4)

1β,5α-Decalindiol[13] was prepared by equilibration of 1,5-decalindiol. Commercial 1,5-decalindiol (5.1 g, 0.03 mole), 3.5 g (0.06 mole) acetone, 8 g (0.04 mole) aluminium isopropoxide and an excess of dry isopropyl alcohol were boiled for 5 h. Acetone and isopropyl alcohol were distilled off and the residue was acidified with 2N sulphuric acid. Extraction with choloroform, evaporation and crystallization from isopropyl alcohol afforded pure 1β,5α-decalindiol. The reaction of this diol with diazomethane[14] gave **4** quantitatively.

$C_{12}H_{22}O_2$: % C (72.73), % H (11.08), % O (16.19). Calc. 72.68; 11.18; 16.13. IR absorptions, cm^{-1}: 428, 582, 840, 888, 927, 990, 1011, 1090, 1108, 1140, 1182, 1200, 1236, 1257, 1340. M.p. 42–43 °C.

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