Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Spectra of Some Pentose and Hexose Aldopyranoses[1]

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Received July 18, 1969

Abstract: Natural-abundance ^{13}C spectra of selected pentose and hexose aldopyranoses are reported and discussed. The ^{13}C chemical shifts of these substances are shown to be heavily dependent upon the proximity of the substituents on the pyranose ring.

Various investigations[3-5] have evinced the utility of proton magnetic resonance (pmr) spectroscopy for establishing the configuration and conformation of carbohydrates in solution. Through applications of the Karplus relationship, the conformations of the pyranose forms of many of the common pentoses and hexoses in aqueous solution have been deduced. Although the proton resonances of the sugars are often heavily overlapped, it has been possible to identify many of them with the aid of double-resonance techniques. Furthermore, a system of empirical rules has been shown to be quite successful in the calculation of proton chemical shifts in pyranose rings.[3]

During studies of the ^{13}C nuclear magnetic resonance (cmr) spectra of the inositols[6] it was found that carbon chemical-shift differences could be explained in terms of steric hindrance or proximity effects. It was of interest to extend these studies to include those sugars which occur in aqueous solution in the form of the pyranose ring. It was anticipated that the ^{13}C spectra of such sugars would provide an experimental test of the method of calculating chemical shifts which resulted from the inositol study. Subsequent to the completion of this research, a study of the ^{13}C nmr spectra of carbohydrates was published by another group.[7] To the extent to which comparison is possible, the results of these two independent studies are in accord, though they differ slightly in experimental detail.

Experimental Section

Spectra of the carbohydrates were taken in aqueous solution (*ca.* 5 *M*) using the digital frequency spectrometer described previously.[8] 1,4-Dioxane (*ca.* 10%) was used as an internal reference. Sugars with unsubstituted anomeric hydroxyl groups were examined in mutarotational equilibria, and relative peak heights were used to distinguish the resonances of the carbons of the two anomers.

Proton decoupling was achieved either by noise decoupling[7,9] or by single-frequency decoupling.[8] While the latter method was more tedious, it yielded additional data which often proved valuable in the establishment or confirmation of resonance assignments.

The methyl glucosides were prepared and separated by standard literature procedures,[10] as was 3-O-methylglucose.[11] A sample of D-allose was generously provided by Professor S. J. Angyal. All other compounds were obtained from commercial sources and used without purification.

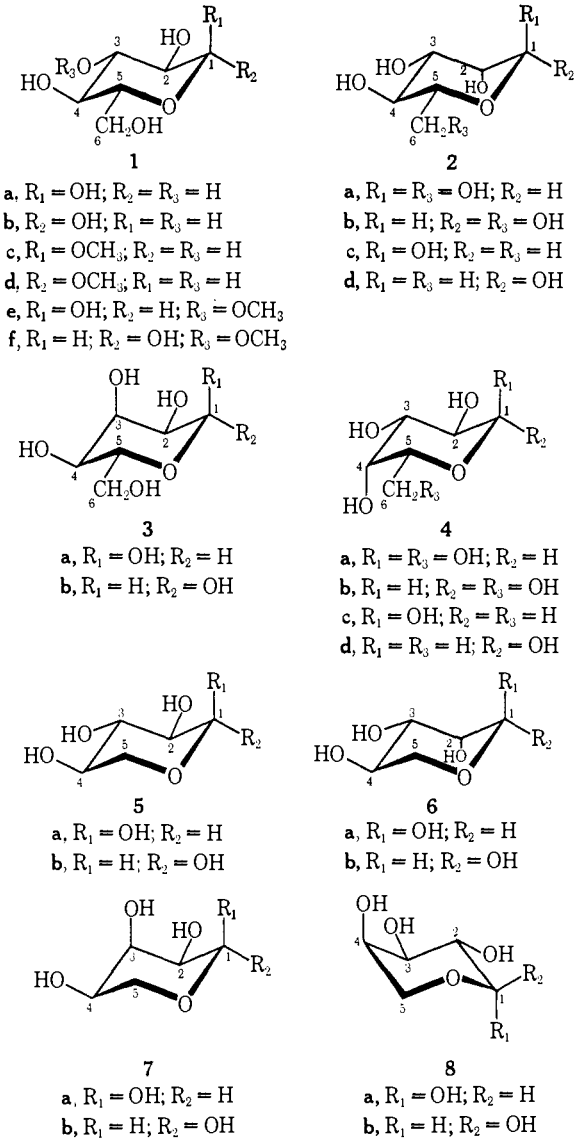
All chemical shifts in this paper are given in parts per million upfield from external carbon disulfide. On this scale, the chemical shift of 1,4-dioxane (10% in water) is 126.1 ppm.

Results and Discussion

Assignment of Resonances. The ^{13}C chemical shifts of the aldoses and aldose derivatives studied in this research are gathered in Table I. The assignments shown in this table are derived largely from correlations of the observed chemical-shift differences with those which would be expected from changes in configuration and conformation. These assignments have been extended and corroborated by comparison of the proton-decoupling frequencies (pdf) with the pmr spectra of these compounds, in those cases wherein the latter data are available.[3-5]

Throughout the series of hexoses studied (Figure 1), the resonances of the anomeric carbons are at substantially lower fields than those of the remaining pyranose carbons, and the identification of these resonances in each spectrum is therefore straightforward. In most cases, the sugars were studied as equilibrium mixtures of mutational isomers because the longer scanning periods required for natural-abundance cmr spectra precluded examination of solutions before mutarotation is well advanced. The published[4] data on the constitution of the equilibrium mixtures could often be used in conjunction with relative peak heights to distinguish the C-1 resonances of the α and β anomers. Identification of these resonances was corroborated by consideration of their proton-decoupling frequencies. In all cases, the proton-decoupling frequency associated with the C-1 resonance of the anomer in which the proton at carbon 1 is equatorial corresponded to the lower field proton in the pmr spectrum. This result is in agreement with the general fact that equatorial protons come

(1) Supported in part by Public Health Service Grant No. 11072-0607 from the Division of General Medical Services.
(2) National Institutes of Health Postdoctoral Fellow, 1967-1969.
(3) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966).
(4) S. J. Angyal, *Angew. Chem.*, **81**, 172 (1969).
(5) J. C. Jochims, G. Taigel, A. Seeliger, P. Lutz, and H. E. Driersen, *Tetrahedron Lett.*, 4363 (1967).
(6) D. E. Dorman, S. J. Angyal, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 1351 (1970).
(7) (a) L. D. Hall and L. F. Johnson, *Chem. Commun.*, 809 (1969). (b) After this paper was submitted, the cmr spectrum of a mixture of α- and β-D-glucopyranoses enriched in ^{13}C has been published and interpretated by A. S. Perlin and B. Casu, *Tetrahedron Lett.*, 2921 (1969). The spectrum is in good agreement with the one we report below but the assignments proposed for the C2 and C3 resonances of the α form are reversed from our assignments.
(8) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 2967 (1967).
(9) F. J. Weigert, M. Jautelat, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, 60, 1162 (1968).
(10) M. L. Wolfrom, Ed., "Methods in Carbohydrate Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, section 84.
(11) (a) Reference 10, Vol. 2, section 78; (b) W. L. Glen, G. S. Myers, and G. A. Grant, *J. Chem. Soc.*, 2568 (1951).



1

a, $R_1 = OH; R_2 = R_3 = H$
b, $R_2 = OH; R_1 = R_3 = H$
c, $R_1 = OCH_3; R_2 = R_3 = H$
d, $R_2 = OCH_3; R_1 = R_3 = H$
e, $R_1 = OH; R_2 = H; R_3 = OCH_3$
f, $R_1 = H; R_2 = OH; R_3 = OCH_3$

2

a, $R_1 = R_3 = OH; R_2 = H$
b, $R_1 = H; R_2 = R_3 = OH$
c, $R_1 = OH; R_2 = R_3 = H$
d, $R_1 = R_3 = H; R_2 = OH$

3

a, $R_1 = OH; R_2 = H$
b, $R_1 = H; R_2 = OH$

4

a, $R_1 = R_3 = OH; R_2 = H$
b, $R_1 = H; R_2 = R_3 = OH$
c, $R_1 = OH; R_2 = R_3 = H$
d, $R_1 = R_3 = H; R_2 = OH$

5

a, $R_1 = OH; R_2 = H$
b, $R_1 = H; R_2 = OH$

6

a, $R_1 = OH; R_2 = H$
b, $R_1 = H; R_2 = OH$

7

a, $R_1 = OH; R_2 = H$
b, $R_1 = H; R_2 = OH$

8

a, $R_1 = OH; R_2 = H$
b, $R_1 = H; R_2 = OH$

Figure 1. The common hexose and pentose aldopyranoses.

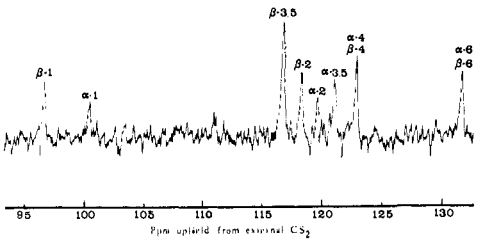


Figure 2. Natural-abundance ^{13}C spectrum of the anomeric mixture of α- and β-D-glucose (**1a** and **1d**).

into resonance at lower fields than do chemically similar axial protons.[3,12] These criteria allow straightforward assignment of the C-1 resonances.

Because only the hydroxymethyl carbons would be expected to appear as triplets in the undecoupled spectra, the C-6 resonances are also readily identified. It is found that the C-6 resonances of an anomeric pair are at least partially superimposed in all cases, as would

(12) See J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Ltd., London, 1966, p 696.

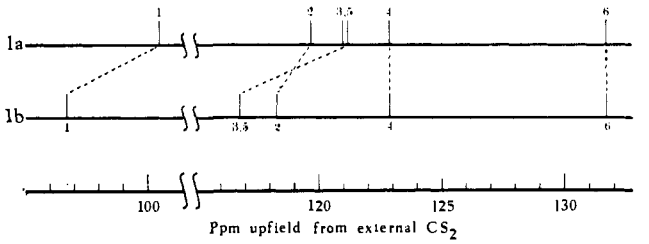


Figure 3. Correlation of the cmr spectra of α- (**1a**) and β-D-glucopyranose (**1b**).

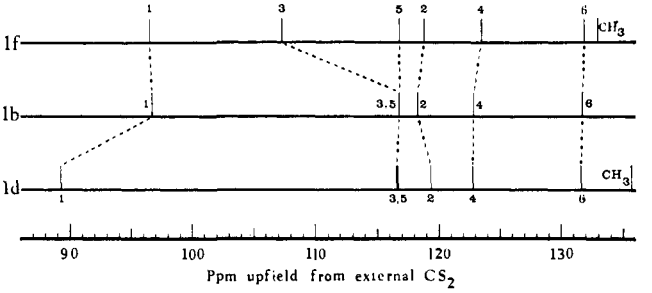


Figure 4. Correlation of the cmr spectra of β-D-glucopyranose (**1b**), methyl β-D-glucopyranoside (**1d**), and 3-O-methyl-β-D-glucopyranose (**1f**).

be expected from the attenuation of steric or proximity effects with distance. It is also evident from Table I that the resonances of these carbons remain relatively constant throughout the series of hexoses studied, and are always the highest field peaks in the spectra of the unsubstituted hexoses.

Because of these regularities, the identification of the C-1 and C-6 resonances of the D-glucose (**1**) spectrum (Figure 2) is straightforward, leaving eight unassigned peaks in the spectrum of the anomeric mixture of α- (**1a**) and β-glucopyranose (**1b**). Relative peak heights can be used to assign these resonances to either the α or β anomer. There is one peak at 122.9 ppm which is common to both anomers and seems most reasonably assigned to carbon 4 on the basis that this center is relatively remote from the anomeric center. The remaining peaks (Figure 3) show a general upfield shift for change of the anomeric hydroxyl group from equatorial to axial, again as would be predicted from the expected increase in steric crowding accompanying such an epimerization.[6]

It was observed during the study of the inositols[6] that methylation of a hydroxyl group effected an 8–11 ppm downfield shift in the position of the resonance of the directly attached (*i.e.*, α) carbon, a shift which is consistent with the results of other research.[13] When both the methoxyl and the adjacent hydroxyl groups were equatorial, the methylation shift at the β carbons was found to be less than one part per million. More remote carbon nuclei were generally shifted less than ± 0.3 ppm, regardless of the configuration of the attached hydroxyl group. For this reason, it was anticipated that interpretation of the glucose spectra would be facilitated by a study of various O-methyl derivatives.

Comparison (Figure 4) of the spectra of β-D-glucopyranose (**1b**) and methyl β-D-glucopyranoside (**1d**) shows

(13) F. J. Weigert, Ph.D. Thesis, California Institute of Technology, Pasadena, Calif., 1968, p 211.

Table I. ^{13}C Chemical Shifts[a] in Aldopyranoses and Their Derivatives

Compd	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3
1a	100.5	119.7	121.0 or 121.2	122.9	121.0 or 121.2	131.7	
1b	96.7	118.3	116.8	122.9	116.8	131.7	
1c	93.4	119.3	121.0 or 121.2	122.8	121.0 or 121.2	131.8	137.7
1d	89.3	119.4	116.6 or 116.7	122.8	116.6 or 116.7	131.6	135.6
1e	100.4	121.4	109.8	123.4	121.2	131.8	132.6
1f	96.5	118.8	107.3	123.6	116.8	131.8	132.9
2a	98.6	121.8	122.2	125.6	120.3	131.5	
2b	99.1	121.5	119.4	125.9	116.8	131.5	
2c	98.6	121.6	122.7	120.3	124.4	175.7	
2d	99.0	121.2	119.6	120.7	120.7	175.7	
3a	99.8	120.9 or 121.4	120.0	125.0	120.9 or 121.4	130.6	
3b	99.1	119.1	121.4	125.7	121.2	131.2	
4a	100.3	123.3	124.1	123.3	122.3	131.4	
4b	96.0	120.5	119.7	123.8	117.6	131.6	
4c	100.3	123.1	124.3	120.7	126.5	176.9	
4d	96.2	120.7	119.5	121.1	122.0	176.9	
5a	100.4	119.6	121.0	123.1	131.6		
5b	95.9	118.4	116.7	123.3	129.5		
6a	98.5	122.0	122.4	125.0	129.6		
6b	98.5	122.7	119.8	125.9	128.6		
7b	98.6	121.4	124.0	125.1	129.6		
8a	100.0	126.4	126.4	123.8	130.2		
8b	95.8	120.6	120.1	123.9 or 124.1	123.9 or 124.1		

[a] In parts per million upfield from external CS_2.

that the C-1 resonance is shifted downfield 7.4 ppm by methylation of the anomeric hydroxyl group. With the exception of one pair of peaks, the remainder of these spectra are superimposable. This is in full accord with the results of the inositol study, since it would be predicted that methylation at carbon 1 would effect shifts only in the C-1 and C-2 resonances. Hence this comparison allows the identification of the C-2 resonances of **1b** and **1d**. Furthermore, it allows the tentative assignment of the resonance at 122.8 ppm of the spectrum of **1d** to carbon 4.

There remain to be assigned in the spectrum of β-glucopyranose (**1b**) only the resonance positions for C-3 and C-5 and these appear to coincide at 116.8 ppm. Verification of the over-all assignments is available from comparison of the spectrum of **1b** with that of 3-O-methyl-β-D-glucopyranose (**1f**). It is seen from Figure 4 that the chemical shifts of carbons 1 and 6 are changed by less than ±0.2 ppm by the methylation of the C-3 hydroxyl group. Since carbon 5, as carbon 1, is γ to the methyl group, it would also be likely to show only a small methylation shift. The C-2 and C-4 resonances would be expected to undergo a methylation shift of about 0.5–1.0 ppm, while the C-3 resonance should be shifted downfield by over 8 ppm. Reference to Figure 4 shows that these expectations are fulfilled.

It is seen, therefore, that the spectra of **1b**, **1d**, and **1f** can be correlated to yield a complete assignment of the resonances to specific carbons. A similar comparison of spectra leads to a full interpretation of the spectra of **1a**, **1c**, and **1e**. As observed in the inositol study,[6] an axial methoxyl group (**1c**) has little more effect upon the chemical shift of the γ carbon resonances than a hydroxyl group, a rather surprising phenomenon in view of the potential steric interactions. A possible explanation of this observation is that the rotamers wherein the O-methyl group is directed away from the axial protons at carbons 3 and 5 are by far the most highly populated.

Having obtained a satisfactory interpretation of the spectrum of glucose, the assignment of the resonances of D-mannose (**2a**, **b**) can be begun by the now routine identification of the C-1 and C-6 resonances (*cf.* Table I and Figure 5). The expectation that the axial hydroxyl group at carbon 2 would have little effect upon the chemical shift of the C-5 resonance leads to assignment of the peaks at 116.8 and 120.3 ppm to the C-5 resonances of β- (**2b**) and α-D-mannopyranose (**2a**), respectively. Because carbon 4 is γ to the axial C-2 hydroxyl group, its resonance would be expected to be shifted 2–3 ppm upfield[6] from its position in the glucose

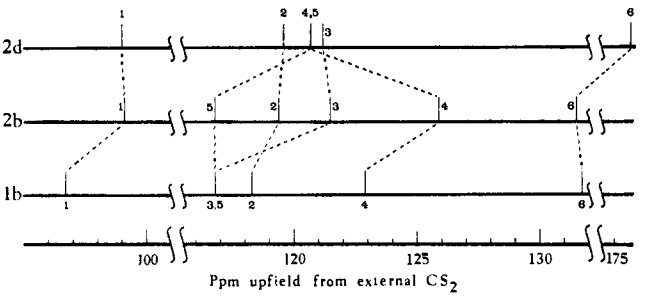


Figure 5. Correlation of the cmr spectra of β-D-glucopyranose (**1b**), β-D-mannopyranose (**2b**), and β-L-rhamnopyranose (**2d**).

Table II. Comparison of Pmr Results[a] with Proton-Decoupling Frequencies[b]

Compound	C-2		C-3		C-4		C-5		C-6[c]
	Pmr	Pdf	Pmr	Pdf	Pmr	Pdf	Pmr	Pdf	Pdf
1a	1.42	1.47		1.23		1.23		1.23	0.83
1b	1.72 (1.77)	1.60		1.53		1.80		1.53	1.40
2a	0.94	0.80		1.10		1.10		1.27	0.90
2b	1.24	1.30		1.43		1.53		1.50	1.37
3b	1.56	1.47	0.72 (0.77)	1.00	(*Ca.* 1.3)	1.57		1.73	1.43
4a	1.47	1.37		1.33		1.37		1.27	1.50
4b	1.13	1.20	*Ca.* 0.95	1.13	0.71	0.77	*Ca.* 0.95	0.97	0.93
5a	1.63	1.70		1.70		1.53		1.43	
5b	1.38	1.27	1.17	1.13	1.07	0.90	Ax. 1.28 Eq 0.65	0.87	
6a	1.18	1.20		1.27		1.20		1.37	
6b	0.90	1.27		1.47		1.20	Ax. 1.62 Eq 0.85	1.60	
7b	1.38	1.40	0.87	0.97	1.20	1.13		1.30	
8a	1.42	1.40	1.42	1.40	1.27	1.30		1.10	
8b	1.02	1.10	0.85	0.93	0.57	0.57		0.57	

[a] Data taken from ref 3, except values in parentheses, which were derived from ref 5. [b] Chemical shifts are given in parts per million upfield from the H-1 resonance of each anomer. [c] No pmr values were available.

spectrum, and hence the resonances at about 125 ppm are assigned to this carbon. The remaining two pairs of peaks may be distinguished by comparison of the proton-decoupling frequencies to the published[3] pmr chemical shifts (*cf.* Table II), which show that the peaks at 121.8 and 121.5 ppm are due to the 2-carbons of the α and β anomer, respectively.

The spectrum of L-rhamnose (**2c** and **2d**; the compounds studied are actually enantiomers of these drawings) provides a unique test for the veracity of the above assignment. From Figure 5, it is seen that the C-1 resonances of β-D-mannopyranose (**2b**) and α-L-rhamnopyranose (**2d**) are not very different, data which reflect the large separation of C-1 and C-6. Since carbons 2 and 3 are also distant from the site at which **2b** and **2d** differ, their resonances should not be very different in the spectra of these two compounds. On this basis the assignment of all the resonances except those due to C-4 and C-5 is possible in both **2c** and **2d**, and in the spectrum of the latter these resonances are isochronous at 120.7 ppm. Because the chemical shifts of the C-4 resonances of **2c** and **2d** should not be very different, the peak at 120.3 ppm can be assigned to the C-4 resonance of **2c**. It is to be noted that these assignments specify that the C-5 resonance of rhamnose undergoes a 4-ppm downfield shift upon hydroxylation at C-6, while the C-4 resonance experiences a concomitant 5 ppm upfield shift. These shifts are in broad agreement with the results of a thorough study of the ^{13}C spectra of cyclic and continuous-chain alcohols.[14]

The aqueous solution of D-allose (**3**) consists of both furanose and pyranose forms, and the complexity of the mutarotational equilibrium makes interpretation of the spectrum difficult. Only the β-pyranose (**3b**) predominates to a sufficient extent to allow specific proton-decoupling frequencies to be obtained. Comparison of these values with the pmr spectrum[3,5] (*cf.* Table II) allows the full assignment of the spectrum of **3b**. The correlation of proton-decoupling frequencies and proton chemical shifts seems particularly poor for carbons 3 and 4, but this may be due to uncertainties in the pmr data. The resonances of α-allopyranose (**3a**) could be identified in some cases, but the chemical-shift values entered into Table I for this anomer must be considered as tentative.

Proton-decoupling frequencies were especially helpful in the interpretation of the spectrum of D-galactose (**4a** and **4b**). Reference to Table II shows that all the resonances of **4b** can be assigned by this means. The correlation of values for C-3 of **4b** is poorer than usual, but the matching throughout the remainder of the spectrum is good enough to overrule this objection. The proton-decoupling frequencies also limit the possible assignments for C-2 of **4a** to two peaks.

Extension of this assignment is possible through comparison of the spectra of D-galactose and L-fucose (**4c**, **d**; the fucose anomers studied are enantiomeric to these drawings). Figures 6 and 7 show that the spectrum of β-L-fucopyranose (**4d**) can be easily assigned such that the C-1, C-2, and C-3 resonances of **4b** and **4d** are not different by more than ± 0.2 ppm, as was observed for mannose (**2a**, **b**) and rhamnose (**2c**, **d**). In the spectra of these earlier examples, there is also a downfield shift at carbon 5 of about 4 ppm upon hydroxylation at carbon 6, and the 122.0-ppm peak of the spectrum of **4d** is assigned to C-5 upon the assumption that a similar shift will obtain in this case. These assignments specify that the upfield shift at carbon 4 due to C-6 hydroxylation is about 2.5 ppm in the case of **4d** and **4b**, whereas the analogous shift in the mannose system was approximately 5 ppm. This difference is probably due to the fact that these systems differ in configuration at carbon 4.

Assuming that **4a** and **4c** will show shifts similar to those of **4b** and **4d**, the spectra of the former two sugars can be assigned as shown in Figures 6 and 7. The completed assignments indicate that the C-4 and C-6 resonances of **4a** and **4b** have different chemical shifts, an unusual circumstance which suggests that the two anomers differ slightly in average conformation. As before, the upfield shifts at carbons 3 and 5 upon going from the β to the α anomer are roughly equivalent, and both are larger than the upfield shift of carbon 2. The shifts upon reductive dehydroxylation at carbon 6 of **4a** and **4b** are also very similar.

(14) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **91**, 1338 (1969).

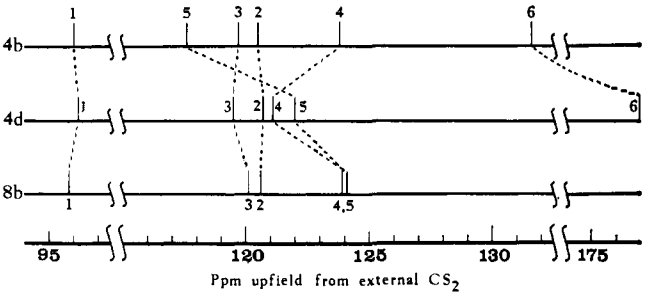


Figure 6. Correlation of the cmr spectra of α-D-arabinopyranose (**8b**), β-L-fucopyranose (**4d**), and β-D-galactopyranose (**4b**).

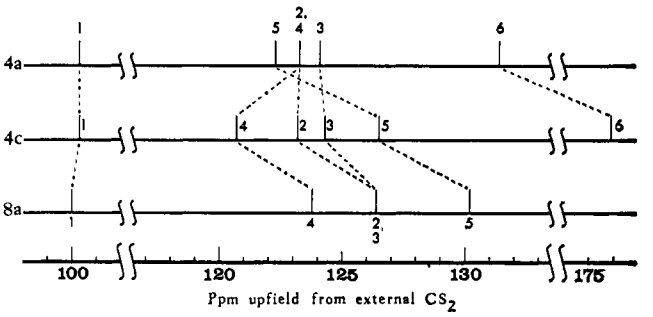


Figure 7. Correlation of the cmr spectra of β-D-arabinopyranose (**8a**), α-L-fucopyranose (**4c**), and α-D-galactopyranose (**4a**).

Interpretation of the spectra of the pentoaldopyranoses is complicated by the more variable conformational equilibria of these compounds. Lacking the stabilizing influence of the bulky hydroxymethyl group, the pentopyranoses exist in conformations which are determined by the steric arrangement of the hydroxyl groups around the ring. The available evidence[3,4] suggests that both anomers (**5a** and **5b**) of D-xylopyranose as well as the β anomer of D-xylose (**6b**) exist preferentially in the same conformation as their homomorphous hexoses, while α-D-arabinopyranose (**8b**) occurs in a conformation which is the mirror image to that of its homomorphous hexose, β-D-galactopyranose (**4b**). Under these circumstances it may be anticipated that the resonances of carbons 1, 2, and 3 of these pentoses would not be much shifted from their positions in the homomorphous hexoses. This hypothesis, which finds some precedence in the pmr studies of these compounds,[3] is supported by the positions of the easily identified C-1 resonances of these substances. As seen in Table III, this criterion allows identification of the resonances of carbons 2 and 3 in the spectra of **5a**, **5b**, and **8b**. In the case of **6b**, only the C-3 resonance can be assigned on this basis.

Table III. Comparison of ^{13}C Chemical Shifts of Homomorphous Carbohydrates

Homomorphous series	Compd	C-1	C-2	C-3	C-4	C-5	C-6
1	**5a**	100.4	119.6	121.0	123.1	131.6	
	1a	100.5	119.7	121.0	122.9	121.0	131.7
				or		or	
				121.2		121.2	
2	**5b**	95.9	118.4	116.7	123.3	129.5	
	1b	96.7	118.3	116.8	122.9	116.8	131.7
3	**6a**	98.5	122.0	122.4	125.0	129.6	
	2c	98.6	121.6	122.7	120.3	124.4	175.7
	2a	98.6	121.8	122.2	125.6	120.3	131.5
4	**6b**	98.5	122.7	119.8	125.9	128.6	
	2d	99.0	121.2	119.6	120.7	120.7	175.7
	2b	99.1	121.5	119.4	125.9	116.8	131.5
5	**7b**	98.6	121.4	124.0	125.1	129.6	
	3b	99.1	119.1	121.4	125.7	121.2	131.2
6	**8a**	100.0	126.4	126.4	123.8	130.2	
	4c	100.3	123.1	124.3	120.7	126.5	176.9
	4a	100.3	123.3	124.1	123.3	122.3	131.4
7	**8b**	95.8	120.6	120.1	124.1	124.1	
	4d	96.2	120.7	119.5	121.1	122.0	176.9
	4b	96.0	120.5	119.7	123.8	117.6	131.6

Carbon 5 of the pentopyranose ring system is directly attached to two protons, and should thus appear as a triplet in the absence of proton decoupling. Unfortunately, the undecoupled spectra are complex and difficult to interpret, and only the C-5 resonances of **6a**, **6b**, and **7b** can be identified in this way. However, because the two protons on carbon 5 are nonequivalent, single-frequency proton decoupling should be rather inefficient and, therefore, the C-5 resonances could often be identified by their broad appearance in the single-frequency decoupled spectrum.

Most of the remaining peaks may be assigned by comparison of the proton-decoupling frequencies and pmr spectra. As seen from Table II the pmr spectra of the pentoses are better understood than those of the hexoses, a fact which makes this basis of assignment particularly useful. The very poor correlation in the case of **6b** is doubtless due to the fact that the proton-decoupling frequency of the C-1 resonance of this substance cannot be accurately determined because of its overlap with the C-1 resonance of **6a**.

Comparison of the homomorphous series in Table III and Figures 6 and 7 reveals some interesting generalizations. It is first noted that the resonances of carbons 1, 2, and 3 are relatively constant throughout these series, even in no. 3 where the members of the homomorphous series are known[4] to have different average conformations. It is somewhat more surprising to note that in most cases the resonance of carbon 4 is "unaffected" by the presence of the hydroxymethyl group at carbon 5. This phenomenon probably results from cancellation of shielding and deshielding effects, because the C-4 resonances of the 6-deoxyhexoses are significantly different from the other members of their homomorphous series. Finally, the C-5 resonances are subject to large downfield shifts upon addition of the side chain.

The interpretation of the spectra of the pentoses is less secure than in the cases of the hexoses, and verification by the study of appropriate derivatives is badly needed. Still, the importance of steric effects continues to be evident in these examples, and there is strong indication that natural-abundance cmr spectroscopy will prove a valuable tool in the conformational analysis of these compounds.

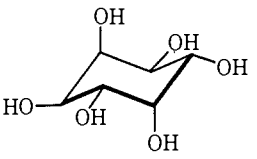
Correlation with the Spectra of the Inositols. During the study of the cmr spectra of the inositols[6] it was observed that a system of empirical constants could be derived and used to correlate the chemical shifts of inositol carbons. It was important to test the utility of this method for correlation of the cmr chemical shifts of the carbohydrates which occur in the pyranose forms in solution. The inositol study showed that carbon chem-

Table IV. Correlation of Calculated and Empirical Carbon Chemical Shifts of Pyranoses

Compounds	Conformation	C-1 Emp	C-1 Calcd	C-2 Emp	C-2 Calcd	C-3 Emp	C-3 Calcd	C-4 Emp	C-4 Calcd	C-5 Emp	C-5 Calcd
1a	C1	100.5		119.7	120.0	121.1[a]	119.6	122.9	122.2	121.1[a]	119.6
1b	C1	96.7		118.3		116.8		122.9		116.8	
2a	C1	98.6	101.1	121.8	122.1	122.4	121.3	125.6	125.0	120.3	118.9
2b	C1	99.1	98.4	121.5		119.4	118.5	125.9	125.7	116.8	116.1
3a	C1	99.8	98.2	121.0[b]	121.7	120.0	119.1	125.0	123.9	121.0[b]	122.2
3b	C1	99.1	99.5	119.1	120.0	121.4		125.7	124.6	121.2	119.6
4a	C1	100.3	100.5[c]	123.3	122.8	124.1	121.3	123.3	123.8[c]	123.3	121.3
4b	C1	96.0	96.0	120.5	121.1	119.7	118.5	123.8		117.6	118.5
5a	C1	100.4		119.6	120.1	121.0	119.5	123.1	122.6	131.6	132.3
5b	C1	95.9		118.4		116.7		123.3		129.5	
6a	C1		101.0		123.3		121.2		125.4		131.6
		98.5		122.0		122.4		125.0		129.6	
	1C		98.0		122.9				124.6		134.0
6b	C1	98.5	97.6	122.7		119.8	118.4	125.9	126.1	128.6	128.8
7b	C1		98.7		120.1				125.0		132.3
		98.6		121.4		124.0		125.1		129.6	
	1C		101.0[c]		121.0		122.9		121.7[c]		133.3
8a	1C		100.4[c]		122.9		121.2		124.0[c]		134.0
		100.0		126.4		126.4		123.8		130.2	
	C1		100.4		123.3				127.8		131.6
8b	1C	95.8	95.2	120.6	121.2	120.1	118.4	124.0[a]		124.0[a]	131.2

[a] These values are averages of two possible assigned resonances. [b] Owing to the complex mutarotational equilibrium, these chemical shifts are tentative. [c] δ_a is assumed to be zero in these calculations.

ical-shift differences could be correlated with changes in the configurations of the other asymmetric centers of the molecule. For inositol carbons bearing an equatorial hydroxyl group, β_e was taken to represent the shift caused by a change in the configuration of the hydroxyl group on the immediately adjacent carbon[15] from the equatorial to the axial disposition, while γ_e and δ_e represented the shifts associated with like changes in configuration of hydroxyl groups on γ and δ carbons, respectively. For carbons bearing an axial hydroxyl group, the empirical constants β_a, γ_a, and δ_a were defined in an entirely analogous fashion. Best values for these constants as obtained from the spectra of the inositols by a least-squares analysis follow: $\beta_e = +1.7 \pm 0.3$ ppm; $\gamma_e = +2.8 \pm 0.3$ ppm; $\delta_e = -0.7 \pm 0.5$ ppm; $\beta_a = +0.6$ ppm;[17] and $\gamma_a = 2.3$ ppm.[17,18]



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Using these constants, the chemical shift of carbon 1 of β-D-galactopyranose (**4b**), for example, will differ from its chemical shift in β-D-glucopyranose by δ_e, while the chemical shifts of the C-3 resonances of α- and β-D-xylopyranose (**5a** and **5b**, respectively) will be expected to differ by γ_e.

For the purpose of calculating the spectra of the pyranoses, two distinct reference points are adopted for each carbon of the pyranose ring. For the hexoses, the spectrum of β-glucopyranose (**1b**) gives convenient reference points for carbons bearing a single equatorial hydroxyl or hydroxymethyl group are surrounded by carbons all with equatorial substituents. For carbons bearing axial hydroxyl groups and surrounded by carbons bearing only equatorial substituents, the spectra of α-D-glucopyranose (**1a**), β-D-mannopyranose (**2b**), β-D-allopyranose (**3b**), and β-D-galactopyranose (**4b**) provide reference points for carbons 1, 2, 3, and 4, respectively. Reference points for the pentoses are established in an analogous fashion. The L-pentoses exist in the 1C conformation[19] and for these sugars the calculated shift values in Table IV are those for the corresponding D-enantiomers.

The chemical shifts calculated in this manner are compared to the empirical spectra in Table IV. The correlation in the case of the hexopyranoses is poorer than observed for the inositols,[6] the standard deviation being about 1.2 ppm. Correspondence between calculated and experimental C-2 and C-4 resonances is best (standard deviation equalling 0.6 and 0.8 ppm, respectively) and worst for the C-3 resonances (1.7 ppm). For most examples the calculated values are too low, and the correlation would be bettered by adjustment of the reference points.

The degree of correspondence of calculated and empirical values among the pentoses is similar, the calculated values again being usually low. As might be expected, those substances which should exist as a rapidly equilibrating mixture of conformations rather than one classical chair form give the poorest correlation. Calculated and empirical chemical shifts for the pentose C-5 resonances show little correspondence at all, but since the method of calculation was derived for hydroxymethine groups this is to be expected.

This method of correlating of chemical shifts of pyranose carbons is therefore moderately successful and roughly comparable to the correlations found for carbon shifts for alcohols relative to hydrocarbons[14]

(15) The designation of this change as occurring at the "β carbon" is in accord with correlations of the chemical shifts in other systems.[14,16]

(16) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967).

(17) Insufficient examples were available to provide estimates of reliability for these values.

(18) The low solubility of *neo*-inositol **9** precluded estimation of δ_a.

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and ketones relative to hydrocarbons.[20] It is probable that at least part of the deviations arises from subtle differences in conformations. In any event, the heavy dependence of ^{13}C chemical shifts upon steric forces in these systems heralds the development of a potent tool in the study of conformations.

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Acknowledgment. The authors are indebted to Professor S. J. Angyal for generous advice and gifts of samples.

Carboxylic Acid–Amine Equilibria in Nonaqueous Solvents[1,2]

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Received April 14, 1969

Abstract: A survey of the infrared and ultraviolet spectra of mixtures of amines and carboxylic acids has shown that the expected formation of ion pairs A^-BH^+ and AHA^-BH^+ often takes place. However, tertiary amines exhibit two types of abnormal behavior. In solvents of low dielectric constant such as carbon tetrachloride, cyclohexane, or carbon disulfide strong tertiary amines such as triethylamine interact with carboxylic acids such as acetic acid and benzoic acid by hydrogen bond association with little ionization. Furthermore, the ionization which does occur in solvents such as chloroform or acetonitrile leads to unusual species. There is an absence of identifiable NH^+ infrared absorption and the whole curve is underlaid by a strong genreal absorbance. These spectra have been interpreted qualitatively and in two cases also quantitatively.

Because an understanding of acid–base equilibria underlies much of chemistry, the development of modern techniques has led to a rejuvenation of interest in medium strength acids and bases, particularly with reference to nonaqueous systems.[3] Techniques that have been applied include conductivity,[4] indicator titrations,[3] measurements of ultraviolet,[5] infrared[6–12] and nmr spectra,[13] potentiometric titrations,[14] measurements of colligative properties,[15,16] calorimetric measurements,[17] and measurements of dielectric constants.[18] Chemical methods based on reaction kinetics might be included, but reaction systems are usually too complicated to provide firm conclusions about acid–base equilibria.[19,20]

Each technique provides useful types of information. The purpose of the present work is to develop further the spectrophotometric techniques. In favorable systems these permit direct observation of ion pair and other equilibria and hence serve to complement techniques which depend primarily on observation of free ions or which count the number of molecules present.

The present work has been greatly facilitated by the pioneering studies of Barrow and his students[6–10] and by other studies, only a selection of which has been specifically cited. Yet there are two fundamental points upon which we disagree with previous workers. (1) We interpret the spectra of solutions of acetic acid and triethylamine in nonpolar solvents such as carbon tetrachloride as indicative of hydrogen bonding without ionization. Previous workers have suggested the formation of 2:1 salts AHA^-BH^+ and 1:1 salts A^-BH^+.[6,12] (2) Systems of tertiary amines and carboxylic acids show a broad relatively strong general absorbance which we interpret as indicative of uncertainty in the position of the proton. This phenomenon is much less pronounced for mixtures of carboxylic acids with primary or secondary amines and does not occur with mixtures of amines and phenols.

Qualitative Results. Typical ir spectra are shown in Figure 1 and uv spectra are shown in Figure 2. In a solvent such as dimethyl sulfoxide, addition of sufficient triethylamine to a solution of benzoic acid causes disappearance of the benzoic acid peak at 1714 cm^{-1} and appearance of typical benzoate peaks at 1575 and 1604 cm^{-1} (Figures 1-1 and 1-8). It is also possible to identify the NH^+ absorption at 2450 and 2600 cm^{-1} (Figures 1-3 and 1-8). These spectral features indicate that ionization has occurred. Other evidence shows that there is relatively little dissociation into free ions.

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