Carbohydrate Research, 58 (1977) 9–20

PREDICTING CIRCULAR-DICHROISM SPECTRA OF PYRANOID MONOSACCHARIDES*

W. CURTIS JOHNSON, JR.

Department of Biochemistry and Biophysics, Oregon State University, Corvallis, Oregon 97331 (U. S. A.)

(Received June 16th, 1976; accepted for publication in revised form, November 15th, 1976)

ABSTRACT

Fragment spectra are presented that may be summed algebraically to predict the vacuum-ultraviolet, circular-dichroism spectra of certain pyranoid monosaccharides. It is shown that a limited number of these fragment spectra can be used to calculate a larger number of circular-dichroism spectra that had been measured previously. Furthermore, the circular-dichroism spectra of a number of other monosaccharides, whose spectra have not yet been measured, can be predicted.

INTRODUCTION

One of the goals of our research into the vacuum-ultraviolet, circular dichroism (c.d.) of monosaccharides is the formulation of empirical rules to relate the conformation of mono-, oligo-, and poly-saccharides to these measurements. Such rules have been developed by a number of workers for the optical rotation of sugars at the sodium D line (see, for instance, refs. 1–4). As a first attempt to relate carbohydrate configuration to this single-wavelength measurement, Hudson[1] developed his "Rules of Isorotation". Subsequently, Whiffen[2], Brewster[3], and Lemieux and Martin[4] developed simple, empirical rules that are generally applicable.

Kauzmann *et al.*[5] have shown that optical activity arises from the interaction of a group with the rest of the molecule. If an empirical approach is to be consistent with their theoretical basis, it must consider all possible interactions between the various groups that make up the molecule. One might consider only contributions from all ways of pairing the groups in the molecule (the principle of pairwise interaction) as one simplifying approximation. As a second approximation, one might consider only interactions between groups that are physically near one another (the near-neighbor approximation). The general rules developed previously for predicting optical rotation at the sodium D line are consistent with the principle of pairwise

*Optical Properties of Sugars. Part V.

interactions in the near-neighbor approximation. They may be used to predict reliably the sign and magnitude of the optical rotation for pyranoid sugars at the sodium D line.

C.d. bands can now be measured for unsubstituted, cyclic sugars by using modern vacuum-ultraviolet instrumentation[5]. These measurements are more useful than measurements at the sodium D line because they contain much more information. One way to utilize this information is to develop a set of rules analogous to those of Whiffen, Brewster, or Lemieux and Martin, that will relate these measurements to the conformations of the sugars.

Recently, we have measured the c.d. of α- and β-D-glucopyranose, α- and β-D-galactopyranose, α-D-xylopyranose, three pyranoid ketoses, and twelve methyl aldopyranosides in aqueous solution[6]. We compared the spectra of structurally related monosaccharides using c.d. difference spectra. According to the principle of pairwise interaction, these difference spectra reflect the changes in group interactions between the two molecules compared. The similarities between the difference spectra for pyranoses and methyl pyranosides having identical changes in near-neighbor group-interactions suggests that a catalog of "fragment" c.d. spectra might be compiled. The idea is that such fragment spectra could be summed algebraically to give a good prediction of the c.d. spectrum of a sugar of given configuration and conformation. This report takes the initial steps toward producing such a catalog of fragment spectra, with the hope that it will be useful for purposes of identification of sugars, determining configuration, and investigating conformation and solvent interaction.

DISCUSSION

Most asymmetric molecules exhibit c.d. bands, not because the chromophores themselves are intrinsically dissymmetric, but because they interact with the remainder of the molecule. According to the pairwise principle, an asymmetric molecule may be divided into symmetrical groups so that the optical activity is given as the sum of pairwise interactions between these groups. It is convenient to divide monosaccharides into the chromophoric functional-groups $\mathrm{HC(OH)}$, $-CH_2OH$, $-\mathrm{C(H)OC(H)}-$, and $\mathrm{C(H)OMe}$.

It will be assumed that the minor conformers present in aqueous solution may be overlooked, and each monosaccharide discussed here is in its pyranose ring-form in the $^4C_1$ conformation for both D and L families. Likewise, it is assumed that comparisons are possible, even though bond lengths and bond angles may vary somewhat. Then, for sugars that differ only at a single configurational center, c.d. difference spectra should reveal the changes in the interactions, involving the groups attached to this center, with other groups in the molecule.

Fragment spectra. — The key to compiling a catalog of fragment spectra is to

realize that the xyloses and xylosides become symmetrical if the functional group on the anomeric carbon atom is replaced by hydrogen. Thus the c.d. spectrum that we have measured for each of these compounds is completely attributable to the presence of the functional group on the anomeric carbon atom, and results from the interactions of this group with the other groups in the molecule. This conclusion does not necessarily mean that the anomeric group is the chromophore, however. These c.d. spectra are thus difference spectra themselves, and are also fragment spectra of the type that we seek. The c.d. spectra of α- and β-D-xylose and methyl α- and β-D-xyloside are presented in Fig. 1 as the basic fragment spectra in this catalog.

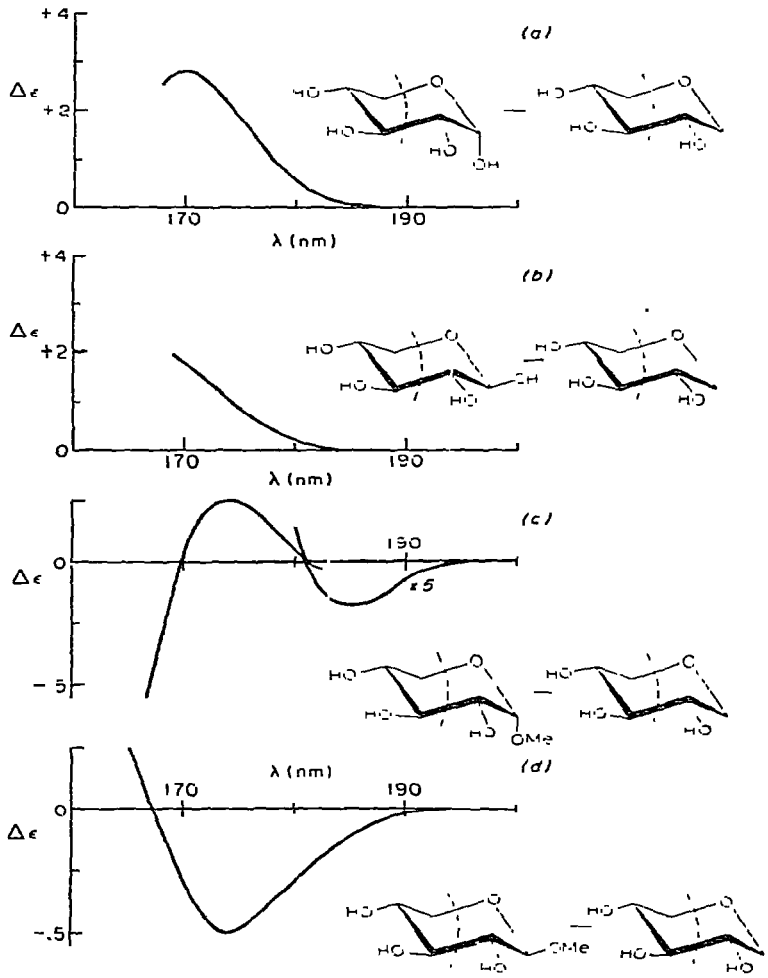

Fig. 1. Basic c.d. fragment spectra: (*a*) α-D-xylose; (*b*) β-D-xylose; (*c*) methyl α-D-xyloside, and (*d*) methyl β-D-xyloside.

Fig. 2 presents fragment spectra for changes at the anomeric carbon atom. These are the average of very similar difference spectra that result for both D-xylose and D-glucose pairs. Figs. 2a and 2b show the change in c.d. that results on changing a pyranose to a methyl pyranoside for the α and β pairs, respectively. Fig. 2c shows the change in c.d. attributed to a change from the β to α configuration at C-1 for pyranoses, whereas Fig. 2d gives the same change for pyranosides. In all cases, these c.d. fragment spectra are only valid when the 2-hydroxyl group is equatorial. The c.d. fragment spectra given in Fig. 2 are really redundant. Many combinations of four fragment spectra chosen from the eight presented in Figs. 1 and 2 may be used as an independent set of basic fragment spectra. For instance, one could choose the

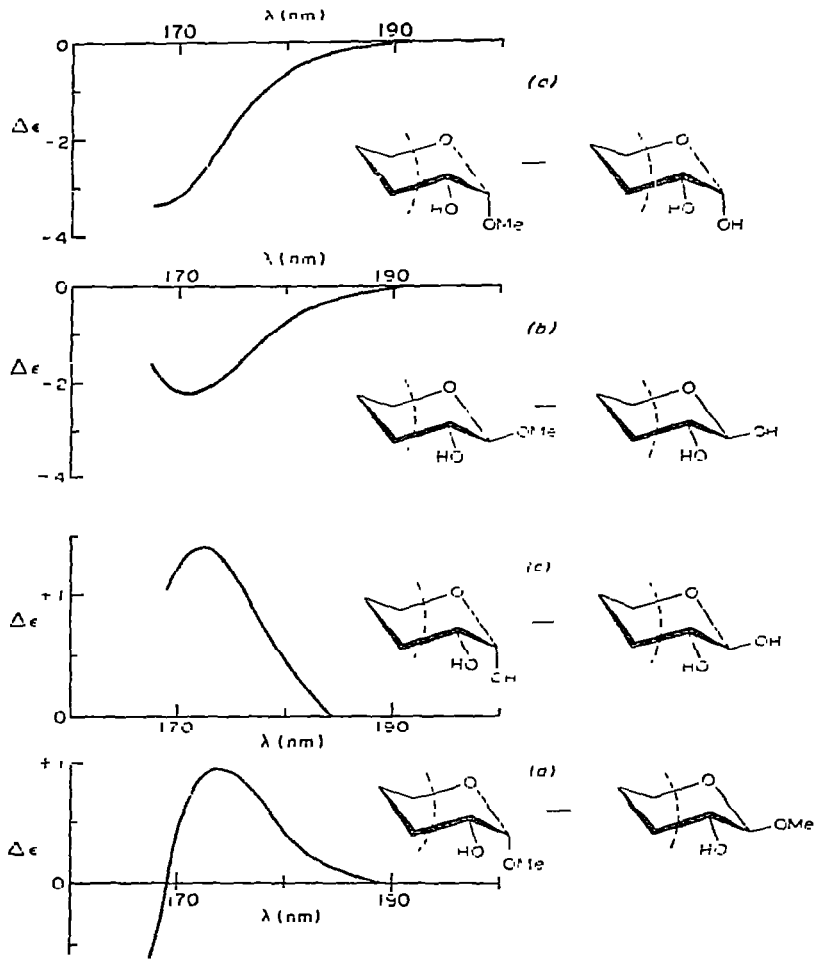

Fig. 2. C.d. fragment spectra for changes at the anomeric carbon atom: (*a*) α-pyranose to methyl α-pyranoside; (*b*) β-pyranose to methyl β-pyranoside; (*c*) β to α for pyranoses; and (*d*) β to α for methyl pyranosides. Each is the average for two or three sugar pairs.

spectrum in Fig. 1a and convert that into the spectra in Figs. 1b, 1c, and 1d by using the fragment spectra presented in Figs. 2a, 2b, and 2c. All eight are presented here so that selection may be made as convenient.

Very similar changes in the c.d. are observed when a hydroxymethyl group is added at C-5 of a pyranose or pyranoside having an equatorial 4-hydroxyl group. Fig. 3a gives the fragment spectrum that is an average of the difference spectra for (α-D-glucose − α-D-xylose), (β-D-glucose − β-D-xylose). (α-D-*manno*-heptulose − α-D-tagatose), (methyl α-D-glucoside − methyl α-D-xyloside), and (methyl β-D-glucoside −

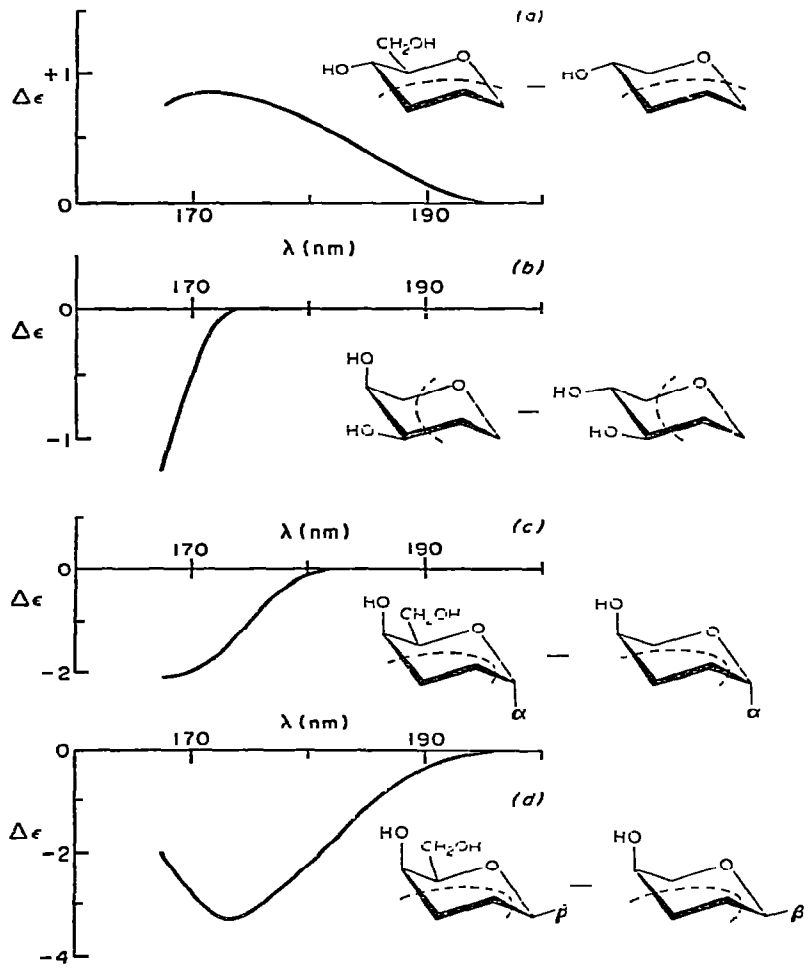

Fig. 3. C.d. fragment spectra: (*a*) addition of a hydroxymethyl group at C-5 with 4-hydroxyl group equatorial, average for five sugar pairs; (*b*) 4-hydroxyl group equatorial to axial, one sugar pair; (*c*) addition of a hydroxymethyl group at C-5 with 4-hydroxyl group axial for α sugars, average for two pairs of sugars; and (*d*) addition of a hydroxymethyl group at C-5 with the 4-hydroxyl group axial for β sugars, average for two pairs of sugars.

methyl β-D-xyloside). The fragment spectrum corresponding to the change in the 4-hydroxyl group of a xylose or xyloside from equatorial to axial is given in Fig. 3b. This fragment spectrum is the result of only one measured pair, (methyl β-L-arabinoside − methyl α-D-xyloside). The fragment spectra for the addition of a 5-hydroxymethyl group to an L-arabinose or methyl L-arabinoside (4-hydroxyl group

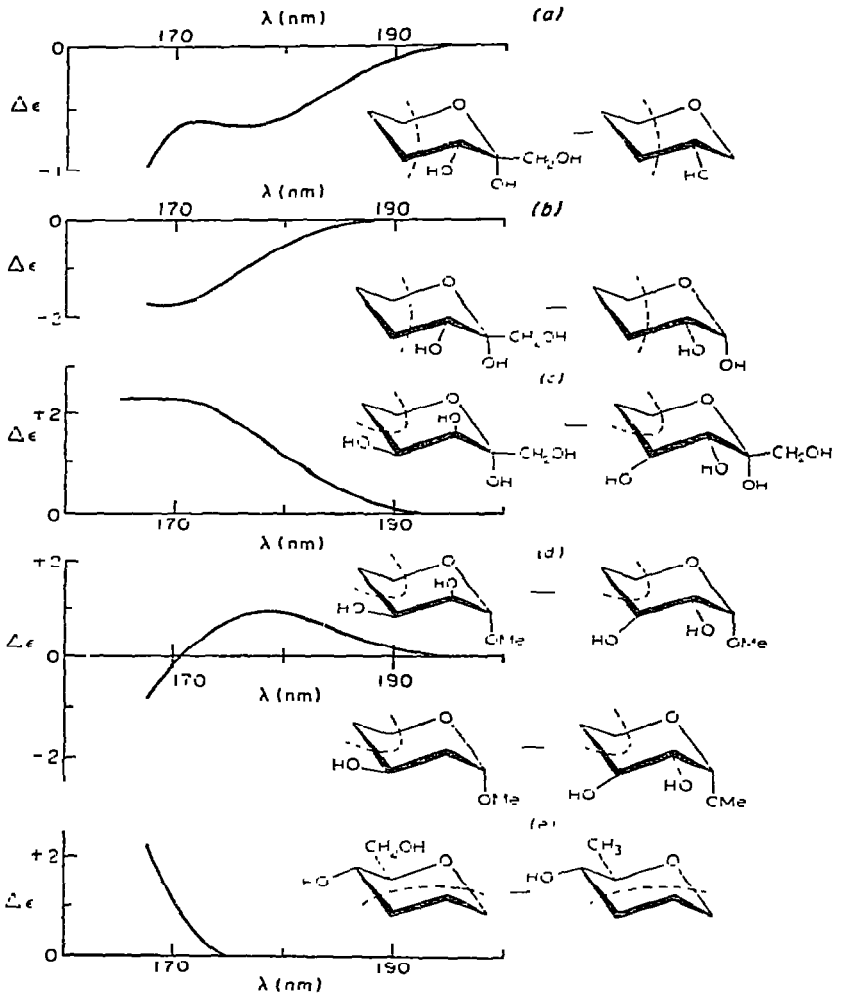

Fig. 4. C.d fragment spectra based on a single pair of sugars: (*a*) addition of an equatorial hydroxymethyl and an axial hydroxyl group to C-1 when 2-hydroxyl group is equatorial; (*b*) addition of an equatorial hydroxymethyl group at C-1 with an axial hydroxyl group at C-1 and an equatorial 2-hydroxyl group; (*c*) equatorial to axial hydroxyl group at C-2 with an equatorial 3-hydroxyl group plus an equatorial hydroxymethyl and an axial hydroxyl group at C-1; (*d*) equatorial to axial hydroxyl group at C-2 (or removal of an equatorial hydroxyl group at C-2) with an equatorial 3-hydroxyl group and an axial methoxyl group at C-1; and (*e*) addition of a hydroxyl group to C-6 when the 4-hydroxyl group is equatorial.

axial) is given for the α and β anomers in Figs. 3c and d, respectively. These two fragment spectra are an average for (D-galactose – L-arabinose) and (methyl D-galactoside – methyl L-arabinoside).

Other fragment spectra for which only one example has been measured are given in Fig. 4. The fragment spectrum in Fig. 4a represents the contribution of an equatorial hydroxymethyl and an axial hydroxyl group on the anomeric carbon atom when the 2-hydroxyl group is equatorial. The contribution of an equatorial hydroxymethyl group on the anomeric carbon atom when there is an axial hydroxyl group on C-1 and an equatorial hydroxyl group on C-2 is given in Fig. 4b. Fig. 4c shows the change in contribution of a 2-hydroxyl group when it is changed from equatorial to axial, provided that the 3-hydroxyl group is equatorial and the anomeric carbon atom has an equatorial hydroxymethyl group and an axial hydroxyl group attached. The fragment spectrum from a 2-hydroxyl group that is changed from equatorial to axial is identical to the fragment spectrum resulting from removal of this group, provided that the 3-hydroxyl group is equatorial and the anomeric carbon atom has an axial methoxyl group. This fragment spectrum is given in Fig. 4d. Fig. 4e shows the contribution of the hydroxyl group of a 5-hydroxymethyl group when the 4-hydroxyl group is equatorial.

Reproducing measured c.d. spectra. — These fragment spectra will only be valuable if they can be used to predict the c.d. spectra of monosaccharides. As a first step in testing their reliability, it will be shown that a limited number of fragment spectra may be used to compute the c.d. spectra of a larger number of compounds for which the spectra have already been measured.

Starting out with the four basic fragment spectra (the spectra of α- and β-D-xylose and the spectra of methyl α- and β-D-xyloside) and adding to each the fragment spectrum for the hydroxymethyl group from Fig. 3a, it should be possible to predict fairly accurately the spectra of four new sugars. Fig. 5 demonstrates that the predicted spectra of α-D-glucose, β-D-glucose, methyl α-D-glucoside, and methyl β-D-glucoside closely match the measured spectra. With five fragment spectra, the spectra of eight different monosaccharides may be calculated.

Although the fragment spectrum of Fig. 3a is due to the presence of the hydroxymethyl group, the hydroxymethyl group is not believed to be the chromophore giving rise to this rotational strength. In previous work[6], we assigned the long-wavelength shoulder beginning at about 195 nm in α- and β-D-glucose to the excitation of nonbonding electrons on the oxygen atom of the pyranose ring. As α- and β-D-xylose also have such an oxygen atom, they must also exhibit such a transition. However, in these two sugars, the band is probably of low intensity, blue-shifted, and buried under the obvious 170-nm band. We consider that the addition of a hydroxymethyl group tends to shield the ring oxygen-atom from the hydrogen-bonding solvent, red-shifting this band by at least 10 nm. The intensity of the band is probably increased because the ring oxygen-atom has more asymmetric, pairwise interactions. The shorter-wavelength bands at about 170 nm are assigned to those hydroxyl groups having some contribution from other ring-oxygen bands. The shorter-wavelength

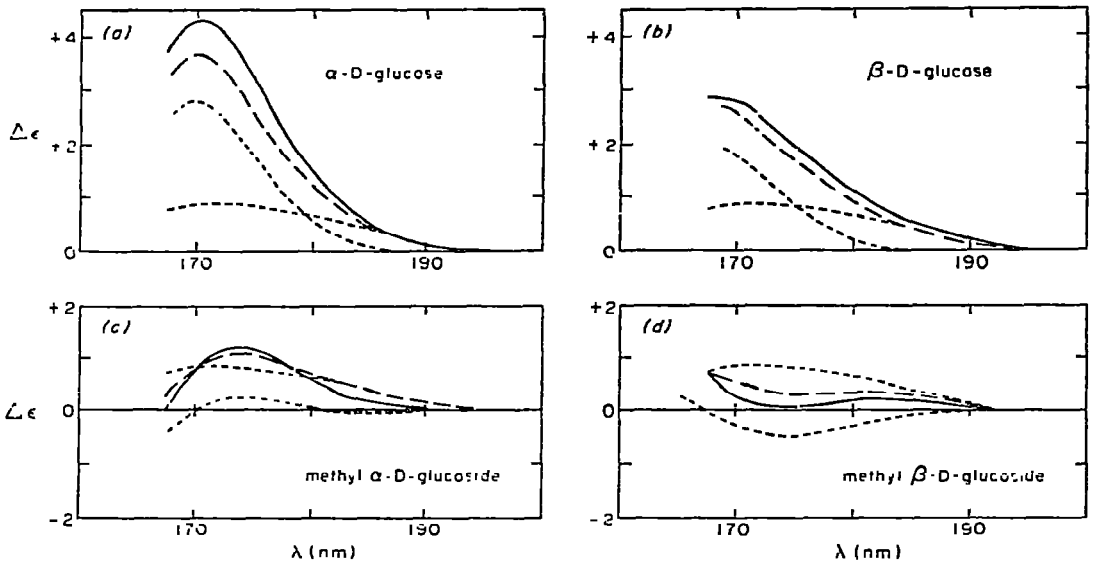

Fig. 5. Measured (——), calculated (– –), and fragment (– – – –) c.d. spectra: (*a*) α-D-glucose; (*b*) β-D-glucose; (*c*) methyl α-D-glucoside; and (*d*) methyl β-D-glucoside.

contribution of the hydroxymethyl fragment spectrum in Fig. 3a is probably a hydroxyl-group contribution.

In the case of the methyl pyranosides, we consider that the methoxyl group already shields the ring-oxygen atom from the hydrogen-bonding solvent. For both the α and β anomers, the band attributable to this chromophore is observed as a low-intensity (and negative) band beginning about 195 nm. The next two bands, observed at about 174 nm and below 168 nm, are assigned to the methoxyl group. The local environment of this group changes to its mirror image on proceeding from the α to the β anomer, and this mirror-image change is consistent with the change in sign of these two bands observed in a number of instances. We would also expect intensity from the hydroxyl groups at wavelengths shorter than 175 nm, as was the case for the pyranoses. Addition of the hydroxymethyl group to C-5 of both anomers of methyl D-xyloside does not shift the ring-oxygen band, but enhances its intensity. The intensity ascribed to the hydroxyl groups in the shorter-wavelength part of this fragment spectrum is also enhanced.

In order to calculate the c.d. spectra of α-D-galactose, β-D-galactose, methyl α-D-galactoside, and methyl β-D-galactoside, it is necessary to know the spectra of the corresponding arabinosides. Only the spectrum of methyl β-L-arabinoside (which corresponds to the spectrum of methyl α-D-galactoside) has been measured. However, it should be possible to calculate the other three c.d. spectra by using the fragment spectra developed here. The fragment spectrum in Fig. 3b gives the c.d. change expected when the 4-hydroxyl group in a xylose or xyloside is changed from equatorial to axial. This fragment spectrum is consistent with our assignment of the

transitions due to nonbonding electrons on the hydroxyl group to transitions at wavelengths shorter than 175 nm. By using this fragment spectrum, it is possible to calculate the c.d. of β-L-arabinose, α-L-arabinose, and methyl α-L-arabinoside from the spectra of the corresponding xyloses and xylosides. It is also possible to calculate the spectra of these three arabinose derivatives from the measured spectrum of the β-L-arabinoside by using the fragment spectra in Fig. 2. Spectra calculated by both methods are presented in Fig. 6. They are very similar.

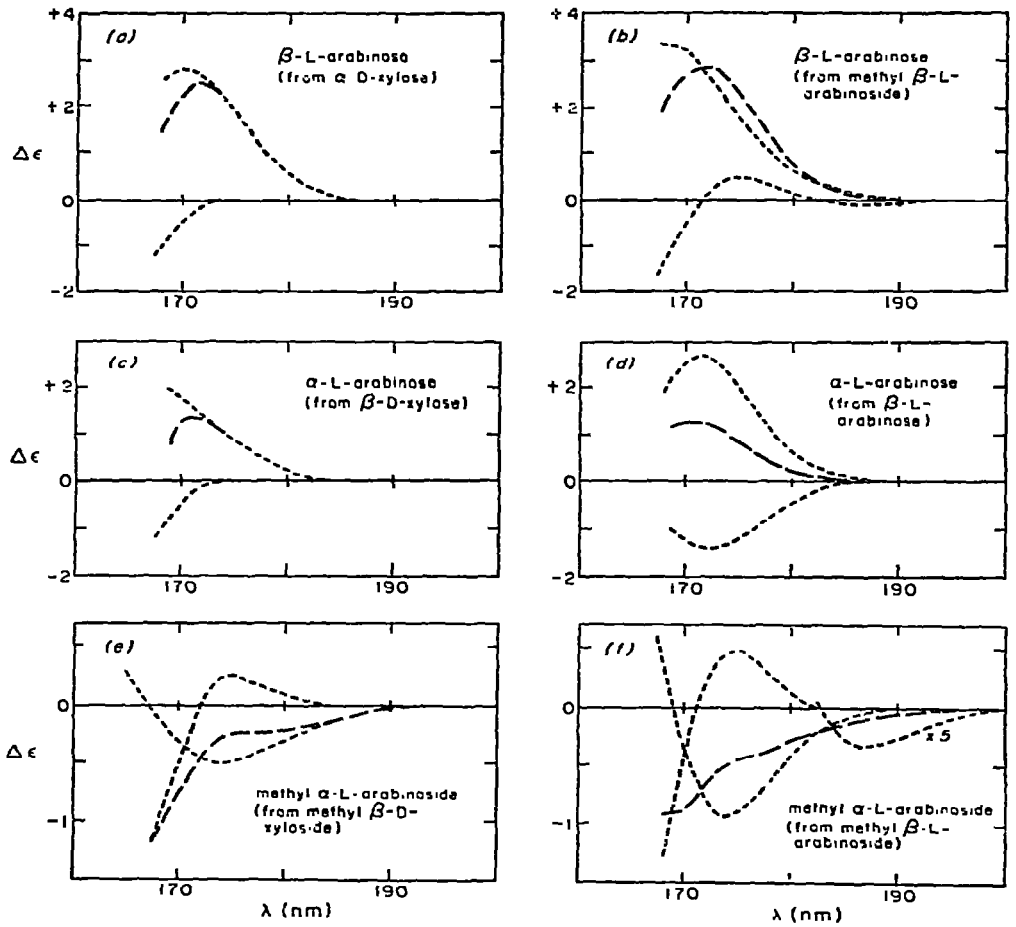

Fig. 6. Predicted (— —), and fragment (----) c.d. spectra: β-L-arabinose calculated from (*a*) α-D-xylose, and (*b*) methyl β-L-arabinose; α-L-arabinose calculated from (*c*) β-D-xylose, and (*d*) average calculated β-L-arabinose; methyl α-L-arabinoside calculated from (*e*) methyl β-D-xyloside, and (*f*) methyl β-L-arabinoside.

It is now possible to calculate the spectra of the four galactose derivatives by using the two fragment spectra presented in Fig. 3c and 3d. One might expect the fragment spectrum due to a 5-hydroxymethyl group when the 4-hydroxyl group is

axial to be independent of the configuration or substitution at the anomeric carbon atom, as it was for the glucose derivatives. This is not so, however. Although the fragment spectra are basically independent of whether the substitution on the anomeric carbon atom is a hydroxyl or a methoxyl group, it does depend on whether the configuration is α or β. We have postulated that solvent interaction with the hemiacetal or acetal group depends on whether this group is α or β, and that this solvent interaction may affect the distribution of rotamers for the exocyclic 5-hydroxymethyl group. The arguments for this idea have been presented previously[6]. The c.d. spectra of α-D-galactose, β-D-galactose, methyl α-D-galactoside, and methyl β-D-galactoside, calculated from the spectra of the corresponding L-arabinose derivatives, are compared with the measured spectra in Fig. 7.

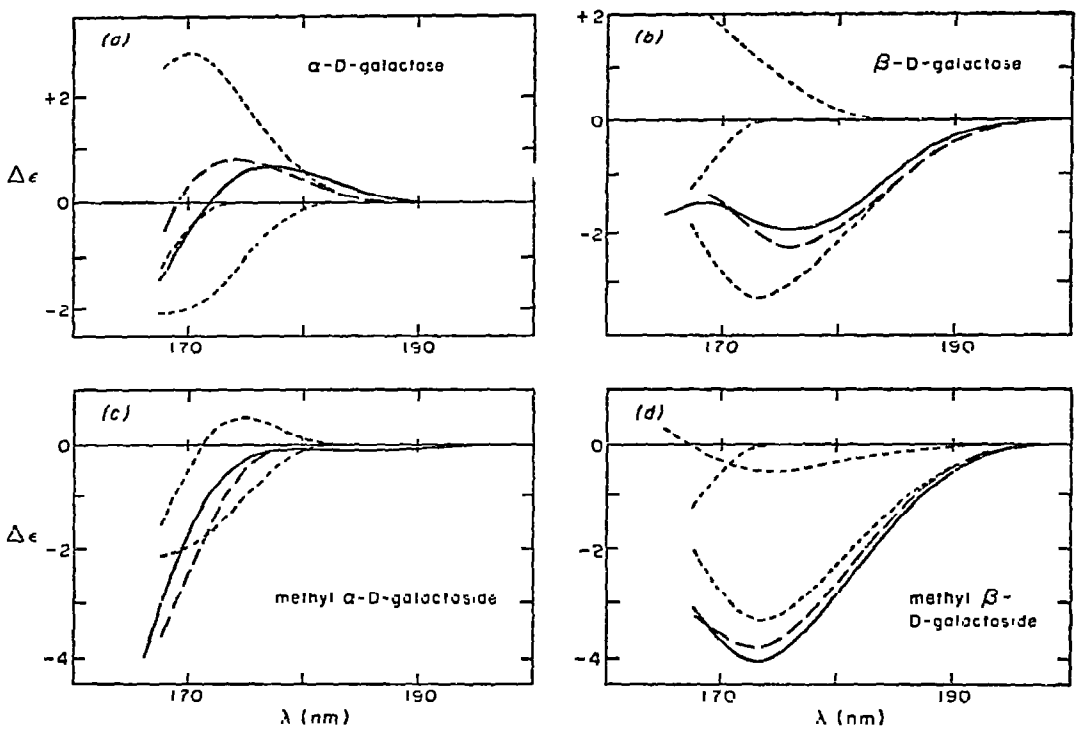

Fig. 7. Measured (——), calculated (– –), and fragment (– – – –) c.d. spectra: (*a*) α-D-galactose; (*b*) β-D-galactose; (*c*) methyl α-D-galactoside; and (*d*) methyl β-D-galactoside.

We have measured the c.d. spectra of other sugars, but they are trivially calculated from these fragment spectra.

Predicting c.d. spectra of sugars not yet measured. — By using the fragment spectra in Figs. 1–4, it is possible to predict the c.d. spectra for quite a number of sugars whose spectra have not yet been measured. A few examples of the kinds of

predictions that may be made are presented in Fig. 8. For instance, the fragment spectrum in Fig. 3b might be utilized to predict the spectra of β-L-fructose or β-L-psicose. Fig. 8a shows the predicted spectrum of β-L-fructose, which is calculated by adding the fragment spectrum in Fig. 3b to the fragment spectrum in Fig. 4a.

The fragment spectrum in Fig. 3a that corresponds to the addition of a hydroxymethyl group at C-5 when the hydroxyl group is equatorial may be used to predict a number of c.d. spectra. For instance, that of α-D-*gluco*-heptulose can be calculated by adding this fragment spectrum to the fragment spectrum in Fig. 4a. The result is shown in Fig. 8b.

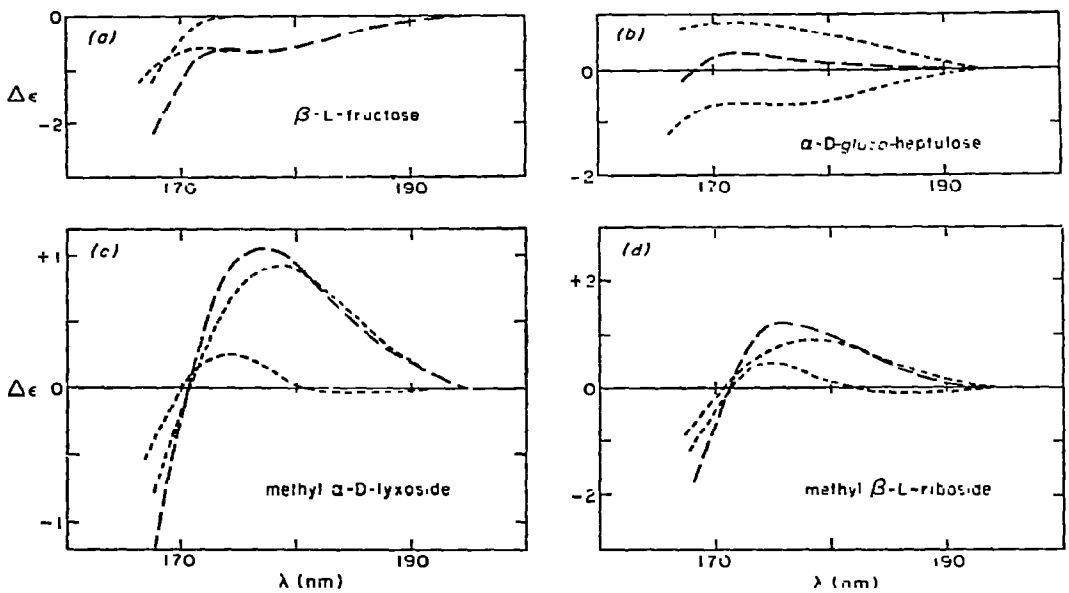

Fig. 8. Predicted (— —), and fragment (----) c.d. spectra: (*a*) β-L-fructose; (*b*) α-D-*gluco*-heptulose; (*c*) methyl α-D-lyxoside; and (*d*) methyl β-L-riboside.

The effect of changing an equatorial 2-hydroxyl group to axial when the 3-hydroxyl group is equatorial and a methoxyl group is α-attached to the anomeric carbon atom is given by the fragment spectrum presented in Fig. 4d. When combined with the spectrum of methyl α-D-xyloside, the c.d. spectrum for methyl α-D-lyxoside may be predicted, as presented in Fig. 8c. The spectra of methyl α-D-taloside and methyl β-L-riboside may be predicted similarly. The spectrum of methyl β-L-riboside is given in Fig. 8d.

Many other c.d. spectra may also be predicted in this way. It will be interesting to see how these predictions compare with the actual c.d. spectra when they are measured.

ACKNOWLEDGMENT

This work was supported by National Science Foundation grant number PCM74-01533-A03.

REFERENCES

1 C. S. HUDSON, *J. Am. Chem. Soc.*, 31 (1909) 66–86; *ibid.*, 47 (1925) 268–280.
2 D. H. WHIFFEN, *Chem. Ind. (London)*, (1956) 964–968.
3 J. H. BREWSTER, *J. Am. Chem., Soc.*, 81 (1959) 5475–5483; *ibid.* 5483–5493; *ibid.* 5493–5500.
4 R. U. LEMIEUX AND J. C. MARTIN, *Carbohydr. Res.*, 13 (1970) 139–161.
5 W KAUZMANN, F. B. CLOUGH, AND I. TOBIAS, *Tetrahedron*, 13 (1961) 57–105.
6 R. G. NELSON AND W. C JOHNSON, JR., *J. Am. Chem. Soc.*, 98 (1976) 4290–4295; *ibid.*, 4296–4301.