

CHEMICAL SHIFTS IN THE NMR SPECTRA OF SUBSTITUTED CYCLOHEXANOLS

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FOR some years it has been known¹ that the NMR signal for axial protons in substituted cyclohexanes² is found at higher field than the signal for corresponding equatorial protons. This result has been rationalized in terms of diamagnetic anisotropy of carbon-carbon bonds³ following a treatment proposed by McConnell⁴. More recently it has been claimed⁵ that the chemical shifts for 21 different substituted cyclohexanols may be consistently interpreted in terms of carbon-carbon bond anisotropy (with regard to magnetic susceptibility) using appropriate parameters. Cyclohexane derivatives are inherently suitable for studies of this type, since their conformations are well understood² and, in many cases, rigid so that the distances between atoms and bonds within the molecule can be computed readily.

¹ R.U. Lemieux, R.K. Kullnig, H.J. Bernstein and W.G. Schneider, J. Amer. Chem. Soc. **80**, 6098 (1958).

² For nomenclature and general background, see E.L. Eliel, Stereochemistry of Carbon Compounds Chap. 8. McGraw-Hill, New York (1962).

³ See L.M. Jackman, Applications of NMR Spectroscopy in Organic Chemistry Chap. 7. Pergamon Press, London (1959).

⁴ H.M. McConnell, J. Chem. Phys. **27**, 226 (1957).

⁵ J.I. Musher, J. Chem. Phys. **35**, 1159 (1961).

We have now examined the NMR spectra of 36 substituted cyclohexanols available in our laboratory, 26 of these different from those previously examined by Musher. The chemical shifts for the carbinol protons in these compounds expressed in cps at 60 Mc/sec downfield from tetramethylsilane are listed in Tables 1 and 2. Table 1 contains data for compounds in which the hydroxyl group is largely or entirely equatorial (and the carbinol proton therefore axial) whereas Table 2 has data for carbinols with predominantly or entirely axial hydroxyl groups and therefore equatorial carbinol protons. Listed in parentheses in the two tables are the data of Musher converted to cps and corrected by a downfield shift of 3 cps to take into account the difference of reference signals (hexamethyldisiloxane in Musher's case, tetramethylsilane in ours).⁶ It is of interest that the chemical shifts of the carbinol protons cover a range of over 100 cps and that there is appreciable overlap between the range of the axial protons (145-225 cps) and that of the equatorial protons (198.5-249.5 cps). In trying to fit our data with the theoretical calculations of Musher⁵ we noted two especially serious discrepancies. One is concerned with the effect of an axial methyl group on an axial proton (entries 8 vs. 20, 12 vs. 8, 13 vs. 6) for which Musher (and, in fact, any treatment^{3,4} based solely on carbon-carbon bond diamagnetic anisotropy) predicts a shielding (amounting to 10 cps), whereas experimentally a deshielding effect of about 10 cps is observed. The other major discrepancy is quantitative in nature: an equatorial 2-methyl group exercises about 4 times the predicted shielding effect of 7 cps (entries 16 vs. 1, 11 vs. 7). There are also other, less

⁶ In some cases, the experimental agreement between our data and Musher's is poor. Our chemical shifts are averaged from repeated up- and down-field scans using at least two different sidebands from a calibrated audio-oscillator for each compound and with the possible exception of entries 10, Tables 1 and 2 (where only a few scans were made) are reproducible to ± 1 cps. There is, however, in some cases, an uncertainty of 1-2 cps as to the exact location of the band center. Cf. ref. 12.

TABLE 1

Chemical Shifts of Carbinol Proton in Equatorial Cyclohexanols^a

Entry	Cyclohexanol	- ν observed ^b	- ν calculated ^c	
			A	B
1	<u>trans</u> -4-t-butyl	202(210.5)	200	203
2	<u>cis</u> -3-t-butyl	206	200	-
3	<u>trans</u> -2-t-butyl	204	200	-
4	menthol	196(199.5)	193 ^d	196.5
5	<u>trans</u> -4-methyl	203(206)	200	203
6	<u>cis</u> -3-methyl	207(213)	200	207.5
7	<u>trans</u> -2-methyl	179(178)	180	178
8	<u>cis</u> -3,3,5-trimethyl	219	220	219.5
9	<u>trans</u> -2-isopropyl	195	193 ^d	195
10	2- α -cholestanol	219	220	-
11	<u>trans</u> -2- <u>trans</u> -6-dimethyl	145	160	150
12	3,3,5,5-tetramethyl	229	240	230
13	3,3-dimethyl	219	220	218
14	<u>trans</u> -2-ethyl	185	183 ^d	-
15	<u>cis</u> -2- <u>trans</u> -6-dimethyl	193	180(e) ^e 200(a) ^e	189.5(e) ^e 201(a) ^e
16	<u>trans</u> -2-methyl- <u>trans</u> -4-t-butyl	176	180	175
17	<u>cis</u> -2-methyl- <u>trans</u> -4-t-butyl	214	200	214.5
18	2,2-dimethyl- <u>trans</u> -4-t-butyl	187	180	186.5
19	2,2-dimethyl	192	180(e) ^e 200(a) ^e	189.5(e) ^e 201(a) ^e
20	<u>cis</u> , <u>cis</u> -3,5-dimethyl	209	200	209
21	<u>trans</u> -4-isopropyl	(209)	200	-
22	<u>trans</u> -2- <u>cis</u> -5-dimethyl	(181)	180	179.5
23	<u>trans</u> -2- <u>trans</u> -5-dimethyl	(208.5)	200(e) ^e 220(a) ^e	188.5(e) ^e 217.5(a) ^e
24	isomenthol	(225)	213(e) ^{d,e} 240(a) ^{d,e}	205.5(e) ^e -
25	<u>cis</u> -2- <u>cis</u> -5-dimethyl	(223.5)	200(e) ^e 220(a) ^e	219(e) ^e 230(a) ^e

^a For footnotes, see Table 2.

TABLE 2

Chemical Shifts of Carbinol Proton in Axial Cyclohexanols^a

Entry	Cyclohexanol	ν observed ^b	ν calculated ^c	
			A	B
1	<u>cis</u> -4-t-butyl	236(242)	240	237
2	<u>trans</u> -3-t-butyl	244	240	-
3	<u>cis</u> -2-t-butyl	249.5	240	-
4	neomenthol	241(241)	239 ^d	-
5	<u>cis</u> -4-methyl	233(234)	240(a) ^e 220(e) ^e	- -
6	<u>trans</u> -3-methyl	238(239)	240(a) ^e 220(e) ^e	241.5(a) 216.5(e)
7	<u>cis</u> -2-methyl	225(224)	220(a) ^e 200(e) ^e	225(a) 217.5(e)
8	<u>trans</u> -3,3,5-trimethyl	246	240	246
9	<u>cis</u> -2-isopropyl	240	239 ^d	-
10	2- β -cholestanol	243	240	-
11	<u>cis</u> -2- <u>cis</u> -6-dimethyl	208	200	208
12	<u>cis</u> -2-ethyl	228.5	230 ^d	-
13	<u>trans</u> -2-methyl- <u>cis</u> -4-t-butyl	214	220	214
14	<u>cis</u> -2-methyl- <u>cis</u> -4-t-butyl	220	220	220
15	<u>trans</u> -3- <u>trans</u> -5-dimethyl	241	240	241
16	2,2-dimethyl- <u>cis</u> -4-t-butyl	198.5	200	196
17	<u>cis</u> -4-isopropyl	(239.5)	240	-
18	<u>cis</u> -2- <u>trans</u> -5-dimethyl	(227)	220	224.5
19	neoisomenthol	(242.5)	239(a) ^{d,e} 240(e) ^{d,e}	- -

^a At 60 Mc/sec downfield from TMS in 10% CCl₄ solution, measured on a Varian HR-60 instrument.

^b Data in parentheses are from ref. 5 (see text).

^c See text.

^d Assuming reasonable distribution of the rotational conformations of the 2-alkyl groups.

^e The two entries correspond to the two possible chair conformations of the ring.

serious discrepancies. We feel that the present data clearly point up a limitation of the theoretical treatment of the chemical shift so far presented and call for a refined interpretation. One of us (J.B.S.) is presently searching for such an interpretation.

From the practical point of view, the shift parameters here established should be useful in structural and configurational assignments of naturally occurring cyclohexanoid alcohols, e.g. in the steroid and terpene series. In this connexion, it is of interest that two empirical correlations of our data have been developed. One of these is

$$-\nu = 240 - 20n,$$

where ν is the predicted shift under the conditions studied (10% CCl_4 solution, TMS standard, 60 Mc/sec frequency) and n is the number of "syn-axial" hydrogens of the carbinol proton under study, as shown in Fig. 1.

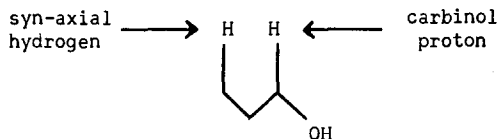


FIG. 1

"Syn-axial" hydrogens.

The shifts predicted by this formula are shown in Tables 1 and 2, column A, and in most cases come within 5 cps of the observed value, although in some cases the difference is greater. The formula has the advantage of requiring no empirical parameters, but it is only very approximate and probably not founded on any clear-cut theoretical principles.

A second, more accurate, correlation employs a set of empirical parameters, distinct for each alkyl group in each position with respect to each type of carbinol hydrogen. These parameters have been determined by a least squares analysis of the data for those compounds which exist entirely, or nearly so, in one conformation assuming that the effects of alkyl groups in

the various positions are additive. In this approach the shifts for the two conformations of cyclohexanol were treated as unknowns. Thus, the analysis provides a shift parameter for each alkyl group and for each of the cyclohexanol conformers. The parameters for the axial carbinol hydrogen (equatorial alcohols) are shown in Table 3 and those for the equatorial carbinol hydrogens (axial alcohols) in Table 4. In Tables 1 and 2, Column B gives the calculated values using these parameters in cases where enough

TABLE 3

Shift Parameters for Equatorial Cyclohexanols^a (in cps)

2-Me (eq.)	-28	2-t-Bu (eq.)	-2
2-Me (ax.)	11.5	3-t-Bu (eq.)	0
3-Me (eq.)	1.5	4-t-Bu (eq.)	-3
3-Me (ax.)	10.5	2-Et (eq.)	-21
4-Me (eq.)	-3	2-i-Pr.(eq.)	-11

^a These values are to be added to a base value of $-v = 206$ cps to obtain the predicted $-v$ (from TMS in 10% CCl_4 at 60 Mc/sec) for the equatorial cyclohexanol with the appropriate alkyl substituent.

TABLE 4

Shift Parameters for Axial Cyclohexanols^a (in cps)

2-Me (eq.)	-17	2-t-Bu (eq.)	7
2-Me (ax.)	-24	3-t-Bu (eq.)	2
3-Me (eq.)	- 0.5	4-t-Bu (eq.)	-5
3-Me (ax.)	5		

^a These values are to be added to a base value of $-v = 242$ cps to obtain the predicted $-v$ (from TMS in 10% CCl_4 at 60 Mc/sec) for the axial cyclohexanol with the appropriate alkyl substituent.

data are available to afford independent checks. The observed shifts are usually within 1 cps of those calculated, suggesting that the assumption of additivity of the shifts caused by alkyl substituents is a good one. This further suggests that any deformation of the cyclohexane ring from the

perfect chair form^{7,8} has little if any effect on the chemical shift of the carbinol proton in the cyclohexanols.

It is interesting to note that one can calculate a value for A_{OH} , the free energy of preference of the hydroxyl group for an equatorial vs. an axial position⁹ using the shift parameters obtained for the two conformations of cyclohexanol by this analysis and the observed shift of cyclohexanol¹⁰ under similar conditions. This leads to the value 1.07 kcal/mole which is in good agreement with that recently reported by Anet¹¹ although somewhat higher than other published values.^{2,7,10,12}

In the equatorial series, omitting the 2-isopropyl compounds for which there are not enough checks, seven parameters (for 2-, 3- and 4-Me and 4-t-Bu plus the base value) are used to correlate seventeen experimentally observed shifts; and in the axial series, six parameters correlate ten observed shifts. Clearly more data are required to establish the generality of these correlations and we hope that other investigations will be encouraged to apply the present approach to a much greater number of compounds.

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⁷ E.L. Eliel, J. Chem. Educ. **37**, 126 (1960).

⁸ J.-C. Richer, L.A. Pilato and E.L. Eliel, Chem. & Ind. 2007 (1961).

⁹ S. Winstein and N.J. Holness, J. Amer. Chem. Soc. **77**, 5562 (1955).

¹⁰ E.L. Eliel and M.H. Gianni, Tetrahedron Letters 97 (1962).

¹¹ F.A.L. Anet, J. Amer. Chem. Soc. **84**, 1053 (1962).

¹² A. Lewin and S. Winstein, J. Amer. Chem. Soc. **84**, 2464 (1962).