The CD in Situ Complexation Method as a Tool for Determination of Absolute Configurations of Cottonogenic Derivatives

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Abstract: An easy and versatile method has been developed for the generation of enhanced Cotton effects (CEs) from optically active substances that are weakly absorbing in the accessible wavelength range. This method involves the *in situ* interaction of chiral carboxylic acids, α-amino acids, amino alcohols, ephedrine isomers, and polynucleic acids with trinuclear metal complexes: $[M_3O(O_2CCH_3)_6L_3]^{n+}$, where M = Fe, Cr, Mn, Rh, Ru, etc., L = water or pyridine, and n = 0 or 1. These derivatives, with their conformational flexibility either reduced or totally restricted, give rise to CEs. Semiempirically based helicity rules and newly established sector rules have been applied for the correlation of the CEs with the absolute configurations.

Introduction

Circular dichroism (CD) can be reliably used for the determination of relative and absolute configurations as well as conformational preferences. This is of major importance both for natural product synthesis and for the development of new synthetic methods. But a common problem encountered with a majority of optically active substances is that, because of their conformational mobility, the weakly absorbing chromophores yield CD spectra that are difficult to interpret. Therefore, questions related to fixing of conformations by suitable derivatives in order to induce intense Cotton effects (CEs) are the main focus of experimental and theoretical studies.[1-11]

In this paper we report a convenient method for determining absolute configurations involving the *in situ* generation of chiral complexes by mixing solutions of chiral substances and trinuclear metal complexes of the general formula $[M_3O(O_2CCH_3)_6L_3]^{n+}$, where M = Fe, Cr, Mn, Rh, Ru, etc., L = water or pyridine, and n = 0 or 1.

The crystal structures of several such complexes in which the oxidation state of the metal atom is M^{II}, M_2^{III}, or M_3^{III} are known.[12] As shown in Figure 1, an oxygen atom is located at the center of an equilateral triangle of metal atoms surrounded by six carboxylate groups positioned in an octahedral arrangement with nearly D_{3h} symmetry.

A number of sector rules correlating the substituent disposition in a chiral metal complex with the d-electron CEs have been
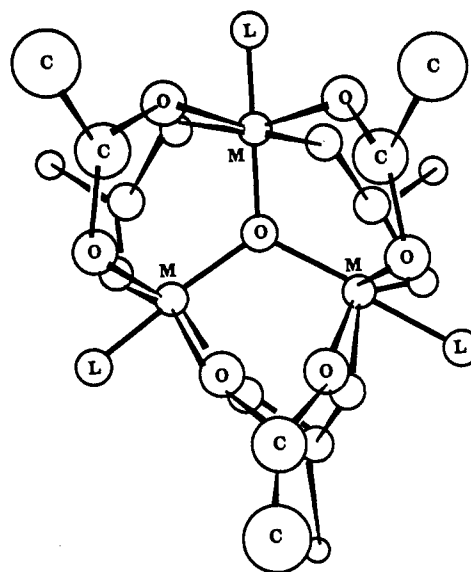

Figure 1. Structural unit of $[M_3O(OOOR)_6L_3]^{n+}$ complex.

reported.[13-20] The simplest sector rule can be built up from the mirror planes of the molecule. In order for a static external

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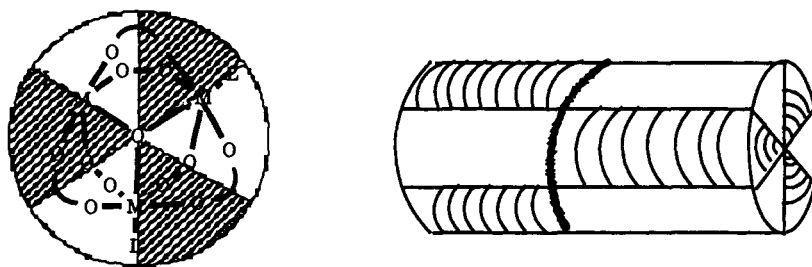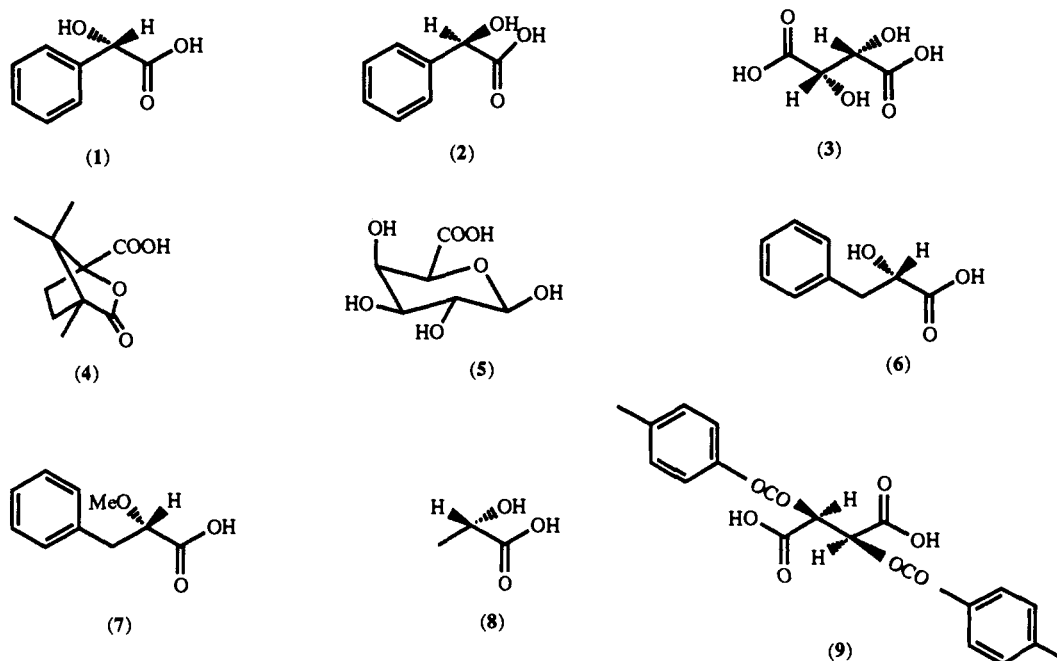(27) Snow, M. R.; Buckingham, D. A.; Marzilli, P. A.; Sargeson, A. M. *Chem. Commun.* **1969**, 891.

Figure 2. (Top) Sector rule represented in terms of a view down the cylinder axis showing both the molecule and the sectors with the notation that the sectors lying below the plane of the three metal atoms are reversed. (Bottom) The second side view is shown without the molecular structure.

Chart I

potential to induce optical activity in a chromophore, it must contain a part which belongs to the pseudoscalar representation of the point group of the chromophore. This pseudoscalar function, which is the scalar product of an axial and a polar vector (i.e., it behaves like a scalar under all transformations except those of reflection and inversion, where it changes sign), plays a dominant role in sector rules.

The pseudoscalar representation in the point groups D_3 and D_{3h} is A_1'', and the simplest symmetry-determined sector rule which is appropriate is then a duodecant rule to which, however, at least for some transitions, additional orbital-determined nodal surfaces have to be added. Substituents which are located in the hatched sectors of the duodecant induce a positive rotational strength in the D_3 components $A_1 \rightarrow A_2$ and a negative rotational strength in the $A_1 \rightarrow E$ components. Converse relations between optical activity and substituent positions apply to the unhatched sectors (Figure 2).

For our purpose it is not necessary to assign individual transitions to the structural problems because it is the net CD that is important for sector rules. In practice, the net CD sign is probably determined by the resultant magnetic dipole-allowed transitions so that only they need be considered.

Results and Discussion

Chiral Carboxylic Acids. Carboxylic acids may be investigated nowadays by chiroptical methods directly without the need of first preparing Cottonogenic derivatives, but several difficulties are encountered: (1) in solution, acids are present as a mixture of monomeric and dimeric forms, each giving its own CD; (2) the anionic species might also be present in appreciable concentration;

(3) the very polar carboxyl group is heavily solvated in solution, and such a chiral solution will contribute to the CD in a nonpredictable way; (4) $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands are very close to each other, so the respective Cotton effects may not unequivocally be disentangled; (5) several conformers are generally present in solution; and (6) if additional chromophores are present in the molecule, the $n \rightarrow \pi^*$ Cotton effect of the acid chromophore might be overlapped by other Cotton effects. All these drawbacks disappear for the metal complexes since conformational mobility is very much reduced by the restricted rotations of the acylate ligands coordinated to the metal atoms. Furthermore, transition-metal ions, when complexed to an optically active ligand, become associated with the symmetry of the ligand, and Cotton effects related to electronic transitions of the metal atom are observed.

In most cases, α-hydroxy carboxylic acids give two characteristic Cotton effects with the complexes FE1, FE4, CR1, and MN1 (complexes I–IV, respectively, see Experimental Section); these can be used for the determination of their absolute configurations. (S)-$(+)$-Mandelic acid (**1**, Chart I), e.g., on treatment in water with both iron complexes FE1 and FE4, generates two major CEs around 400 and 300 nm having negative and positive signs, respectively. The reverse signs are, however, seen for (R)-$(-)$-mandelic acid (**2**) (Figure 3). (S)-$(+)$-Tartaric acid (**3**) and both the iron complexes generate several CEs in DMSO, where the two CEs around 400 and 300 nm, with respective negative and positive signs, may be the diagnostic ones. A solution of $(-)$-camphanic acid (**4**) and FE4 in DMSO gives rise to several CEs, but the two intense CEs around 470 and 370 nm with their respective negative and positive signs seem to be more appropriate for determining the absolute configuration.
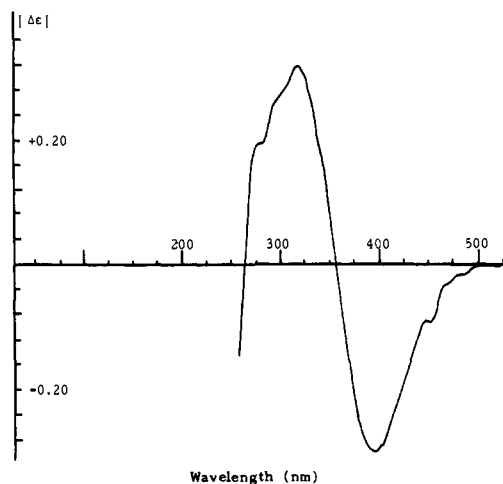
Complexation Method for CD Study of Configurations

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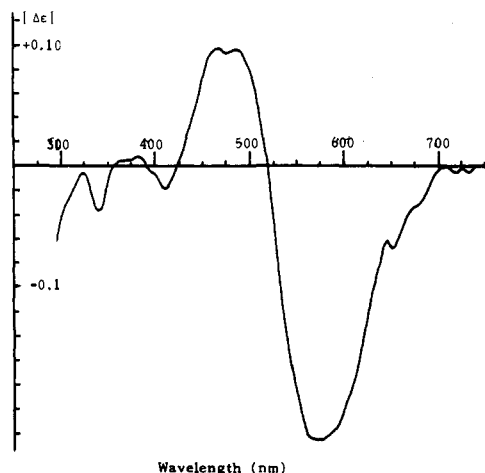**Figure 3.** CD spectrum 1 in water in the presence of FE4.

Figure 4. CD spectrum of 1 in acetonitrile in TMP in the presence of CRI.

Galacturonic acid monohydrate (5) and FE4 afford in TMP a broad positive CD between 450 and 350 nm with a maximum around 375 nm and another negative CE around 290 nm.

Five optically active carboxylic acids are measured with CR1, where compounds 1 and (S)-(-)-3-phenyllactic acid (6) give identical CD spectra characterized by an intense negative CD around 600 nm and a relatively minor positive CE around 450 nm. Compound 2 is the enantiomer of compound 1 and, therefore, shows the reverse CD spectra. Of the several CEs, the largest negative one, which occurs at about 570 nm and which is common to compounds 5 and (S)-(-)-2-O-methyl-3-phenyllactic acid (7), may help in the determination of the absolute stereochemistry (Figure 4).

Six optically active carboxylic acids were measured with MN1 (IV), and all of them showed a positive CE at longer wavelengths and a negative one at shorter wavelengths. Compounds 1, 6, and (S)-(+)-lactic acid (8) show nearly identical CD spectra with a broad, positive band around 500 nm and a negative CD band around 410 nm (Figure 5). 2,3-O,O-Di-p-toluoyltartaric acid (9) affords in TMP a positive CE around 520 nm with a shoulder at 472 nm and a negative CE around 300 nm. For MN1 and (S)-(-)-malic acid (10, Chart II), the two CEs retain their sign sequence, i.e., (+) and (-), but occur at different wavelengths at about 500 and 365 nm, respectively. The CD spectrum of compound 5 is quite different from those of other carboxylic acids, where it is associated with a weak negative CE centered at 640 nm, a strong positive CE at 450 nm, a relatively less strong positive CE at 430 nm, and two minor CEs at 340 and 310 nm with negative and positive signs, respectively. The strong CE at 450 nm may be the diagnostic one for the absolute configuration.
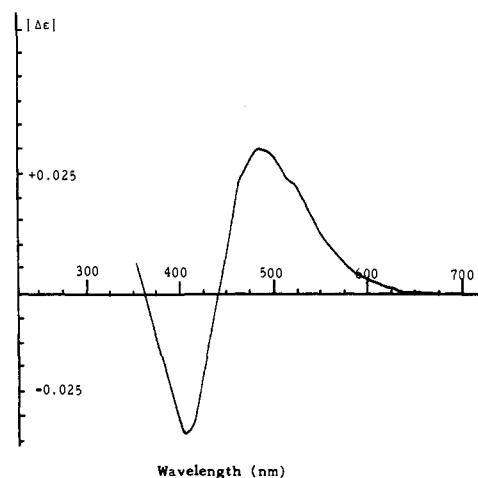

Figure 5. CD spectrum of 8 in TMP in the presence of MNI.

In cases I–III, the CD spectra corresponding to S-isomers are characterized by a negative CE at longer wavelengths and by a positive one at shorter wavelengths, while in case IV, the longer wavelength CE is positive and the shorter wavelength CE is negative.

These observed signs of the CEs of chiral carboxylic acids may be rationalized according to the duodecant rule if it is assumed that the C=O bond of the carboxyl group lies synperiplanar to the nearby C=C bond.

As has been observed in many tris-chelated Co(III) complexes of D_3 symmetry with Λ-configuration,[28-32] the longer wavelength CE belonging to the $A_1 \rightarrow A_2$ component of the octahedral $A_{1g} \rightarrow T_{1g}$ transition is associated with the positive sign, while the shorter wavelength CE corresponding to the $A_1 \rightarrow E$ component of the same transition carries a negative sign, but the net CD for the two components remains positive. The reverse of this, however, holds for the same complexes with Δ-configuration, where the net CD remains negative.

As can be deduced from the CD spectra of chiral carboxylic acids, the net CD remains negative for the chiral carboxylic acids with S-configuration. These may, therefore, be compared with Co(III) complexes with Δ-configuration. On the other hand, the carboxylic acid with R-configuration, where the net CD remains positive, may be compared with Co(III) complexes with Λ-configuration. Thus our *in situ* method confirms the already established stereochemistry of the optically active carboxylic acids.[28-32]

In the duodecant (Figure 2), substituents in hatched regions induce a positive CE through the configurational effect in the $A_1 \rightarrow A_2$ transition, and converse relations between CD and substituent positions apply in the unhatched regions.

α-Amino acids. The protein amino acids isolated from natural sources have been shown to possess both S- and R-configurations at C-2.[33,34] There have been several previous surveys of the optical rotatory dispersion (ORD) and CD data for the common amino acids and hydroxy acids.[35-38] Sulfur-containing amino acids have been studied by several groups of workers,[39-41] and aryl amino acids have been studied in detail.[42]

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Chart II

(10)   (11)   (12)
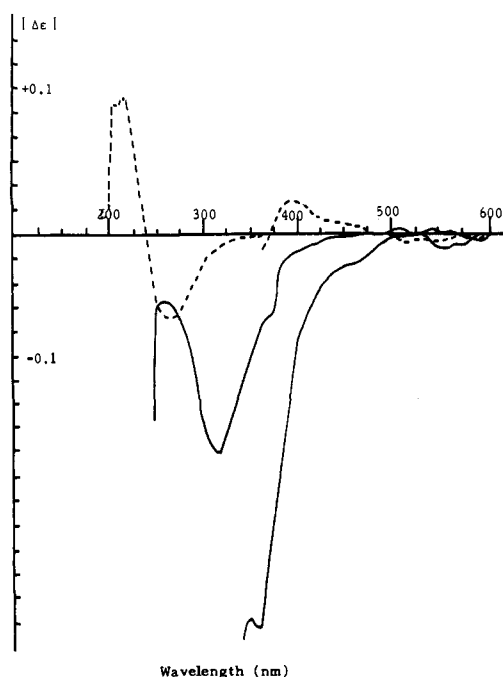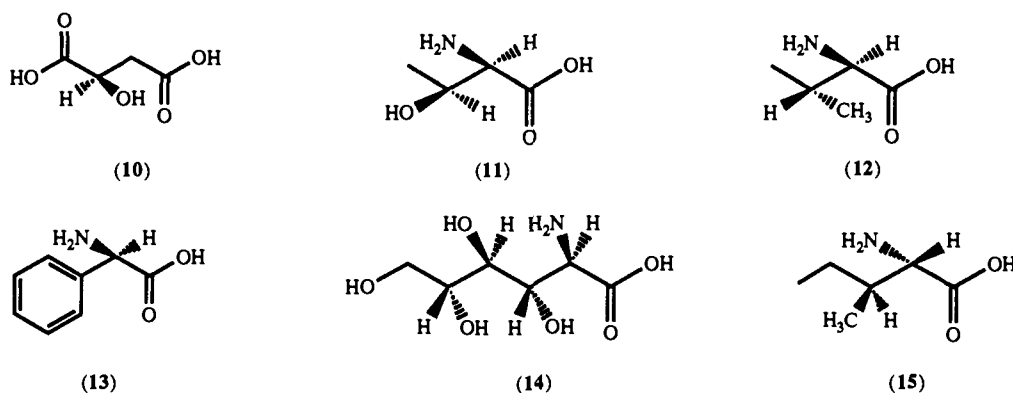

(13)   (14)   (15)

Figure 6. CD spectra of **12** (- - -) in **13** (—) in DMSO in the presence of FE4.

Our present survey reports the CD of *in situ* complexes of 14 amino acids acting as ligands for the oxo-bridged metal carbox-ylates FE1, FE4, CR1, and MN1. These have been examined in DMSO, pyridine, water, trifluoroethanol, and acidic solutions. DMSO was found to be the best solvent for the generation of CEs from the amino acids.

Four amino acids of the *R*-series were measured with complexes I–IV. These were (*R*)-(–)-threonine (**11**), (*R*)-(–)-valine (**12**), (*R*)-(–)-2-phenylglycine (**13**), and (*R*)-(+)-glucosaminic acid (**14**). Compounds **11**, **12**, and **13** yield with complex II broad positive CEs between 550 and 450 nm, negative CEs between 400 and 300 nm, and a positive CE below 300 nm (Figure 6). (*R*)-(+)-Glucosaminic acid (**14**) in water and (*S*)-isoleucine (**15**) in DMSO show with FE1 complex nearly identical CD spectra with positive bands around 400 and 300 nm and negative bands below 300 nm.

The eight amino acids of the *S*-series were also examined for comparison. These were (*S*)-isoleucine (**15**), (*S*)-norleucine (**16**), (*S*)-methylcysteine (**17**), (*S*)-cysteine (**18**), (*S*)-(–)-tyrosine (**19**), (*S*)-3,5-diiodotyrosine (**20**), (*S*)-proline (**21**), and (*S*)-phenyl-

alanine (**22**) (Chart III). Compound **15** exhibits in pyridine identical CD spectra with the iron complexes I and II which are characterized by a distinct positive curve at about 370 nm. One additional negative broad band at about 575 nm and the other positive broad band at 415 nm may be observed.

The CD data for sulfur-containing amino acids are also reported. Compound **17**, for example, shows in DMSO with FE4 a broad positive CD band between 600 and 500 nm and another broad positive CD band between 400 and 300 nm with a maximum at 325 nm. There is also the beginning of a third negative CE below 300 nm. The broad band between 600 and 500 nm turns negative after 1 week of CD measurement of the solution and resolves into two negative CEs, one at about 480 and the other at 440 nm.

Compound **19** measured in DMSO with FE1 affords negative CEs between 500 and 400 nm and a positive one around 300 nm. One additional negative CE occurs below 300 nm. In pyridine the CD spectrum of **19** is identical to that measured in DMSO, but Δε values are increased. The CD curves of (*S*)-proline (**21**) show in pyridine two maxima, the positive one at about 330 nm and the negative one at about 280 nm. Additional positive bands occur around 500 and 415 nm. In TFE, two multiple CEs are observed. The negative one appears between 400 and 350 nm while the positive one occurs between 340 and 300 nm.

Seven amino acids, **11, 12, 13, 15, 17, 20**, and **22**, were measured with CR1 (**III**). Water, acetonitrile, and DMSO were used as the solvents. The CD curves of compounds **11** and **12** show positive CEs between 600 and 500 nm and minor negative CE below 450 nm. Compounds **15** and **22** each yield a broad negative CE between 600 and 500 nm but with a variation of maxima. For instance, in compound **15** this lies around 560 nm and in **22** this is near 500 nm (Figure 7).

Four amino acids, **12, 16, 17**, and **18**, and two dipeptides, (*S*)-alanylglycine (**23**) and acetyl-Ala-Ala (**24**) (Chart III), were measured with MN1 (**IV**). The representative of the *R*-series **12** shows a positive CE around 600 nm, a negative CE between 500 and 400 nm, and a positive CE around 300 nm, while compound **16** of the *S*-series shows the opposite behavior, i.e., the CD band between 500 and 400 nm is associated with positive sign while the band around 300 nm carries the negative sign (Figure 8). Compound **23** yields in DMSO two distinct CEs, a negative one between 600 and 500 nm and a positive one between 500 and 400 nm. Compound **24** produces in DMSO a positive broad band at 615 nm and a relatively stronger negative one around 520 nm. Like for *S*-amino acids, one observes here in both **23** and **24** negative CEs between 400 and 300 nm with an additional positive curve below 300 nm.

From this discussion we come to the conclusion that, in general, amino acids of the *R*-series yield a net negative CD with complexes I, II, and IV. The reverse holds, of course, for the *S*-series. In case III, the net negative CD is associated with *S*-amino acids while the *R*-series show a *net* positive CD. Compound **14** of the

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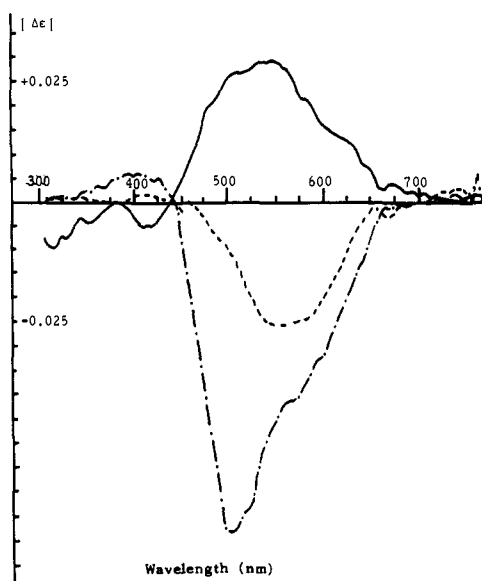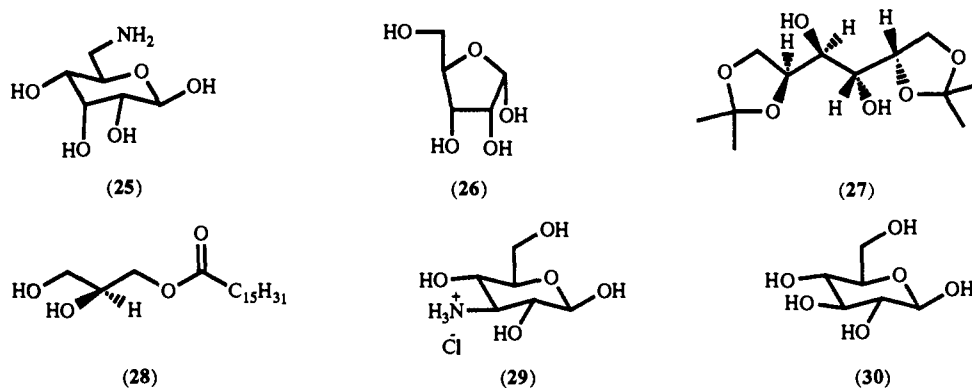
Chart III

(25)   (26)   (27)

(28)   (29)   (30)

Figure 7. CD spectra of **12** (—) in DMSO, **15** (- - -) in acetonitrile, and **22** (—·—) in DMSO in the presence of CRI.
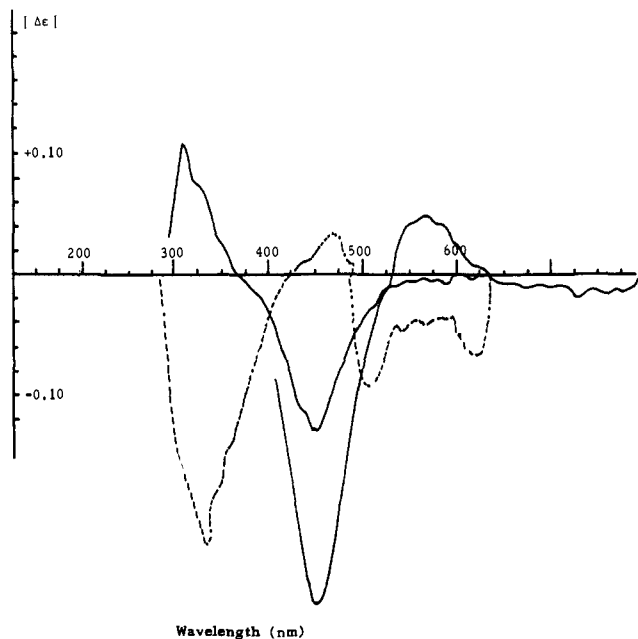

Figure 8. CD spectra of **12** (—) and **16** (- - -) in DMSO in the presence of MNI.

R-series is the exceptional case. Thus the CD results obtained from α-amino acids measured with **III** may be subjected to the proposed duodecant rule according to which duodecant with usual

signs may account for the absolute configurations of amino acids, i.e., the substituents in the hatched sectors contribute positively to the CEs, while those accommodated in the unhatched sectors contribute negatively (Figure 2). As is evident from their CD spectra, the duodecant with unusual signs may be applied to the *in situ* complexes of amino acids measured with **I**, **II**, and **IV**, i.e., the substituents in the unhatched sectors contribute positively, while those in hatched sectors contribute negatively. The results with **III** confirm the already established *S*-configuration of amino acids in the free state where the net CD is negative,[43] while the results with **I**, **II**, and **IV** support the *R*-configuration of Cu(II) complexes of amino acids for which the net CD in the d → d region is also negative.[44]

It should also be emphasized that amino acids or the dipeptides coordinate to the metal ions only when they act as zwitterions. The chelate ring so formed is nearly planar, and the substituents may be below or above this plane depending upon whether their configuration is *S* or *R*. Thus, the substituents attached to the chiral centers may contribute to the optical activity through the vicinal effect which is caused by the chiral centers in the chromophore, and this can also be applied to the α-amino acids which we have taken into account.

Glycols. Several investigations have been made on the ORD and CD of glycol complexes of Mo(IV) and Mo(V).[45-48] We describe here the CD results of the *in situ* complex formation of glycols 6-amino-6-deoxy-D-allose (**25**), D-ribose (**26**), 1,2:5,6-diisopropylidenemannitol (**27**), L-α-stearine (**28**), 3-amino-3-deoxy-D-glucose–HCl (**29**), and D-(+)-glucose–H₂O (**30**) (Chart IV) measured with complexes I–IV. Compounds **25** and **26** measured with iron complexes I and II show nearly identical CD spectra, where the longer wavelength CE is positive and occurs around 500 nm while the shorter, negative CE appears around 400 nm (Figure 9). The weakly acidic solution of compound **27** in pyridine gives CD curves which are characterized by a broad positive CE around 400 nm and negative multiple CEs between 350 and 250 nm. In compounds **29** and **30**, the sign sequence persists but with variation of maxima. For instance, in **29** measured with **I**, the positive CD band between 500 and 400 nm splits into multiple CEs with a maximum around 470 nm, while in **30** measured with **II**, the positive maximum is around 430 nm, shifted to 370 nm in slightly alkaline solution.

The only glycol measured with CR1 in trimethyl phosphate (TMP) is D-sorbitol (**31**, Chart V), for which one finds a negative CE around 620 nm that seems more characteristic of its absolute configuration. An additional minor positive band around 540 nm can also be observed (Figure 10).

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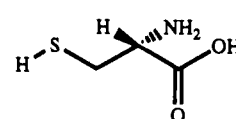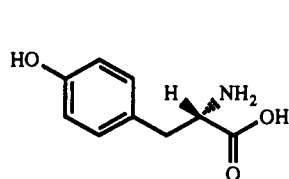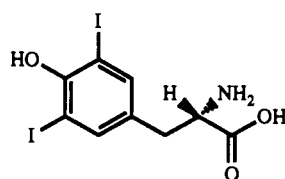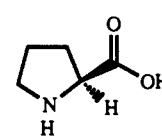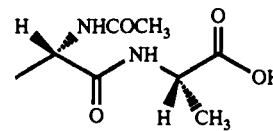
Chart IV
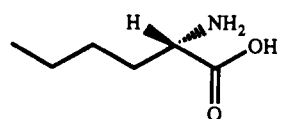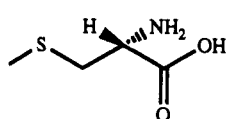
(16) (17) (18)

(19) (20) (21)
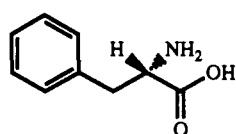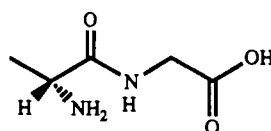
(22) (23) (24)

Chart V
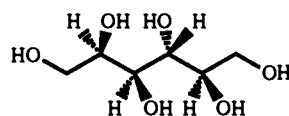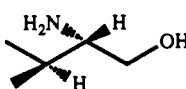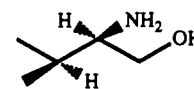
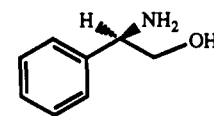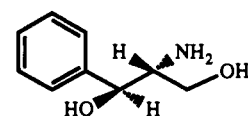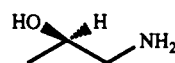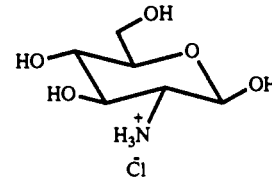(31) (32) (33)
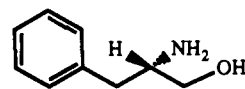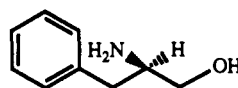
(34) (35) (36)

(37) (38) (39)

The CD of three open-chain glycols **27**, **28**, and **31** were examined with MN1 complex, where one observes two distinct broad CEs between 600 and 500 and 500 and 400 nm which for **27** and **31** are associated with negative and positive signs, while for **28** these are positive and negative, respectively (Figure 11).

As mentioned, the glycols follow helicity rules, and, therefore, one can correlate the diagnostic CEs with the torsion angle. Thus, the glycols showing positive CEs toward longer wavelength with a corresponding negative one toward shorter wavelength follow P-helicity, where the positive CE is correlated with the positive torsion angle. On the other hand, the negative, longer wavelength CE with a corresponding positive, shorter wavelength one occurs with a negative torsion angle; therefore, the glycols exhibiting such characteristics obey M-helicity (Figure 12).

For open-chain glycols, .e.g., **31**, one gets the correct CD sign if one forces the glycol into such a conformation that each –O–C–C–O–R moiety adopts an antiperiplanar conformation. This seems reasonable because in such a conformation the bigger group R avoids steric interactions with the acetate ligands of the complexes I–IV still present.

Several investigations[49,50] show that the ring glycols, e.g. **25**, exist in aqueous solution in the pyranose form and act as either

bidentate or tridentate ligands. In our case the ring glycols may adopt pyranose conformations, but preference is, of course, given to the bidentate ligation rather than to the tridentate one. This is born out by the fact that glycols may complex through either the exchange of two OH groups with the two acetate groups of the same metal maintaining the torsion angle (M–O)–C–C–(O–M) of approximately 60° or the exchange of the two OH groups with the two acetate groups bonded to two metals with a torsion angle (M–O)–C–C–(O–M') of 60°. In tridentate-type ligation, however, the maintenance of the torsion angle of 60° may not be possible, because then we can have a violation of our well-established helicity rule for such compounds.

Amino Alcohols. Amino alcohols generate intense CEs with complexes I–IV, and the characteristic CEs may be compared with the torsion angles and thus follow the helicity rule. Most of the amino alcohols of the same absolute configuration give nearly identical CD spectra with iron complexes FE1 and FE4. For instance, the solution of L-valinol (**32**, Chart V) and FE1

(49) Velluz, L.; Legrand, M. *C. R. Hebd. Seances Acad. Sci. Paris C* **1966**, *263*, 1429.

(50) Park, J. J.; Glick, M. D.; Hoard, J. L. *J. Am. Chem. Soc.* **1969**, *91*, 301.
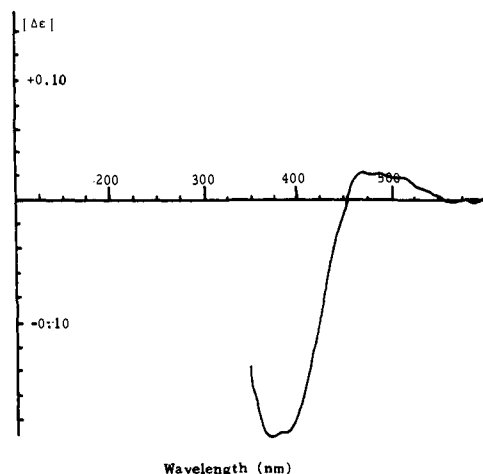
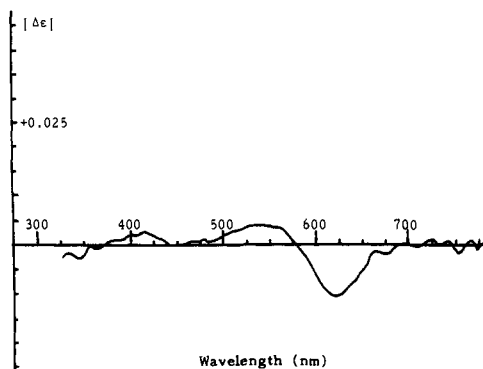**Figure 9.** CD spectrum of **26** in DMSO in the presence of FEI.

Figure 10. CD spectrum of **31** in TMP in the presence of CRI.
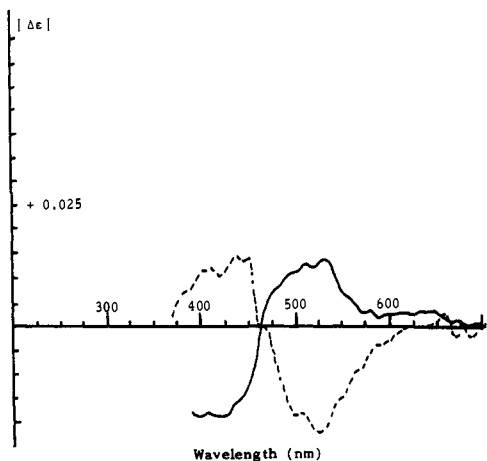

Figure 11. CD spectra of **28** (—) in acetonitrile and **31** (- - -) in ethanol in the presence of MNI.

gives rise to two characteristic CEs around 400 and 300 nm with negative and positive signs which undergo inversion when the solution is heated at 80 °C for 30 min. The inverse spectral behavior is shown by the D-valinol (**33**) (Figure 13). L-Phenylalaninol (**34**), besides several CEs, shows two distinct CEs around 435 and 320 nm with (−) and (+) sign sequence for the same CEs. In L-phenylalaninol (**34**) and D-phenylalaninol (**35**) there is the beginning of the positive and negative CEs below 300 nm, respectively. In D-(−)-2-phenylglycinol (**36**) measured in acetonitrile with I and II, the positive intense CE lies around 430 nm and the negative CE occurs around 315 nm. L-(+)-*threo*-2-Amino-1-phenyl-1,3-propanediol (**37**), like its counterparts, is associated with a negative, longer wavelength CE around 375 nm and a positive, shorter wavelength CE at about 255 nm. The addition of a trace of a base to the solution of **37** does not change
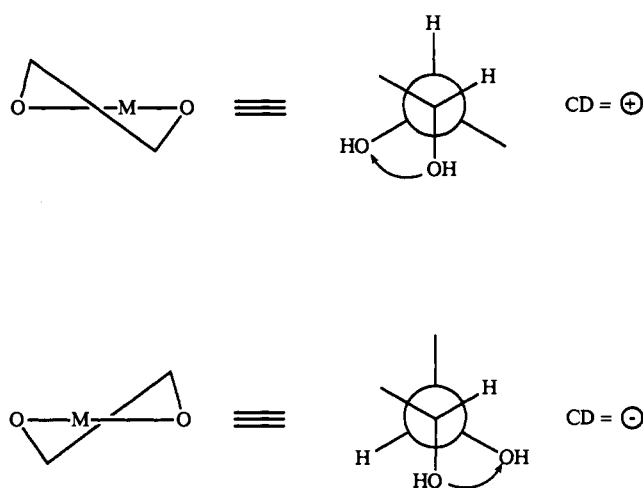

Figure 12. Glycol with positive and negative torsion angles of 60° with the C–C bond lying in front of and behind the metal atom, respectively, as indicated by the drawings to the left.
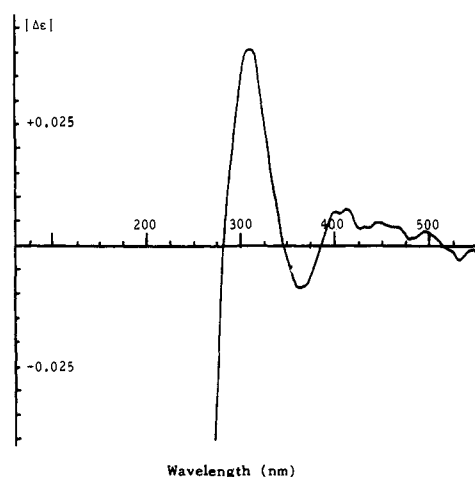

Figure 13. CD spectrum of **32** in DMSO heated at 80° for 30 min in the presence of FEI.

the CD spectrum drastically. Also, no change occurs when the spectrum is measured 1 week after preparation of the solution. (*R*)-(−)-1-Amino-2-propanol (**38**) affords a positive CE toward longer wavelength, around 370 nm, while the negative, shorter wavelength CE occurs at 330 nm.

CR1 (**III**) and amino alcohols yield different CD spectra in different solvents. In ethanol, compound **32**, for instance, gives CD curves around 540 and 400 nm which are negative and positive, respectively. The enantiomeric CD curves correspond to **33**. Compound **34** yields negative CEs around 570 nm, while the positive CD band occurs between 500 and 400 nm. The reverse holds for (**35**) (Figure 13). Compound **39** (Chart V) gives rise to two broad bands, where the stronger, negative one is centered at about 570 nm while the minor, positive one lies between 500 and 400 nm. In acetonitrile, one gets quite different CD spectra where the CEs lie around 630, 560, 500, 430, and below 400 nm with (+), (−), (+), (−), and (+) sign sequence. The CD spectrum for **40** in TMP is identical to that taken for **39** in acetonitrile (Figure 14).

Our CD examination of amino alcohols **32**, **34**, **35**, and **37** and MN1 (**IV**) shows in DMSO the presence of five CEs around 600, 500, 400, 350, and 300 nm, which for the L-series have the sign sequence (+), (−), (+), (−), and (+), while the inverted sign sequence was obtained for the D-series (Figure 15). In ethanol, two broad CD bands corresponding to the L-series are observed. The bands between 600 and 500 nm and around 450 nm are associated with positive and negative signs, respectively. The D-series, as usual, gives the opposite CD spectra.

Chart VI

(40)   (41)   (42)

(43)   (44)   (45)
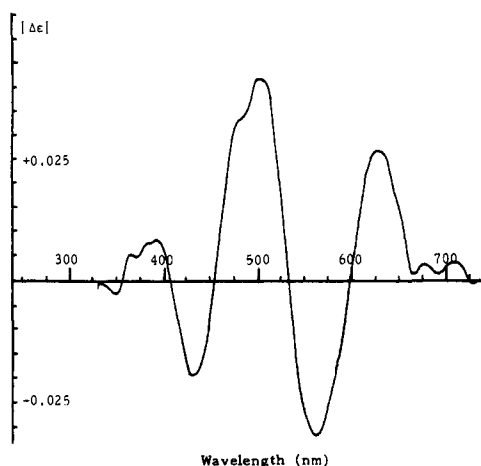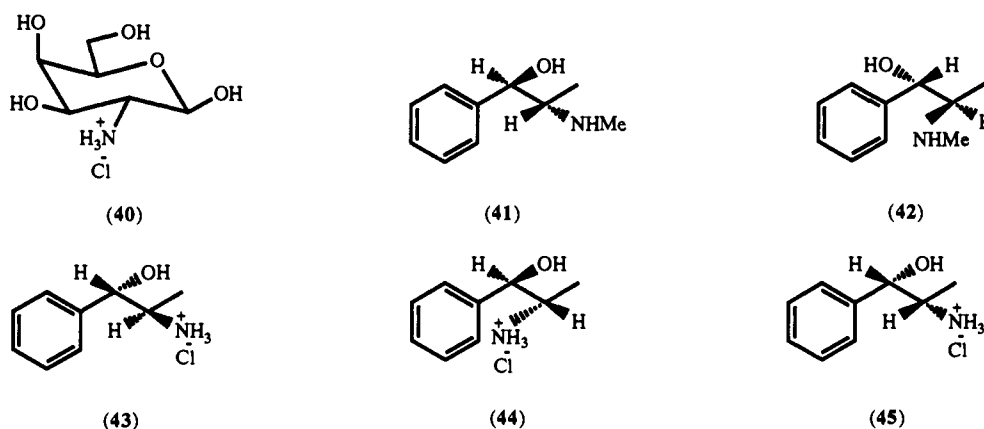
Figure 14. CD spectrum of **39** in acetonitrile in the presence of CRI.
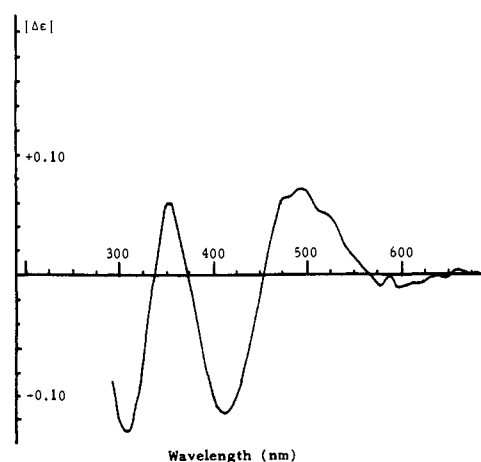
Figure 15. CD spectrum of **32** in DMSO in the presence of MNI.

The results of CD measurements lead to the following conclusion: generally, open-chain amino alcohols of the L-series yield with I–IV the negative, longer wavelength CEs and the positive, shorter wavelength CEs, while the D-series give the positive, longer wavelength CEs and the negative, shorter wavelength CEs. Rigid amino alcohols of the D-configuration such as **39** and **40** (Charts V and VI, respectively) show CD spectra with CEs around 650, 550, 500, 450, and 400 nm with (+),(−),(+),(−), and (+) sign sequence. Hence, for the absolute configuration of L-amino acids, one can make use of the M-helicity rule which can be compared with the negative torsion angle. For the D-series, however, the P-helicity rule which can be compared with the positive torsion angle may be employed.

Ephedrine Isomers. The absolute configurations of ephedrine

isomers with more than one asymmetric center have already been published.[51-53] We are interested in establishing a rapid, convenient method for configurational assignment for the ephedrine isomers based upon CD measurements. These include (1R,2S)-(−)-ephedrine (**41**), (1S,2R)-(+)-ephedrine (**42**), (1S,2R)-(+)-norephedrine hydrochloride (**43**), (1R,2S)-(−)-norephedrine hydrochloride (**44**), (1S,2S)-(+)-Ψ-ephedrin hydrochloride (**45**), (Chart VI) and (1R,2R)-(−)-Ψ-ephedrine (**46**, Chart VII). These drugs measured in DMSO with iron complexes give CEs in the range between 700 and 500 nm. The CD spectra related to these drugs are illustrated as follows.

Compound **41** generates with both iron complexes identical CD spectra with a positive CE around 520 nm, a negative CE at 470 nm, a negative maximum at 430 nm, and a negative CE at about 360 nm (Figure 16). Compounds **42** and **45** give in DMSO identical CEs around 530, 470, and 430, between 400 and 300, and around 280 nm with (−), (+), (−), (+), and (−) sign sequence.

In the case of CR1 (**III**) and ephedrine isomers, the CD range lies between 800 and 300 nm. Several CEs can be observed when acetonitrile is used as solvent. For instance, compound **43** yields CD spectra associated with a negative CE around 610 nm, a negative maximum around 550 nm, a negative CE around 520 nm, and a positive CE at about 450 nm, while compound **44** gives rise, however, to the enantiomorphic CD curves (Figure 17). In ethanol, two broad CD bands can be observed, one between 600 and 500 nm and the other between 400 and 300 nm which for **45** are associated with negative and positive signs. In acetonitrile, **45** gives rise to CEs between 750 and 650 nm and around 610, 550, 470, 420, 390, and 350 nm with (−), (+), (−), (+), (−), (+), and (−) sign sequence.

Unlike the CD spectra of aminopropanol drugs measured with complexes I–III, no coincidence can be found in their CD spectra measured with MN1 (**IV**), probably because of different solvents used in each case. For example, in ethanol, two prominent CEs at about 540 and 410 nm are generated by **41** which can be correlated with the positive torsion angle. On the other hand, **42** in acetonitrile generates two CEs at about 525 and 450 nm with respective negative and positive signs comparable with negative torsion angle (Figure 18). For **46** measured in DMSO, the two CEs around 470 and 310 nm with positive and negative signs may be correlated with the positive torsion angle. In ethanol, however, the two CEs for **45** at about 640 and 520 nm with negative and positive signs may show correlation with the negative torsion angle.
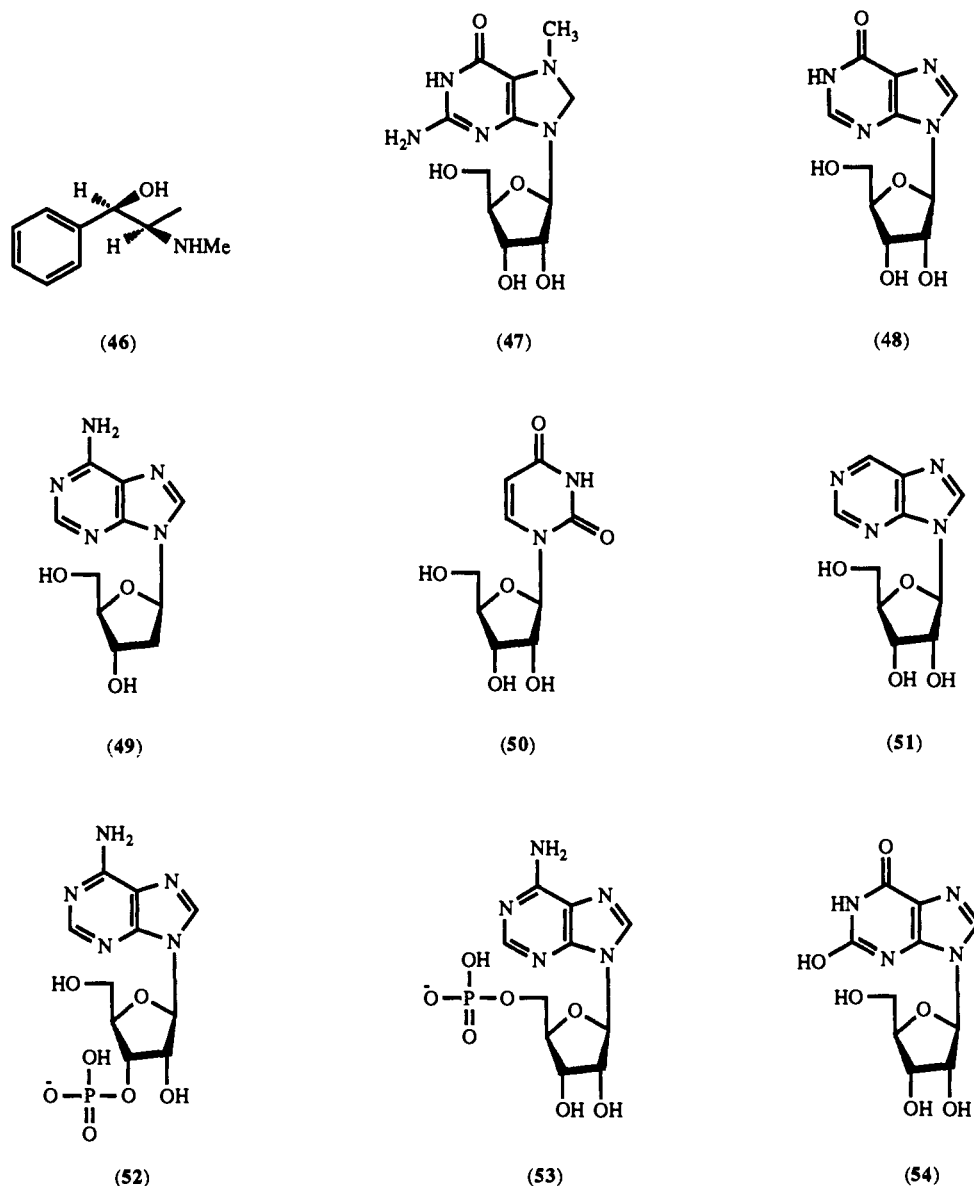
Compounds **42** and **45** measured with FE4 and with the same configuration, *S*, at C-1 afford identical CD spectra with the

(51) Freudenberg, K.; Schoffel, E.; Braun, E. *J. Am. Chem. Soc.* **1932**, *54*, 234.

(52) Rebstock, M. C.; Crooks, H. M.; Controulis, J., Jr.; Bartz, Q. R. *J. Am. Chem. Soc.* **1949**, *71*, 2458.

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Complexation Method for CD Study of Configurations

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Chart VII

(46)

(47)

(48)

(49)

(50)

(51)

(52)

(53)

(54)

difference in amplitude only. Likewise, compounds **41** and **46** show identical results, their amplitudes being the exception. Moreover, the CD spectra of compounds **42** and **45** are enantiomorphic to those recorded for **41** and **46**, respectively. Thus, the only factor with which we can differentiate **42** from **45** and **41** from **46** is the amplitude, which for the *erythro* compounds **41** and **42** is larger than that for the *threo* compounds **45** and **46**. This amplitude difference arises, of course, from the configuration at C-2 rather than that at C-1. C-1 is closest to the aromatic chromophore and dominates, therefore, the spectrum and thus determines the overall sign of the Cotton effect.

Ephedrine isomers follow the semiempirically based helicity rules. In general, *erythro* compounds with 1*S*,2*R* configurations such as **42** obey M-helicity, while those with 1*R*,2*S* configurations such as **41** follow P-helicity. In the *threo* series, the compounds with 1*S*,2*S* configurations such as **45** follow M-helicity, while those with 1*R*,2*R* configurations obey P-helicity. The Newman projection formulae for **41** and **45** are shown for illustration purposes (Figure 19).

Polynucleic Acids. Many attempts have been made to establish the stereochemistry of nucleosides and nucleotides.[54-62] We have also tested the *in situ* method to learn whether it is also applicable

to such aromatic bases for the determination of their absolute configurations. Several CD spectra were measured, and we finally came to the conclusion that the aromatic bases with a ribose moiety containing at least two free OH groups generate Cotton effects.

The CD spectra of nucleosides and nucleotides measured with the iron complexes generate CEs in the range between 700 and 250 nm. 7-Methylguanosine (**47**, Chart VII), for instance, affords in DMSO with FE4 multiple positive CEs in the range between 700 and 400 nm with two maxima around 560 and 490 nm and a positive minimum in between them, occurring around 520 nm. A sharp CD band also appears at about 430 nm. With FE1 in

(54) Guschlbauer, W.; Privat de Garilke, M., *Bull. Soc. Chim. Biol.* **1969**, *51*, 1511.

(55) Ulbricht, T. L. V.; Emerson, T. R.; Swan, R. J. *Biochem. Biophys. Res. Commun.* **1965**, *19*, 643.

(56) Emerson, T. R.; Swan, R. J.; Ulbricht, T. L. V. *Biochem. Biophys. Res. Commun.* **1966**, *22*, 505.

(57) Emerson, T. R.; Swan, R. J.; Ulbricht, T. L. V. *Biochemistry* **1967**, *6*, 843.

(58) Ikehara, M. *Acc. Chem. Res.* **1969**, *2*, 47.

(59) Ulbricht, T. L. V. *Jerusalem Sym. Quantum Chem. Biochem.* **1972**, *4*, 170.

(60) Miles, D. W.; Robins, R. K.; Erying, H. *Proc. Nat. Acad. Sci. U.S.A.* **1967**, *57*, 1138.

(61) Miles, D. W.; Townsend, L. B.; Robins, M. J.; Robins, R. K.; Erying, H. *J. Am. Chem. Soc.* **1971**, *93*, 1600.

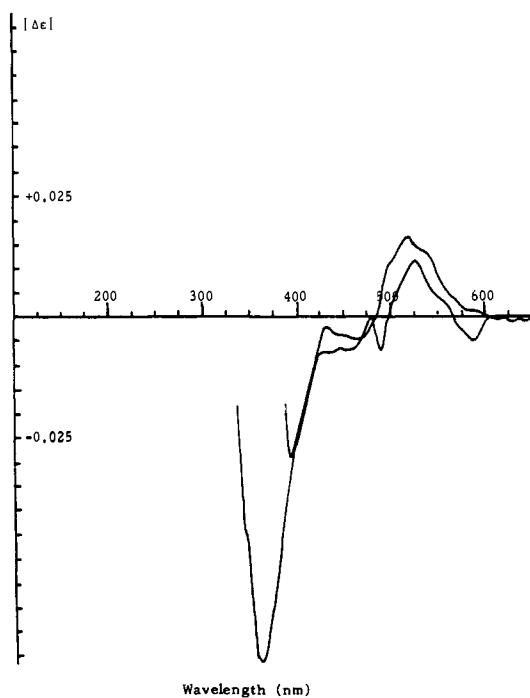(62) Delabar, J. M.; Guschlbauer, W.; Schneider, C.; Thiery, J. *Biochemie* **1972**, *54*, 1041.

Figure 16. CD spectra of **41** in DMSO in the presence of FE4.

Figure 17. CD spectrum of **43** in acetonitrile in the presence of CRI.

Figure 18. CD spectra of **41** (- - -) in ethanol and **42** (—) in acetonitrile in the presence of MNI.

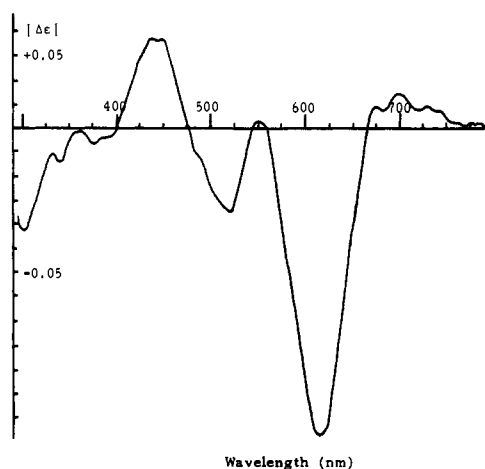**Figure 19.** Newman projection formulae and CD signs of **41** and **45**.

Figure 20. CD spectrum of **48** in TMP in the presence of FE4.

ethanol, the CD spectrum of **47** reveals a broad, positive band with several shoulders between 500 and 450 nm with a maximum around 490 nm. Moreover, the positive minimum occurs around 450 nm, followed by a small, positive CE at about 430 nm. Once again a negative CE at about 365 nm can also be seen. Likewise, inosine (**48**) and FE4 generate in TMP a positive CD maximum around 480 nm associated with a positive minimum at about 450 nm. FE1 and **48** also show in pyridine two positive maxima around 490 and 400 nm with a positive minimum around 450 nm. Below 350 nm, the negative peak is also observable (Figure 20). The spectrum of **49** and FE1 in TMP is not well-resolved. However, we get a better CD spectrum when a trace of acid is added to the solution, resulting in the generation of positive multiple CEs between 550 and 450 nm and two positive CEs around 410 and 370 nm with a positive minimum around 400 nm between them. Uridine (**50**) and FE1 in pyridine and **51** in TMP in the presence of FE4 yield nearly identical CD spectra with a positive CE around 400 nm and a negative CE around 300 nm. In both cases, we observe a positive inflection point at about 500 nm and a negative inflection point near 350 nm. The positive CE around 400 nm and the negative one below 300 nm may be clearly seen for adenosine-5′-monophosphate (**53**) and FE4 in TMP. In
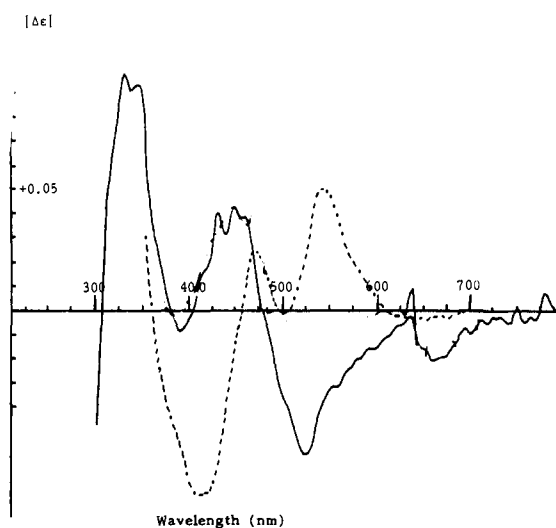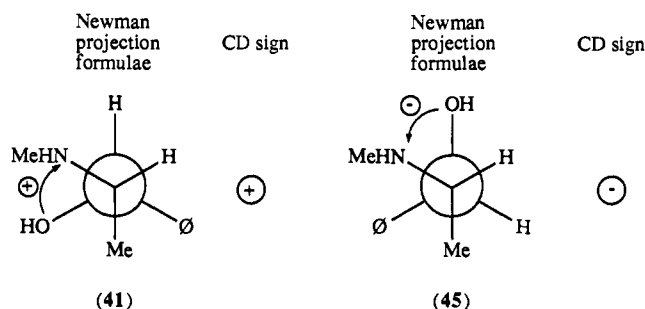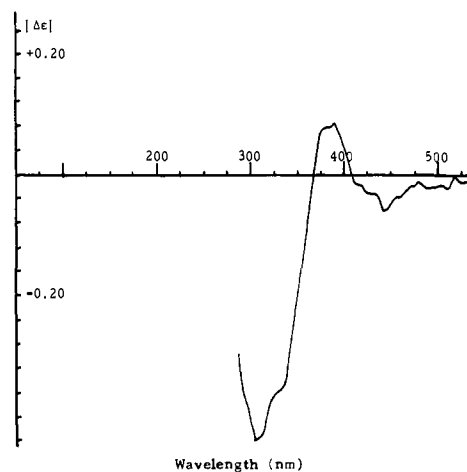
water we observe for **53** and FE4 negative multiple CEs between 700 and 600 nm and positive multiple CEs between 500 and 400 nm.

Polynucleic acids generate also with CR1 enhanced Cotton effects in the range between 700 and 250 nm. The CD spectrum of xanthosine (**54**, Chart VII) taken in TMP reveals a well-defined negative CE around 500 nm which could hardly be seen in DMSO. Compound **47** yields in TMP a broad positive CD band between 700 and 600 nm and a negative one between 600 and 500 nm. A small positive CE around 440 nm is also present. In DMSO, broad, negative multiple CEs between 650 and 450 nm can also be noticed. Inosine (**48**) shows in TMP again a positive CE between 700 and 600 nm with a maximum around 625 nm and a negative one between 600 and 500 nm with a maximum around 560 nm. A broad band of low intensity between 500 and 400 nm
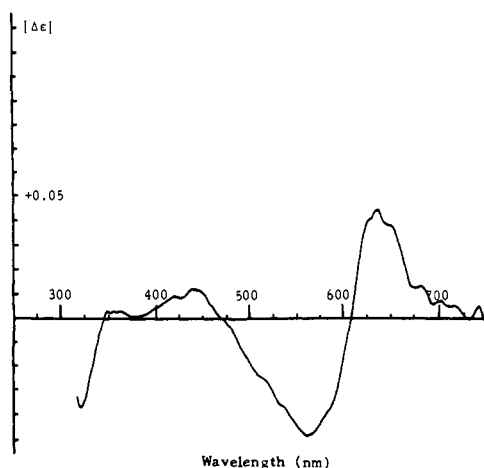
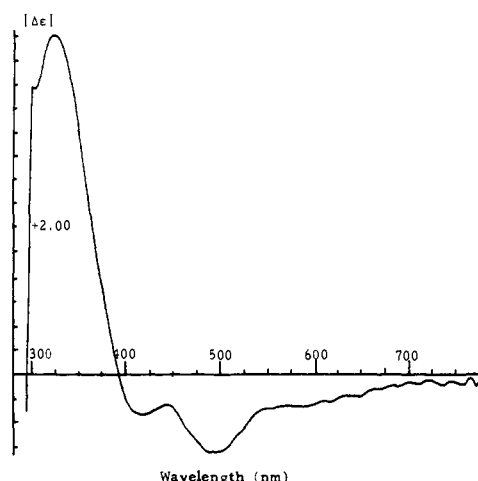**Figure 21.** CD spectrum of **47** in TMP in the presence of CRI.

Figure 22. CD spectrum of **53** in pyridine in the presence of MNI.

is also evident. The CD spectrum of **55** in ethanol reveals a broad, positive CE between 670 and 570 nm with a maximum around 630 nm and a negative broad band between 550 and 450 nm with a maximum around 500 nm. Compound **56** gives in TMP a negative band between 700 and 600 nm with a maximum around 610 nm and a positive band between 550 and 450 nm with a maximum around 490 nm (Figure 21).

With MN1, compound **47** produces in pyridine two prominent multiple CD bands around 500 and 400 nm with a positive minimum between them. For **49** and MN1, one observes negative multiple CEs between 600 and 400 nm with a maximum around 480 nm. A negative minimum around 450 nm can also be seen. Compound **53** gives rise in pyridine to a prominent negative CE around 490 nm, with a negative minimum around 450 nm and an intense positive CE between 400 and 300 with a maximum at about 325 nm (Figure 22).

From the general consideration of the CD spectra of polynucleic acids we conclude that those aromatic bases with a ribose moiety containing at least two free OH groups generate Cotton effects. Enhanced CEs are however, observed when the three hydroxyl groups are not replaced by the phosphate groups. Phosphorylation at position 3′ as in **52** and **55** does not drastically change the CD spectrum. On the other hand, phosphorylation of the hydroxyl group at C-5′ leads to the dramatic change in the CD spectra, and in most cases no CD could be observed as found in guanosine 5′-monophosphate (**57**), xanthosine 5′-monophosphate (**58**), and inosine 5′-monophosphoric acid (**59**) (Chart VIII). Removal of the hydroxyl group at position 2′ of the ribose moiety reduces the intensity of the CEs as examined in 2′-deoxyadenosine (**49**) and 2′-deoxyuridine (**60**). Polynucleic acids may follow helicity rules

which make use of the torsion angle for the determination of the absolute configuration.

As the CD spectra reveal, most of the aromatic bases measured with the complexes I–III generate positive CEs toward longer wavelength and negative CEs toward shorter wavelength, and therefore they can be compared with the positive torsion angle which then follows the P-helicity rule. The reverse holds, of course, for the aromatic bases measured with MN1, except for **47**, for which the longer wavelength CEs are negative and the shorter wavelength CEs are positive and, therefore, they may follow the M-helicity rule.

It would be premature to emphasize the site of complexation whether it occurs at the adjacent carbons C-2′ and C-3′, C-3′ and C-5′, or C-2′ and C-5′. The first and the last type of complexation, however, can be excluded, for in the first case the torsion angle may deviate from the assumed 60° value, whereas in the last case the larger distance between the two carbons may prevent complexation. But the question as to why we observe CEs in compounds **52** and **55** where the phosphate groups are substituted at position 3′ and the two hydroxyl groups at C-2′ and C-5′ remain nonphosphorylated cannot be answered with certainity. Finally, complexation at C-3′ and C-5′ seems more probable, and this has been proved experimentally by using the compounds 2′-deoxyuridine (**60**) and 2′-deoxyadenosine (**49**).

Experimental Section

General Procedures. CD spectra were recorded on a JOBIN-YVON-ISA dichrograph Mark III connected on-line to a PDP-8/e; curve smoothing and calculations of the first derivative of a CD curve were done by the Golay-Savitzky algorithm.

In general, the CD curves obtained in this way remained constant for several days. To establish an equilibrium between the conformers, the CD spectra were in most cases recorded after several hours; in some cases the solution was warmed for 1 h to 50 °C, or a few microdrops of aqueous NaOH, acetic acid, or hydrochloric acid were added, if not mentioned otherwise.

CD spectra are presented as ficticious $\Delta\epsilon$ values, since a mixture of several complexes may be present and dissociation constants are unknown. For analytical purposes only, the signs and relative magnitudes of the CEs are important, not the absolute values.

Preparation of the Metal Complexes. (1) $[Fe_3O(OOCCH_3)_6(H_2O)_3]$ (**Fe1**). According to the method of Chrétien and Lous,[63,64] ferrous chloride, $FeCl_2\cdot4H_2O$ (30 g, 0.15 mol), sodium acetate (30 g, 0.366 mol). and glacial acetic acid (90 mL, 1.57 mol) were dissolved in 150 mL of water and heated at 70 °C under reflux for 3 h, while a constant stream of air was bubbled through it. The dark brown precipitate was washed with ethanol and dried *in vacuo* over silica gel to afford 18.3 g of the product (yield 61%). This complex is slowly decomposed on dissolving in water, methanol, or ethanol, giving an orange-red color characteristic of the triiron(III) complex.

(II) $[Fe_3O(OOCCH_3)_6(H_2O)_3]Cl\cdot5H_2O$ (**FE4**). Sodium acetate (10 g, 0.121 mol) was dissolved in 50 mL of water. The solution was warmed up, and $FeCl_3\cdot6H_2O$ (17 g, 0.063 mol) was gradually added. The chloride separated out immediately on cooling to afford 11.90 g of the product (yield 70%).

(III) $[Cr_3O(OOCCH_3)_6(H_2O)_3]\cdot5H_2O$ (**CR1**). Chromic nitrate, Cr$(NO_3)_3\cdot9H_2O$ (50 g, 0.125 mol) was dissolved in a minimum amount of water. NaOH (20 g, 0.5 mol) in 190 mL of water was slowly added with continuous stirring. The precipitate of $Cr(OH)_3$ was washed with water and dissolved in glacial acetic acid (0.4 mol), and the solution was refluxed for 2 h. The fibrous green crystals which formed on cooling were dried *in vacuo* over silica gel to afford 30 g of the product (yield 60%).

(IV) $[Mn_3O(OOCCH_3)_6(Py)_3]ClO_4$ (**MN1**). This was also prepared according to the published method.[63,64] Pyridine (0.5 g) and $NaClO_4\cdot H_2O$ (0.2 g) were added to an ethanolic solution (10 mL) containing the so-called Mn(III) acetate (0.30 g), and the solution was heated to 50 °C for 20 min and allowed to stand for 30 min at room temperature to give the brown precipitate, which was purified by washing with a small amount of ethanol and then with ether to afford 0.195 g of the product (yield 65%).

(63) Chrétien, A.; Lous, P. *Bull. Soc. Chim. Fr.* **1944**, *11*, 446.
(64) Johnson. M. K.; Powell, D. B.; Cannon, R. D. *Spectrochim. Acta* **1981**, *37A*. 995–1006.

Chart VIII

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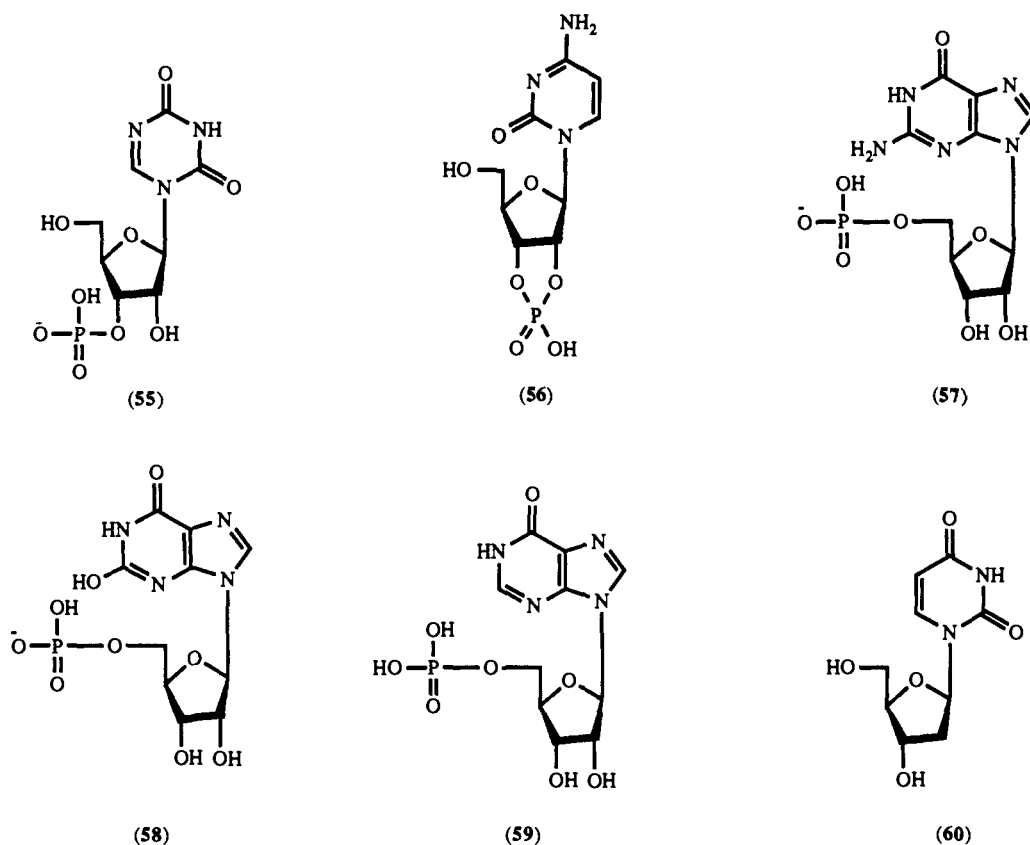
The most commonly used solvents for complexes I–IV are dimethyl sulfoxide (DMSO), acetonitrile, ethanol, water, pyridine, 2,2,2-trifluoroethanol, and trimethylphosphate. For the *in situ* preparation of the complexes, the chiral ligand is added to the stock solution, and the CD spectrum is measured from 800 to 260 nm in cells of 2.0-, 1.0-, 0.5-, 0.2-, and 0.05-cm path length. In general, a ligand concentration of 0.5–1.0 mmol/L is sufficient.

Supplementary Material Available: Tables of CD data with FE1, FE4, CR1 and MN1; Figures 23–43 showing CD curves (34 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.