Absolute Configurational Studies of Vicinal Glycols and Amino Alcohols. I. With $Ni(acac)_2$

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Abstract: A spectroscopic method requiring no substrate derivatization has been developed for absolute configurational studies of glycols and amino alcohols. The substrates which are suited for studies by the $Ni(acac)_2$ method are those containing acyclic primary/secondary (**1–3**), secondary/secondary (**11**), and unhindered secondary/tertiary (**14–16**) vicinal glycols, vicinal primary OH/secondary NH_2 groups (**4–10**), and certain 1,3-glycols (**25–28**). The addition of $Ni(acac)_2$ (acac = acetylacetonate) to a wide variety of model compounds produces induced Cotton effects in both the uv (ca. 300 nm) and d–d regions (ca. 630 nm), the signs of which can be correlated with the absolute configuration of the glycol or amino alcohol. This method utilizes small amounts of material (ca. 10^{-4} *M*) and is applicable to compounds soluble in aprotic and protic (*t*-BuOH) solvents. Studies performed to characterize the species producing the observed CD indicate that the interaction between $Ni(acac)_2$ and a glycol results in complex equilibria, but the main absorbing species results from bidentate addition of the glycol to $Ni(acac)_2$.

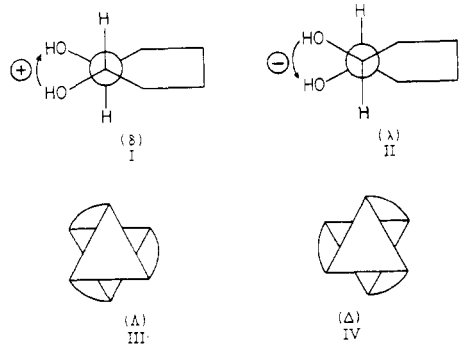
Several spectroscopic methods are known for determining the sense of handedness of cyclic vicinal glycols and amino alcohols. The cuprammonium method,[1] which involves addition of the substrate to an aqueous solution of cuprammonium and measuring the CD at 580–600 nm, has been used extensively in the carbohydrate field. Other CD methods make use of the osmate esters[2] and thionocarbonates.[3] The dibenzoate chirality method,[4] which is based on the theoretically sound exciton coupled transitions,[5] enables one to determine the chiralities of glycols much more remote than vicinal[6] and can be extended to the interactions between various chromophores other than benzoates, e.g., enones,[7,8] lactones, and others.[7] The original dibenzoate chirality method, however, has some disadvantages in that derivatization, which is not facile for tertiary alcohols, is necessary; CD spectra of vicinal dibenzoates which contain competing chromophores are not easy to interpret, and so far it is not applicable to acyclic α-dibenzoates.

We have developed methods[9] for determining the absolute configurations of cyclic and acyclic vicinal glycols and amino alcohols and isolated hydroxyl groups. They require no derivatization and employ small amounts of material; since organic solvents are employed, they are complementary to the cuprammonium method[1] which is carried out in water. In this and the following paper,[10] we describe the scope, limitations, and other aspects of the technique dealing with the vicinal glycols and amino alcohols. The method consists of the addition of a glycol or amino alcohol to a solution of $Ni(acac)_2$ (acac = acetylacetonate) or $Pr(dpm)_3$ (dpm = dipivalomethanato). This mixture forms a complex which results in an induced CD originating in the inorganic ligands. Correlations between the sign of the Cotton effect and the absolute structure of the glycol or amino alcohol lead to an empirical method for the determination of the absolute configurations of unknown compounds.

Studies show that $Ni(acac)_2$ is applicable to the following acyclic groups: primary/secondary (prim/sec), secondary/secondary (sec/sec), *unhindered* tertiary/secondary (tert/sec) α-glycols, and vicinal prim-OH/sec-NH_2 groups. On the other hand, $Pr(dpm)_3$ is complementary and can be used for cyclic α-glycols and *hindered* acyclic tertiary/secondary α-glycols.

In the course of these studies, experiments were carried out to characterize the absorbing species in solution, its stability and structure. Investigations suggest that, in both cases, the complexes consist of complicated equilibria, but the variation of parameters such as concentration, time, and temperature gives some insight into the nature of these species.

Conventions. In the "dibenzoate chirality method," the chirality of a cyclic glycol is defined as being positive for the dihedral relationship depicted as I whereas, in inorganic complexes, it is defined as δ. Conversely, the negative relationship is defined as λ (II). If the glycol is acyclic or is attached to a flexible ring, there would then be two rotameric possibilities for each structure, where the oxygen functions are gauche.



When three bidentate ligands combine with a metal to form an octahedral complex, an enantiomeric mixture results. These are based on the relative helicity shown in III and IV. Here Λ and Δ have a left-handed and right-handed screw sense, respectively, along the threefold axis.

Results and Discussion

(1) Nature of the Induced CD. The addition of a glycol or an amino alcohol to a solution of $Ni(acac)_2$ results in an induced CD in both the uv and d–d regions of the spectrum. Figure 1 shows a typical curve. This is of a mixture of (2*R*,3*R*)-butane-2,3-diol (2.1×10^{-3} *M*) and $Ni(acac)_2$ (5.0×10^{-5} *M*) in CCl_4. Inspection of this curve reveals that the uv region consists of an intense split Cotton effect at 315–293 nm of opposite signs and near equal intensities with a shoulder around 305 nm. The d–d region has a broad transition at ca. 630 nm which is opposite in sign to the transition at 315 nm; in addition there is a small CD around 380 nm, which may or may not be split, but this is of no diagnostic value.

X-Ray studies of anhydrous $Ni(acac)_2$ have shown that it is a trimer in the crystalline state[11] which is retained in aprotic solvents at high concentrations.[12,13] However, this

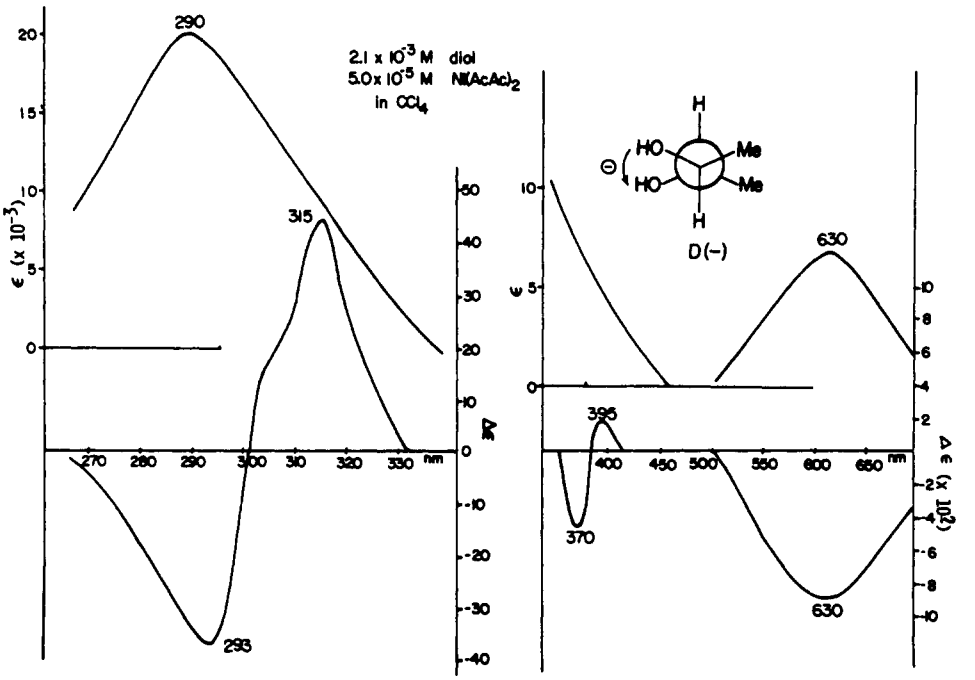


Figure 1. The uv and CD of a mixture of 5.0×10^{-5} *M* $Ni(acac)_2$ and 2.1×10^{-3} *M* (2*R*,3*R*)-butane-2,3-diol in CCl_4.

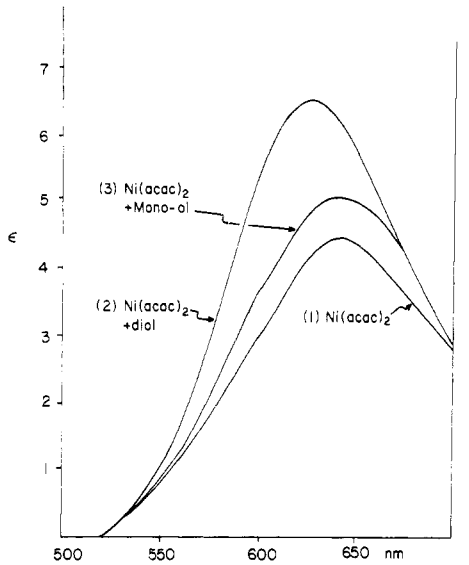


Figure 2. The uv, in CCl_4, of: (1) an 8.33×10^{-4} *M* solution of $Ni(acac)_2$; (2) a mixture of 8.33×10^{-4} *M* $Ni(acac)_2$ and 3.33×10^{-2} *M* (2*R*,3*R*)-butane-2,3-diol; (3) a mixture of 8.33×10^{-4} *M* $Ni(acac)_2$ and 3.33×10^{-2} *M* (2*R*)-3-methylbutan-2-ol.

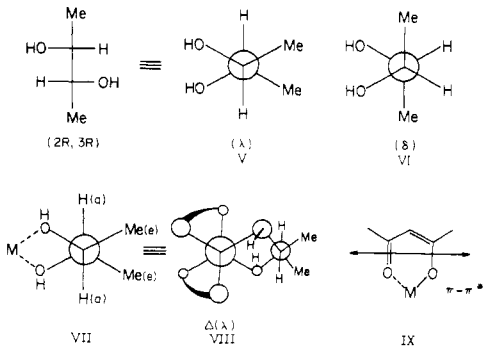


Figure 3.

breaks down to a monomer in protic solvents[12,14] and at higher temperatures.[15] In both its trimeric form and base adduct monomeric form, the Ni complex assumes an essentially octahedral shape.[16,17] If the Lewis base B is a monodentate ligand, then a 1:2 $Ni(acac)_2 \cdot B_2$ complex is formed in which the bases are usually disposed trans to each other. On the other hand, the addition of a bidentate ligand to $Ni(acac)_2$ forms a 1:1 complex in which the bases, out of necessity, assume a cis relationship (e.g., $Ni(acac)_2(en)$ where en = ethylenediamine[16,18]).

In all probability then, the CD depicted in Figure 1 results from the bidentate addition of (2*R*,3*R*)-butane-2,3-diol to $Ni(acac)_2$. Further corroboration for this hypothesis is found in the following experiments. The addition of monofunctional alcohols to $Ni(acac)_2$ [e.g., (2*R*)-octan-2-ol (2×10^{-3} *M*) to $Ni(acac)_2$ (5×10^{-5} *M*) in CCl_4] does not give rise to an induced CD. Also, the geometry of chelation is reflected in the d-d region of Ni.[16,19] Figure 2 shows the change in uv intensity of the transition at ca. 620 nm when either a glycol (curve 2) or monofunctional alcohol (curve 3) is added to $Ni(acac)_2$. The greater enhancement for the glycol is indicative of cis chelation.

The actual structure of the absorbing species in solution is of course more complicated than that suggested above. (2*R*,3*R*)-Butane-2,3-diol (B–B) (where B denotes a nucleophile) can adopt either one of the two conformers, λ or δ (V and VI, Figure 3), in which the hydroxyl relations are gauche. Both λ and δ conformers can add bidentally to $Ni(acac)_2$ to give the $Ni(acac)_2 \cdot$B–B complex, where the interligand relations can be either Δ (as in VIII) or Λ. The total number of possible structures for the complex in solution is therefore four, Δ(λ), Δ(δ), Λ(λ), and Λ(δ).

One would expect an equilibrium mixture in solution where the percentages of species would result from their relative energies which would be affected by the environment. In considerations of such relative energies, we have ignored monodentate interactions since they do not seem to produce induced CD's in this system.

There are several ways to identify which of the four complexes is the main absorbing species giving the CD in Figure 1. The first is to look at the steric interactions in the formed

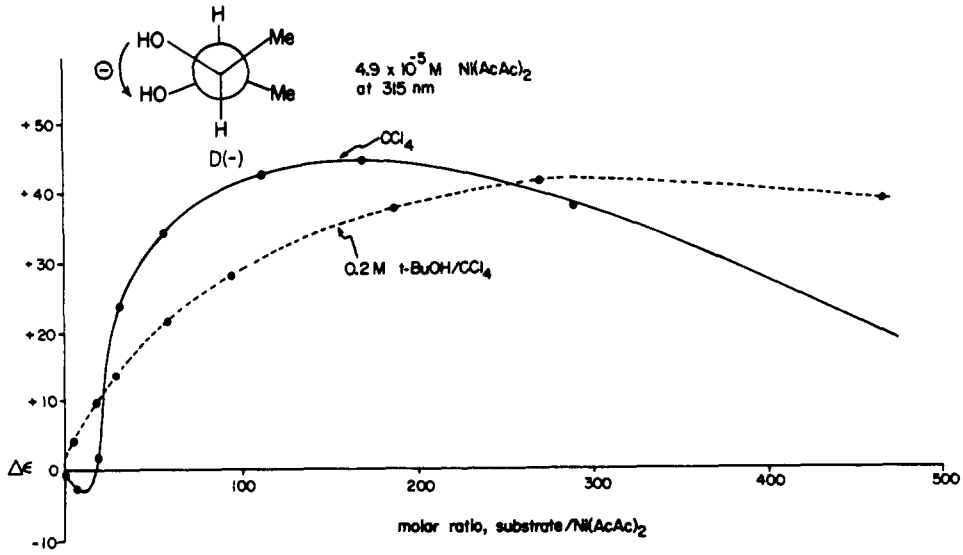


Figure 4. Variation of $\Delta\epsilon$ at 315 nm for $Ni(acac)_2$ (4.9×10^{-5} *M*) with increasing concentrations of (2*R*,3*R*)-butane-2,3-diol in CCl_4 (—) and in 0.2 *M* *t*-BuOH-CCl_4 (- - -).

complexes. The method developed by Bailer and Corey[20] consists of treating the metal-bidentate (1,2-bidentate) complex as a five-membered ring system. Then the substituents on that ring can be either axial or equatorial (Figure 3, VII). When this five-membered ring is part of an octahedral complex, a second ring on the metal is then axial to the substituents on the first ring (see VIII). The minimization of steric interaction between the axial substituents should suggest which of the complexes is the most stable. In most complexes studied thus far, it was found that formation of complexes with their bulky groups in an axial position δ (or VI, Figure 3) were less stable by at least 1 kcal, relative to when the groups are equatorially disposed.[21] In the example presented here, the main interacting conformer would thus be λ (or V, Figure 3), resulting in either $\Delta(\lambda)$ (VIII) or $\Lambda(\lambda)$.

Decisions between these two are more difficult because the energetic differences are slight. This was verified by inspecting a model using the dimensions from the crystal structure of $Ni(acac)_2(B)_2$[22] (where B = pyridine *N*-oxide, and are cis to each other) and substituting (2*R*,3*R*)-butane-2,3-diol for $(B)_2$. A nonambiguous decision between the two structures could not be made.

This, of course, is a very crude method for determining the nature of the $Ni(acac)_2$-glycol complexes in solution since neither the bite of the glycol nor the other dimensions of the complex are known. It is presented here only as a model, to get some feeling for the most probable structures in solution.

An alternative approach to this problem is to interpret the d-d region of the CD in terms of the structure of the absorbing species. Various publications have appeared which relate the signs of Cotton effects in this region to the absolute configuration of Co complexes.[21b,23] This method has recently been extended to Ni complexes,[24] and the absorption at ca. 600 nm has been assigned to a $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ transition. Mason has interpreted the sign of this Cotton effect in terms of absolute configuration of several Ni complexes. A negative sign indicates a Δ configuration, whereas a positive sign indicates a Λ configuration. [Although the complexes treated in our studies are of lower symmetry, Mason's results suggest that the $Ni(acac)_2$-glycol complex giving an extremum at 630 nm in Figure 1 has a Δ configuration. Thus the total shape of the complex would be $\Delta(\lambda)$ (see VIII in Figure 3).]

A third approach is to interpret the uv region of the CD in terms of structure. If the absorptions are due to the long axis polarized π-π^* transitions solely in the acac ligand (see IX in Figure 3), then dipolar interactions of these transitions should conform to the exciton formalism.[25] The uv region would then consist of two extrema of opposite signs and near equal intensities; if the longer wavelength absorption has a negative sign, the ligands complexed to the Ni would have a Δ relationship. This then suggests that the absorbing species depicted in Figure 1 should have a Λ configuration and is in variance with that deduced from the d-d region. However, this is analogous to the situation found in the case of $(+)\text{-}Co(acac)_2(en)^+$. Here, the interpretation of CD in the d-d region in terms of absolute configuration is opposite to that found in the uv region, provided the latter transitions conformed to the exciton formalism.[26] The probable explanation for these seeming contradictions is that the ellipticity observed in the uv region is due mainly to $d\pi$-π^* transitions rather than pure π-π^* transitions, and thus they do not conform to the exciton formalism.

In any case, the lack of certainty over the exact nature of the transitions in the uv region does not seem to diminish the usefulness of this method as a structural probe.

(2) Equilibrium Studies. Several concentration dependence curves are reproduced in Figure 4. The graph shows a change of $\Delta\epsilon$ with increasing molar ratio of (2*R*,3*R*)-butane-2,3-diol for a 5×10^{-5} *M* concentration of $Ni(acac)_2$. As can be seen, there is a reversal in the sign of the Cotton effect at a low molar ratio when the solvent is CCl_4, but the sign is constant (at least to a molar ratio of 1:1) if the solvent is a 0.2 *M* mixture of *t*-BuOH in CCl_4. Figure 5 reproduces the actual curves at these lower concentrations, and Figure 6 shows the effect of the addition of various amounts of *t*-BuOH to a 7:1 glycol:$Ni(acac)_2$ ratio in CCl_4 where the $Ni(acac)_2$ concentration is ca. 5×10^{-5} *M*. However, it is interesting to note that, at higher $Ni(acac)_2$ concentration, e.g., 1×10^{-3} *M*, there was no reversal in sign at the low substrate-$Ni(acac)_2$ ratio of 2:1 in 100% CCl_4.

An attractive rationalization for this curious behavior at lower molar ratios is that it is due to some intermediate species. It has been noted above that $Ni(acac)_2$ is preferentially a trimer in solution[12,13] but breaks down to a monomer in protic media. Fackler[27] has shown that the addition of pyridine to $[Ni(acac)_2]_3$ causes the breakdown of the trimer to monomer $[Ni(acac)_2py_2]$ via an intermediate with

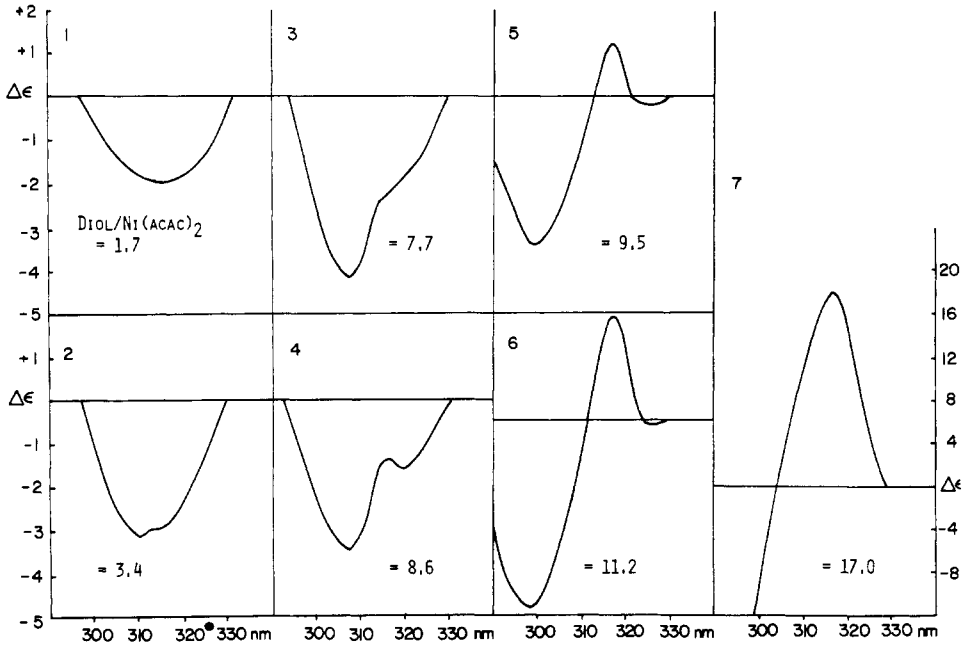


Figure 5. The CD of a mixture of $Ni(acac)_2$ (7.0×10^{-5} *M*) and increasing concentrations of (2*R*,3*R*)-butane-2,3-diol. The molar ratios of diol/Ni are: (1) 1.7:1; (2) 3.4:1; (3) 7.7:1; (4) 8.6:1; (5) 9.5:1; (6) 11.2:1; and (7) 17.0:1.

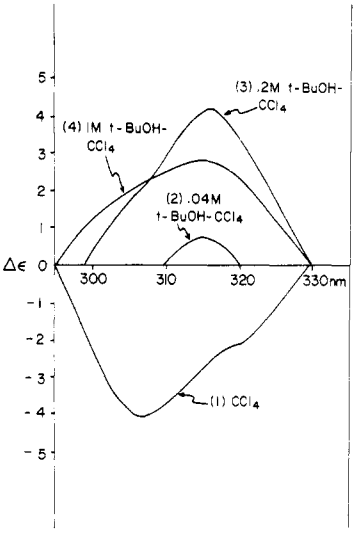


Figure 6. Curve 1: CD of a mixture of $Ni(acac)_2$ (7.0×10^{-5} *M*) and (2*R*,3*R*)-butane-2,3-diol (5.0×10^{-4} *M*) in CCl_4. Curve 2: CD of a mixture of $Ni(acac)_2$ (4.0×10^{-5} *M*) and the diol (2.8×10^{-4} *M*) in a 0.04 *M* *t*-BuOH-CCl_4 solution. Curve 3: same mixture as in curve 2, in a 0.2 *M* *t*-BuOH-CCl_4 solution. Curve 4: same mixture as in curve 2, in a 1 *M* *t*-BuOH-CCl_4 solution.

the stoichiometry of $[Ni(acac)_2]_2py$.

The equilibrium being studied here as suggested by the series of curves in Figure 5 would then consist of two absorbing species, namely, a dimeric (or polymeric) complex at low glycol concentrations ($[Ni(acac)_2]_n$·B-B) and a monomeric species which predominates at higher glycolic concentrations. Corroboration for this hypothesis is found in the concentration studies of other inorganic complexes. $Co(acac)_2$, which like $Ni(acac)_2$ is polymeric in solution,[28] also exhibits an inversion in the sign of the Cotton effect at low molar ratios of (2*R*,3*R*)-butane-2,3-diol. On the other hand, $Ni(dpm)_2$ is a monomer in solution[29] and, significantly, does not invert under similar circumstances.

The addition of *t*-BuOH also upsets this equilibrium in favor of the monomeric species as seen in Figures 4 and 6. Here *t*-BuOH competes more effectively for sites on the Ni with the shared acac ligands of the trimer. Any additional substrate, e.g., a glycol, would then only have to compete for sites with *t*-BuOH in a monomeric $Ni(acac)_2$ complex. The fact that no sign reversal is observed at high $Ni(acac)_2$ concentrations (vide supra) can presumably be attributed to complex equilibria in which the monomeric species makes a dominant contribution.

The equilibrium is also sensitive to changes in temperature. Figure 7 depicts the CD resulting from a 7:1 glycol: $Ni(acac)_2$ mixture at 28 and at 11°; the concentrations were specifically selected so that at 28° there was essentially no observable absorption (see Figure 4). As can be seen from the CD, monomeric species predominates at lower temperatures. As the temperature is further lowered even smaller molar ratios give positive CD's, e.g., a 4.6:1 (2*R*,3*R*)-butane-2,3-diol-$Ni(acac)_2$ at −3° has a $\Delta\epsilon_{315}$ of +8.2. This temperature effect is also seen at very high molar ratios (Figure 8). These data suggest that the monomeric complex is thermodynamically more stable than any intermediate species and its formation is exothermic.

(3) Measurements and Interpretation. Table I gives the results obtained upon the addition of $Ni(acac)_2$ to various glycols and amino alcohols, both cyclic and acyclic. As described earlier, the chirality is predicted on the basis of the conformer having the bulkier substituents toward the rear (▽ or λ, Figure 3). The conditions used in making the measurements vary depending on the structure of the organic substrate. What follows is a general description of the conditions used, the interpretation of the CD obtained, and the utility of this method in determining the absolute configuration of natural products.

Solvents. Figure 9 shows the decrease in the size of the Δε with increasing concentration of various competing nucleophiles. The effectiveness with which the added solvent competes for sites on the $Ni(acac)_2$ depends on its nucleophilicity and bulk. In general then the solvents of choice should be aprotic, e.g., CCl_4, $CHCl_3$, and *n*-hexane. However, *t*-BuOH can also be used as a solvent since although it is protic, its bulk inhibits association with $Ni(acac)_2$ and hence the $Ni(acac)_2$-glycol complex is not disrupted. Figure 10

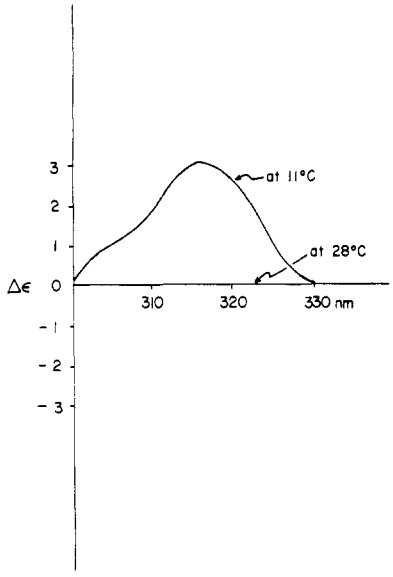


Figure 7. CD of a mixture of $Ni(acac)_2$ (5.0×10^{-5} *M*) and (2*R*,3*R*)-butane-2,3-diol (3.5×10^{-4} *M*) at 28° (baseline) and 11° (curve) in CCl_4.

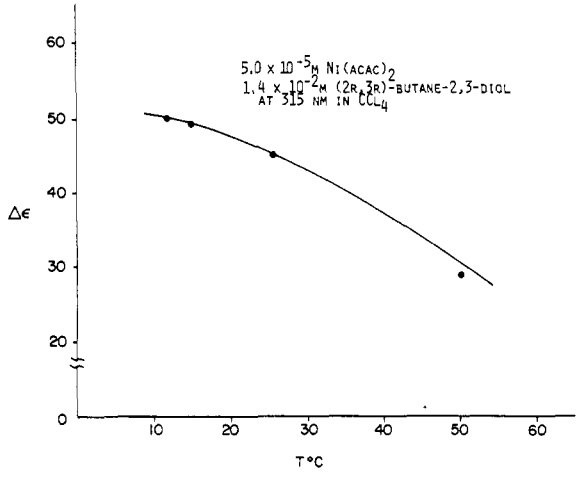


Figure 8. Variation of Δε at 315 nm with temperature for a mixture of $Ni(acac)_2$ (5.0×10^{-5} *M*) and (2*R*,3*R*)-butane-2,3-diol (1.4×10^{-2} *M*) in CCl_4.

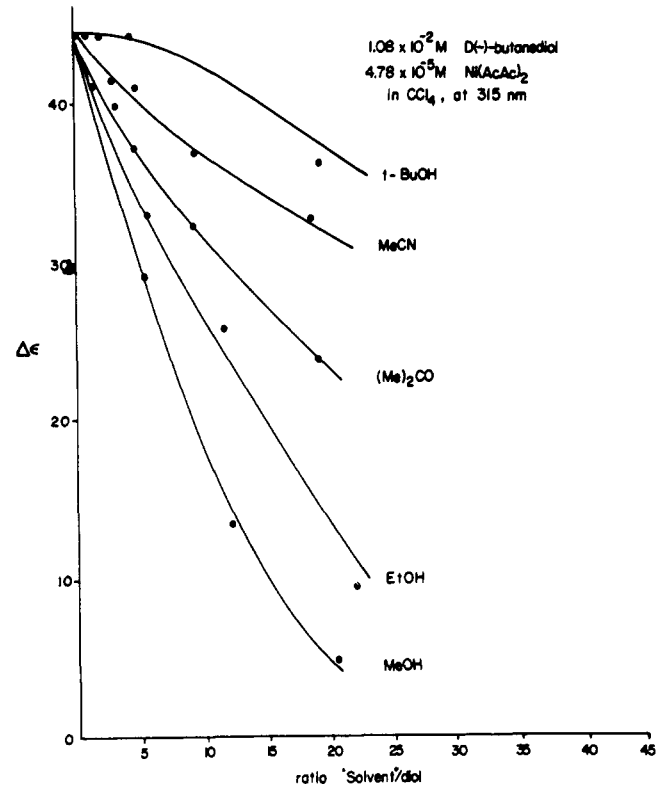


Figure 9. CD observed at 315 nm, when various competing solvents are added to a mixture of 1.08×10^{-2} *M* (2*R*,3*R*)-butane-2,3-diol and 4.78×10^{-5} *M* $Ni(acac)_2$ in CCl_4.

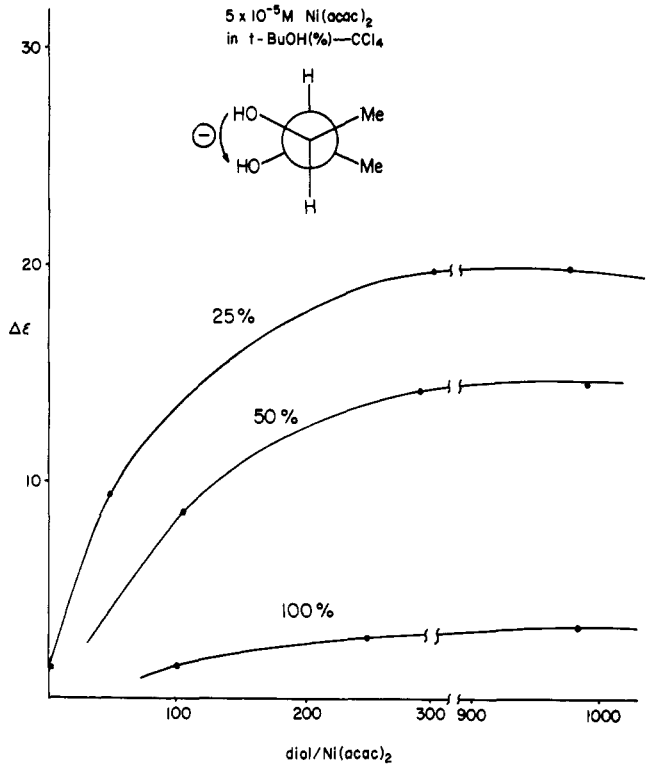


Figure 10. Variation of the CD observed at 315 nm for a $Ni(acac)_2$ (5×10^{-5} *M*) solution with increasing concentrations of (2*R*,3*R*)-butane-2,3-diol in 25% *t*-BuOH-CCl_4, 50% *t*-BuOH-CCl_4 and 100% *t*-BuOH solutions.

shows that, even in 100% *t*-BuOH, an induced CD is observed. Not only does the use of *t*-BuOH expand this technique to compounds slightly soluble in aprotic solvents but, as previously noted, the addition of *t*-BuOH to CCl_4 retards the inversion of the CD at low molar ratios.

Conditions for Measurement. The preferred solvent system for a measurement is an approximately 0.2 *M* *t*-BuOH-CCl_4 solution (see Figure 6). For compounds less soluble in CCl_4 this percentage can be increased as high as 100% *t*-BuOH; solvents such as acetonitrile or acetone can also be employed (Figure 9). The use of *t*-BuOH, unfortunately, does not completely negate the possibility of seeing an inversion of the CD at low molar ratios for some compounds. It is therefore suggested that at least a 10:1 substrate:Ni(acac)$_2$ molar ratio is used for measurements of spectra.

The concentration of $Ni(acac)_2$ has been set at ca. 5×10^{-5} *M*. This can be varied depending on the sensitivity of the instrument used and the type of compound measured. The latter part of this statement can be demonstrated in the following manner. The maximum intensity for glycols is found to occur at a molar ratio (glycol:Ni(acac)$_2$) of greater than 100:1 (Figure 4). On the other hand, the maxima for amino alcohols occur around 10:1, with smaller Δε's (ca. 10). The differences in the concentration dependence be-

Table I

Entry	Compd	Predicted chirality	Molar ratio (sub/Ni)	CD Spectra		Solvent
				uv, nm[a]	d–d, nm[a]	
1	(2*S*)-4-Methylpentane-1,2-diol[b]	(+)	23:1	–45.0 (316) +31.5 (294)	+0.09 (625)	CCl_4
2	(2*S*)-2-Phenylethane-1,2-diol[b]	(+)	20:1	–24.0 (316) +20.0 (293)	+0.041 (620)	CCl_4
3	4-Pregnen-20β,21-diol-3-one	(+)	2:1	–0.6 (311)[e]	+ 0.003 (640)	CCl_4
4	(2*S*)-Propane-1-hydroxy-2-amine[c]	(+)	14:1	–6.3 (317) +4.4 (292)		*n*-hexane
5	(2*S*)-3-Chloropropane-2-hydroxy-1-amine[d]	(+)	14:1	+1.1 (319) –1.0 (290)		CCl_4
6	(2*R*)-Butane-1-hydroxy-2-amine[c]	(–)	10:1	+4.7 (317) –2.8 (289)	–0.004 (660) –0.004 (580)	*n*-hexane
7	(2*S*)-4-Methylpentane-1-hydroxy-2-amine[b]	(+)	10:1	–4.5 (317) +3.0 (293)		CCl_4
8	(2*R*)-4-Methylpentane-1-hydroxy-2-amine[b]	(–)	11:1	+3.1 (317) –1.5 (292)		CCl_4
9	(2*S*)-3-Methylpentane-1-hydroxy-2-amine[b]	(+)	30:1	–8.7 (317) +6.0 (292)		CCl_4
10	(2*S*)-3-Phenylpropane-1-hydroxy-2-amine[b]	(+)	15:1	–4.2 (317) +3.0 (293)	+0.004 (600)	CCl_4
11	(2*R*, 3*R*)-Butane-2,3-diol	(–)	40:1	+40.0 (315)[f] –35.0 (293)	–0.085 (630)	CCl_4
12	(2*S*,3*S*)-3-Phenylpropane-3-hydroxy-2-amine	(+)	30:1	+17.2 (315) –16.8 (290)	+0.015 (635)	0.2 *M* *t*-BuOH–CCl_4
13	(2*R*,3*R*)-3-Phenylpropane-(*N*-methyl)-3-hydroxy-2-amine	(–)	30:1	+19.0 (313)[f] –9.0 (288)	–0.04 (620)	CCl_4
14	(2*S*)-3-Methylbutane-2,3-diol[c,g]	(+)	40:1	–40.0 (315) +41.0 (292)	+0.12 (620)	CCl_4
15	(3*S*)-2,5-Dimethylhexane-2,3-diol[h]	(+)	50:1	–22.0 (315) +16.0 (293)		CCl_4
16	(3*R*)-2,5-Dimethylhexane-2,3-diol[h]	(–)	40:1	+15.0 (315) –11.0 (293)		CCl_4
17	(4*S*)-2-Methyl-5-ethylpentane-4,5-diol[h]	(+)	60:1	–1.1 (317)[j] +0.5 (292)	+0.025 (623)	0.2 *M* *t*-BuOH–CCl_4
18	5α-Cholestane-3β,20,22-triol (18)[i]	(–)	24:1	+0.03 (315) –0.02 (293)		CCl_4
19	(2*S*, 3*S*)-3-Phenylpropane-2-amine-1,3-diol	(–)	15:1	+7.1 (315)		0.2 *M* *t*-BuOH–CCl_4
20	(2*R*,3*R*)-3-Phenylpropane-(*p*-nitro)-2-amine-1,3-diol	(+)	10:1	–7.0 (315)		2% *t*-BuOH–CCl_4
21	5α-Cholestane-2α,3α-diol	(+)	15:1	–35.2 (316)[f] +27.2 (293)	+0.05 (625)	CCl_4

22	5α-Cholestane-2β,3β-diol	(−)	27:1	−29.0 (317)[f] +16.5 (293)		CCl_4
23	(1*S*, 2*S*)-1,2-Dihydroxy-1,2,3,4-tetrahydronapthalene[k]	(+)	20:1	−21.8 (316) +9.8 (288)		0.2 *M* *t*-BuOH–CCl_4
24	(1*S*,2*S*)-1,2-Dihydroxy-1,2-dihydronaphthalene[k]	(+)	16:1	−7.3 (316)		0.2 *M* *t*-BuOH–CCl_4
25	2-Deoxy-D-ribose	(+)	200:1	−0.7 (315) +0.8 (288)		50% *t*-BuOH–CCl_4
26	Illudin S (26)	(−)	2:1	+3.3 (315)[e] −1.0 (300)		0.2 *M* *t*-BuOH–CCl_4 at 10°
27	Methyl phytaccinate (27)[l]	(+)	2:1	−1.0 (315)	+0.04 (635)	0.2 *M* *t*-BuOH–CCl_4
28	Methyl arjunolate (28)	(+)	9:1	−23.6 (314)[f] +11.4 (288)		CCl_4
29	4-Pregnen-17α,20β-diol-3-one	(+)	3:1	−3.0 (319)		0.2 *M* *t*-BuOH–CCl_4
30	Carbohydrate derivative (30)[m]	(−)	200:1	+0.9 (315) −0.6 (292)		50% *t*-BuOH–CCl_4
31	Carbohydrate derivative (31)[m]	(+)	200:1	−1.0 (316) +0.4 (288)		50% *t*-BuOH–CCl_4

[a] The $\Delta\epsilon$ is based on the concentration of Ni(acac)$_2$ unless otherwise noted. [b] Prepared by the $LiAlH_4$ reduction of the corresponding acids. [c] Gift of Professor A. Kjaer, Copenhagen. [d] Gift of Dr. R. Paul, Lederle Laboratories. [e] The $\Delta\epsilon$ is based on the concentration of the substrate. The Ni(acac)$_2$ was added as a solid and its concentration is approximately 5×10^{-5} *M*. [f] The concentration of Ni(acac)$_2$ is 1×10^{-3} *M*. [g] Gift of Professor H. Mosher, Stanford. [h] See ref 9b. [i] Gift of Dr. H. Mori, Teikoku Hormone Co. [j] The molar ratio is 27:1, and the solvent is CCl_4. [k] Gift of Professor M. Nakazaki, Osaka University. [l] Gift of Professor Y. Shimizu, University of Rhode Island. [m] Gift of Dr. D. Horton, The Ohio State University.

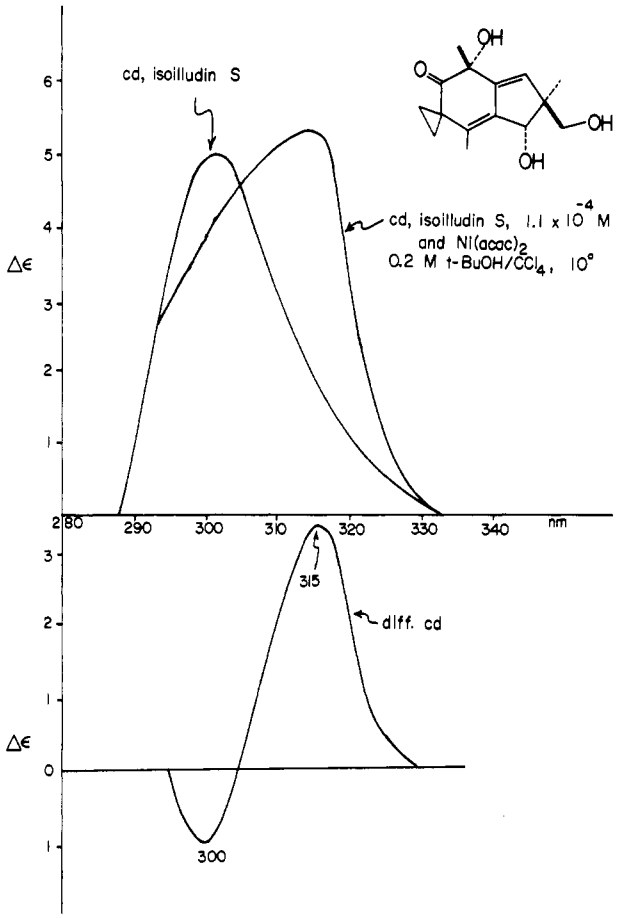


Figure 11. The CD of isoilludin S (1.1×10^{-4} *M*) and that with Ni(acac)$_2$ added as a solid (ca. 5×10^{-5} *M*), in a solution of 0.2 *M* *t*-BuOH–CCl_4 at 10°. Lower trace is the difference curve.

tween alcohols and amino alcohols can be explained in terms of the greater nucleophilicity of the amino group over an alcohol. At higher molar ratios, one would expect the formation of a diamine complex, where the amino groups can come from two different amino alcohols. They would undoubtedly be trans to each other, and thus the complex would have little dissymmetry. Here a 5×10^{-5} *M* solution of Ni(acac)$_2$ and a 5×10^{-4} *M* solution of amino alcohol would be the optimum conditions.

The measurement of compounds which also have a competing enone presents several problems. The first and most obvious is that, since an enone system, such as cholest-4-en-3-one, absorbs in the same region of the uv as the Ni(acac)$_2$ complex, a high substrate concentration would make the observation of an induced CD difficult. A second problem is that complexation with Ni(acac)$_2$ was found to lower the CD intensity on the high energy side of the enone absorption. See Figure 11 (or Table I, entry **26**) for data of an enone.

Although this latter problem has a deleterious effect on the general usefulness of this technique, it was unexpected and therefore interesting. We have reported previously that Cu(hfac)$_2$ also affects the ketone and enone absorptions,[30] but that Pr(dpm)$_3$ has little or none.[9] This parallels the results obtained from the NMR of ligands complexed to these reagents. There it was concluded that shifts resulting from complexation with transition metals can occur via a contact or pseudo-contact mechanism (for Ni(acac)$_2$ primarily contact)[31] but that lanthanide shifts occur through a pseudo-contact mechanism.[32] This suggests that the changes seen in the CD absorptions for Ni and Cu are due to some mix-

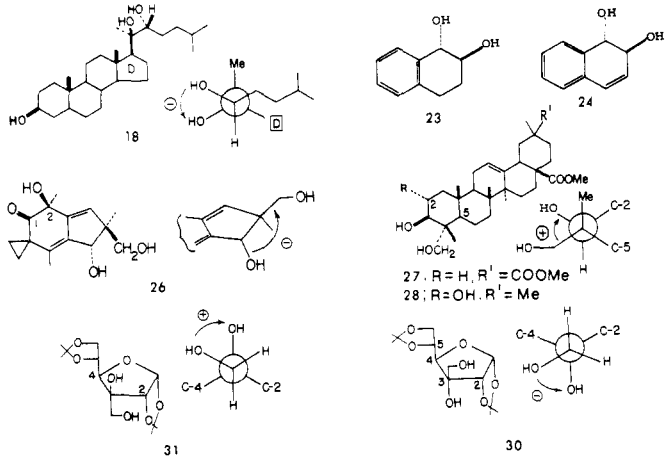
ing of the metal electron density with the enone energy levels.

These problems may be circumvented, with some difficulty, by lowering the substrate concentration, with a concomitant lowering of the temperature to enhance any induced CD's and by adding $Ni(acac)_2$ to model compounds that contain all other functionalities excepting the glycol moiety in order to determine the effect of $Ni(acac)_2$ on competing absorbing systems. The use of both of these devices will be demonstrated in the next section.

Another approach is to use the d–d region of the CD for diagnostic purposes. This has the advantage of being free of most transitions associated with organic compounds. It also has the advantage that, at lower molar ratios, there is no inversion of the CD. The major drawback is that the $\Delta\epsilon$'s are small (ca. 0.01) and are difficult to measure even with relatively high concentrations of $Ni(acac)_2$ and the substrate, e.g., 1×10^{-3} *M* $Ni(acac)_2$ with the usual molar ratio.

Interpretation. Table I gives the predicted chirality and the observed signs of the Cotton effects in both the uv and the d–d regions of the CD for a wide range of glycols and amino alcohols. It can be seen that *the sign of the CD for the d–d transition invariably agrees with the predicted chirality, while the longer wavelength extremum in the uv region is opposite to it.* The size of the $\Delta\epsilon$ for unhindered acyclic glycols and amino alcohols is relatively large. It is for these types of compounds that this method is the most useful, and it provides a very sensitive technique for the determination of the absolute configuration of natural products using only minute quantities of those compounds.

Entries **25, 26, 27,** and **28** are noteworthy in that they contain a cyclic 1,3-glycol moiety. Here the results obtained agree with those for 1,2-glycols. Entry **28** contains two glycol moieties, a rigid 1,2-glycol and a flexible 1,3-glycol. Since the latter has a more favorable bite, the CD obtained is due to the 1,3-diol. These examples show that the method can be employed to determine the chirality of 1,3-diols containing a primary hydroxyl function.



Entries **19** and **20** contain three neighboring groups. Here steric considerations dictate that complexation occurs primarily with the prim-OH/sec-NH_2. The extension of this type of analysis to more complicated or less obviously hindered systems should naturally be done with a great deal of care.

Compounds that are sparingly soluble in CCl_4 are dealt with by using higher concentrations of *t*-BuOH as in entries **25, 30,** and **31.** Compounds with competing enone systems can be handled in several ways. Entry **26** (Table I and Figure 11) was taken by adding $Ni(acac)_2$ as a solid to a known solution of **26,** or isoilludin S.[33] The difference in CD between that of entry **26** itself and **26** in the presence of $Ni(acac)_2$ is depicted in Figure 10. Control measurements with illudin S[33] (Me instead of CH_2OH and the substituents at C-1 and C-2 interchanged) showed that the CD was not affected by the addition of $Ni(acac)_2$. Therefore, the change in CD shown in Figure 11 is not due to complexation to the hydroxy ketone moiety.

Another approach to compounds containing ketones is to use the d–d region for interpretive purposes. This is demonstrated for entry **3.** Here the predicted chirality is positive. Thus one obtains a negative Cotton effect at 311 nm and a positive one at 640 nm. Either transition can be used diagnostically.

Limitations. (1) The result obtained for entry **21** agrees with prediction, but that for entry **22** disagrees. Although the latter anomaly is presumably caused by the 10-Me group, more data are necessary to clarify this point. Thus the $Ni(acac)_2$ method is not applicable at this stage to ordinary cyclic α-glycols. However, the cyclic α-glycols can be determined by the $Pr(dpm)_3$ method. It appears that $Ni(acac)_2$ can be used for compounds such as the important naphthalene metabolites entries **23** and **24.**[34]

(2) Hindered sec/tert acyclic glycols (entries **17** and **18**) give only small intensities; however, it is these types of compounds that can be handled successfully with $Pr(dpm)_3$.[9]

(3) Compounds such as entries **5** and **12,** which contain a relatively unhindered amine and a hindered hydroxyl group, give anomolous results. This is probably due to the more effective binding of an amine over a hydroxyl group (amines themselves induce CD's, whereas hydroxyls do not). Combining this with the unhindered nature of the amino group would result in something other than the bidentate binding hypothesized here; perhaps monodentate binding. Although the d–d transition at ca. 630, entry **12,** agrees with the predicted chirality, a new transition is observed at ca. 500 that does not appear in other spectra. To further corroborate the hypothesis that the binding for these two compounds is different, entry **13,** the *N*-methyl analog of entry **12** was measured. The results with this more hindered amine are now consistent with that obtained for the other compounds.[35]

Experimental Section

The CD measurements were made on a Jasco J-40 spectropolarimeter, the CD temperature dependence studies on a Cary 6001 attachment on a Cary spectropolarimeter, and the uv on a Cary 16 spectrophotometer. Spectrograde hexane and CCl_4 were dried over molecular sieves; acetone and CH_3CN were distilled from P_2O_5 and *t*-BuOH from CaH_2 prior to use.

$Ni(acac)_2$ was purchased as the monohydrate and used without purification. $Co(acac)_2$ was purchased from Aldrich and used without purification. $Ni(dpm)_2$ was synthesized according to the literature.

The concentration studies were done by the dilution technique. A known amount of substrate is dissolved in a premixed solution of $Ni(acac)_2$, and volumetric samples of this solution were then diluted with solutions of the same $Ni(acac)_2$ concentration.

The spectra were usually measured by taking a 5×10^{-5} *M* solution of $Ni(acac)_2$ in a 0.2 *M* *t*-BuOH–CCl_4 and dissolving the glycol or amino alcohol, the concentration of which was at least ten times that of the $Ni(acac)_2$. Solubilization can be speeded up by warming the solution to 50° without any deleterious effect on the $Ni(acac)_2$. The following are some selected examples of the actual measurements.

Case 1. (2*R*)-Butane-1-hydroxy-2-amine, 2.1 mg (entry **6**), was dissolved in 5 ml of a 4.8×10^{-5} *M* solution of $Ni(acac)_2$ in 0.2 *M* *t*-BuOH–CCl_4. This was diluted to $1/10$ with the same solution of $Ni(acac)_2$, and the spectrum was taken in a sample cell of path length 1 cm: $\Delta\epsilon_{317}$ +9.0; $\Delta\epsilon_{289}$ −5.3.

Case 2. Methyl arjunolate, 22.5 mg (entry **28**), was dissolved in 5 ml of a 1×10^{-3} *M* solution of $Ni(acac)_2$ in CCl_4. The CD of the d–d region was taken in a 1-cm sample holder; $\Delta\epsilon_{635}$ 0.04. The uv

region was taken in a 0.1-cm sample holder: $\Delta\epsilon_{314}$ −23.6; $\Delta\epsilon_{288}$ +11.4.

Case 3. (2*S*,3*S*)-3-Phenylpropane-2-amine-1,3-diol, 0.63 mg (entry **19**; K & K), was dissolved in a 5.0×10^{-5} *M* solution of $Ni(acac)_2$ in 0.2 *M* *t*-BuOH–CCl_4. A CD taken in a 1-cm sample holder resulted in $\Delta\epsilon_{315}$ +7.1.

References and Notes

(1) R. E. Reeves, *Adv. Carbohydr. Chem.*, **6**, 107 (1971); S. T. K. Bukhari, R. D. Wrixon, A. I. Scott, and A. D. Wrixon, *Chem. Commun.*, 1580 (1968); *Tetrahedron*, **26**, 3653 (1970).
(2) E. Bunnenberg and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5953 (1960); see also A. I. Scott and A. D. Wrixon, *Chem. Commun.*, 1184 (1969).
(3) A. H. Haines and C. S. P. Jenkins, *Chem. Commun.*, 350 (1969).
(4) N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **91**, 3789 (1969).
(5) N. Harada and K. Nakanishi, *Acc. Chem. Res.*, **5**, 257 (1972), and references cited therein.
(6) S. L. Chen, N. Harada, and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 7352 (1974).
(7) M. Koreeda, N. Harada, and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 266 (1974).
(8) V. Delaroff and R. Viennet, *Bull. Soc. Chim. Fr.*, 277 (1972).
(9) Preliminary accounts have been published: (a) K. Nakanishi and J. Dillon, *J. Am. Chem. Soc.*, **93**, 4058 (1971); (b) K. Nakanishi, D. A. Schooley, M. Koreeda, and J. Dillon, *Chem. Commun.*, 1235 (1971); (c) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 4057, 4059 (1974).
(10) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.* **97**, following paper in this issue.
(11) G. J. Bullen, R. Mason, and P. Pauling, *Inorg. Chem.*, **4**, 456 (1965).
(12) D. P. Graddon and E. C. Watten, *Nature (London)*, **190**, 906 (1961).
(13) F. A. Cotton and J. P. Fackler, Jr., *J. Am. Chem. Soc.*, **83**, 2818 (1961).
(14) J. P. Fackler, Jr., *J. Am. Chem. Soc.*, **84**, 24 (1962).
(15) J. P. Fackler and F. A. Cotton, *J. Am. Chem. Soc.*, **83**, 3775 (1961).
(16) J. T. Hashagen and J. P. Fackler, Jr., *J. Am. Chem. Soc.*, **87**, 2821 (1965).
(17) For reviews of this and other topics concerning the chemistry of β-ketoenolate transition metal complexes, see: D. P. Graddon, *Coord. Chem. Rev.*, **4**, 1 (1969).
(18) T. S. Kannan and A. Chakravorty, *Inorg. Chem.*, **9**, 1153 (1970).
(19) See, for example: A. B. P. Leven, "Inorganic Electronic Spectroscopy", Elsevier, New York, N.Y., 1968, p. 134.
(20) E. J. Corey and J. C. Bailar, Jr., *J. Am. Chem. Soc.*, **81**, 2620 (1959).
(21) (a) J. R. Gollogly and C. J. Hawkins, *Inorg. Chem.*, **8**, 1168 (1968); (b) C. J. Hawkins, "Absolute Configuration of Metal Complexes", Wiley-Interscience, New York, N.Y., 1971.
(22) W. De W. Horrocks, Jr., D. H. Templeton, and A. Zalkin, *Inorg. Chem.*, **7**, 1552 (1968).
(23) A. J. McCaffery, S. F. Mason, B. J. Norman, and A. M. Sargeson, *J. Chem. Soc. A*, 1304 (1968); B. Bosnich and J. MacB. Harrowfield, **94**, 3425 (1972).
(24) M. J. Harding, S. F. Mason, and B. J. Peart, *J. Chem. Soc.*, 955 (1973).
(25) B. Bosnich, *Acc. Chem. Res.*, **2**, 266 (1969).
(26) L. J. Boucher, *Inorg. Chem.*, **9**, 1202 (1970).
(27) J. P. Fackler, Jr., *J. Am. Chem. Soc.*, **84**, 24 (1962).
(28) D. P. Graddon, *Nature (London)*, **195**, 891 (1961).
(29) J. P. Fackler, Jr., and F. A. Cotton, *J. Am. Chem. Soc.*, **82**, 5005 (1960).
(30) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 4055 (1974).
(31) D. R. Eaton and W. D. Phillips, *Adv. Magn. Reson.*, **1**, 103 (1965).
(32) W. De W. Horrocks, Jr., J. P. Sipe, III, and D. Sudnick, "Nuclear Magnetic Shift Reagents", R. E. Sievers, Ed., Academic Press, New York, N.Y., 1973.
(33) T. C. McMorris and M. Anchel, *J. Am. Chem. Soc.*, **85**, 831 (1963).
(34) H. Ziffer, D. M. Jerina, D. T. Gibson, and V. M. Kobal, *J. Am. Chem. Soc.*, **95**, 4048 (1973).
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Absolute Configurational Studies of Vicinal Glycols and Amino Alcohols. II. With $Pr(dpm)_3$

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Abstract: A spectroscopic method requiring no substrate derivatization has been developed for absolute configurational studies of glycols and amino alcohols. The substrates which are suited for studies by the $Pr(dpm)_3$ method are complementary to those suited for study by the $Ni(acac)_2$ method, and are cyclic (**1–11**) and hindered acyclic secondary/tertiary (**15–19**) vicinal glycols. The method consists of measuring the CD of substrate and $Pr(dpm)_3$ dissolved in a dry nonpolar solvent. The solution shows an induced split Cotton effect consisting of two peaks of opposite sign and near equal intensity centered at ca. 300 nm. The longer wavelength extremum is positive for cyclic α-glycols of positive chirality and negative for glycols of negative chirality. Studies indicate that the size of the Cotton effect amplitude varies with concentration, time, and temperature. These data suggest that the observed CD results from formation of an unstable bidentate adduct between the glycol and $Pr(dpm)_3$. Several examples of the application of this method to compounds of unknown absolute configuration are presented.

In our previous papers,[1,2] we discussed the general usefulness of $Ni(acac)_2$ as a structural probe. Here we will present the scope and limitations of $Pr(dpm)_3$. We have reported its application to cyclic glycols,[3] and this was extended in a limited way to acyclic secondary/tertiary (sec/tert) α-glycols during the course of absolute configurational studies of the insect juvenile hormone.[4] More recently, it was shown that $Pr(dpm)_3$ can be used for cyclic α-hydroxyamines and certain monofunctional amines.[5] Studies carried out on a variety of substrates and at different concentrations show that the $Pr(dpm)_3$ reagent is complementary to the $Ni(acac)_2$ reagent and is more suited for cyclic vicinal glycols and hindered sec/tert vicinal glycols. In contrast to $Ni(acac)_2$, the solvent should be vigorously dried and nonpolar.

Results and Discussion

A split CD curve centered at ca. 300 nm is observed immediately upon addition of an optically active glycol or amino alcohol to a solution of $Pr(dpm)_3$ (dpm = dipivalomethanato; sometimes called thd = 2,2,6,6-tetramethyl-3,5-heptadionato). A typical curve, a 1:1 mixture of cholest-5-ene-3β,4β-diol and $Pr(dpm)_3$ in CCl_4 is depicted in Figure 1. The observed Cotton effect consists of two extrema of opposite signs and near equal intensities. The amplitudes of these extrema are concentration dependent as shown in Figure 2 for a cyclic case and Figure 3 for an acyclic case.

Tables I and II give the results obtained for a series of cyclic and acyclic glycols and amino alcohols. The chirality of a cyclic glycol moiety is defined as being negative or posi-