Conformational and Long-range Low Field Steric Deuterium Isotope Effects on Carbon Chemical Shifts

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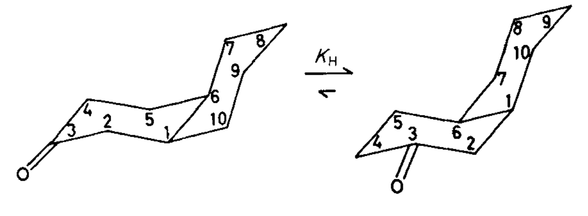
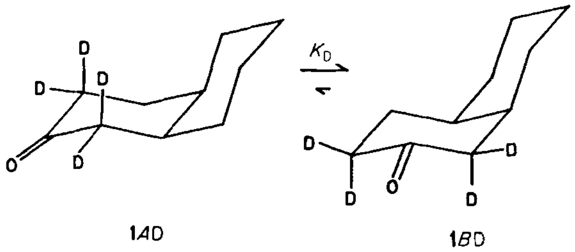
Comparison of the room and low temperature (203 K) ^{13}C NMR spectra of 3-*cis*-bicyclo[4.4.0]decanone and its 2,2,4,4-tetradeuterio isotopomer provides information about the deuterium isotope effect on the conformational equilibrium in this compound. Four-bond low field deuterium isotope effects on some carbon chemical shifts are observed. These effects can be used for unambiguous assignment of the ^{13}C lines to carbon atoms in alicyclic compounds.

Deuterium isotope effects have been used in ^{13}C NMR spectroscopy since the very first experiments on the recording of ^{13}C NMR signals.[1] Specific deuteration is a useful technique for the assignment of ^{13}C signals to deuterated carbon atoms,[1,2] and also to the carbons in β-position to deuterium, due to the high field intrinsic isotope effects of approximately 0.1 ppm.[3] Quite long-range deuterium isotope effects have sometimes been observed with modern instrumentation.[4] These effects were explained by Anet as equilibrium chemical shift isotope effects,[5] caused by the slightly different equilibrium constants between the equilibrating species in the protio and deutero compounds. Quite large splittings have been observed in various rapidly equilibrating carbonium ion systems due to the large chemical shift differences (>200 ppm) between the exchanging nuclei.[6] In neutral compounds these differences are much smaller (<10 ppm) and, therefore, quite high resolution is needed for the determination of these relatively small isotope effects in a conformational equilibrium. Nevertheless, isotopic perturbation of a degenerate conformational equilibrium was observed by Anet *et al.* in 1,1,3,3-tetramethylcyclohexane due to the different energies of the 1,3-diaxial interactions between the $CH_3—CH_3$ and $CH_3—CD_3$ groups.[7] In the present study we have measured the deuterium isotope effect caused by the different energies of the *gauche* interactions between the carbon atoms bonded to deuterium (D) or protium (H) nuclei. *gauche* Interactions are most important in the determination of conformations of aliphatic and alicyclic compounds, but have much lower conformational energies than the 1,3-diaxial interactions.



1*A*H 1*B*H



1*A*D 1*B*D

A mixture of 3-*cis*-bicyclo[4.4.0]decanone (**1**H) (*cis*-2-decalone) and its 2,2,4,4-tetradeuterio derivative (**1**D) was investigated. Compound **1** exists in a conformational equilibrium (**1***A* ↔ **1***B*) at room temperature, with conformation **1***B* being the more favoured; conformation **1***A* involves one additional hydrogen-mediated *gauche* interaction and is therefore less stable. This difference is sometimes termed as the 3-alkylketone effect.[8] From the spectrum taken under the conditions of slow exchange at 203 K, **1***B* is favoured with an equilibrium constant of $K_{203} = 1B/1A = 1.70$, corresponding to $\Delta G = 0.88\ \text{kJ mol}^{-1}$ ($0.21\ \text{kcal mol}^{-1}$) and leading to $K_{313} = 1.16$. Practically the same room temperature equilibrium constant can be calculated from the recent data on the 186 K spectrum of **1**.[9] Our measurements show that some assignments given in Ref. 9 for **1** should be changed (see Table 1).

An equimolar mixture of **1**H and **1**D was measured at room temperature for an estimation of the deuterium isotope effect on the conformational equilibrium **1***A* ↔ **1***B*. The effects on C-1,5,6,10 are connected with intrinsic isotope shifts. The expected splittings for C-7, C-8 and C-9, caused by the equilibrium isotope effect, must have nearly equal values, because the differences in the chemical shifts of these atoms in the two conformations have approximately the same values (Table 1, 5.9, 6.1 and 6.9 ppm, respectively). As can be seen in Table 2, only the line corresponding to C-8, which is separated by five bonds from the deuterons, is split by 0.02 ppm at room temperature. C-8 resonates at a lower field in the deuterium isotopomer of **1**, corresponding to a shift of the equilibrium towards **1***A* in the deuterated ketone

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Table 1. Carbon chemical shifts[a] of 3-*cis*-bicyclo[4.4.0]decanone (1) and *cis*-3-*cis*-bicyclo[4.4.0]decanol (2)

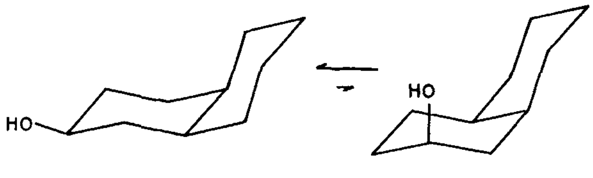
Compound and conformer	T (K)	C-1	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10
		Carbon atoms								
1H	313	38.8	45.5	39.5	29.0	35.3	28.6	23.3	24.1	29.2
1*A*H	203	37.7	42.3	37.4	32.3	34.8	24.9	26.6	20.0	31.1
1*B*H	203	39.4	48.3	41.5	27.2	34.6	30.8	20.5	26.9	26.4
2H	313	35.0	35.3	30.2	30.1	35.2	26.0	26.8	21.1	31.9

[a] In ppm from TMS.

by approximately 1%. This is caused by weaker *gauche* interactions in **1**AD as compared to **1**AH. The CD_2 group acts as if it were smaller than the CH_2 group.

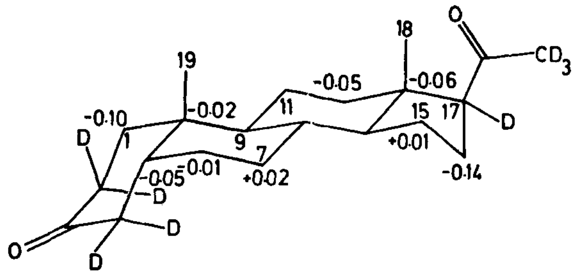
The puzzling lack of high field deuterium equilibrium effects on C-7 and C-9 can be explained by the existence of low field intrinsic four-bond deuterium isotope effects. The presence of these effects was confirmed from the spectrum taken under conditions of slow exchange. At 203 K the signal from C-8, which was split at room temperature, gives a single line, confirming the equilibrational origin of the splitting of the signal from C-8 under the conditions of fast exchange. Four-bond deuterium low field isotope shifts occur at conformationally well-defined positions, and are observed only at C-7 and C-9 of **1***A*. In **1***B* the deuterium-bonded carbon atoms C-2 and C-4 are not in *gauche* interactions with C-7 and C-9. The observed trends fit nicely the model of Cheney and Grant for calculating the steric γ-effects from the steric compression between the CH groups.[10] Since a CD_2 group is effectively smaller than a CH_2 group, this compression is smaller in the first case and a low field steric intrinsic isotope effect is expected.

The presence of low field deuterium steric intrinsic four-bond isotope shifts was also observed in a mixture of 2,2,4,4-tetradeuterio-*cis*-3-*cis*-bicyclo[4.4.0]-decanol and the undeuterated alcohol. In this case no cooling is needed, because conformation **2***A* is strongly favoured over **2***B* due to the strong 1,3 diaxial interaction in **2***B*. The content of the less stable conformer was in this case estimated as approximately 2.5%.[9] No equilibrium isotope effect is observed, therefore, on C-8, but the C-7 resonance is shifted by 0.02 ppm and C-9 by 0.01 ppm to lower field in the deuterated compound. A larger low field effect on C-7 is expected from the two *gauche* interactions with the deuterated carbon atoms. It follows from the deuterium isotope effects that some assignments given for **2** in Ref. 9 should be changed.



2*A* **2***B*

As another example, a mixture of 2,2,4,4,17,21,21,21-octadeuterio-5β,3,20-pregnanedione (**3**) and the undeuterated steroid was measured. The low field deuterium isotope shift (0.02 ppm) for one of the two close lines at 26.8 and 27.6 ppm enables one to reverse the original assignment of C-6 and C-7.[11] A low field isotope effect is also observed for C-15 (0.01 ppm), but is not measurable for C-9. Line broadening is evident for many lines of the steroid skeleton, but the resolution at 50.3 MHz is not high enough to measure the long-range 3- and 4-bond deuterium isotope shifts on C-9, C-11, C-14, C-18 and C-19.



3D

CONCLUSIONS

Deuterium substitution effects can be analysed in terms of intrinsic and equilibrium isotope shifts. Equilibrium isotope effects can be safely measured from the splittings of the ^{13}C NMR signals of carbon

Table 2. Deuterium isotope effects[a] on carbon chemical shifts of 3-*cis*-bicyclo[4.4.0]decanone (1) and *cis*-3-*cis*-bicyclo[4.4.0]decanol

Compound and conformer	T (K)	Two-bond		Three-bond		Four-bond		Five-bond
		C-1	C-5	C-6	C-10	C-9	C-7	C-8
1D−1H	313	−0.09	−0.08	−0.03	−0.06	0	0	0.02
1*A*D-1*A*H	203	−0.03	−0.08	−0.02	0	0.02	0.02	0
1*B*D-1*B*H	203	−0.08	−0.13	−0.04	−0.09	0	0	0
2D-2H	313	−0.17	−0.18	−0.03	−0.04	0.01	0.02	0

[a] In ppm.

atoms separated by at least five bonds from the deuterons. Long-range intrinsic low field four-bond deuterium isotope effects indicate the presence of *gauche* conformations with the participation of deuterons. Long-range isotope effects are useful for the assignment of ^{13}C NMR spectra.

EXPERIMENTAL

All spectra were recorded on a Bruker CXP-200 spectrometer at 50.3 MHz. Samples were examined as 5–10% w/w solutions in a mixture of $CHCl_3$ and CD_2Cl_2 in 5 or 10 mm o.d. tubes. Mixtures of deuterated and undeuterated compounds with different ratios of the isotopomers were measured. The typical resolution was approximately 0.3 Hz (0.006 ppm). For the determination of small splittings, narrow spectral windows (~300 Hz) and 32 K FT were used. The radiofrequency pulse width was 6 μs, which corresponds to a 30° flip angle. Approximately 1000 scans were accumulated for the FT measurements.

Compound **1** was prepared from commercially available **2**. **2D** was prepared from **1D** by the action of $LiAlH_4$. Compound **3** was commercially available (Calbiochem). The deuterated ketones were prepared according to Ref. 2.

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