# Circular Dichroism of Nucleosides. I. Anomeric Pairs of the D-Pentofuranosides of Adenine

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**Abstract:** The ultraviolet (uv) absorption and circular dichroism (CD) spectra were obtained for the $\alpha$ and $\beta$ anomers of the four D-pentofuranosides of adenine in water, ethanol, and, in four cases, dimethyl sulfoxide. In addition to the two broad envelopes centered near 260 and 206 nm observed in uv spectra, CD spectra possess a third envelope centered near 220 nm. Similar but oppositely signed CD was observed not for anomeric pairs but for those nucleosides that are enantiomer-like at $C_1'$, $C_2'$, and $C_3'$. The enantiomer-like pairs are $\alpha$-ara–$\beta$-xylo, $\alpha$-xylo–$\beta$-ara, $\alpha$-lyxo–$\beta$-ribo, and $\alpha$-ribo–$\beta$-lyxo. The CD behavior of the $\alpha$-lyxo–$\beta$-ribo pair is different from that of the others; this difference may be related to the atypical furanose ring puckering in these nucleosides ($C_3'$ instead of $C_2'$ puckering). Analysis of the shapes of the uv and CD envelopes and of the changes in shapes for a solvent change from water to ethanol suggests the resolution of these spectra into six transitions centered near 270, 260, 250, 225, 215, and either 206 or 198 nm. Although the configuration of the $C_2'$–$O_2'$ bond is the primary steric factor affecting the rotational strength of four of these transitions and of the 260-nm envelope, well-defined effects of the configuration of the $C_3'$–$O_3'$ bond are also observed. The 270- and 225-nm transitions are tentatively assigned as $n \rightarrow \pi^*$ transitions. This assignment suggests that the rotational strength of $n \rightarrow \pi^*$ transitions may be as large as or larger than $\pi \rightarrow \pi^*$ transitions in adenine nucleosides.

Optical rotatory dispersion and circular dichroism (CD) measurements have proven to be valuable tools in the study of nucleoside structure.[1,2] For example, empirical rules have been established relating the sign of the long-wavelength Cotton effect to anomeric configuration.[1] Recent work[3-5] has focused attention on the sensitivity of CD measurements to structural features of (primarily) pyrimidine nucleosides. Due to their weak rotational strengths, purine nucleosides have not been studied as extensively; however, recent advances in instrumentation have made it possible to obtain satisfactory CD spectra for these molecules.

This report presents the CD spectra of both the $\alpha$ and $\beta$ anomers of the four D-pentofuranosides of adenine. The solvents used were water, ethanol, and, in four cases, dimethyl sulfoxide (DMSO). The spectra were resolved into six electronic transitions between 300 and 195 nm. The variations in sign and magnitude of each of these transitions were correlated with specific structural features of the nucleosides. Two of the six transitions are tentatively assigned as $n \rightarrow \pi^*$ transitions.

## Experimental Section

**CD measurements** in the wavelength range 320–195 nm were made with a Durrum-Jasco ORD/UV-5 spectropolarimeter equipped with a Sproul Scientific SS-20 CD modification and a programmed 15-Å slit width control (Durrum Instrument Co., Palo Alto, Calif.). An Osram Xenon arc lamp (450 W) was used as the light source. The cell compartment was continually purged with dry prepurified nitrogen and all measurements were made at ambient temperatures (~25°). Solutions were contained in silica cells of various path lengths (0.01–1.0 cm). Time constants of 1 and 4 sec and low scanning speeds (50–100 nm/hr) were used. The instrument was calibrated with *d-10*-camphorsulfonic acid supplied by the Durrum Instrument Co. (0.307° ellipticity for 0.1% solution in a 1.0-cm cell at 290.5 nm). The calibration of the spectropolarimeter was routinely checked; deviations in the molar ellipticity of the standard were kept to within 1%.

Numerous CD spectra were recorded at sensitivity settings of 1.0 and 2.0 mdeg/cm for each of several concentrations for every compound studied. CD spectra were found to be independent of concentration for all solvents used (water, ethanol, and DMSO) over the range 0.4–4.0 $\times 10^{-4}$ *M*.

The CD spectra are expressed in terms of molar ellipticity, $[\theta]$ in deg l./(mol cm), defined by

$$[\theta] = \frac{100\psi}{lm} \qquad (1)$$

where $\psi$ is the measured ellipticity in degrees, $l$ is the path length in centimeters, and $m$ is the concentration in moles/liter. Precision in $[\theta]$ was judged to be ~2 and ~5% for wavelength regions 350–220 and 220–195 nm, respectively. For compounds with molar ellipticities less than 3000 deg l./(mol cm), all measurements were made using the 1.0-mdeg sensitivity setting. Precision in these experiments was judged to be approximately half the values given above. The RMS noise level was 0.4–0.8-mdeg ellipticity.

**Ultraviolet absorption** (uv) spectra were obtained using a Cary 14 spectrophotometer. Quartz cells of 1.0-cm path length were used for water and ethanol solutions and 0.2-cm cells for dimethyl sulfoxide solutions. The optical density at 259 nm was used to determine the concentration of the nucleoside solutions. The concentration of the solution calculated from the optical density (assuming a molar extinction coefficient ($\epsilon_m$) of 14,900 l./(cm mol)[6]) was compared to the concentration calculated from the amount of sample weighed.[7] After correcting for hydration, the concentrations calculated using the two methods agreed to within 2%.

**Resolution of Spectra.** The CD and uv spectra were magnified to scales of 1 cm = 500 deg l./(mol cm) and 1 cm = 100 l./(mol cm), respectively. Each spectrum was matched to a curve synthesized by summing a minimum number of Gaussian curves. The Gaussian curves were allowed to vary in position, sign, height, and width. This was accomplished using a DuPont 310 Curve Resolver.[8]

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(7) The author is indebted to Mr. John Gee, Mr. Dennis Jarvis, Mrs. Dorothy Palomeque, and Miss Kathleen Ue for technical assistance in obtaining the uv spectra.
(8) The author is indebted to Mr. David N. Smith and the DuPont Instrument Co. for providing the use of this instrument.

**Table I.** Uv Absorption Data

| Compd | Solvent[a] | Long-wavelength envelope[b] $\epsilon_{270} \times 10^{-4}$ | λ, nm | $\epsilon_{max} \times 10^{-4}$ | $\epsilon_{250} \times 10^{-4}$ | λ, nm | $\epsilon_{min} \times 10^{-4}$ [c] | Short-wavelength envelope λ, mn | $\epsilon_{max} \times 10^{-4}$ |
|---|---|---|---|---|---|---|---|---|---|
| Adenine | Water, pH 7.0 | 0.89 | 261 | 1.33 | 1.04 | 226 | 0.26 | 207 | 2.27 |
| | Water, pH 1.3 | 1.06 | 262.5 | 1.27 | 0.98 | 229 | 0.26 | 204 | 1.86 |
| | Ethanol | 0.96 | 261 | 1.36 | 1.04 | 226 | 0.21 | 208 | 2.22 |
| | DMSO | 1.14 | 262.5 | 1.33 | 0.99 | | | | |
| β-Ribo | Water, pH 7.0 | 0.95 | 259 | 1.50 | 1.21 | 227 | 0.25 | 206 | 2.12 |
| | Water, pH 1.3 | 0.96 | 257 | 1.47 | 1.21 | 229 | 0.35 | 206 | >2.1 |
| | Ethanol | 1.11 | 259 | 1.50 | 1.14 | 228 | 0.31[d] | 206 | 2.08 |
| | DMSO | 1.26 | 262.5 | 1.44[e] | 1.03 | | | | |

[a] All solutions were at neutral pH (7.0 ± 0.4) except where noted. [b] Distinction between envelope and bands or transitions within the envelope is made under Results. [c] For nucleoside solutions older than 1 week, $\epsilon_{min}$ values were observed to increase as much as twofold. [d] $\epsilon_{min}$ for the α anomers was 0.29; $\epsilon_{min}$ for β anomers varied from 0.29 to 0.38. [e] $\epsilon_{max}$ value for β-ara was 1.37, $\epsilon_{max}$ value for β-ribo, α-lyxo, and β-xylo was the same (1.44).

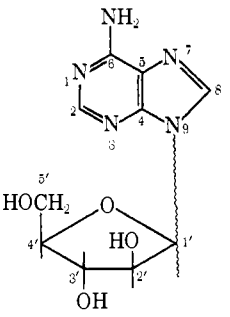
Each Gaussian represents a transition in the CD and uv spectra. The rotational strength, $R(j)_i$ (cgs-esu), for each transition $i$ for each nucleoside $j$ was calculated using eq 2[6] where $\theta_i$ is the molar ellipticity and $\lambda_i$ is the wavelength at the center of transition $i$ while $\Delta_i$ is its half-width at $\theta_i/e$.

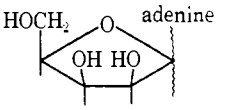
$$R(j)_i = 1.233 \times 10^{-42}\theta_i\Delta_i/\lambda_i$$

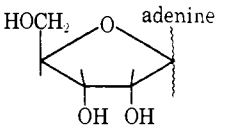
**Materials.** The compounds studied are listed below and referenced to the method of synthesis. Unless otherwise noted, all nucleosides were synthesized in the Department of Bioorganic Chemistry at Stanford Research Institute, Menlo Park, Calif.: 9-(α-D-arabinofuranosyl)adenine[9] (α-ara); 9-(β-D-arabinofuranosyl)adenine[10] (β-ara); 9-(α-D-lyxofuranosyl)adenine[11] (α-lyxo); 9-(β-D-lyxofuranosyl)adenine[12] (β-lyxo); 9-(α-D-ribofuranosyl)-adenine[13] (α-ribo); 9-(β-D-ribofuranosyl)adenine[14] (β-ribo); 9-(β-L-ribofuranosyl)adenine[15] (β-L-ribo); 9-(α-D-xylofuranosyl)adenine[16] (α-xylo); 9-(β-D-xylofuranosyl)adenine[17] (β-xylo); adenine.[18]

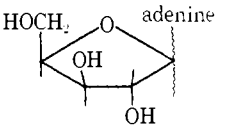
The structures of the furanoside moieties of these nucleosides are given below. All the nucleosides were paper chromatographically homogeneous[19] except for β-xylo (1–3% impure) and α-ribo (less than 0.5% adenine contamination).

The CD and uv spectra were recorded for solutions of glass-distilled water, absolute ethanol, and spectroscopic grade DMSO.




## Results and Discussion

**Ultraviolet Absorption Spectra.** The uv spectra for the four anomeric pairs of the D-pentofuranosides of adenine in a given solvent are essentially identical. They are represented in Table I by the spectral parameters of β-ribo. A typical uv spectrum in water and in ethanol has a broad asymmetric absorption region centered near 260 nm, a minimum at 227–228 nm, and another broad absorption region centered near 206 nm. Since such broad absorption regions (both in the uv and CD) contain contributions from more than one electronic transition, the word "envelope" will be used to describe them.

Changing the solvent from water to ethanol does not change the value or position of the maxima, and the minimum is red-shifted only 1 nm. However, this change increases the absorption near 270 and 215 nm and decreases the absorption near 250 nm for each nucleoside studied.

Since DMSO absorbs very strongly below 250 nm, only the 260-nm envelope can be measured in this solvent. For the four nucleosides studied (β-ara, β-ribo, β-xylo, and α-lyxo), changing the solvent from water to DMSO red-shifts the 260-nm envelope to 262.5 nm and significantly decreases its $\epsilon_{max}$ value. The 262.5-nm envelope is very asymmetric, and the $\epsilon_m$ values observed near 280 nm are approximately three times the corresponding values observed in water.

The $\epsilon_m$ values for adenine are also shown in Table I. In general, the effects of solvent changes on the uv spectra of adenine parallel the effects observed with the nucleosides. However, the 260-nm envelope of adenine red-shifts ~1.5 nm when the pH is changed from 7 to 1.3, while β-ribo exhibits a blue shift of 2 nm for this change. The spectrum of adenine at pH 7 has a 270-nm shoulder, which is not resolved in the uv spectra of any of the nucleosides and which is enhanced for a solvent change from water to ethanol.

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(19) Paper chromatography systems used included 5% $Na_2HPO_4$, *n*-BuOH–$H_2O$ saturated and *n*-BuOH–HOAc–$H_2O$ (4:1:5).

**Table II.** Circular Dichroism of the α- and β-D-Pentofuranosides of Adenine

| Compd | Solvent[a] | First CD envelope[b] λ, nm | First CD envelope [θ]max | Second CD envelope λ, nm | Second CD envelope [θ]max | Third CD envelope λ, nm | Third CD envelope [θ]max |
|---|---|---|---|---|---|---|---|
| α-Lyxo | Water | 260 | 3750 | 214 | 870 | | (−) |
| | Ethanol | 260 | 3970 | | (+) | | |
| | DMSO | 269 | 5000 | | | | |
| β-Lyxo | Water | 257 | −3540 | 218 | −6090 | | (+) |
| | Ethanol | 258 | −4730 | 220 | −5790 | | (+) |
| α-Ribo | Water | 256 | 5410 | 225 | 3940 | 204 | −13,600 |
| | Ethanol | 257 | 5030 | 225 | 4030 | | (−) |
| β-Ribo | Water, pH 7.0 | 265 | −2970 | 225 | 1450 | | |
| | | | | 213 | 1300 | 196 | −8,700 |
| | Water, pH 1.3 | 253 | −3600 | 225 | 2000 | 206 | −13,000 |
| | Ethanol | 268 | −3860 | 226 | 2410 | | (−) |
| | | | | 216 | 2360 | | |
| | DMSO | 269 | −4860 | | | | |
| α-Ara | Water | 259 | 3570 | 214 | 4430 | | (−) |
| | Ethanol | 259 | 3650 | 216 | 8730 | | (−) |
| β-Ara | Water | 258 | −5380 | 227 | −2200 | 205 | 11,700 |
| | Ethanol | 259 | −7450 | 229 | −3470 | ~205 | 16,500 |
| | DMSO | 262 | −6340 | | | | |
| α-Xylo | Water | 258 | 6960 | 226 | 2150 | 205 | −15,400 |
| | Ethanol | 259 | 8360 | 228 | 4200 | 206 | −19,900 |
| β-Xylo | Water | 259 | −2410 | 212 | −6040 | | (+) |
| | Ethanol | 259 | −3330 | 215 | −9600 | | (+) |
| | DMSO | 264 | −3450 | | | | |

[a] pH of all solutions was neutral (7.0 ± 0.4) except where noted. [b] Distinction between envelope and bands is made under Results.

**Pentofuranoside Configuration.** Before analyzing the CD spectra in detail, it is useful to discuss the configuration of the four pentofuranosides found in these nucleosides.

In the two-dimensional representation of the pentofuranosides presented in the Experimental Section, the $C_2'$–$O_2'$, $C_3'$–$O_3'$, and $C_1'$–$N_9$ (glycosyl) bonds, taken in pairs, are directed on the same (cis) or opposite (trans) side of the plane of the furanose ring. In this representation, the eight nucleosides can be arranged in pairs that are enantiomer-like at $C_1'$, $C_2'$, and $C_3'$. For example, both α-lyxo and β-ribo have their $C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds trans to the $C_1'$–$N_9$ bond. The other enantiomer-like pairs are α-xylo-β-ara, α-ara-β-xylo, and α-ribo–β-lyxo.

In reality, the furanose ring assumes a puckered configuration that displaces the $C_2'$ and/or $C_3'$ atoms from the plane of the furanose ring to either the same side (endo) or opposite side (exo) of the ring as the $C_5'$ atom. The $C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds are oriented either axially or equatorially.

Sundaralingam and coworkers have formulated general rules concerning furanose ring puckering in nucleosides.[20–22] In this scheme, the preferred puckering for α anomers is $C_2'$ exo, while for β anomers it is $C_2'$ endo. The arrangement of the $N_9$, $C_1'$, and $C_2'$ atoms in α anomers is the mirror image of the arrangement in β anomers.[20]

Based on these considerations, the following assignments of sugar conformation for the enantiomer-like pairs appear plausible. The puckering in α-ara is $C_2'$ exo. If this is the case, the $C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds are equatorial.[22] The puckering in β-xylo is $C_2'$ endo, with the $C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds equatorial. The puckering is $C_2'$ exo for α-xylo and $C_2'$ endo for β-ara, with the $C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds axial in both nucleosides. The puckering is $C_2'$ exo for α-ribo and $C_2'$ endo for β- lyxo, with the $C_2'$–$O_2'$ bond axial and $C_3'$–$O_3'$ bond equatorial in both nucleosides.

However, these generalizations do not apply to β-ribo, since X-ray crystallographic studies of adenosine,[23] adenosine 3′-phosphate,[24] and adenosine 5′-phosphate[25] show that the sugar conformation in each case is $C_3'$ endo. For $C_3'$ endo puckering, the $C_2'$–$O_2'$ bond is axial and the $C_3'$–$O_3'$ bond is equatorial. Since the α anomer that forms the enantiomer-like pair with β-ribo should have a puckering that is the mirror image of $C_3'$ endo, it is reasonable to expect α-lyxo to be $C_3'$ exo, with $C_2'$–$O_2'$ axial and $C_3'$–$O_3'$ equatorial.

**Circular Dichroism Spectra in Water.** The CD spectra of the α and β anomers in water are shown in Figures 1a and 1b, respectively, and the spectral parameters are summarized in Table II. The typical CD spectrum has broad envelopes centered near 260, 220, and either 205 or 196 nm. As observed for other purines,[1] α anomers have positive and β anomers have negative 260-nm envelopes.

It can be seen that the CD maxima of **the 260-nm envelope** are within 1 nm of the absorption maximum for α-ara, α-lyxo, α-xylo, β-ara, and β-xylo. The CD maxima of the enantiomer-like pair α-ribo–β-lyxo are blue-shifted from the absorption maximum 3 and 2 nm, respectively. In contrast, the CD maximum of β-ribo is red-shifted 6 nm from the absorption maximum.[26] Each member of the enantiomer-like pair α-lyxo–β-ribo has an unusually large molar ellipticity on the red side of the 260-nm envelope. This results in envelope shapes for α-lyxo and β-ribo that are quite different from the others.

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(25) J. Kraut and L. H. Jensen, *ibid.*, 16, 79 (1963).
(26) Comparison of the CD spectrum of β-ribo with those in the literature is found in a later section of this report.

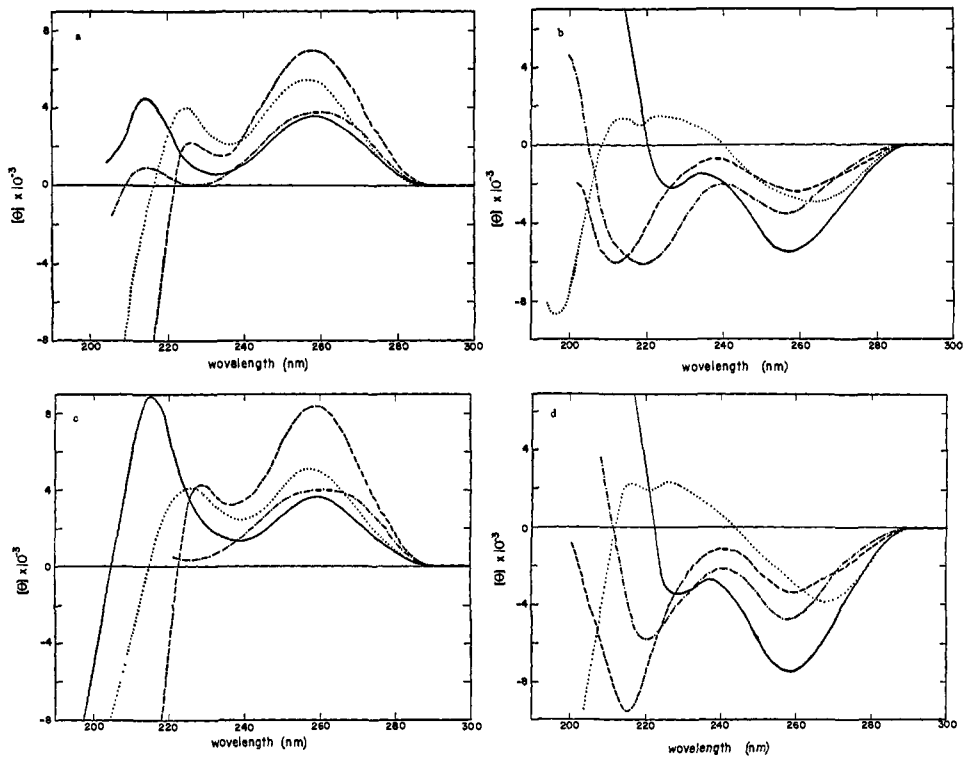



Figure 1. (a) Circular dichroism spectra of the 9-(α-D-pentofuranosyl)adenines in water: α-ara (——), α-lyxo (–·–·), α-ribo (····), α-xylo (– – –); (b) circular dichroism spectra of the 9-(β-D-pentofuranosyl)adenines in water: β-ara (——), β-lyxo (–·–·), β-ribo (····), β-xylo (– – –); (c) circular dichroism spectra of the 9-(α-D-pentofuranosyl)adenines in ethanol: α-ara (——), α-lyxo (–·–·), α-ribo (····), α-xylo (– – –); (d) circular dichroism spectra of the 9-(β-D-pentofuranosyl)adenines in ethanol: β-ara (——), β-lyxo (–·–·), β-ribo (····) β-xylo (– – –).

The nucleosides that have their $C_2'$–$O_2'$ bonds cis to their glycosyl bonds (β-ara, β-lyxo, α-xylo, and α-ribo) have larger molar ellipticities at 260 nm than do those nucleosides with a trans arrangement of these bonds. α-Xylo and β-ara have the largest ellipticities at 260 nm of the α and the β anomers, respectively. In each case, the $C_2'$–$O_2'$ bond is cis to the glycosyl bond and axial and the $C_3'$–$O_3'$ bond is trans to the glycosyl bond and axial. α-Ara and β-xylo have the smallest ellipticities at 260 nm of the α and the β anomers, respectively. In each case, the $C_2'$–$O_2'$ bond is trans to the glycosyl bond and equatorial and the $C_3'$–$O_3'$ bond is cis to the glycosyl bond and equatorial. The nucleosides of the two enantiomer-like pairs that have intermediate values for the ellipticity at 260 nm have their $C_2'$–$O_2'$ bonds cis to their $C_3'$–$O_3'$ bonds.

**The 220-nm envelopes** for all the nucleosides except α-ribo and α-lyxo appear from their curve shapes to be composed of two transitions, one centered near 225 nm and the other near 215 nm.

The 225-nm transition is positive for α-ribo, α-xylo, α-ara, and β-ribo, and negative for β-lyxo, β-ara, and β-xylo. This transition is absent in the CD spectrum of α-lyxo. The enantiomer-like pair α-lyxo–β-ribo, which exhibits unusual CD near 260 nm, also displays unusual CD near 225 nm. Specifically, this transition is missing for α-lyxo and the sign of this transition for β-ribo is opposite from the sign observed for the other β nucleosides. For the other enantiomer-like pairs, the sign of the 225-nm transition is the same as the sign of the 260-nm envelope. As observed for the 260-nm envelope, the nucleosides having the largest molar ellipticities at 225 nm have their $C_2'$–$O_2'$ bond cis to the glycosyl bond and axial.

The 215-nm transition is positive for α- and β-ara, α-lyxo and β-ribo, negative for α- and β-xylo and β-lyxo, and absent for α-ribo. There is no apparent correlation between the sign and magnitude of the 215-nm transition with configuration. For the β-nucleosides, negative transitions are observed for $C_3'$–$O_3'$ cis and positive transitions are observed for $C_3'$–$O_3'$ trans to the glycosyl bond; for the α nucleosides, negative or no transition is observed for $C_2'$–$O_2'$ cis and positive transitions are observed for $C_2'$–$O_2'$ trans to the glycosyl bond.

**The short-wavelength region** has an envelope centered near 196 nm for β-ribo and near 205 nm for α-ribo, α-xylo, and β-ara. With the exception of β-ribo, the short-wavelength envelope appears to be negative for α anomers and positive for β anomers.

The α and β nucleosides of an enantiomer-like pair have closely related CD spectra between 300 and 220 nm. In addition, the transitions that occur in this wavelength range are strongly influenced by the configuration of those bonds ($C_1'$–$N_9$, $C_2'$–$O_2'$, and $C_3'$–$O_3'$) that define the enantiomer-like pairs. This description does not apply to the 215-nm transition since only those enantiomer-like pairs with their $C_2'$–$O_2'$ bonds trans to their $C_3'$–$O_3'$ bonds have similar but opposite CD near 215 nm. This transition may be influenced by the $C_5'$ atom rather than by those bonds that define an enantiomer-like pair.

The spectrum for β-ribo differs from each of three different spectra reported in the literature. Miles,

*et al.*,[4] present a CD spectrum with maxima at 260 nm ([θ] = −2450), at 219 ([θ] = −1950), and near 195 ([θ] = 3100). Voelter, *et al.*,[27] report a spectrum with maxima at 265 nm ([θ] = −2500) and at 225 ([θ] = 2000) and a short-wavelength negative envelope. Warshaw and Cantor[28] report still a different spectrum, with maxima at 263.5 nm ([θ] = −3800) and at 227 ([θ] = 1100) and a short-wavelength negative envelope. In addition to the discrepancies in position, sign, and magnitude of the three CD envelopes, none of these spectra show the 220-nm envelope resolved into the two transitions shown in Figure 1b.

For this study, chromatographically pure[16] β-ribo was obtained from two commercial sources;[14] the CD spectra of these samples were identical within experimental error. In addition, the spectrum for β-L-ribo was recorded and found to be the mirror image of β-D-ribo, as shown in Figure 2. The spectra for β-D- and β-L-ribo were also recorded with the Jasco spectropolarimeter in the laboratory of Dr. J. T. Yang,[29] with the same results.

The resolution of the 220-nm envelope for β-ribo into transitions at 225 and 215 nm is probably the most significant deviation of the spectrum reported here. Although very small, the 215-nm transition is measurable in both water and ethanol (see Figure 1d), not only for β-ribo but also for its 2′- and 3′-*O*-methyl derivatives.[30]

The CD spectrum for β-ara shown in Figure 1b differs from the spectrum presented for this compound by Guschlbauer and de Garilhe.[31] The positive transition at 295 nm reported by these workers was not observed in any nucleoside spectrum recorded in this study.

**Circular Dichroism in Ethanol and Dimethyl Sulfoxide.** The CD spectra of the α and the β anomers in ethanol are shown in Figures 1c and 1d, respectively, and their spectral parameters are given in Table II. The CD spectra of each nucleoside in water and ethanol are compared directly in Figure 3. The magnitudes of the three CD envelopes are generally greater in ethanol than in water. Except for β-ribo, the CD and absorption maxima of the 260-nm envelopes in ethanol occur within 1 or 2 nm of the CD and absorption maxima in water. The CD maximum for β-ribo is red-shifted 3 nm from the CD maximum in water and 8 nm from the absorption maximum. The solvent change from water to ethanol changes the shapes of the 260-nm CD envelopes: the long-wavelength sides of these 260-nm envelopes for α- and β-lyxo, β-ribo, and β-xylo are enhanced; the entire 260-nm envelopes of the α-xylo–β-ara enantiomer-like pair are enhanced, and the short-wavelength sides of the 260-nm envelopes of α- and β-ribo are reduced. The maxima of the second CD envelopes are red-shifted when compared to water; this may be the result of large increases in the magnitudes of their neighboring, oppositely signed envelopes. Despite these differences, the correlations between furanoside structure and CD spectra described for aqueous solutions also hold for ethanol solutions. This finding supports both the observations concerning nucleoside configuration in water and the correlation of configuration with CD spectra.

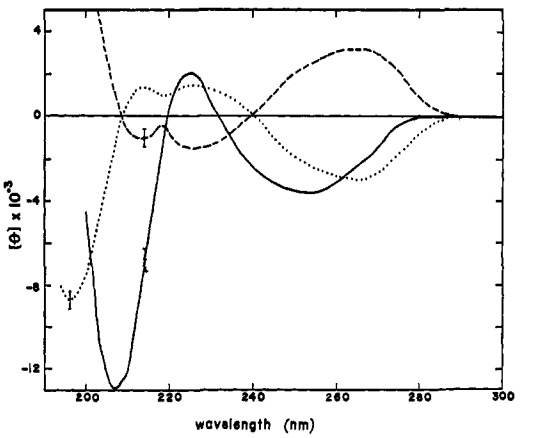



Figure 2. Circular dichroism spectra of β-L-ribo in water at pH 7 (– – –), and of β-ribo in water at pH 7 (. . . .) and pH 1.3 (——).

The CD spectra for β-ara, β-ribo, β-xylo, and α-lyxo in DMSO are shown in Figure 3, and their spectral parameters are given in Table II. Since DMSO absorbs strongly below 250 nm, only the long-wavelength envelope can be measured in this solvent. For β-ara and β-xylo, the CD maxima are close to the absorption maximum for adenine nucleosides in DMSO (262.5 nm), and the $[\theta]_{max}$ values are similar to the values observed in ethanol. For α-lyxo and β-ribo, the CD maxima are red-shifted 6.5 nm from the absorption maximum, and the $[\theta]_{max}$ values are ~25% larger than the values observed in ethanol. The positions and shapes of the long-wavelength CD and uv envelopes in DMSO are sufficiently different from those in water and ethanol to suggest that these nucleosides assume a different conformation in DMSO. Since the CD spectra of α-lyxo and β-ribo in DMSO are mirror images, it is likely that the conformations of those bonds that define this enantiomer-like pair are closer to being mirror images in DMSO than in water and ethanol. These suggestions are discussed more fully in the second paper in this series.[30]

**Resolution of the Spectra.** Each electronic transition of the adenine chromophore makes a contribution at the same wavelength in the uv, CD, and magnetic circular dichroism (MCD) spectra. By approximating each transition with a Gaussian curve, it should be possible to construct the uv, CD, and MCD spectra from a sum of such curves. Such sets of Gaussian curves must be centered at the same wavelengths in the uv, CD, and MCD spectra; however, their sign, height, and width need not be the same in the different spectra.

Since there may not be a unique resolution for a particular spectrum, a proposed resolution was subjected to the following constraints. It was required, first, that the complete set of uv and CD spectra of the adenine pentofuranosides in water be matched with the same number of Gaussian curves centered at the same wavelengths; second, that the available MCD spectra be matched using this same set of Gaussian curves; third, that the uv and CD spectra of the adenine pentofuranosides in ethanol be matched with this same set of Gaussian curves allowing for only small solvent shifts

(27) W. Voelter, R. Records, E. Bunnengerg, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 6163 (1968).
(28) M. M. Warshaw and C. R. Cantor, *Biopolymers*, **9**, 1079 (1970).
(29) The author gratefully acknowledges the cooperation of Dr. Y. T. Yang, University of California at San Francisco, and the use of his spectrophotometer.
(30) J. S. Ingwall, unpublished results.
(31) W. Guschlbauer and M. P. de Garilhe, *Bull. Soc. Chim. Biol.*, **51**, 1511 (1969).

**Table III.** Resolution of CD Spectra

| | α-Xylo | | α-Ribo | | α-Lyxo | |
|---|---|---|---|---|---|---|
| | Water | Ethanol | Water | Ethanol | Water | Ethanol |
| $\lambda_i$, nm | 270 | 271 | 270 | 271 | 271 | 272 |
| $[\theta]_i$ | 2,300 | 3,100 | 1,300 | 1650 | 1750 | 2200 |
| $R_i \times 10^{42}$ | 95 | 140 | 45 | 75 | 70 | 100 |
| $[\theta]_{260}$ | 4,450 | 5,350 | 3,200 | 3250 | 2550 | 2650 |
| $R_{260} \times 10^{42}$ | 220 | 225 | 150 | 155 | 130 | 130 |
| $[\theta]_{250}$ | 4,000 | 4,400 | 3,600 | 2750 | 1950[a] | 2400[a] |
| $R_{250} \times 10^{42}$ | 225 | 270 | 215 | 165 | 105 | 155 |
| Sum of $R_i \times 10^{42}$ within first CD envelope | 540 | 665 | 410 | 395 | 305 | 385 |
| $[\theta]_{225}$ | 2,400 | 4,800 | 4,050 | 4050 | 0 | 0 |
| $R_{225} \times 10^{42}$ | 120 | 315 | 220 | 265 | | |
| $[\theta]_{215}$ | −5,750 | −6,000 | 0 | 0 | 1100[b] | 1600 |
| $R_{215} \times 10^{42}$ | −180 | −260 | | | 40 | 70 |
| Sum of $R_i \times 10^{42}$ within second CD envelope | −60 | 65 | 220 | 265 | 40 | 70 |
| $\lambda_i$ (nm) | 206 | 206 | 206 | 200 | 197 | (−) |
| $[\theta]_i$ | −15,400 | −19,000 | −12,000 | −9200 | −4000 | |
| $R_i \times 10^{42}$ | −740 | −1,140 | −505 | −565 | −200 | |

[a] Transition centered at 249 nm. [b] Transition centered at 214 nm. [c] Transition centered at 212.5 nm.

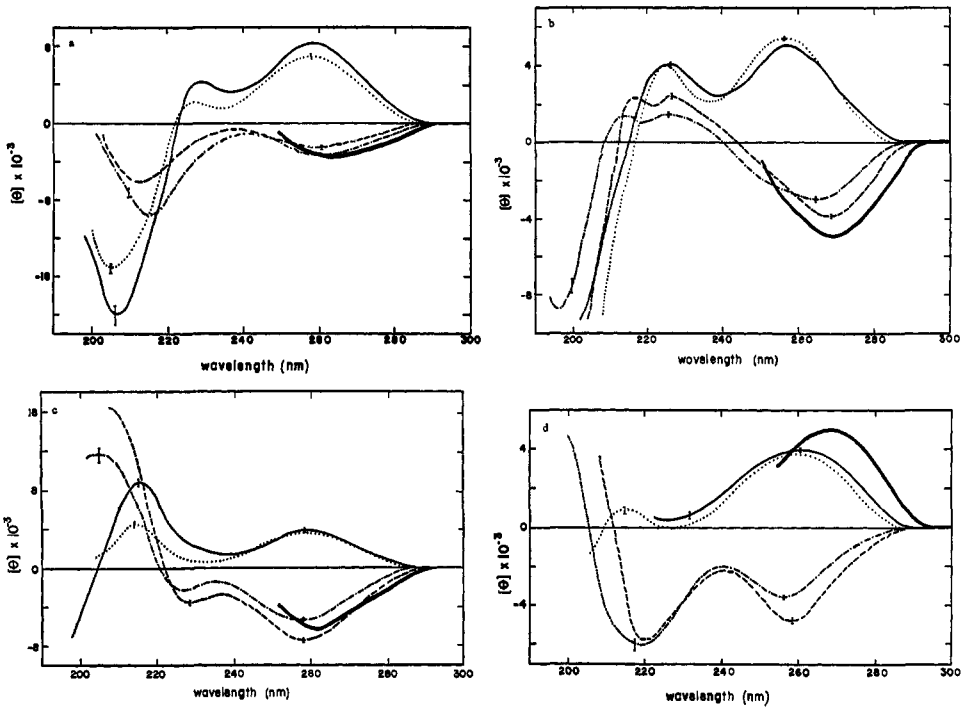



Figure 3. (a) Circular dichroism spectra of α- and β-xylo: α-xylo in ethanol (——), α-xylo in water (· · · ·), β-xylo in water (– – –), β-xylo in ethanol (–·–·), β-xylo in DMSO (——); (b) circular dichroism spectra of α- and β-ribo: α-ribo in ethanol (——), α-ribo in water (· · · ·), β-ribo in water (–·–·), β-ribo in ethanol (– – –), β-ribo in DMSO (——); (c) circular dichroism spectra of α- and β-ara: α-ara in ethanol (——), α-ara in water (· · · ·), β-ara in water (–·–·), β-ara in ethanol (– – –), β-ara in DMSO (——); (d) circular dichroism spectra of α- and β-lyxo: α-lyxo in DMSO (——), α-lyxo in ethanol (——), α-lyxo in water (· · · ·), β-lyxo in water (–·–·), β-lyxo in ethanol (– – –).

of the transitions; and fourth, that the half-band widths of the CD transitions be no greater than the half-band widths of the corresponding uv transitions[32] (<15 nm[33]).

The Gaussian curves that account for the uv, CD, and MCD spectra are centered near 270, 260, 250, 225, 215, and either 206 or 198 nm. The transitions near 225 nm, 215 nm, and the low-wavelength transition are clearly evident by visual inspection of the CD curves. The resolution of the 260-nm envelope into transitions near 270, 260, and 250 nm is consistent with the observed asymmetry in the shapes of the uv and CD 260-nm envelopes and with the changes in the shapes of these envelopes accompanying a solvent change from water to ethanol, as described above.

The resolution of the 260-nm envelope into three transitions is also supported by analysis of the MCD spectra of adenine and of β-ribo presented by Djerassi and coworkers.[27] The MCD spectrum of adenine at pH 7 resolves the 260-nm envelope into three transitions: a negative band with a shoulder and a positive band which can be matched by summing Gaussian curves centered near 270, 262, and 252 nm, a resolution

(32) W. Moffitt and A. Moscowitz, *J. Chem. Phys.*, 30, 648 (1959).
(33) R. W. Woody, personal communication.

| α-Ara | | β-Ara | | β-Lyxo | | β-Ribo | | β-Xylo | |
|---|---|---|---|---|---|---|---|---|---|
| Water | Ethanol | Water | Ethanol | Water | Ethanol | Water | Ethanol | Water | Ethanol |
| 270 | 271 | 270 | 270 | 272 | 273 | 270 | 271 | 272 | 272 |
| 1600 | 1600 | −2,300 | −3,300 | −700 | −1150 | −2150 | −3,200 | −1200 | −2000 |
| 65 | 75 | −95 | −150 | −30 | −45 | −90 | −160 | −50 | −100 |
| 2000 | 2200 | −3,650 | −4,700 | −2150 | −3400 | −1750 | −1,600 | −1750 | −2050 |
| 85 | 95 | −175 | −210 | −100 | −160 | −65 | −70 | −65 | −80 |
| 2250 | 2150 | −3,150 | −4,200 | −2250 | −2350 | −1450 | −950 | −1500 | −1550 |
| 120 | 120 | −155 | −220 | −120 | −130 | −55 | −35 | −70 | −75 |
| 270 | 290 | −425 | −580 | −250 | −335 | −210 | −265 | −185 | −255 |
| 800 | 2300 | −2,300 | −4,250 | −3750 | −3750 | 1500 | 2,300 | −1600 | −2800 |
| 35 | 125 | −140 | −280 | −225 | −255 | 100 | 165 | −95 | −170 |
| 4400[b] | 8750 | 3,400 | 7,300 | −3700[b] | −3900 | 1200[c] | 1,700 | −5700[c] | −8300[c] |
| 175 | 375 | 115 | 335 | −215 | −245 | 30 | 40 | −330 | −430 |
| 210 | 500 | −25 | 55 | −440 | −500 | 130 | 205 | −425 | −600 |
| (−) | 195 | 205 | 205 | 198 | 206 | 196 | 200 | (+) | (+) |
| | −8200 | 11,700 | 16,400 | 5300 | 7100 | −7950 | −12,200 | | |
| | −335 | 705 | 1,000 | 200 | 340 | −400 | −600 | | |

close to the proposed adenine nucleoside resolution. When the pH is changed from 7 to 2, the 270- and 252-nm transitions increase in intensity and the 262-nm transition is no longer delineated. Overlapping bands of opposite sign may conceal the presence of additional transitions. This situation may occur in the MCD spectrum of β-ribo at pH 7, which is very similar to the MCD spectrum of adenine at pH 2. It can be matched by summing Guassian curves centered near 270, 260, and 250 nm.

The parameters describing each transition $i$ for each nucleoside $j$, and the associated rotational strengths $R(j)_i$, are given in Table III for CD spectra obtained in water and in ethanol. The half-band widths observed for the individual transitions are ~10 nm ($[\theta]_{270}$ and $[\theta]_{260}$), ~11 ($[\theta]_{250}$), 10–12 ($[\theta]_{225}$), ~7 ($[\theta]_{215}$), and 8–10 ($[\theta]_{206}$). A representative resolution (for β-ribo) is shown in Figure 4.

A consideration of the separate ranking of the α and β anomers according to the magnitudes of their rotational strengths, $|R(j)_i|$, obtained from spectra in water and in ethanol, reveals enantiomer-like pairs occupying corresponding positions within this ranking. In addition, relationships between $|R(j)_i|$ and the orientation of the $C_2'$–$O_2'$ and/or $C_3'$–$O_3'$ bonds with respect to the glycosyl bond are revealed. These relationships form the basis for the following discussion of the individual transitions. Conclusions were not found to be substantially changed if alternate but similar resolutions were considered.

**For the 270-nm transition** the configurational feature that correlates with large $|R_{270}|$ is the $C_3'$–$O_3'$ bond trans to the glycosyl bond; $R_{270}$ for those nucleosides with the $C_3'$–$O_3'$ bond trans is 1.5–2 times larger than for those with the $C_3'$–$O_3'$ bond cis. Changing the solvent from water to ethanol typically red-shifts and broadens this transition and increases $|R_{270}|$ 50–100%. The per cent contribution of this transition to the total $R(j)$ of the 260-nm envelope varies with configuration: $R_{270}$ of β-ribo ($C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds both trans) contributes *ca.* 50%, $R_{270}$ of β-lyxo ($C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds both cis) contributes only *ca.* 10%, and $R_{270}$ values of the other nucleosides contribute *ca.* 25%.

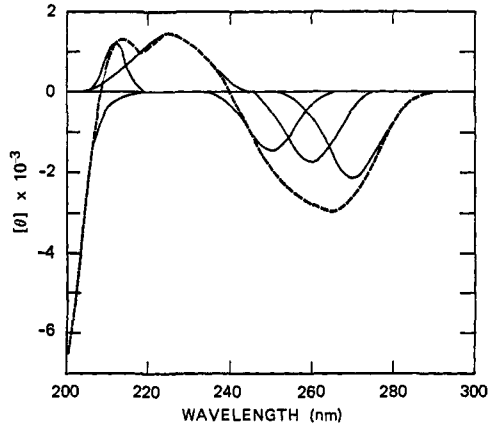



Figure 4. Resolution of the circular dichroism spectrum of β-ribo in water. Note that the 250- and 212-nm transitions are unusually narrow.

**The 260-nm transition** is largest for those nucleosides with their $C_2'$–$O_2'$ bond cis to the glycosyl bond and axial; $R_{260}$ for these nucleosides is about twice as large as for those with their $C_2'$–$O_2'$ bond trans. For a given configuration of the $C_2'$–$O_2'$ bond (*i.e.*, either cis or trans), nucleosides with the $C_3'$–$O_3'$ bond trans have $|R_{260}|$ about 1.5 times larger than do those with the $C_3'$–$O_3'$ bond cis. The α nucleosides of the enantiomer-like pairs have larger $|R_{260}|$ values than do the β nucleosides. Except for β-lyxo, there is little change in $|R_{260}|$ for a solvent change from water to ethanol. The contribution this transition makes to $R(j)$ of the first CD envelope is *ca.* 40% for all nucleosides in both water and ethanol.

The characteristics of the **250-nm transition** are similar to those of the 260-nm transition. The $|R_{250}|$ of nucleosides with their $C_2'$–$O_2'$ bond cis and axial is about twice as large as for those with this bond trans, and the α nucleosides of the enantiomer-like pairs have larger $|R_{250}|$ than do the β nucleosides. A solvent change from water to ethanol decreases $|R_{250}|$ of α- and β-ribo *ca.* 30%, while $|R_{250}|$ for the other nucleosides either increases (for the α-xylo–β-ara pair and α-lyxo, each of which has its $C_3'$–$O_3'$ bond trans to the glycosyl bond)

or remains the same (for the α-ara–β-xylo pair and β-lyxo, each of which has its $C_3'$–$O_3'$ bond cis). This transition also contributes *ca.* 40% to the $R(j)$ of the first CD envelope, except for β-ribo (*ca.* 25% in water and *ca.* 13% in ethanol).

**For the 225-nm transition** $C_2'$–$O_2'$ cis to the glycosyl bond and axial is again correlated with large $|R_{225}|$. Members of the enantiomer-like pair α-lyxo–β-ribo must be excluded from the usual ranking by $|R(j)_t|$ because of their unusual behavior. Both of these nucleosides behave similarly in this region, exhibiting small positive CD; this behavior may be related to their atypical furanose ring puckering ($C_3'$ instead of $C_2'$ puckering). The $|R_{225}|$ values of α-ribo and β-lyxo ($C_2'$–$O_2'$ and $C_3'$–$O_3'$ both cis) in water are about the same and are *ca.* 75% larger than the values of $|R_{225}|$ for α-xylo and β-ara ($C_2'$–$O_2'$ cis and $C_3'$–$O_3'$ trans). In ethanol, all four nucleosides have the same $|R_{225}|$ ($\sim 280 \pm 30 \times 10^{-42}$), strongly supporting the contention that the CD near 225 nm is related to the configuration common to these four nucleosides. The solvent change from water to ethanol broadens the half-band widths from ~10 to ~12 nm and increases $|R_{225}|$ up to fourfold.

**The 215-nm transition** exhibits sign reversals within the groups of α and β anomers. In contrast to the previous four transitions described above, $|R_{215}|$ cannot be correlated with the configuration of those bonds defining enantiomer-like pairs. In both water and ethanol, α- and β-xylo exhibit negative CD at 215 nm and α- and β-ara exhibit positive CD. This is an unusual example of anomeric pairs having a CD transition of the same sign; however, these nucleosides arranged into enantiomer-like pairs have oppositely signed CD near 215 nm. These nucleosides, each with its $C_2'$–$O_2'$ bond trans to its $C_3'$–$O_3'$ bond, generally have larger $|R_{215}|$ values than do those with a cis arrangement of these bonds. For a solvent change from water to ethanol, $|R_{215}|$ values for α- and β-ara and α-lyxo increase two–threefold.

The positions and $[\theta]_{max}$ values for **the low-wavelength transition** can be directly obtained from the spectra for β-ara, α- and β-ribo, and α-xylo. For spectra that delineate only part of the low-wavelength envelope, the positions and $[\theta]_{max}$ values were estimated using the curve resolver. This was done for spectra of α- and β-lyxo in water and α-ara, α-ribo, and β-lyxo in ethanol. The $|R_t|$ values of this transition are largest for α-xylo and β-ara ($C_2'$–$O_2'$ cis); the transition is centered at 205–206 nm, coincident with the uv maximum. For β-lyxo and β-ribo, the transition is centered near 196 nm in water but is red-shifted 4 and 8 nm, respectively, when the solvent is changed to ethanol; for α-ribo, the same solvent change blue-shifts the transition 6 nm.

**The CD Envelopes.** The three CD envelopes of the adenine pentofuranosides do not occur in signed pairs, nor is there evidence for signed pairs of transitions. This is in contrast to the observation of Miles, *et al.*,[4] that the 220-nm and the low-wavelength envelopes of several adenine pentofuranosides occur in signed pairs.

The $|R(j)|$ values of **the 260-nm envelope** of those nucleosides with $C_2'$ furanose ring puckering generally increase with a solvent change from water to ethanol: *ca.* 35% for the β nucleosides, *ca.* 25% for α-xylo, but not at all for α-ara and α-ribo. The $|R(j)|$ values of the α nucleosides of the enantiomer-like pairs are *ca.* 50% larger than $|R(j)|$ values of the β-nucleosides in water, but only *ca.* 15% larger in ethanol. These observations suggest that the enantiomer-like pairs are closer to being mirror images in ethanol than in water. In addition, these observations may indicate that the population of anti conformers is smaller in water than in ethanol solutions, and that the population of anti conformers in both solvents is smaller for β nucleosides than for α nucleosides. Alternatively, slight changes in furanose conformation and/or the $C_1'$–$N_9$ torsion angles may be the cause of the increases in $|R(j)|$ values.

The nucleosides with $C_3'$ furanose ring puckering, α-lyxo and β-ribo, behave differently. The $|R(j)|$ values of both 260-nm envelopes are enhanced *ca.* 25% with a solvent change from water to ethanol, and $|R(j)|$ of α-lyxo is *ca.* 45% larger than $|R(j)|$ of β-ribo in both water and ethanol. Changes in the population of syn–anti conformers and/or changes in the $C_1'$–$N_9$ torsion angles of these nucleosides apparently occur to the same extent for this solvent change.

A recent study of vicinal effects on the CD of pyrimidine nucleosides[5] suggests that $R(j)$ values of the long-wavelength CD envelope for nucleosides with $C_2'$–$O_2'$ cis are at least twice those for nucleosides with a trans arrangement of these bonds. It is also suggested that a change from $C_3'$–$O_3'$ trans to cis reduces these $|R(j)|$ values *ca.* 10%. Similar trends were observed for the purine nucleosides of this study.

The configuration of the $C_2'$–$O_2'$ bond appears to be the primary steric factor affecting the $|R(j)|$ values in both water and ethanol, but well-defined effects of the configuration of the $C_3'$–$O_3'$ bond on $|R(j)|$ values are also observed. The $|R(j)|$ values of nucleosides with $C_2'$–$O_2'$ cis and axial and $C_3'$–$O_3'$ trans and axial (α-lyxo–β-ara) are about twice as large as those of nucleosides with $C_2'$–$O_2'$ trans and equatorial and $C_3'$–$O_3'$ cis and equatorial (α-ara–β-xylo). However, when the $C_2'$–$O_2'$ and $C_3'$–$O_2'$ bonds are both cis (α-ribo–β-lyxo), the $|R(j)|$ values of the envelope are only 1–1.3 times larger than when the $C_2'$–$O_2'$ and $C_3'$–$O_3'$ bonds are both trans to the glycosyl bond (α-lyxo–β-ribo). When the $C_2'$–$O_2'$ bond is cis (and axial), a change in configuration of the $C_3'$–$O_3'$ bond from trans to cis decreases $|R(j)|$ values 30–70%; when the $C_2'$–$O_2'$ bond is trans (axial or equatorial), $|R(j)|$ values decrease *ca.* 10–15%.

**The 220-nm CD Envelope.** The signs of the 225- and 215-nm transitions are the same for each member of every enantiomer-like pair except α-xylo–β-ara, with the $|R(j)|$ values of the 220-nm envelope being two–three times larger for the β anomers than for the α anomers. Since the 225- and 215-nm transitions have opposite signs for α-xylo–β-ara, the 215-nm transition is part of the low-wavelength envelope in the spectra for these nucleosides.

**Assignment of Transitions.** Simpson and coworkers[3] concluded from studying the depolarization of fluorescence of adenine that the 260-nm envelope is composed of two $\pi \rightarrow \pi^*$ transitions—the major transition centered near 260 nm and the other near 250 nm. Cohen and Goodman[35] concluded from studying luminescence

(34) P. R. Callis, E. J. Rosa, and W. T. Simpson, *J. Amer. Chem. Soc.*, 86, 2292 (1964).
(35) B. J. Cohen and L. Goodman, *ibid.*, 87, 5487 (1965).

of purines that the 260-nm envelope contains an n → π* transition. Assignment of the 270-nm transition as n → π* and the 260- and 250-nm transitions as π → π* is consistent with these conclusions and is supported by the following observations made in this study.

The 270-nm transition is characterized by low $\epsilon_m$ and low $R(j)$. Upon changing the solvent from water to ethanol, the 270-nm transitions undergo a small but reproducible red shift, the half-band widths broaden, and $|R(j)|$ values increase 50–100%; for the same solvent change, the 260- and 250-nm transitions do not change position, their half-band widths do not broaden, and there is little enhancement of $|R(j)|$ values. Upon changing the solvent from water to DMSO, the 270-nm transition red-shifts ~10 nm while the 260-nm transition red-shifts only ~5–6 nm. Furthermore, for a pH change from 7 to 1.3, the 270-nm transition apparently blue-shifts 30 nm while the 260- and 250-nm transitions undergo no change in position (see Figure 2).

The 225-nm transition may also be an n → π* transition since it occurs at the uv minimum. The half-band widths and $|R_{225}|$ values increase upon changing the solvent from water to ethanol, behavior similar to that of the 270-nm transition (presumably n → π*) and in contrast to that of the 260- and 250-nm transitions (π → π*). An estimate of the ratio of the rotational strength to the dipole strength (the anisotropy factor)[36] for the 225-nm transition is an order of magnitude larger than for the 260- and 250-nm transitions (~$10^{-4}$ compared to ~$10^{-5}$). This is consistent with the assignment of the 225-nm transition as an n → π* transition.

These assignments suggest that $R(j)$ values of n → π* transitions in adenine nucleosides can be as large as or larger than $R(j)$ values of π → π* transitions (for example, for β-ribo). They also suggests that the intensity of n → π* transitions can be large in MCD spectra.

**Acknowledgments.** The author is grateful to Drs. Leon Goodman and Peter Lim for arranging for support of this work.

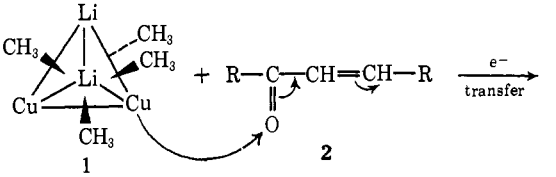
(36) The dipole strength for each transition $i$ was calculated using the equation $D_i = 1.63 \times 10^{-38} \epsilon_i \Delta_i / \lambda_i$, where $\epsilon_i$ is the molar extinction coefficient and $\lambda_i$ is the wavelength at the center of transition $i$ while $\Delta_i$ is its half-width at $\epsilon_i/e$.

# Communications to the Editor

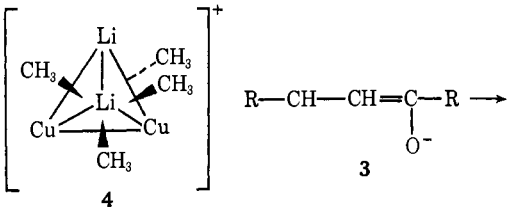
## Reactions Involving Electron Transfer. III. The Conjugate Addition of Lithium Dimethylcuprate to α,β-Unsaturated Carbonyl Compounds[1]

*Sir:*

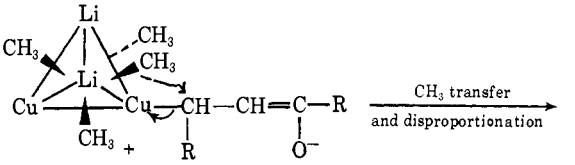
The introduction of lithium dialkyl- (or diaryl-) cuprates [$LiR_2Cu(I)$] as selective reagents for the conjugate addition of alkyl or aryl groups to unsaturated carbonyl compounds[2] has led to the widespread utilization of these reagents both for conjugate additions and for the related generation of specific enolate anions.[3] The reaction was suggested[2] to involve an initial electron transfer from the cuprate **1** (which we tentatively formulate as a dimeric tetrahedral structure analogous to other "ate" complexes[4]) to an unsaturated carbonyl compound **2** to form an intermediate anion radial **3** and an electron-deficient metal cluster such as **4**. Rebonding of **3** and **4** followed by the intramolecular rearrangement of a methyl group (*i.e.*, **5**) from the metal




1 2




4 3




5


6

cluster to carbon accounts for the retention of stereochemistry observed with alkyl and vinyl groups[5] and

(1) Supported by Public Health Service Grant No. RO1-CA-12634 from the National Cancer Institute.

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