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THE ^{13}C-N.M.R. SPECTRA OF INOSITOLS AND CYCLOHEXANEPENTOLS: THE VALIDITY OF RULES CORRELATING CHEMICAL SHIFTS WITH CONFIGURATION

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ABSTRACT

The ^{13}C-n.m.r. spectra of the eight diastereomeric inositols and the ten diastereomeric cyclohexanepentols have been recorded and all of the signals have been assigned by a variety of methods. The additive empirical constants used to correlate the configuration of hydroxyl groups with the ^{13}C-chemical shifts differ, in the latter group, from those derived for the inositols; the removal of one hydroxyl group had altered the "rules" considerably. A better correlation was found between the spectra of the cyclohexanepentols and those of the inositols derived therefrom, in each case, by the addition of an equatorial hydroxyl group.

INTRODUCTION

When the ^{13}C-n.m.r. spectra of the sugars were first investigated, the cyclitols were initially studied as useful model compounds. The spectra of four inositols were fully assigned[1] and a system of empirical shielding parameters was derived in order to provide "rules" for estimating the changes in chemical shifts due to variations of the configuration at various points in the molecules. This method was then used to assist in the assignments of the ^{13}C-n.m.r. spectra of simple sugars[2], but it was only moderately successful. Que and Gray[3] used such rules on 1,5-anhydrohexitols, but obtained different values for the empirical parameters. Perlin and his collaborators[4,5] have used such rules extensively, but they introduced additional parameters. Paulsen and coworkers[6] found that the method gave satisfactory results when applied to 1,6-anhydrohexoses, but they, again, used different values for the empirical parameters.

These "rules" for configurational changes lack a theoretical basis and, despite their many applications, evaluations of ^{13}C-n.m.r. spectra by such rules are not always satisfactory and can lead to wrong assignments[7–10]. In order to find out whether the rules can be improved or suitably modified, we studied the ^{13}C-n.m.r.

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spectra of the cyclohexanepentols[11]. This is a particularly appropriate group of compounds, because the ten cyclohexanepentols constitute one of the largest all-known family of diastereomers in organic chemistry. Moreover, for each but one compound (the 1,2,3,4/5-isomer), only one of the chair forms needs to be considered because the other one, having one or several pairs of *syn*-axial hydroxyl groups, would be considerably less stable. We anticipated difficulties in assigning every resonance of each isomer; however, the chemical shift of the methylene carbon atom is unequivocal for each isomer, and it can be seen how it is affected by epimerization at any position, or combination of positions, in the cyclohexane ring. The opportunity was also taken to consider the ^{13}C-n.m.r. spectra of the four inositols which were not recorded in the 1970 paper[1] on cyclitols.

ASSIGNMENT OF CHEMICAL SHIFTS

A. Inositols

The spectra of four inositols were fully assigned by Dorman *et al.*[1]. During our work on complex formation of polyols with cations, we realized that one of their assignments was erroneous. The ^{13}C-n.m.r. spectrum of 3-*O*-methyl-*epi*-inositol[12] has a signal at δ 71.2 (originally assigned to C-3 of *epi*-inositol), but not at 67.8 (originally assigned to C-6) (Table I). On the other hand, in the spectrum of 6-*O*-methyl-*epi*-inositol[13], there is a signal at δ 67.4, but none at 71.1. The assignments of C-3 and C-6 therefore need to be reversed (and are shown thus in Table I). The

TABLE I

^{13}C SHIELDINGS OF THE INOSITOLS[a]

	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
scyllo-Inositol (135/246)	74.7	74.7	74.7	74.7	74.7	74.7
myo-Inositol (1235/46)	72.1	[73.2]	72.1	73.4	75.3	73.4
chiro-Inositol (125/346)	[72.6]	71.5	73.8	73.8	71.5	[72.6]
epi-Inositol (12345/6)	72.7	[75.5]	67.8	[75.5]	72.7	71.1
epi-Inositol, 3-*O*-methyl-	72.6	[72.6]	76.5	[72.6]	72.6	71.2
epi-Inositol, 6-*O*-methyl-	71.9	[75.3]	67.4	[75.3]	71.9	81.0
neo-Inositol (123/456)	70.3	[72.6]	70.3	70.3	[72.6]	70.3
muco-Inositol (1245/36)	73.2	73.2	71.0	73.2	73.2	71.0
allo-Inositol (1234/56)[b] (1)	72.7	71.1	71.1	72.7	70.5	70.5
allo-Inositol[c] (1a)	[75.3]	66.6	[75.6]	70.4	68.0	[72.8]
cis-Inositol (123456/0)[d]	68.9	[74.5]	68.9	[74.5]	68.9	[74.5]

[a]P.p.m. from Me_4Si. The original data[1] for the first four compounds were converted by using the factor 193.5 p.p.m. (ref. 8, p. 459). Square brackets denote carbon atoms bearing axial hydroxyl groups. In solution, *muco*-, *allo*-, and *cis*-inositols are 50:50 mixtures of the two chair forms; when their interconversion is fast on the n.m.r. time-scale, each signal represents the average of the signals of a carbon bearing an axial and a carbon bearing an equatorial hydroxyl group. [b]At 95°. [c]At −20°. [d]At 2°.

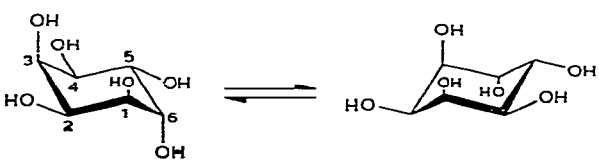
original assignments[1] were made by single-frequency proton decoupling. The signals of H-3 and H-6 overlap; under such conditions, the decoupling method gives ambiguous results.

Application of the Koch–Stuart method[14] of deuterium exchange to *myo*-inositol has recently shown[15] that the assignments of this inositol had also been in error. After 20-min treatment of *myo*-inositol with Raney nickel in deuterium oxide, the ^{1}H-n.m.r. spectrum showed that the signal of H-1 and H-3 (dd, $J_{1,2}$ 3, $J_{1,6}$ 10 Hz) had decreased to 38% of its original size; that of H-4 and H-6 (t, $J_{4,5}$ 10 Hz) still integrated at almost 2 H. In the ^{13}C-n.m.r. spectrum of this sample, however, the signal at δ 73.4 (originally assigned to H-1 and H-3) integrated at almost 2 C and that at 72.1 (assigned to H-4 and H-6) as ~0.7 C. Hence, these two assignments have to be reversed. Here, again, single-frequency proton decoupling led to erroneous assignments; although the two proton signals are clearly separated at 250 MHz, they overlap at 100 MHz.

The ^{13}C-n.m.r. spectra of the other inositols are now described (Table I). That of *neo*-inositol (1,2,3/4,5,6) could not be recorded in 1970 because of its very low solubility in water (0.1%). The Fourier-transform spectrometers can now cope with this difficulty. Because of its high order of symmetry, the spectrum of *neo*-inositol shows only two lines, in the ratio 2:1; their assignment is trivial.

The remaining isomers, *cis*- (1,2,3,4,5,6/0), *allo*- (1,2,3,4/5,6), and *muco*-inositol (1,2,4,5/3,6), each have two chair forms which are magnetically equivalent, being either identical or enantiomorphous. For each of them, a spectrum would therefore be expected which is the average of that of the two chair forms. However, the chair–chair inversion of *cis*-inositol is slow on the n.m.r. time-scale[16], presumably because each hydroxyl group has to pass between two *cis*-hydroxyl groups during this process. In fact, the ^{1}H-n.m.r. spectrum taken at ambient temperature shows separate signals for the axial and the equatorial protons[17]. Similarly, the ^{13}C-n.m.r. spectrum shows separate signals for the carbons bearing axial and those bearing equatorial hydroxyl groups; averaging does not occur at ambient temperature. (The same behaviour is shown by 1,2,3,4,5,6/0-hexamethylcyclohexane[18] and cyclohexane-1,2,3,4,5,6/0-hexacarboxylic acid[19].) To obtain sharper lines, the spectrum was run at 2°. The assignments were readily made by comparison with the spectrum of *epi*-inositol.

During the interconversion of the two chair forms (**1a** and **1b**) of *allo*-inositol, only two hydroxyl groups have to pass between two *cis*-hydroxyl groups. Nevertheless, this hindrance makes the interconversion slower than in most cyclohexane deriva-



1a 1b

tives[16]. At ambient temperature, the spectrum of *allo*-inositol was indistinct, indicating incomplete averaging; the temperature had to be increased to 95° in order to obtain a spectrum of three sharp lines. At −20°, in a 1:1 mixture of deuterium oxide and tetradeuteriomethanol, the spectrum of the separate chair forms was obtained as six sharp lines. Those at δ ~75 represent the two carbon atoms carrying the *syn*-axial hydroxyl groups, and the one at δ ~67 the carbon atom between them (see Discussion). Since the average values for pairs of carbon atoms are known from the 95° spectrum, the other member of each pair can readily be found. The chemical shifts are close to those expected from a comparison with those of *epi*-inositol (Table I).

muco-Inositol gives a spectrum of two lines, in the proportion 2:1, indicating rapid interconversion of the two chair forms; the assignments are trivial.

B. Cyclohexanepentols

All of the ten possible cyclohexanepentol isomers[11] were available for this study. Complete assignment of all signals in their ^{13}C-n.m.r. spectra is a difficult task; several methods were used, but ultimately some signals were assigned only tentatively (Table II). The assignment of the high-field signal in each spectrum to C-6 is, of course, unambiguous.

The best, wholly unequivocal, method for assigning ^{13}C resonances is by isotopic labelling. The use of deuteration for assigning ^{13}C resonances is based on the observation that conversion of C-H to C-D perturbs the substituted carbon atom so that it disappears from the n.m.r. spectrum[20] or appears as a small triplet[10,21]. The chemical shift of the deuterium-substituted carbon atom can therefore be assigned. In addition, carbon atoms β to the deuterium atom show small upfield-

TABLE II

^{13}C SHIELDINGS OF THE CYCLOHEXANEPENTOLS[a]

Cyclohexanepentol	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
135/24-	69.4	77.7	74.9	77.7	69.4	37.5
124/35- (4)	[69.1]	74.4	73.4	78.1	69.1	35.8
1235/4- (3)	67.2	[73.6]	72.5	75.0	70.0	34.6
15/234-	68.3	75.1	[73.4]	75.1	68.3	37.6
1245/3-	[71.0]	74.7	71.3	74.7	[71.0]	32.6
12345/0-	67.9	[74.2]	68.6	[74.2]	67.9	30.2
134/25-	69.8	75.4	71.8	[73.1]	[69.4]	34.2
123/45-	66.7	[73.6]	70.7	71.3	[68.6]	33.1
125/34-	67.2	[72.5][b]	[72.7][b]	73.0	68.7	34.3
125/34-, 5-*O*-methyl-	67.2	[72.4][b]	[72.5][b]	71.5	78.3	30.8
1234/5- (6)	[70.3]	71.4	[73.2]	74.6	67.2	34.4

[a]P.p.m. from Me_4Si. Square brackets denote carbon atoms bearing axial oxygen atoms. [b]Assignment uncertain.

shifts (0.02–0.17 p.p.m.) due to the "β-isotope effect"[10,22]. This method has been applied to 1,2,3,5/4-cyclohexanepentol.

2 3

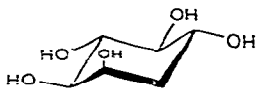
It was shown[23] that when 2,3,4,6/5-pentahydroxycyclohexanone (**2**) is dissolved in deuterium oxide, base-catalysed deuterium exchange occurs at different rates on the two carbon atoms adjacent to the keto group. We chose conditions so that almost complete exchange (~95%) occurred on one carbon atom, but only 75% on the other. Hydrogenolysis[24] then gave DL-1,2,3,5/4-cyclohexanepentol (**3**) fully deuterated at C-1, but only partially at C-5. The signal at δ 67.2 had almost disappeared from the spectrum and that at δ 70.0 had diminished; hence, these are the signals of C-1 and C-5, respectively. The spectrum of a mixture of the deuterated and an undeuterated sample (1 : 1) showed the signal at δ 73.6 as two equal lines (β-effect 0.06 p.p.m.) and that at 75.0 as two unequal lines (β-effect 0.07 p.p.m.); hence, these are the signals of C-2 and C-4, respectively. The signal of the methylene group showed a β-effect of 0.19 p.p.m. The only signal in the spectrum unaffected by deuteration, at δ 72.5, is therefore assigned to C-3.

The assignment of the spectrum of 1,3,5/2,4-isomer is quite easy, because the compound is symmetrical. Hence, the one-carbon resonance at δ 74.8 is that of C-3, and only the two two-carbon resonances need to be assigned. The one at higher field (δ 69.4) is assigned to the carbon atoms adjacent to the methylene group (C-1 and C-5). Although this assignment appears unequivocal, it was checked by the deuteration method. When 2,4,6/3,5-pentahydroxycyclohexanone was deuterated, as described above, and then reduced to the cyclohexanepentol[24], the signal at δ 69.4 did, indeed, disappear.

Since none of the other pentahydroxycyclohexanones are readily available, this method of assignment was not further pursued.

Another method of assigning ^{13}C resonances is by single-frequency proton decoupling[1], but the results are reliable only if the signals are well separated in the ^{1}H-n.m.r. spectrum. The spectrum of 1,3,4/2,5-cyclohexanepentol fulfils this requirement[25]. Each proton resonance was in turn selectively irradiated and the collapse of signals observed in the ^{13}C-n.m.r. spectrum, which was thereby fully assigned.

The ^{1}H-n.m.r. spectrum of 1,2,4/3,5-cyclohexanepentol (**4**) was also well resolved at 270 MHz [n.m.r. data (D_2O): δ 1.55 (ddd, $J_{1,6}$ 2.3, $J_{5,6}$ 12.2, $J_{6,6'}$ −14.0 Hz, H-6), 2.10 (dt, $J_{1,6'}$ 4.2, $J_{5,6'}$ 4.6 Hz, H-6'), 3.25 (t, $J_{3,4}$ 9.2, $J_{4,5}$ 9.3 Hz, H-4), 3.49 (dd, $J_{2,3}$ 9.7, $J_{1,2}$ 2.9 Hz, H-2), 3.56 (t, H-3), 3.76 (ddd, H-5), and 4.06 (q, H-1)]. Single-frequency proton decoupling allowed complete assignment of the ^{13}C-n.m.r. spectrum.



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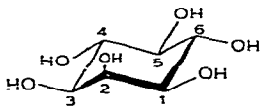

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Yet another method was used to assign the spectrum of 1,2,5/3,4-cyclohexanepentol, because its 5-methyl ether was available[26]. Its ^{13}C-n.m.r. data are shown in Table II. Methylation causes a downfield shift of ~10 p.p.m. of the signal of the carbon atom carrying the methoxyl group, and a smaller upfield shift of those of the two neighbouring carbon atoms[1]. The signals which have not altered on methylation are therefore those of C-1, C-2, and C-3; the one at δ 67.2 is obviously that of C-1, but the assignments of the other two are uncertain. The upfield and downfield shifts define the signals of C-4 and C-5.

The spectra of 1,2,3,4,5/0-, 1,5/2,3,4-, and 1,2,4,5/3-cyclohexanepentols are readily assigned. Since these compounds are symmetrical, the one-carbon signal is that of C-3; the two-carbon signals are assigned by comparison with the spectra of the 1,3,5/2,4-isomer and *epi*-inositol or 1,2,4/3,5-cyclohexanepentol, respectively (Table II). These conclusions were confirmed by comparing the spectra with those of monobenzyl ethers (which were the intermediates in their syntheses[26]). The ^{13}C-n.m.r. spectrum of 3-*O*-benzyl-1,2,4,5/3-cyclohexanepentol has signals at δ 32.3, 70.9 (2 C), 73.9 (2 C), 75.4, and 80.2 (CH_2Ph). The signal at δ 71.0 in the spectrum of the parent pentol had not shifted and therefore represents C-1 and C-5; that at 74.7 moved upfield and therefore represents C-2 and C-4. The spectrum of 1-*O*-benzyl-1,2,3,4,5/0-cyclohexanepentol has signals at δ 28.3, 67.8, 68.4, 70.9, 71.3, 74.5, and 75.1 (CH_2Ph). One of the carbon signals of the parent pentol at δ 67.9 had shifted downfield, and one at 74.2 upfield, confirming the assignment given in Table II.

The spectra of two cyclohexanepentols, the 1,2,3/4,5- and the 1,2,3,4/5-isomers, remained unassigned. The ^{1}H-n.m.r. spectrum of the former is not well resolved even at 250 MHz; in that of the latter, three of the proton signals overlap. It was hoped to make the ^{13}C assignments by the use of the rules correlating chemical shifts with configuration.

DISCUSSION

The empirical configurational rules predict the shielding effect on ^{13}C-chemical shifts of changing an equatorial to an axial hydroxyl group; the α-, β-, γ- and δ-carbon atoms are affected (the α-carbon is the one bearing the hydroxyl group).

First, the chemical shift of the methylene carbon atom was studied, comparing it for various isomers with that for the (all equatorial) 1,3,5/2,4-cyclohexanepentol, to obtain values for the β and γ effects. Dorman *et al.*[1] distinguished β^a and β^e shielding effects, depending on whether the carbon to be observed carries an equatorial or an axial hydroxyl group. In the present case, there is no hydroxyl substituent;

our β and γ values should be close to β^e and γ^e. An axial hydroxyl group on the β-carbon atom shifts the signal of the methylene carbon atom by −1.7 p.p.m. (upfield); one on the γ-carbon atom, by −2.9 p.p.m. Two identical configurational changes cause a shift more than double that caused by one: two axial hydroxyl groups on β-carbon atoms give a shift of −4.9, and two on γ-carbon atoms, −7.3 p.p.m. These effects are therefore not strictly additive. The δ effect is very small, as shown by 1,2,4,5/3-cyclohexanepentol.

When there are two axial hydroxyl groups far apart, their effect is approximately additive: in 1,2,3/4,5-cyclohexanepentol, the combined β and γ effects result in an upfield shift of 4.4 p.p.m.; but in the 1,3,4/2,5-isomer, with adjacent β and γ axial hydroxyl groups, the combined effect is hardly greater than that of a β hydroxyl group alone.

When the effect of the epimerization of a hydroxyl group on the other carbon atoms is considered, similar considerations apply, but there are some exceptions. The signal of the α-carbon atom shifts upfield by 2–4 p.p.m. When epimerization occurs at C-2, the result is quite predictable and the spectrum of 1,2,3,5/4-cyclohexanepentol could have been assigned on the basis of the configurational effects. However, when the axial hydroxyl group is introduced adjacent to the methylene group, there is no α-effect, and no γ-effect on the carbon atom on the other side of the methylene group (see the 1,2,4/3,5-isomer). This is surprising, because in cyclohexanols, with methylene groups on each side of the hydroxyl group, the α- and the γ-effects are larger than in cyclitols[2,7]. A somewhat similar case, however, is that of the carbon atom adjacent to the methylene group in pyranoses: *e.g.*, there is very little α-effect in going from xylopyranose to arabinopyranose[4] (C-4) or from sorbopyranose to fructopyranose[9] (C-5).

The α-effect is small ($\sim$1.5 p.p.m.) when the β-carbon atom carries an axial hydroxyl group, and negligible or even positive (downfield) when the γ-carbon atom bears an axial hydroxyl group.

The effect of inverting a hydroxyl group is small on a β-carbon bearing an axial hydroxyl group (Dorman *et al.*[1] gave −0.6) and strongly *downfield* on a γ-carbon atom bearing an axial hydroxyl group (Dorman *et al.*[1] gave +2.3 p.p.m.). This latter effect, coupled with the previously mentioned α effect, means that two *syn*-axial hydroxyl groups cause the carbons which bear them to appear further downfield than other carbons with axial hydroxyl groups; this is a feature that is readily recognized. More remarkably, the signal of the carbon atom between those carrying the *syn*-axial hydroxyl groups, if it bears an equatorial hydroxyl group, appears at exceptionally high field (see, for example, C-3 in *epi*-inositol); this, again, is diagnostically useful. Perlin and co-workers[4] noticed this effect and accounted for it by introducing a special *cis* effect. Paulsen also noticed this effect[6] and took care of it by using a very large value (−5.8) for β^e, unsuitable for some other compounds. It seems best to regard this *ax–eq–ax* situation as a special one. Other examples of it are found in the spectra of some methyl ketopyranosides[9]. The large upfield shift of the central carbon atom only occurs when it carries an equatorial hydroxyl group (the *ax–ax–ax* situa-

tion occurs in *muco*-inositol and in 1,6-anhydro-β-D-glucopyranose[4], and the shift of C-3 seems to be normal in each case); it is probably due to increased *gauche* OH–OH interactions.

In summary, it may be noted that the α-shielding effect is ~ −2 p.p.m., but it is smaller when the β-carbon atom carries an axial hydroxyl group, and it is negligible when the β-carbon atom has no hydroxyl group or the γ-carbon atom carries an axial hydroxyl group; β^e is ~ −2, but β^a is smaller; γ^e is ~ −2 and γ^a ~ +2.5 p.p.m. The signal of a carbon atom in the middle of an *ax,eq,ax*-triol sequence is shifted by ~ −7 p.p.m. Because of the wide scatter of the values, we refrain from defining them more closely.

By the use of these shielding effects, the ^{13}C spectrum of 1,2,3/4,5-cyclohexanepentol can be assigned (Table II). The two high-field signals certainly represent the carbon atoms adjacent to the methylene group; the low-field signal is undoubtedly that of C-2. However, the two signals at δ 70.7 and 71.3 are too close to each other for unequivocal assignment. These assignments were partially confirmed by the proton-coupled ^{13}C-n.m.r. spectrum of the pentol, in which the signals at δ 68.6 and 73.6 appeared as doublets ($^1J_{C-H}$ 148.9 Hz), confirming that they are signals of the carbon atoms carrying axial hydroxyl groups[5]. The other signals were doublets of quartets or doublets of quintets.

Application of these shielding effects to the spectrum of 1,2,3,4/5-cyclohexanepentol, however, does not lead to unequivocal assignments. Undoubtedly, the signal at δ 67.2 is that of C-5. Comparison with the 1,5/2,3,4-isomer indicates that the signal of C-4 is probably at δ 74.6, and that at 73.2 can then be assigned to C-3, one of the carbon atoms carrying the *syn*-axial hydroxyl groups. The other signals remain unassigned.

Another approach was therefore tried, in which the substitution effect was used instead of the configurational effect. Since introduction (or removal) of an *axial* hydroxyl group causes substantial changes in the ^{13}C spectrum, the spectra of the cyclohexanepentols were compared with those of inositols containing an additional *equatorial* hydroxyl group. Each cyclohexanepentol can be derived from one inositol by removal therefrom of an equatorial hydroxyl group; *e.g.*, removal of HO-4 (or HO-6) from *myo*-inositol (**5**) would give the 1,2,3,5/4-pentol (**3**); removal of HO-1 (or HO-3) would give the 1,2,4/3,5-pentol (**4**).

Table III shows a comparison of the spectra of nine cyclohexanepentols with those of the corresponding homomorphous inositols (for discussion of the 1,2,3,4/5-pentol, see below). In the pentols, C-1 and C-5 resonate at higher field by −3.2 to −5.3 p.p.m. (average −4.5), owing to the removal of the inductive effect of the oxygen atom from the neighbouring carbon atom. On going from inositols to pentols, the signals of C-2 and C-4 shift downfield by 1.0 to 3.0 p.p.m. (average +2.0) when these carbon atoms carry equatorial hydroxyl groups; this is probably an antiperiplanar effect[28]. However, when C-2 or C-4 carries an axial hydroxyl group, its signal is not substantially altered, the shift ranging from −1.3 to +1.0 p.p.m. The signal of C-3 is only slightly shifted (by 0.0 to +0.8 p.p.m.). These changes correspond well

TABLE III

CORRELATION BETWEEN THE ^{13}C-N.M.R. SPECTRA OF CYCLOHEXANEPENTOLS AND HOMOMORPHOUS INOSITOLS[a]

Pentol	*Chemical shift (p.p.m. from Me_4Si)*				
	C-1	*C-2*	*C-3*	*C-4*	*C-5*
1,3,5/2,4-inositol[b]	69.4 74.7 (−5.3)	77.7 74.7 (+3.0)	74.9 74.7 (+0.2)		
1,2,4/3,5-inositol[c]	[69.1] [73.2] (−4.1)	74.4 72.1 (+2.3)	73.4 73.4 (0.0)	78.1 75.3 (+2.8)	69.1 73.4 (−4.3)
1,2,3,5/4-inositol[c]	67.2 72.1 (−4.9)	[73.6] [73.2] (+0.4)	72.5 72.1 (+0.4)	75.0 73.4 (+1.6)	70.0 75.3 (−5.3)
1,5/2,3,4-inositol[c]	68.3 73.4 (−5.1)	75.1 72.1 (+3.0)	[73.4] [73.2] (+0.2)		
1,2,4,5/3-inositol[d]	[71.0] [75.5] (−4.5)	74.7 72.7 (+2.0)	71.3 71.1 (+0.2)		
1,2,3,4,5/0-inositol[d]	67.9 72.7 (−4.8)	[74.2] [75.5] (−1.3)	68.6 67.8 (+0.8)		
1,3,4/2,5-inositol[e]	69.8 73.8 (−4.0)	75.4 73.8 (+1.6)	71.8 71.5 (+0.3)	[73.1] [72.6] (−0.5)	[69.4] [72.6] (−3.2)
1,2,3/4,5-inositol[f]	66.7 70.3 (−3.6)	[73.6] [72.6] (+1.0)	70.7 70.3 (+0.4)	71.3 70.3 (+1.0)	[68.6] [72.6] (−4.0)
1,2,5/3,4-inositol[e]	67.2 71.5 (−4.3)	[72.5][g] [72.6] (−0.1)	[72.7][g] [72.6] (+0.1)	73.0 71.5 (+1.5)	68.7 73.8 (−5.1)

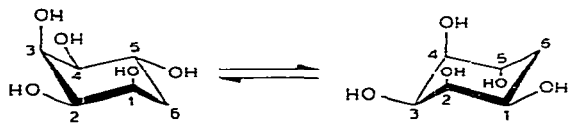
[a]Square brackets denote carbon atoms bearing an axial hydroxyl group. The differences between the chemical shifts of the pentols and the inositols are shown in brackets. For the symmetrical pentols, the equivalent mirror-image carbon atoms are not listed. The carbon atoms of the inositols are arranged so as to show the homomorphous relationship; their numbering is therefore not necessarily in accordance with the headings. [b]*scyllo*-Inositol. [c]*myo*-Inositol. [d]*epi*-Inositol. [e]*chiro*-Inositol. [f]*neo*-Inositol. [g]Assignment uncertain.

with those found in acyclic compounds[5]: on going from ethane-1,2-diol to ethanol, the signal of C-1 shifts by −4.6 p.p.m.; from propane-1,3-diol to propan-1-ol, by +1.9 p.p.m.

These changes, caused by an additional equatorial hydroxyl group, are more consistent than those predicted by the configurational rules. On the basis of such comparison with the homomorphous inositols, most of the signals in the spectra of the cyclohexanepentols could have been assigned. If the shifts caused by elimination of the equatorial hydroxyl groups are given the values −4.5 ±0.9 for the β-carbon, +2.0 ±1.0 for a γ-carbon with an equatorial hydroxyl group, 0 ±1.0 for a γ-carbon with an axial hydroxyl group, and 0.4 ±0.4 for a δ-carbon, correct assignments are obtained for all the signals of the 1,3,5/2,4, 1,2,4/3,5, 1,2,3,5/4, 1,5/2,3,4, 1,2,4,5/3, and 1,2,3,4,5/0 isomers. The assignments postulated for the 1,2,3/4,5 isomer are thereby confirmed and the signals of C-3 and C-4 are assigned. (The signal C-2 in the 1,2,3,4,5/0-isomer falls slightly outside the calculated range, but the assignment is nevertheless unambiguous.) The signals for C-1 and C-5 of the 1,3,4/2,5-isomer and

for C-2, C-3, and C-4 of the 1,2,5/3,4-isomer cannot be assigned unambiguously by this method, as they are too close to each other. However, the other signals in the spectra of these two pentols are correctly assigned.

The last isomer, 1,2,3,4/5-cyclohexanepentol, can now be considered. In contrast to all the other isomers, this compound is not overwhelmingly in one chair form. The calculated free-energy difference[29] between its two chair forms is only 1.9 kJ.mol^{-1}, and the coupling constants in its ^{1}H-n.m.r. spectrum show[12] that, in aqueous solution, it is a 4:1 mixture of the two chair forms, **6a** and **6b**. Chemical shifts have been calculated for each chair form. For **6a**, comparison with *epi*-inositol (1,2,3,4,5/6) and use of the above parameters gives the values (C-1 to C-5): 70.1–71.9, 68.8–70.8, 75.5–76.3, 73.7–75.7, and 65.7–67.5. For **6b**, comparison with *allo*-inositol (**1a**) gives the values: 65.0–66.8, 74.6–76.6, 66.6–67.4, 74.3–76.3, and 67.4–69.2. Combining these two sets of values in the proportion of 4:1 gives the values 69.1–70.9, 70.0–72.0, 73.7–74.5, 73.8–75.8, and 66.0–67.8. The experimental data fit into these ranges (C-3 being slightly outside it), giving the assignments shown in Table II. Although they appear to be unequivocal, it appeared desirable to check them. In the ^{1}H-n.m.r. spectrum of the pentol, the proton signals are not all separated, but those of H-2 and H-4 appear clearly at high field[12]. These signals were irradiated, and the resulting collapse of the signals in the ^{13}C-n.m.r. spectrum proved that C-2 indeed resonates at δ 71.4 and C-4 at 74.6.



6a 6b

Another table, similar to Table III, has been set up, comparing the spectra of the cyclohexanepentols with homomorphous inositols containing an additional *axial* (rather than equatorial) hydroxyl group. This table was incomplete, because, in two cases, the relevant inositol is *muco*-inositol, for which the individual chemical shifts are not known (only the averages of pairs of shifts, see Table I). The scatter of values is greater in this case than in Table III, *e.g.*, the shift of the β-carbon atoms varies from −4.2 to +0.6 p.p.m. This comparison appears to be of little value, and the table is therefore not reproduced here. Que and Gray[3] assigned the ^{13}C-n.m.r. spectra of the hexuloses by comparison with those of the 1,5-anhydrohexitols, deriving the former from the latter by addition of an *axial* hydroxyl group. More than one third of their assignments proved to be false[9].

CONCLUSIONS

The shift rules in consequence of configurational changes are a rather unsatisfactory method for assigning ^{13}C-chemical shifts. The shifts are sensitive to minor

structural and conformational changes, and the shift differences are by no means constant. Such a change as removal of one hydroxyl group alters the rules altogether. In the present instance, although the spectra of nine diastereomers had been assigned, the configurational rules did not enable us to assign that of the tenth isomer with confidence.

When such rules are used for the assignment of spectra (to save the very considerable time and effort involved in the application of better methods), several model compounds of assured assignment should be available for comparison. The structural and configurational change between the compounds with assigned and with unassigned spectra should be restricted to one carbon atom, and should not involve an axial hydroxyl group vicinal to, or *syn*-axial with, another axial hydroxyl group. Even then, the assignment may be uncertain for carbon atoms whose chemical shifts differ by only 1–2 p.p.m.

EXPERIMENTAL

Published procedures were used for the synthesis of *neo*-[30], *cis*-[31], *allo*-[32], and *muco*-inositol[33]; 1,3,5/2,4- and DL-1,2,3,5/4-cyclohexanepentol were prepared by hydrogenolysis of the corresponding inososes[11]. D-1,2,3/4,5-Cyclohexanepentol was a gift from Dr. G. E. McCasland (University of San Francisco); the syntheses of the other isomers are described in the preceding paper[26].

The n.m.r. spectra were recorded with a Varian XL-100 and a Cameca 250 spectrometer (in Grenoble) and with a JEOL JNM-FX-100 spectrometer (in Sydney) for solutions in deuterium oxide. Chemical shifts are in p.p.m. downfield from external tetramethylsilane; 1,4-dioxane (δ_C 67.4) was used as internal standard.

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