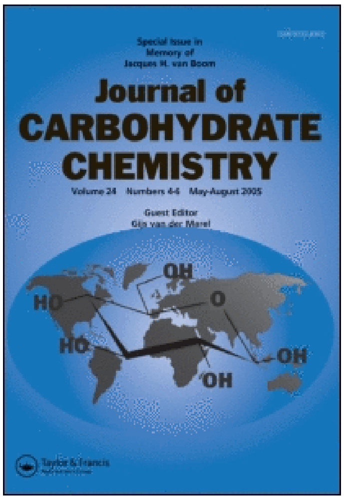

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Grindley, T. Bruce and Wickramage, Chandra(1985) 'Structural Assignments of Ethylidene Acetals by NMR Spectroscopy', Journal of Carbohydrate Chemistry, 4: 2, 171 — 192

To link to this Article: DOI: 10.1080/07328308508058830

URL: http://dx.doi.org/10.1080/07328308508058830

J. CARBOHYDRATE CHEMISTRY, 4(2), 171-192 (1985)

STRUCTURAL ASSIGNMENTS OF ETHYLIDENE ACETALS BY NMR SPECTROSCOPY

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Received November 12, 1984 - Final Form February 14, 1985

ABSTRACT

The ^1H and ^{13}C NMR spectra of ethylidene derivatives of simple diols and of carbohydrates were measured to determine whether NMR parameters could be found which could be related to structure. Four NMR parameters were considered; the chemical shifts of the acetal proton and carbon, the $^2J_{C,H}$ value between the acetal proton and methyl carbon and the $^1J_{C,H}$ value of the acetal carbon. The values of these parameters were all somewhat related to ring-size; the $^2J_{C,H}$ value was most closely related. The sign of $^2J_{C,H}$ was shown to be positive for 2-methyl-1,3-dioxolane and 2-methyl-1,3-dioxane by means of selective population transfer experiments. Comparison of the ^{13}C NMR chemical shifts of the acetal with the parent diol was found to give information about acetal location.

INTRODUCTION

Ethylidene acetals have been extensively employed as protecting groups for diols, particularly of those derived from carbohydrates.[1] The normal method of acetal formation involves use of paraldehyde and an acid catalyst. Such conditions yield products formed under thermodynamic control. The products are as fully acetalated as possible and the acetal rings are normally substituted 1,3-dioxane rings, the most stable type of ring for acetals derived from aldehydes.[1] More recently, it has been found that vinyl ethers react with polyols under conditions of kinetic control to give different types of products.[2]

Structures of all types of acetals have traditionally been determined by chemical methods. However, spectral methods are faster and can often remove ambiguity in structural assignment.

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^1H NMR spectroscopy would not be expected to be as useful for structural elucidation of compounds containing ethylidene acetals as it is for benzylidene acetals because the signal of the ethylidene acetal proton appears in a region from about 4.5 to 5.2 ppm where it often overlaps with those of anomeric and other secondary protons. In addition, this signal appears as a quartet increasing the likelihood of overlap.

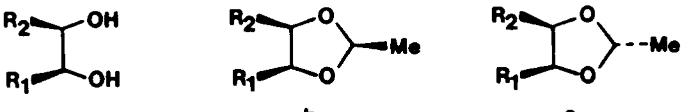
^{13}C NMR spectroscopy has been shown to be particularly useful for the determination of acetal structure.[3-8] A number of ^{13}C NMR parameters were demonstrated to indicate benzylidene acetal configuration[3] and ring size.[4] Subsequently, it was shown that ^{13}C NMR parameters gave information about ring size[5,6,7] and conformation[6] of isopropylidene acetals. The location of an isopropylidene or cyclohexylidene acetal can often be determined by comparison of the chemical shifts of the acetal with its precursor diol.[8] This publication reports an examination of the ^1H and ^{13}C NMR spectra of ethylidene acetals to determine whether useful structural correlations can be made.

RESULTS AND DISCUSSION

Model Compounds

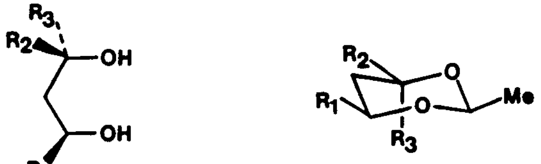
There have been extensive studies of the ^1H and ^{13}C NMR chemical shifts of 1,3-dioxolanes[9-11] and 1,3-dioxanes.[12-15] Little coupling constant data was available. Most of the literature ^{13}C NMR data has been measured in chloroform-*d* while the ^1H NMR data has been measured in carbon tetrachloride. For this study, chloroform-*d* was chosen as sole solvent because most carbohydrate ethylidene acetals are soluble in it. Table 1 lists the NMR data for model compounds, some of which is literature data.[9-12]

The most readily measured NMR parameter is the chemical shift of the acetal proton. As with the chemical shift of the benzylidene acetal proton,[4,16] its position reflected ring-size for common types of acetals; signals with shifts from 4.90 to 5.15 ppm normally arose from 2-methyl-1,3-dioxolane rings, while those with shifts from 4.60 to 4.75 ppm arose from six-membered rings. However, 2-methyl-1,3-dioxane rings with axial substituents at position-4 or -6 and also 2-methyl-1,3-dioxepane rings gave values which were often within the range observed for 2-methyl-1,3-dioxolane derivatives. The observation that the chemical shift ranges for these two less common types of acetals overlapped with those of the five-membered ring derivatives was also made for the analogous benzylidene acetals.[4] The values for ethylidene acetals were about 1 ppm less than those of the structurally analogous benzylidene acetals,[4] greatly increasing the chance of overlap with signals from secondary hydrogens of carbohydrates.



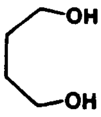
a b c

1 $R_1 = R_2 = H$
2 $R_1 = Me \quad R_2 = H$
3 $R_1 = R_2 = Me$

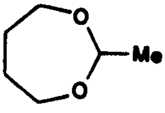


a b

4 $R_1 = R_2 = R_3 = H$
5 $R_1 = Me \quad R_2 = R_3 = H$
6 $R_1 = R_2 = Me \quad R_3 = H$
7 $R_1 = R_3 = Me \quad R_2 = H$



8a



8b

The ^{13}C NMR chemical shift of the acetal carbon is also readily accessible experimentally. The data in Table 1 indicated that these shifts were related to ring size; the signals from typical 2-methyl-1,3-dioxolanes appeared at shifts from 100 to 103 ppm, while those from 2-methyl-1,3-dioxanes fell in a range of 98.0 to 99.8 ppm. Moreover, 2-methyl-1,3-dioxanes with axial substituents at position-4 or -6 could be readily identified by the observation of comparatively upfield signals at 91 to 93 ppm (see ref. 12 for additional examples).

Unfortunately, the ^{13}C NMR shifts observed for two less common types of ethylidene derivatives fell across the ranges

Table 1. Useful NMR Results for Model Ethylidene Acetals and their Precursor Diols

Compound	^{13}C NMR Chemical Shifts (ppm)							$^{13}C-^{1}H$ Coupling Constants (Hz)		^{1}H NMR Chemical Shifts (ppm)	
	C-1^{a}	C-2^{a}	C-3^{a}	C-4^{a}	C-5^{a}	acetal C	methyl C	^{1}J acetal C	^{2}J methyl C	acetal H	methyl
1a	63.7	63.7									
1b	65.0	65.0				101.6	19.8	165.0	5.9	4.93	1.31
2a	67.8	68.3	18.9								
2b	71.1	73.0	18.9			101.8	20.3	164.2	6.0	5.06	1.35
2c	72.0	71.9	18.5			100.8	20.3	164.7	6.0	5.12	1.31
3b^{b}	15.6	74.5	74.5	15.6		100.0	20.8	c	c	c	c
3c^{b}	14.3	74.1	74.1	14.3		99.3	21.2	c	c	c	c
4a	59.2	34.9	59.2								
4b	66.8	25.9	66.8			99.3	21.4	158.2	1.3	4.67	1.27
5a	60.0	40.8	66.3	23.5							
5b	66.4	33.0	72.6	21.8		98.9	21.3	158.6	1.4	4.66	1.27
6a	24.0	68.4	46.6	68.4	24.0						
6b	21.7	72.2	40.5	72.2	21.7	98.4	21.2	158.1	0.9	4.70	1.32
7a	23.5	64.9	46.3	64.9	23.5						
7b	21.9	67.4	36.6	68.0	17.2	91.2	21.5	159.2	1	5.02	1.25
8a	62.0	29.9	29.9	62.0							
8b	65.2	29.5	29.5	65.2		99.5	20.7	163.6	2.6	4.86	1.24

a. acetal carbons numbered as in their precursor diols. b. ref. 9. c. not recorded.

noted above. The ^{13}C NMR chemical shifts of acetal carbons of ethylidene groups in seven-membered rings were highly variable, particularly when the carbohydrate examples were included (see Table 2), ranging from 95 to 100 ppm. The signal of the acetal carbon of 4,5-cis,trans-disubstituted-2-methyl-1,3-dioxolanes appeared in the region where most derivatives of 2-methyl-1,3-dioxane absorb and those of more highly substituted 2-methyl-1,3-dioxane derivatives appeared at still higher field.[9] Thus the chemical shifts of both the acetal proton and the acetal carbon can be helpful but consideration of their values will not always yield unambiguous assignment of acetal ring size.

A parameter which is almost as accessible experimentally as the ^{13}C NMR chemical shift of the acetal carbon is the $^{2}J_{C,H}$ value between the acetal hydrogen and the methyl carbon of the ethylidene group. The signal of this carbon in the coupled ^{13}C NMR spectrum is split by the three directly bonded hydrogens and by this geminal coupling. Further splitting by couplings to other hydrogen atoms are very small since any additional couplings must occur across more than three bonds. In practice, the signal of the methyl carbon in the fully coupled ^{13}C NMR spectrum appears as a sharp quartet of doublets (or singlets) with considerably greater intensity than the signals for the other carbons which have numerous geminal and vicinal coupling constants to hydrogen atoms. The value of this $^{2}J_{C,H}$ value is closely related to ring size, having values of 6 Hz for 2-methyl-1,3-dioxolane derivatives, 1.4 Hz for 2-methyl-1,3-dioxane derivatives and 2.6 Hz for 2-methyl-1,3-dioxepane (Table 1).

Ayras[17] had measured the absolute values of geminal coupling constants of methyl carbons in a number of systems including the 5- and 6-membered parent compounds here (1b and 4b). From a linear correlation of $^{2}J_{C,H}$ values and $^{2}J_{H,H}$ values, Ayras[17] suggested that the signs of the $^{2}J_{C,H}$ values for compounds 1b and 4b are both positive. Selective population transfer (SPT) experiments[18] have been performed here to confirm this sign assignment.[17] Most SPT experiments[18] have been performed on AMX systems. The spins involved here are the acetal hydrogen, the methyl carbon and the methyl hydrogens, which form an AMX_3 system. As far as we are aware, an AMX_3 case has not been examined in an SPT experiment although a related experiment has been performed on an AX_3 case.[19]

Figure 1 shows the energy level diagram for the AMX_3 system. Figure 2 shows a stick diagram of the relavent part of the

TABLE 2. Useful NMR Results for Carbohydrate Ethylidene Acetals and their Precursors

Compound	^{13}C NMR Chemical Shifts (ppm)								^{13}C-^{1}H Coupling Constants (Hz)		^{1}H NMR Chemical Shifts (ppm)	
	C-1	C-2	C-3	C-4	C-5	C-6	acetal C	methyl C	^{1}J acetal C	^{2}J methyl C	acetal H	methyl
9a[a]	55.1	71.6	70.2	69.7	70.4	63.7						
9b	55.8	72.13[b]	70.8[b]	69.1[b]	70.21[b]	68.4	100.4	19.9	157.4	1.3	4.721	1.33
9c	55.8	72.16[b]	70.8[b]	69.1[b]	70.16[b]	67.8	100.3	19.9	158.3	1.3	4.723	1.33
9d	55.8	72.2	71.2	70.2	76.1	67.8	102.2	20.1	166.2	5.9	5.07	1.38
9e	56.0	71.8[b]	71.0[b]	70.0[b]	75.9	66.9	101.8	19.6	165.4	5.5	4.98	1.36
10a[c]	101.1	72.5	74.2	70.7	72.3	61.7						
10b	100.2	72.8	71.0	80.7	62.5	68.5	99.7	20.3	159.4	1	4.72	1.37
10c	99.0	78.8	76.9	79.0	62.1	68.6	99.8 95.5 95.5	20.4 20.9 20.9	159.4 164.8 164.8	1.3 2.0[b,d] 1.7[b,d]	4.60 5.05 5.12	1.36 1.36 1.36
10d	98.8	78.5	71.2	78.3	61.9	68.5	99.8 97.5 97.2	20.4[b] 19.6[b] 21.7[b]	160.4 167.3 159.4	1 2.5 1	4.73 5.20 5.06	1.37[b] 1.41[b] 1.33[b]
11a[e]	63.7	71.3	69.6	69.6	71.3	63.7						
11b	68.6[b]	59.5	81.8	81.8	66.4	69.0[b]	98.8 98.7 98.3	20.4 20.4 19.4	159±3 159±3 170±3	1.1 1.1 2.8	4.70 4.70 4.97	1.33 1.33 1.21

a. ref.8. b. signals may be interchanged. c. in water-$\underline{d}_2$ (ref. 23). d. from spectrum of a sample in a 1:1/chloroform-$\underline{d}$:acetone-$\underline{d}_6$ solution, shifts 95.2 and 94.7 ppm. e. in dimethyl sulfoxide-$\underline{d}_6$ (ref. 24).

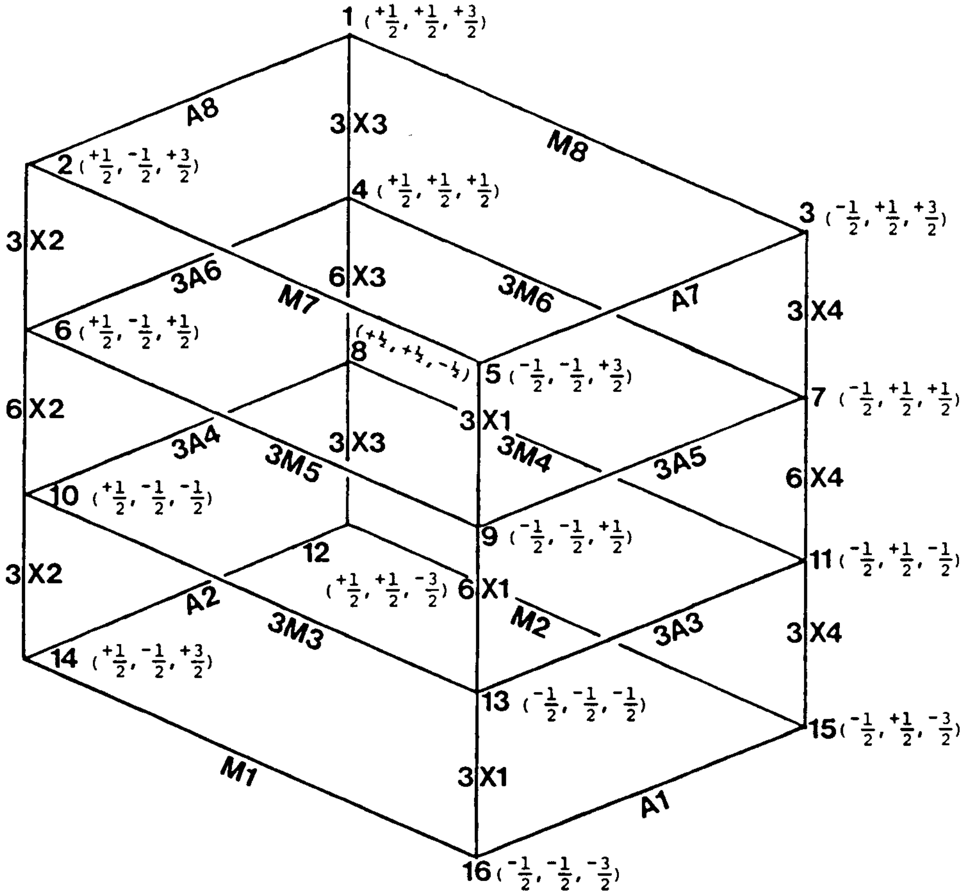


Fig. 1. Energy level diagram for an AMX_3 system. Energy levels are at the corners while transitions are along vertical and horizontal lines. There are 3 degenerate energy levels at the corners labelled 4, 6 - 11 and 13.

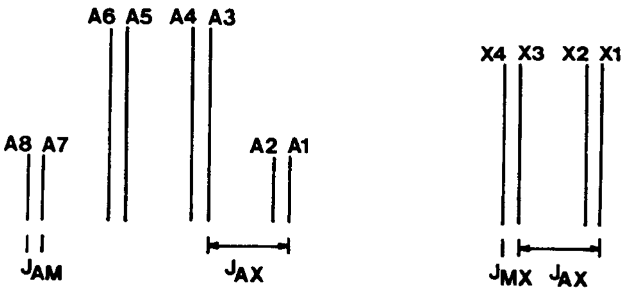


Fig. 2. Stick diagram of the A and X parts of an AMX_3 system. Lines are numbered assuming all coupling constants are positive.

spectrum with the lines numbered assuming that all coupling constants are positive. It is well established that the signs of both $^1J_{C,H}$ and $^3J_{H,H}$ are positive.[20] A negative value for $^2J_{C,H}$ would interchange the positions of lines A_1 and A_2, A_3 and A_4, A_5 and A_6 and A_7 and A_8. The intensities of the lines A_1, A_2, A_3, A_4, A_5, A_6, A_7 and A_8 are proportional to $(1:1:3:3:3:3:1:1)\gamma c$ respectively before irradiation. Irradiation of one of the X transitions with a selective Π pulse affects the populations for the connected energy levels. For instance, consider irradiation of the transitions labelled X_1 (see Figure 1). The population of each energy level will be altered by a factor γ_H/γ_C for each transition connecting the energy level. Thus levels 16 and 13 will be depleted by $3\ \gamma_H/\gamma_C$. Levels 9 and 5 will be enriched by $3\ \gamma_H/\gamma_C$. Transitions A_1, A_3, A_5 and A_7 are affected while A_2, A_4, A_6 and A_8 are not. Calculated intensity changes from irradiation of the line X_1 expressed as ratios of their original intensities are -11, -3, +5 and +13 for A_1, A_3, A_5 and A_7 respectively. Observed changes for the signals for the methyl carbon of compound <u>1b</u> on irradiation of line X1 were -4, -0.6, +2 and +6 in good agreement with the order predicted (compare top and bottom levels of Figure 1). Similar or poorer results are normally observed with SPT experiments[18] due to a number of experimental and theoretical difficulties; obtaining low power pulses which rotate the magnetization of only one line exactly π radians, positioning the pulse exactly at the desired line, keeping the pulse short enough that secondary population transfers do not occur. Figure 3 shows that irradiation of the four X lines of <u>1b</u> gave consistent results. The experiment unambiguously demonstrated that the $^2J_{C,H}$ value, 5.9 Hz, has a positive sign.

Figure 4 shows the results for 2-methyl-1,3-dioxane (<u>4b</u>). The $^2J_{C,H}$ value in this compound is 1.3 Hz and this small a splitting is not evident at the sweep width at which the fully coupled top spectrum is displayed. The requirement that the selective pulse irradiate only the desired X line in the ^{13}C satellite part of the proton signals for the methyl group is much more difficult to achieve for this compound. Nevertheless, the results shown in figure 4 are only in accord with a positive sign for the $^2J_{C,H}$ value. The earlier prediction of sign[17] was correct.

Confirmation that this very small latter value was positive indicates the precision of the relationship of Ayras[17] and strongly suggests that $^2J_{C,H}$ is affected by the same factors that

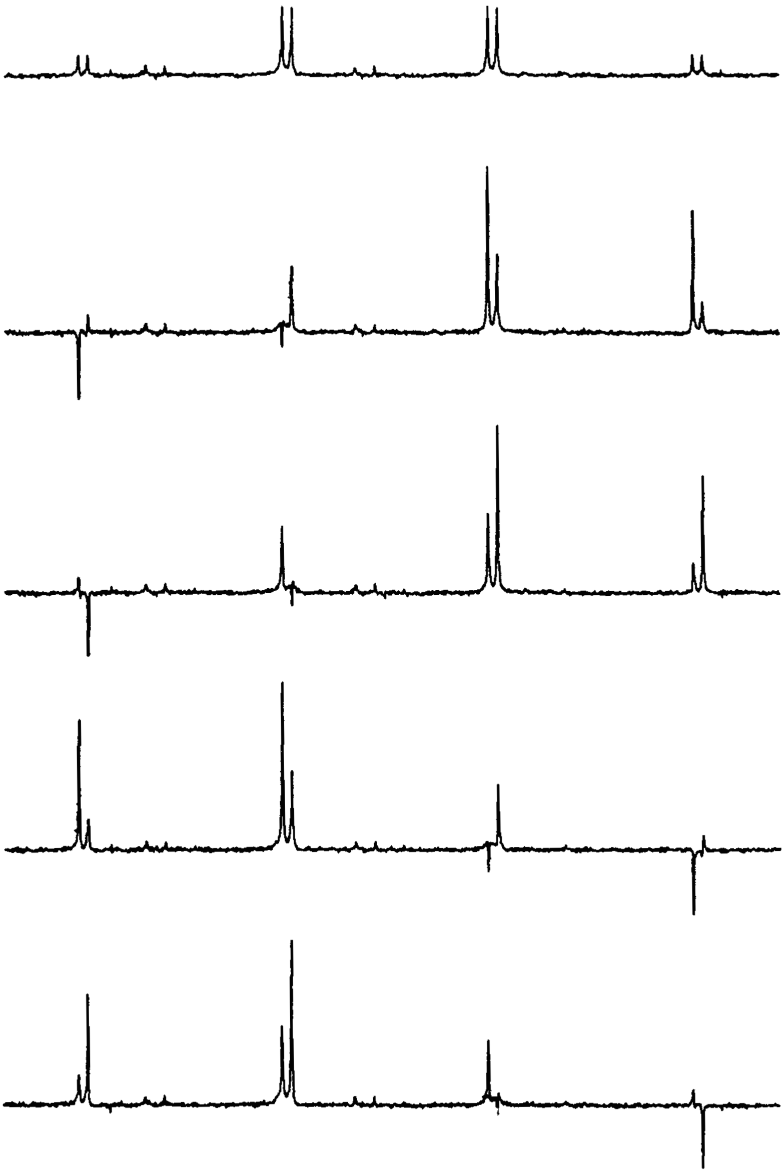


Fig. 3. Selective population transfer experiments on 2-methyl-1,3-dioxolane. The spectra show the signals of the methyl carbon. From the top, these signals are shown with no irradiation, with irradiation at line X4 of the methyl proton signals in the ^{1}H NMR ^{13}C satellite spectrum, at line X3, at line X2, and at line X1.

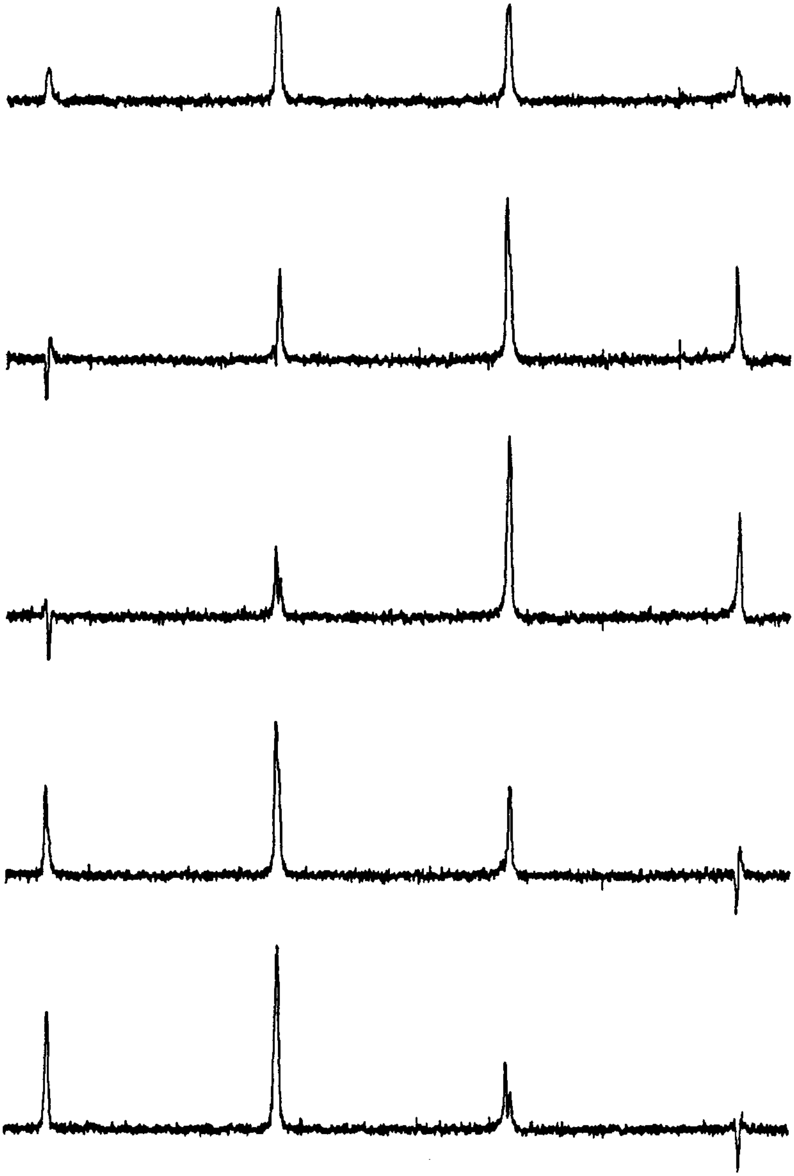


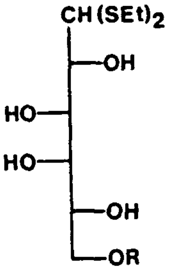
Fig. 4. Selective population transfer experiments on 2-methyl-1,3-dioxane. From the top, the signals shown are the methyl carbon when there is no irradiation and when there is irradiation at lines X4, X3, X2, and X1 of the methyl protons.

determine the size of $^{2}J_{H,H}$ at least for the types of groups considered. These factors include the presence of electronegative groups and lone pairs and their geometrical relationship to the CH_2 group, the H-C-H bond angle and hybridization effects.[21] Consideration of the range of $^{2}J_{H,H}$ values observed for $-OCH_2O-$ groups[21,22] and Ayras's relationship suggests that the range of $^{2}J_{C,H}$ values will be from about +6 to 0 Hz. Deviation from the values of 5.9, 1.3 and 2.6 Hz obtained for the parent five-, six- and seven-membered ethylidene acetal rings can be related to conformational and bond-angle effects as for $^{2}J_{H,H}$ values for related methylene derivatives.

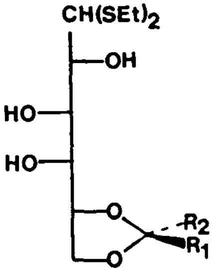
A fourth potential NMR parameter for use as an aid to structural assignments is the $^{1}J_{C,H}$ value for the acetal carbon. The magnitude of this parameter was related to ring size as it is for benzylidene acetals[4] (see Table 1). The values observed for five-membered rings fell in a narrow range from 164.2 to 165.0 Hz. Similarly those in 2-methyl-1,3-dioxanes had a small range of values from 158.1 to 159.2 Hz. The value in 2-methyl-1,3-dioxepane was intermediate. Measurement of these values was more difficult than for benzylidene acetals. Not only were the coupled ^{13}C NMR signals of these acetal carbons split by the $^{3}J_{C,H}$ coupling to the hydrogens on the same carbons as the acetal oxygens (as are benzylidene acetal carbons) but also by the $^{2}J_{C,H}$ couplings to the methyl hydrogens. Thus, the S/N ratio for these signals were always smaller than for the acetal methyl signals.

Confirmation of the distinction between six- and seven-membered ring-size for isopropylidene, cyclohexylidene and methylene acetals can be obtained by comparing the carbon-13 chemical shifts of the initial diol with those the resulting acetal.[8] For C-2 of a 1,3-propanediol derivative, an upfield shift of 8-9 ppm was observed while the effects for 1,4-propanediol derivatives were small.[8] This upfield shift was smaller if the resulting 1,3-dioxane acetal had equatorial substituents on both carbon-4 and -6.[8] Similar effects were evident when the chemical shifts of ethylidene acetals were compared with those of their precursor diols. Upfield shifts ranging from 7.8 to 9.7 ppm were observed here for most 2-methyl-1,3-dioxane derivatives. The chemical shift of the signal for carbon-5 of cis,cis-2,4,6-trimethyl-1,3-dioxane was 6.1 ppm upfield of that of the same carbon of the precursor diol, consistent with a similar attenuation on 4- or 6-equatorial substitution observed for the other acetals.[8]

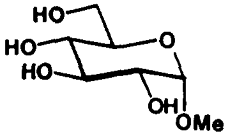
Carbohydrate examples



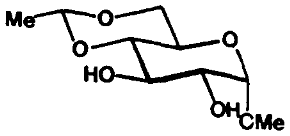
9a , R = H
9b and 9c ,
R = CHMeOEt



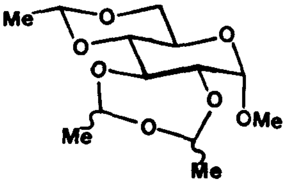
9d R_1 = Me R_2 = H
9e R_1 = H R_2 = Me



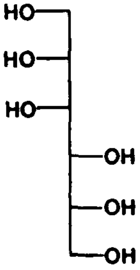
10a



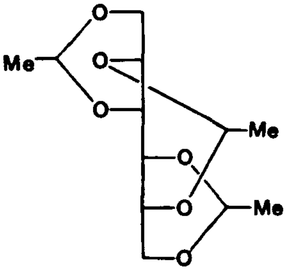
10b



10c and 10d



11a



11b

A range of carbohydrate derivatives were prepared to illustrate the most common types of ethylidene acetals encountered in carbohydrate chemistry. Table 2 lists the NMR data for these compounds and their precursor alcohols. Table 3 lists the ranges of useful parameters defined by both the carbohydrate examples and the model compounds. For the 1,3-dioxolane and 1,3-dioxane derivatives the values of all parameters discussed earlier fall within the ranges defined by the model compounds or slightly extend these ranges.

TABLE 3. Summary of Useful NMR Parameters for Structural Assignment of Ethylidene Acetals

Type of Ring	NMR Chemical Shifts (ppm)			^{13}C NMR Chemical Shift Differences (ppm)[a]		$^{13}C-^{1}H$ Coupling Constants (Hz)	
	^{1}H NMR shift	^{13}C NMR shifts		for carbons α to oxygen	for carbons β to oxygen	^{2}J methyl C	^{1}J acetal C
	acetal H	acetal C	acetal Me				
1,3-dioxolane	4.93- 5.12	99.2- 102.2	19.8- 20.3	1.3- 5.7	b	5.5- 6.0	164.2- 166.2
1,3-dioxane with no axial substituents at C-4 or C-6	4.60- 4.73	98.4- 99.8	20.3- 21.3	2.5- 10.0	-7.8 - -10.2	0 - 1.4	158.2- 160.4
1,3-dioxane with an axial substituent at C-4 or C-6	5.02	91.2- 93.4	25.2	c	c	c	c
1,3-dioxepane	4.86- 5.20	95.5- 99.5	19.4- 21.7	0.2- 6.0	-0.4	1.7- 2.8[d]	159.4- 170

a. value from the acetal - value from the same carbon of the precursor diol.
b. none in the 1,3-dioxolane ring. c. none measured d. one exception discussed in text.

Considerable variation was noted in most parameters for the five seven-membered ring ethylidene groups. The ^{1}H NMR chemical shifts of the acetal protons were larger in the carbohydrate examples, ranging from 4.97 to 5.20 ppm, as compared to 4.86 ppm in 8b. The ^{13}C NMR chemical shifts of the acetal carbons were less downfield, 95.5 - 98.3 ppm, as opposed to 99.5 ppm in 8b. The values of $^2J_{C,H}$ between the acetal hydrogen and the methyl carbon were the most consistent parameter; four of the five values fell in the range 1.7 - 2.8 Hz, close to the value of 2.6 Hz observed for 8b. The value for one ethylidene group in compound 10d was <1 Hz. This smaller value is probably associated with an unusual conformation about the -OCHMeO- group. The considerable variation observed in $^2J_{H,H}$ values in 1,3-dioxepanes has been associated with conformational changes.[22] $^1J_{C,H}$ values also ranged considerably from 160.4 to 170 Hz, with four values 164.8 Hz or larger. The small value was associated with the ethylidene group for which a small $^2J_{C,H}$ value was measured. Small values of $^1J_{C,H}$ in seven-membered ring benzylidene derivatives were shown to be caused by unusual conformations of the seven-membered ring.[4,25]

In related work, it was demonstrated that the location of a five-membered isopropylidene or cyclohexylidene ring could be determined by comparing the chemical shifts of the carbons in the acetal with those in the precursor alcohol.[8] The signals of alcohol carbons directly attached to oxygen atoms were shifted downfield on acetal formation by significant amounts, > 2 ppm. Similar observations were made here for five-membered ethylidene acetals (see Table 1). Formation of six-membered isopropylidene and cyclohexylidene derivatives of diols had very small effects on the chemical shifts of these carbon atoms because the β-effect of the acetal carbon was offset by the two γ-effects of its substituents, particularly the large γ-*gauche* effect of the axial substituent.[8] In contrast, formation of 2-methyl-1,3-dioxane rings resulted in downfield shifts for the signals of those carbons that became carbon-4 or -6 of the 1,3-dioxane ring of 4.9 to 7.6 ppm for primary carbons and 2.5 to 10.0 ppm for secondary carbons. These shifts can be used for structural assignment if the carbon signals can be assigned.

Compounds 9b and 9c are members of a class of ethylidene acetal for which no model compounds were prepared, the acyclic acetal. The values observed for most of the parameters, including the $^1J_{C,H}$ and $^3J_{C,H}$ values and the chemical shift of the acetal proto were within the ranges observed for 2-methyl-1,3-dioxanes.

The ^{13}C NMR chemical shift of the acetal carbon was larger than in 1,3-dioxanes. This difference probably reflects the lack of substitution on the ethoxy group of 9b and 9c as compared to the cyclic compounds. Apparently, the values of most of these NMR parameters are influenced primarily by whether or not the groups about the acetal center are staggered. These two acyclic acetals probably adopted the conformation in which the COCO dihedral angles about the acetal group have +gauche,+gauche angles (or -,-), rather than the less favorable +gauche,-gauche angles of a 1,3-dioxane ring.[27]

It is worth noting that during the preparation of one type of carbohydrate derivative, results were obtained which were somewhat different from a report in the literature[2], possibly as a result of different isolation procedures. The product of ethylidenation of D-galactose diethyl dithioacetal with ethyl vinyl ether was fractionated by column chromatography. ^{13}C NMR spectroscopy showed that the first fraction was a complex mixture containing more than one type of ethylidene acetal. The second fraction was a mixture of the two 5,6-O-ethylidene derivatives, from which both the previously isolated compound 9d[2] and its epimer 9e were obtained by recrystallization. The previously isolated compound 9d, the major product of the two, was assigned the S (or trans) configuration in the 5,6-O-ethylidene ring from the downfield shift of the signal from its acetal proton in comparison with that from 9e.[11,26] The third fraction was a mixture of the two possible 6-O-(1-ethoxyethyl)-D-galactose diethyl diacetal derivatives, whereas a single isomer had been isolated previously.[2] Again, the compound isolated previously was obtained by recrystallization. The ratio of yields of the 5,6-O-ethylidene derivative to the acyclic compound was much lower here than previously.[2]

In a second case, it was discovered that a product which had hitherto been considered to be a single compound[28] was in fact a mixture of two compounds. Methyl 4,6-O-ethylidene-2,3-O-oxidodiethylidene-α-D-glucopyranoside was prepared by reaction of methyl α-D-glucopyranoside with paraldehyde and acid as previously and had physical constants which matched those in the literature.[28] The 4,6-O-ethylidene group should be present in one configuration, the R configuration, which has the methyl group in the more stable equatorial orientation. However, variation in configuration at the two new chiral centres in the 2,3-O-oxidodiethylidene ring could conceivably give four stereoisomers.

^{13}C NMR spectra of the product showed that it was a mixture of two compounds which were separated by careful column chromatography. The configurations of the ethylidene groups in the seven-membered rings of the two isomers were not assigned. However, the observation of similar ^{13}C NMR chemical shifts for C-2 and quite different chemical shifts for C-3 for the two isomers indicated that the two isomers have the same configuration at the new chiral centre closest to C-2 and are different at the other centre.

CONCLUSIONS

The values taken by a number of NMR parameters are related to ring size. The two parameters which are often easiest to measure, the chemical shifts of the acetal proton and carbon are helpful in assignment of ring size, particularly if both are available, but do not provide unambiguous assignments. The magnitude of the $^{2}J_{C,H}$ value between the ethylidene methyl carbon and the acetal proton is comparatively easy to measure and is the most reliable indicator of ring size. The location of an ethylidene acetal can often be determined if the ^{13}C NMR chemical shifts of the acetal and its precursor alcohol can be assigned. Significant downfield shifts were observed for the carbons attached to the oxygen atom bonded to the acetal carbon in five- and six-membered ring derivatives.

EXPERIMENTAL

General Methods

Melting points were determined by using a Fischer-Johns melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on samples dissolved in chloroform-*d*- with tetramethylsilane present as an internal reference. ^{1}H NMR spectra were recorded at 79.6 or 361.07 MHz on Varian CFT-20 or Nicolet NT-360 NB spectrometers respectively. ^{13}C NMR spectra were recorded on the same spectrometers at 20 or 90 MHz. ^{1}H NMR coupling constants were obtained from first order analyses except where noted. ^{13}C NMR chemical shifts at 20 MHz were obtained from spectra recorded using 8K data points, 0.9 sec acquisition times and 34° pulse angles and at 90 MHz from spectra using 32K data points, at least 1 sec acquisition times and 60° pulse angles. Where ^{13}C NMR chemical shifts have been compared with those of the same compounds from the literature,[9,12] reproducibility was within 0.3 ppm for all shifts and was normally within 0.1 ppm. Coupling constants were measured with acquisition times 1.5 sec or greater. Chemical shifts for the model compounds were assigned from the off-resonance decoupled or fully coupled spectra. For one compound, trans-2,4-dimethyl-1,3-dioxolane, assignments for C-4 and C-5 differed from those in the literature.[9] The coupled spectrum clearly showed that the downfield signal was a triplet and hence must be assigned to C-5. ^{13}C NMR chemical shifts for the compounds 9b-e, 10b and 11b were obtained by consideration of substituent effects on the shifts of their starting materials which had been assigned previously.[23,24] Assignments of the 90 MHz ^{13}C NMR signals of 10c and 10d were made by single frequency decoupling of the fully assigned ^{1}H NMR spectra. The SPT experiment was performed as by Cyr et al.[18] Mass spectra were measured with a CEC 21-104 mass spectrometer operating at 70 eV ionizing voltage and an inlet temperature of 110 °C. TLC was performed on 0.25 mm thick Merk Silica Gel 60F-254 glass plates cut to be approximately 7 cm long. Plates were developed by spraying with a 2% ceric sulfate solution in 1 M sulfuric acid and heating for a few minutes at 150 °C. The term pet ether refers to petrolium ether 30-60 °C unless otherwise indicated. Eluent systems used consisted of mixtures of pet ether and ethyl acetate: A, 6:1; B, 3:2 and mixtures of chloroform and acetone: C, 4:1; D, 1:1. Anhydrous p-toluenesulfonic acid was obtained from commercial monohydrate by heating 5h at 56 °C in a drying pistol under vacuum (0.5 mm) in the presence of phosphorous pentoxide. N,N-dimethylformamide (DMF) was purified by distillation from calcium hydride.

Model compounds were prepared from the appropriate diol and paraldehyde or ethoxyethene under acid catalysis and had physical constants similar to literature values. 1,3:2,5:4,6-Tri-O-ethylidene-D-mannitol (11b) was prepared from mannitol and paraldehyde in the presence of p-toluenesulfonic acid, mp 172-173 °C (lit.[29] 172 °C), $[\alpha]^{25}_{D}$ -72.5° (c 1.6, chloroform) (lit.[29] -72.3°).

Ethylidenation of D-galactose diethyl dithioacetal (9a)

A solution of compound 9a (4.86 g, 17.0 mM), ethoxyethene (1.449, 20 mM) and anhydrous p-toluenesulfonic acid (50 mg) in DMF (40 mL) was stirred at room temperature for 2.5 h. Sodium carbonate (0.5 g) was added, and the reaction mixture was stirred a further 0.5 h then filtered and concentrated. Chloroform was added and the mixture was kept overnight in the refrigerator. The starting material which deposited was removed by filtration and the solution concentrated to a white solid (5.23 g). The solid was fractionated by chromatography on silica gel (300 g) using solvent C as eluent. Two unidentified fractions were obtained (0.42 g and 0.19 g both shown by ^{13}C NMR to contain mixtures of compounds each with more than one ethylidene group, then fraction A (0.414 g) and fraction B (2.05 g).

Fraction A, a solid, was shown to be a mixture of two compounds by ^{1}H and ^{13}C NMR spectroscopy. Recrystallization from dichloromethane-pet. ether gave *S*-5,6-*O*-ethylidene-*D*-galactose diethyl dithioacetal (9d),); mp 122-123 °C (lit.[2] 120 °C) $[\alpha]_D^{26}$ 68.1° (c 1.27, chloroform) (lit.[2] +72 2°); R_F 0.75 in solvent D; ^{1}H NMR data δ: 1.29 (t, 6H, J = 7.4 Hz, 2 $\mathrm{SCH_2\underline{CH_3}}$), 1.38 (d, 3H, J = 4.8 Hz, ethylidene Me), 2.61, 2.63 (2d, 2H, J = 8.1, 7.4 Hz, OH-3, OH-4), 2.68-2.72 (complex m, 4H, 2 $\mathrm{S\underline{CH_2}CH_3}$), 3.40 (d, 1H, J = 1.3 Hz, OH-2), 3.61 (dt, 1H, $J_{3,4}$ = $J_{4,OH-4}$ = 7.4, $J_{4,5}$ = 4.1 Hz, H-4), 3.82 (t, 1H, $J_{5,6}$ = $J_{6,6'}$ = 8.2 Hz, H-6), 3.89 (br d, dd after exchange, 1H, $J_{1,2}$ = 9.1 , $J_{2,3}$ = 0.8 Hz, H-2), 3.97 (t, d after exchange, 1H, $J_{3,4}$ = 7.9 Hz, H-3), 4.03 (d, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 4.20 (dd, 1H, $J_{5,6'}$ = 6.7, $J_{6,6'}$ = 8.3 Hz, H-6'), 4.29 (m, H-5), 5.17 (q, 1H, J = 4.7 Hz, acetal H) ; ^{13}C NMR data δ: 14.3, 14.7 (2 $\mathrm{S\underline{CH_2}CH_3}$), 15.3 ($\mathrm{O\underline{CH_2}CH_3}$), 23.9,25.4 (2 $\mathrm{SCH_2\underline{CH_3}}$), 61.5 ($\mathrm{OCH_2\underline{CH_3}}$), for other data, see Table 2.

The mother liquor on concentration and recrystallization from the same solvent gave *R*-5,6-*O*-ethylidene-*D*-galactose diethyl dithioacetal (9e); mp 107-109 °C; $[\alpha]_D^{26}$ 74.0° (c 0.80, chloroform); R_F 0.68 in solvent D; ^{1}H NMR data δ : 1.296, 1.301 (2t, 6H, J = 7.5, 7.4 Hz, 2 $\mathrm{SCH_2\underline{CH_3}}$), 1.36 (d, 3H, J = 5.4 Hz, ethylidene Me), 2.64-2.80 (complex m, 4H, 2 $\mathrm{S\underline{CH_2}CH_3}$), 2.83, 3.30, 3.31 (3d, 3H, J = 8.5, 3.7, 3.1 Hz, OH-3, OH-4, and OH-2, respectively), 3.72 (ddd, dd after exchange, 1H, $J_{2,OH}$ = 3.0, $J_{1,2}$ = 9.3, $J_{2,3}$ = 0.9 Hz, H-2), 3.80 (dd, 1H, $J_{5,6}$ = 5.3, $J_{6,6'}$ = 11.2 Hz, OH-6), 4.04 (d, 1H, $J_{1,2}$ = 9.3 Hz, H-1), 4.03-4.12 (complex m, 3H, H-4, H-5, H-6'), 4.51 (t, d after exchange, 1H, $J_{3,4}$ = 8.8 Hz, H-3), 5.12 (q, 1H, J = 5.1 Hz, acetal H); ^{13}C NMR data : 14.5, 14.6 (2 $\mathrm{SCH_2\underline{CH_3}}$), 15.3 ($\mathrm{OCH_2\underline{CH_3}}$), 23.9, 25.4 (2 $\mathrm{S\underline{CH_2}CH_3}$), 61.6 ($\mathrm{O\underline{CH_2}CH_3}$), for other data, see Table 2.

Fraction B, a solid, was a mixture of the two isomers of 6-*O*-(1-ethoxyethyl)-*D*-galactose diethyl dithioacetal (9b and 9c); mp 116-117 °C (lit.[2] 113 °C) ; $[\alpha]_D^{24.5}$ 54.1° (c 1.03, chloroform) (lit.[2] 64°); R_F 0.65 in solvent D; ^{1}H NMR data δ: 1.20 (t, 3H, J = 7.1 Hz, $\mathrm{OCH_2\underline{CH_3}}$), 1.286, 1.288 (2t, 6H, J = 7.4, 7.5 Hz, 2 $\mathrm{SCH_2\underline{CH_3}}$), 1.33 (d, 3H, J = 5.3 Hz, acetal $\mathrm{CH_3}$), 2.65-2.79

(complex m, 4H, 2 $SC\underline{H}_2CH_3$), 2.84, 3.04, 3.07, 3.10, 3.23, 3.42, 3.43 (7d, about 4H, J = 9.1, 7.2, 6.1, 6.6, 5.4, 3.2 and 3.1 Hz, OHs of 9b and 9c, 9c, 9b, 9b, 9c, 9c and 9b, respectively), 3.49, 3.52 (2q, 2H, J = 7.1, 7.1 Hz, $OC\underline{H}_2CH_3$ in 9b and 9c), 3.46-3.91 (complex m), 4.06 (d, 1H, J = 9.1 Hz, H-1 in 9b and 9c), 4.09 (m, 1H), 4.721, 4.723 (2q, 1H, J = 5.4, 5.3 Hz, acetal H in 9c and 9b) ; ^{13}C NMR data δ: 14.4, 14.6 and 14.5, 14.6 (2 $SCH_2C\underline{H}_3$ groups in 9b and 9c), 23.5, 25.7 (2 $SCH_2\underline{CH_3}$ groups), for other data, see Table 2; m/z: 358 (0.5%, M•), 312 (5.5%, M-HOEt), 251 (2.2%, 312-EtS•), 233 (7.8%, 251-H_2O), 189 (7.6%), 177 (8.1%), 159 (8.0%), 137 (10.7%), 136 (20.8%), 135 (100%, +CH(SEt)$_2$), 107 (13%), 105 (17.9%), 103 (11.8%), 75 (15.9%), 73 (60.4%).

Ethylidenation of methyl-α-D-glucopyranoside (10a)

A solution of compound 10a (5.0 g) in a mixture of paraldehyde (50 mL) and conc sulfuric acid (10 drops) was stirred 14 h. Chloroform (250 mL) was added and the clear solution was treated with solid potassium carbonate (5 g), stirred a few minutes then filtered. Concentration under reduced pressure gave a white solid (8.44 g). Part of this solid was recrystallized from ethanol as previously[28] to give white crystals of methyl 4,6-O-ethylidene-2,3-O-oxidodiethylidene-α-D-glucopyranoside, mp 180-182 °C (lit.[28] 182.5-183.5 °C), $[\alpha]_D^{26}$ +85.0° (c 4, chloroform) (lit.[28] +83.5°). Part of the solid (3g) was very carefully fractionated by column chromatography on silica gel (300 g) using solvent A as eluent into two components, 10c (0.071 g, R_F = 0.31) and 10d (2.46 g, R_F = 0.25), two of the four possible isomers involving configurational change in the 2,3-O-oxidodiethylene ring of methyl 4,6-O-ethylidene-2,3-O-oxidodiethyl-α-D-glucopyranoside. 10c had mp 145-146 °C; $[\alpha]_D^{26}$ +108.0° (c 1.52, chloroform); ^{13}C NMR data δ : 55.3 (OCH_3), for other data, see Table 2; ^1H NMR data (361.07 MHz-data for the 7 glucose hydrogens obtained by iterative spectral simulation using the program LAME[30], standard deviations for parameters were 0.000011 to 0.000014 ppm for chemical shifts and 0.005 to 0.011 Hz for coupling constants), δ: 1.334 (d, 3H, J = 5.26 Hz, ethylidene Me), 1.367 (d, 3H, J = 5.01 Hz, ethylidene Me), 1.414 (d, 3H, J = 5.32 Hz, ethylidene Me), 3.309 (t, 1H, $J_{3,4}$ = 9.45, $J_{4,5}$ = 9.54 Hz, H-4), 3.411 (s, 3H, OCH_3), 3.458 (d of d, 1H, $J_{1,2}$ = 3.63, $J_{2,3}$ = 8.57 Hz H-2), 3.529 (t, 1H, $J_{5,6ax}$ = 10.45, $J_{6ax,6eq}$ = -10.32 Hz, H-6 ax), 3.690 (t of d, 1H, $J_{5,6eq}$ = 4.95 Hz, H-5), 4.125 (d of d, 1H, H-6eq), 4.243 (t, 1H, H-3), 4.725 (q, 1H, J = 5.02 Hz, acetal H), 4.829 (d, 1H, H-1), 5.047 (q, 1H, J = 5.29

Hz, acetal H), 5.205 (q, 1H, J = 5.27 Hz, acetal H). 10d had mp 191-192 °C; $[\alpha]_D^{26}$ 82.9° (c 1.59, chloroform); ^{13}C NMR data δ: 55.1 (OCH_3), for other data,see Table 2; ^1H NMR data (361.07 MHz - data from simulation as for compound 10c) δ: 1.376 (d, 6H, J = 5.12 Hz, 2 ethylidene Me), 1.393 (d, 3H, J 5.30 Hz, 1 ethylidene Me), 3.356 (t, 1H, $J_{3,4}$ = 9.48, $J_{4,5}$ = 9.55 Hz, H-4), 3.417 (s, 3H, OCH_3), 3.526 (t, 1H, $J_{5,6ax}$ = 10.44, $J_{6eq,6ax}$ = -10.34 Hz, H-6 ax), 3.601 (d of d, 1H, $J_{1,2}$ = 3.75, $J_{2,3}$ = 8.73 Hz, H-2), 3.693 (t of d, $J_{5,6eq}$, = 4.91 Hz, H-5), 3.949 (t, 1H, H-3), 4.110 (d of d, 1H, H-6eq), 4.734 (q, 1H, J = 5.04 Hz, acetal H), 4.789 (d, 1H, H-1), 5.127 (q, 1H, J = 5.28 Hz, acetal H), 5.200 (q, 1H, J = 5.28 Hz, acetal H).

Methyl 4,6-O-ethylidene-α-D-glucopyranoside (10b)

Compound 10b was prepared from the mixture of 10c and 10d (3.0 g) as previously.[28] The title compound was recrystallized twice from chloroform-pet ether to give colorless crystals, mp 74-75 °C (lit.[28] 77 °C); $[\alpha]_D^{26}$ 103.0° (c 1.39, water) (lit.[28] 109.1°); ^{13}C NMR data δ: 55.1 (OCH_3), for other data, see Table 2; ^1H nmr data (79.6 MHz) δ : 1.37 (d, 3H, J = 5.0 Hz, acetal Me), 2.31 (br s, 1H, OH), 3.42 (s, 3H, OCH_3), 3.13 - 4.18 (complex m, 7H), 4.72 (q, 1H, J = 5.0 Hz, acetal H), 4.74 (d, 1H, J = 3.4 Hz, H-1).

ACKNOWLEDGEMENTS

TBG thanks the Natural Sciences and Engineering Research Council of Canada for an operating grant. We thank ARMRC for the 361 MHz ^1H and 90 MHz ^{13}C NMR spectra and particularly Bruce MacDonald for carefully performing the SPT experiments.

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