

Figure 2. The bulk relationship presented results in a negative Cotton effect at *ca.* 333 nm. Here L, M and S stand for large, medium, and small groups, respectively.

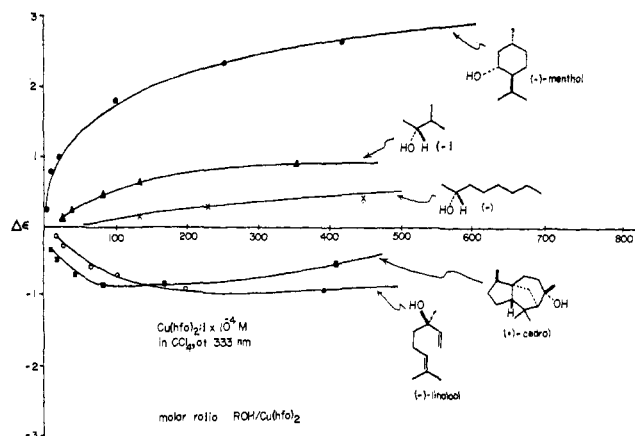


Figure 3. The variation of the  $\Delta\epsilon$  at 333 nm for  $\text{Cu}(\text{hfac})_2$  ( $1.0 \times 10^{-4} M$ ) with increasing concentration of alcohol in  $\text{CCl}_4$ .

A typical curve is shown in Figure 1. It consists of long wavelength maxima at *ca.* 333 and 321 nm and a short wavelength of opposite sign at *ca.* 300 nm (split CD). This is similar to those found for the  $\text{Pr}(\text{dpm})_3$ ,  $\text{Ni}(\text{acac})_2$ , and dibenzoate chirality methods. For purposes of interpretation, only the longest wavelength extrema is chosen. Comparison of the CD data and the known configurations of these compounds leads to the following correlation. A model of the compound in question is observed from the direction of the functional group (Figure 2a). If the bulk relationship<sup>7</sup> between the substituents at the asymmetric carbon is as presented in Figure 2b, *i.e.*, counterclockwise, then a negative Cotton effect will be observed at *ca.* 333 nm.

As has been reported in previous studies, the magnitude of  $\Delta\epsilon$  is related to the dryness of solvent and the concentration of optically active species (Figure 3). For these reasons the following procedure is recommended for measurements. A solution  $10^{-4} M$  in  $\text{Cu}(\text{hfac})_2$  and from  $10^{-2}$  to  $10^{-3} M$  in alcohol is mixed in dry hexane or  $\text{CCl}_4$ . The results obtained upon the addition of  $\text{Cu}(\text{hfac})_2$  to various alcohols are presented in Table I.

The bulk relationships of the substituents around most of the isolated hydroxyl groups follow directly from the drawings. Difficulties arise in compounds such as **10** where nonneighboring carbons play a dominant roll. Here space filling models have to be employed to distinguish the importance of those carbons.

Addition of the Cu reagent to ketones and enone systems produces changes in the CD extrema. This

(6) The strong uv transition permits usage of dilute substrate solutions (*ca.*  $10^{-3} M$ ). Andersen, *et al.*, have independently developed a similar method employing the d-d transition of  $\text{Eu}(\text{fod})_3$ ; however, this method necessitates the usage of more concentrated solutions, 0.04–0.17 M. See N. H. Andersen, B. J. Bottino, A. Moore, and J. R. Shaw, *J. Amer. Chem. Soc.*, **96**, 603 (1974).

(7) Polarizabilities of substituents seem to be relatively unimportant; if they were dominating, the predicted results in pantolactone **13** would be opposite to that observed.

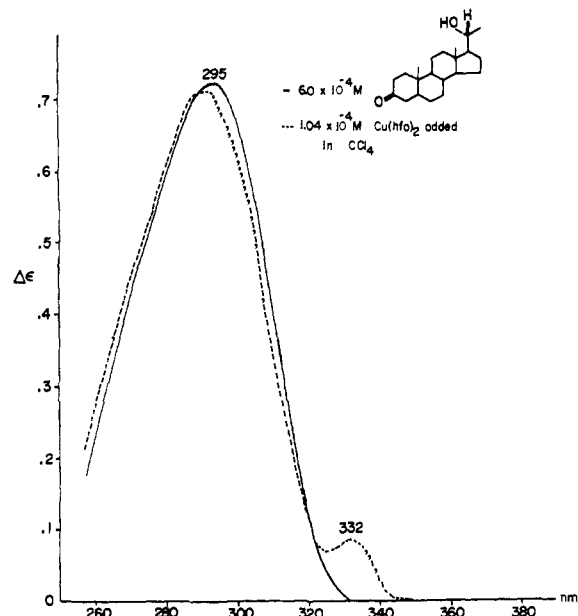


Figure 4. (—) The CD resulting from entry ( $6.0 \times 10^{-4} M$ ). (---) That resulting upon the addition of  $1.04 \times 10^{-4} M$   $\text{Cu}(\text{hfac})_2$  in  $\text{CCl}_4$ .

behavior precludes the use of compounds containing enones, since the uv bands are at *ca.* 340 nm and in the same region used in this method. On the other hand unhindered ketones (**3** and **12**) can be used since the CD resulting from the hydroxyl groups falls at a longer wavelength (Figure 4).

We have not as yet extended this method to amines but the few cases studied gave results similar to those of alcohols; however, the extreme of the amine– $\text{Cu}(\text{hfac})_2$  complexes are at *ca.* 310 nm.

Care should be taken in the interpretation of results obtained from compounds containing ketones with, nearby chiral centers<sup>8</sup> and derivatized hydroxyl groups *e.g.*, OAc or OBz, since these also give induced CD's.<sup>9,10</sup>

(8) Evidently ketones which have a chiral center close to the oxygen, *e.g.*, camphor, give an induced CD from the interaction with  $\text{Cu}(\text{hfac})_2$ ; however, this does not occur in cases where the ketone is not close to a bulky center, *e.g.*, cholestan-3-one.

(9) Acetylation of entry **1** results in a 65% reduction of the observed CD.

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## Use of Complexing Agents for Determining the Absolute Configurations of $\alpha$ -Glycols and $\alpha$ -Amino Alcohols. Basic Systems

Sir:

We previously reported that  $\text{Pr}(\text{dpm})_3$  can be used for determining the absolute configuration of cyclic  $\alpha$ -glycols,<sup>1</sup> and this was extended in a limited way to acyclic *sec/tert*  $\alpha$ -glycols during the course of absolute configurational studies of the insect juvenile hormone.<sup>2</sup> As the measurements are run in organic solvents, the

(1) K. Nakanishi and J. Dillon, *J. Amer. Chem. Soc.*, **93**, 4058 (1971).

(2) K. Nakanishi, D. A. Schooley, M. Koreeda, and J. Dillon, *Chem. Commun.*, 235 (1971).

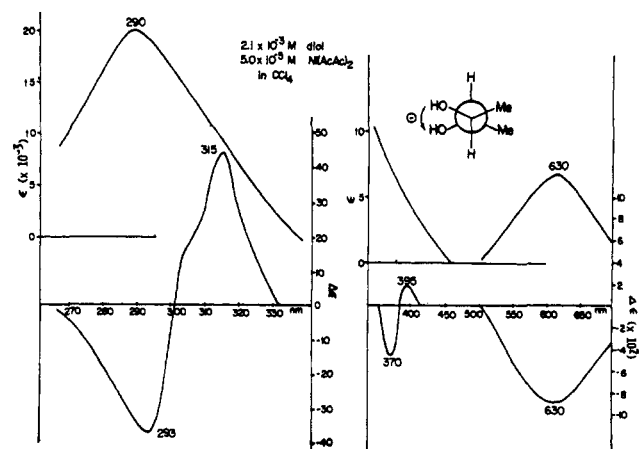


Figure 1. UV and CD of a mixture of  $2.1 \times 10^{-3} M$  (2*R*,3*R*)-butane-2,3-diol and  $5.0 \times 10^{-5} M$  Ni(acac)<sub>2</sub> in CCl<sub>4</sub>.

method is complementary to the Cupra-A method<sup>3</sup> which is carried out in aqueous solutions. Subsequent studies to generalize this method to neighboring bifunctional systems have shown that the use of Ni(acac)<sub>2</sub> (nickel(II) acetylacetonate) in conjunction with Pr(dpm)<sub>3</sub> offers a general method for determining the absolute configurations of various glycols and amino alcohols, acyclic as well as cyclic. An extension of this method to more complex compounds is presented in the following paper.<sup>4</sup>

As in the case of Pr(dpm)<sub>3</sub>, the addition of substrate to the Ni(acac)<sub>2</sub> solution results in an induced exciton-split type CD centered at 300 nm (Figure 1).<sup>5</sup> The chirality of cyclic cases follows from models, whereas for acyclic cases it is that conformer which has its bulkier group(s) in pseudoequatorial orientation(s). Results obtained for conformational unit I are summarized in Table I. A left-handed screw rotation

Table I. Sign of the First Cotton Effect Obtained with Conformational Unit I.

	Ni(acac) <sub>2</sub> (315 nm)	Pr(dpm) <sub>3</sub> (310 nm)
Cyclic	+	-
Acyclic		
Prim/sec	+	+
Sec/sec	+	+
Sec/tert	+	-

along the central C-C bond is defined as a negative chirality. Note that all signs for the Ni cases are consistent and opposite to the chirality I, whereas signs for the Pr complexes depend on the substrate type.

A comparison of the characteristics of the two reagents is given in Table II. In general, the Ni reagent is

(3) R. E. Reeves, *Advan. Carbohyd. Chem.*, **6**, 107 (1971); S. T. K. Bukhari, R. D. Guthrie, A. I. Scott, and A. D. Wrixon, *Chem. Commun.*, 1580 (1968); *Tetrahedron*, **26**, 3653 (1970).

(4) J. Dillon and K. Nakanishi, *J. Amer. Chem. Soc.*, **96**, 4059 (1974).

(5) The complexes formed with Ni(acac)<sub>2</sub> show in addition, a weak split CD at 395(+)/370(-) and a negative CD (d-d transition) at 630 nm. This aspect is discussed in ref 4.

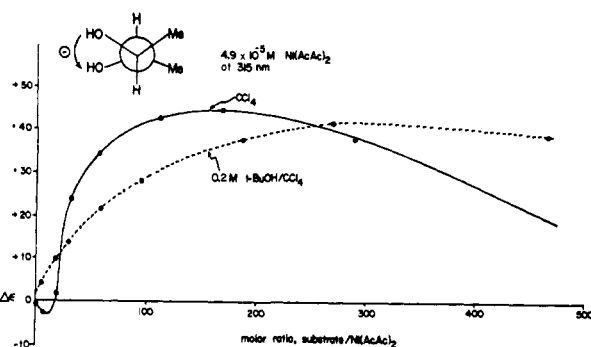


Figure 2. Variation of  $\Delta\epsilon$  at 315 nm for Ni(acac)<sub>2</sub> ( $4.9 \times 10^{-5} M$ ) with increasing concentrations of (2*R*,3*R*)-butane-2,3-diol in CCl<sub>4</sub> (—) and in 0.2 *M* *t*-BuOH-CCl<sub>4</sub> (---).

Table II. A Comparison of Conditions and Characteristics of the Ni(acac)<sub>2</sub> and Pr(dpm)<sub>3</sub> Reagents

	Ni(acac) <sub>2</sub> <sup>a,b</sup>	Pr(dpm) <sub>3</sub> <sup>a</sup>
Solvent	Dry hexane, CCl <sub>4</sub> , CHCl <sub>3</sub> , <i>t</i> -BuOH, CH <sub>3</sub> CN, acetone <sup>c</sup>	Dry hexane, CCl <sub>4</sub> , CHCl <sub>3</sub>
Reagent concn	$5 \times 10^{-5} M$ <sup>d</sup>	$1 \times 10^{-4} M$
Molar ratio	$\alpha$ -Amino alcohol; 5-20:1	1-5:1
(subst:reag)	$\alpha$ -Glycol; 20-200:1	1-5:1
$\Delta\epsilon$	$\alpha$ -Amino alcohol; 3-10 <sup>e</sup> $\alpha$ -Glycol; 5-60 <sup>e</sup>	1-8 <sup>e</sup>
Stability	Several days	Several hours
$\lambda_{max}$	315/295	310/290

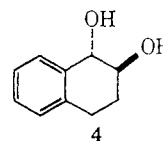
<sup>a</sup> The CD measurements were taken on a Jasco J-40 instrument.

<sup>b</sup> The Ni reagent (monohydrate) was purchased from Aldrich and used without purification. <sup>c</sup> Spectrograde hexane and CCl<sub>4</sub> were dried over molecular sieves; CH<sub>2</sub>Cl was freed of EtOH; *t*-BuOH was distilled from CaH<sub>2</sub>; CH<sub>3</sub>CN and acetone were distilled from P<sub>2</sub>O<sub>5</sub> prior to use. <sup>d</sup> Unlike Pr(dpm)<sub>3</sub>, Ni(acac)<sub>2</sub> can be solubilized by warming to 50° without any harmful effects. <sup>e</sup> The  $\Delta\epsilon$  is based on the concentration of the inorganic complex.

Table III. Cyclic Glycols (in CCl<sub>4</sub>)

Entry	Compound	Chirality	Ni(acac) <sub>2</sub>	Pr(dpm) <sub>3</sub>
1	Cholest-5-ene-3 $\beta$ ,4 $\beta$ -diol	(-)	-323/+302 <sup>b</sup>	(-) <sup>1</sup>
2	5 $\alpha$ -Cholestane-2 $\beta$ ,3 $\beta$ -diol	(+)	-323/+302	(+) <sup>1</sup>
3	5 $\alpha$ -Cholestane-2 $\alpha$ ,3 $\alpha$ -diol	(+)	-318/+301	(+) <sup>1</sup>
4	Compound 4 <sup>a</sup>	(+)	-316/+294	(-)
5	Cholestane-3 $\beta$ ,5 $\alpha$ ,6 $\alpha$ -triol 3-acetate	(-)	Nil	(-) <sup>1</sup>

<sup>a</sup> Gift from Professor M. Nakazaki, Osaka University; R.

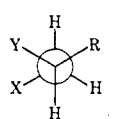
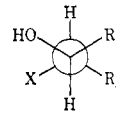
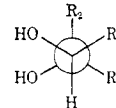


Miura, S. Honmaru, and M. Nakazaki, *Tetrahedron Lett.*, 5271 (1968). <sup>b</sup> Complexation is presumably affected by the 10-Me group.

more stable and more versatile and gives larger  $\Delta\epsilon$ 's than Pr(dpm)<sub>3</sub>. Relatively high concentrations of substrate to reagent have to be used for Ni(acac)<sub>2</sub> due to the fact that at low concentrations there is a reversal in the sign of the Cotton effect,<sup>6</sup> Figure 2. This limi-

(6) Unlike Pr(dpm)<sub>3</sub> which is monomeric<sup>7</sup> in aprotic solvents, Ni(acac)<sub>2</sub> is primarily trimeric.<sup>8</sup> The reversal in sign presumably results from interaction of the substrate with some intermediate species which at

Table IV. Acyclic Glycols and Amino Alcohols

Classes	Entry	Compound	Sign of the Cotton effect		
			Ni(acac) <sub>2</sub> 315/295 nm	Pr(dpm) <sub>3</sub> <sup>a</sup> ca. 310 nm	
	Prim/sec	<b>6-8</b>	X = Y = OH; R = Me <sup>i,l</sup> <i>i</i> -Pr, <sup>d,i</sup> Ph <sup>d,i</sup>	(+)/(−) <sup>b</sup>	(+) <sup>b</sup>
		<b>9-13</b>	X = OH; Y = NH <sub>2</sub> ; R = Me, <sup>f,i</sup> Et, <sup>f,i</sup> <i>i</i> -Bu, <sup>e,i</sup> <i>sec</i> -Bu, <sup>d,i</sup> CH <sub>2</sub> Ph <sup>d,i</sup>	(+)/(−) <sup>b</sup>	(+) <sup>b</sup>
		<b>14</b>	X = NH <sub>2</sub> ; Y = OH; R = CH <sub>2</sub> Cl <sup>d,g</sup>	(−)/(+) <sup>b,m</sup>	(+) <sup>b</sup>
	Sec/sec	<b>15-17</b>	X = OH; R <sub>1</sub> = R <sub>2</sub> = Me, Et, <sup>i</sup> CH <sub>2</sub> CH <sub>2</sub> Br <sup>i,l</sup>	(+)/(−) <sup>b</sup> (+)/(−) <sup>c</sup>	(+) <sup>b</sup>
		<b>18</b>	X = NH <sub>2</sub> ; R <sub>1</sub> = Ph; R <sub>2</sub> = Me <sup>d</sup>	(−)/(+) <sup>b,m</sup>	(+) <sup>b</sup>
	Sec/tert	<b>19</b>	R <sub>1</sub> = R <sub>2</sub> = Me <sup>d,f,h</sup>	(+)/(−) <sup>b</sup>	(+) <sup>e,m</sup>
		<b>20, 21</b>	R <sub>1</sub> = <i>i</i> -Bu; R <sub>2</sub> = Me, <sup>e,k</sup> Et <sup>e,k</sup>	(+)/(−) <sup>b</sup>	(−) <sup>e</sup>

<sup>a</sup> Only the longer  $\lambda$  was measured for Pr(dpm)<sub>3</sub>. <sup>b</sup> In CCl<sub>4</sub>. <sup>c</sup> In hexane. <sup>d</sup> The enantiomer was in fact measured. <sup>e</sup> Both enantiomers were measured. <sup>f</sup> Gift from Professor A. Kjaer, Copenhagen. <sup>g</sup> Gift from Dr. R. Paul, Lederle Laboratories. <sup>h</sup> Gift from Professor H. Mosher, Stanford. <sup>i</sup> Prepared by LiAlH<sub>4</sub> reduction of the corresponding acid. <sup>j</sup> Prepared according to literature. <sup>k</sup> See ref 2. <sup>l</sup> Only the Ni reagent was measured. <sup>m</sup> See text.

tation, however, is obviated to a great extent by addition of 0.2 M *t*-BuOH to the solution to be measured, Figure 2,<sup>10</sup> and allows lowering of the substrate/Ni ratio to 1:1<sup>11</sup> (usage of *t*-BuOH has other advantages).<sup>†</sup>

Results obtained with a variety of compounds are summarized in Tables III and IV. For the Pr(dpm)<sub>3</sub> reagent, it appears that discriminating steric environments, *i.e.*, sec/tert cases, are necessary for it to exhibit CD signs identical with those for cyclic compounds (Table I); the reversal in signs for the prim/sec and sec/sec cases, and the unhindered cyclic and sec/tert cases (entries 4 and 19, respectively), is presumably caused by this. In contrast, it appears that the angle and steric allowances for the formation of the Ni complex is more restricted and hence the cyclic sec/tert compound 5 gives no CD with Ni(acac)<sub>2</sub>.

Finally, amines<sup>12</sup> are much more nucleophilic than hydroxyl groups and compounds such as (+)-1-phenyl-1-aminoethane give relatively large CD's with both Pr(dpm)<sub>3</sub> and Ni(acac)<sub>2</sub> by themselves.<sup>13</sup> Therefore, care must be taken in the interpretation of the results for compounds such as 14 and 18, where the amino group is much less hindered than the hydroxyl group.

higher substrate concentration breaks into monomeric species.<sup>9</sup> The lower molar ratio for amino compounds for Ni reagent is probably due to the greater nucleophilicity of the amino group.

(7) J. S. Ghotra, F. A. Hart, G. P. Moss, and M. L. Staniforth, *J. Chem. Soc., Chem. Commun.*, 113 (1973).

(8) J. P. Fackler and F. A. Cotton, *J. Amer. Chem. Soc.*, **83**, 3775 (1961).

(9) J. P. Fackler, *J. Amer. Chem. Soc.*, **84**, 24 (1962).

(10) The *t*-BuOH helps to break up the Ni(acac)<sub>2</sub> trimer. This is not effective for compounds such as entry 3, Table III, presumably due to the rigid dihedral angle, or entry 8, Table IV, which has a very hindered hydroxyl group. For these compounds it is necessary to use ratios of 10–20 to 1, glycol to Ni(acac).

(11) Lowering the temperature effects results similar to *t*-BuOH addition. A 2:1 D-(−)-butane-2,3-diol:Ni(acac)<sub>2</sub> mixture at −3° has a  $\Delta\epsilon_{315} = +8.5$  as compared to a value of  $\Delta\epsilon_{315} = -2.0$  at room temperature (see Figure 2).

(12) Application of the Pr(dpm)<sub>3</sub> method to a limited class of amines and correlation of absolute configuration with the Cahn, Ingold, Prelog nomenclature has recently been published. See G. N. Mitchell and F. I. Carroll, *J. Amer. Chem. Soc.*, **95**, 7912 (1973).

(13) This observation has been extended to a general method for the treatment of isolated hydroxyl groups. J. Dillon and K. Nakanishi, *J. Amer. Chem. Soc.*, **96**, 4055 (1974).

On the basis of these observations and unpublished observations we recommend that in general Pr(dpm)<sub>3</sub> be used for cyclic compounds and sterically hindered sec/tert acyclic cases, whereas Ni(acac)<sub>2</sub> be used for acyclic cases.<sup>14</sup>

(14) Supported by NSF GP 40087.

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### Use of Complexing Agents for Determining the Absolute Configurations of $\alpha$ -Glycols and $\alpha$ -Amino Alcohols. Applications to Complex Natural Products

Sir:

In our previous paper we reported the use of Ni(acac)<sub>2</sub> and Pr(dpm)<sub>3</sub> for the determination of the absolute configuration of simple  $\alpha$ -amino alcohols and  $\alpha$ -glycols,<sup>1</sup> where we used primarily aprotic solvents and the uv CD region. In the following, this technique has been extended to the use of protic solvents and to the d-d region of the CD. This and previously reported methods<sup>1</sup> will be used in the interpretation of more complicated systems.

When Ni(acac)<sub>2</sub> is the reagent, varying amounts of *t*-BuOH can be added to CCl<sub>4</sub> (Figure 1), a feature which greatly expands the applicability of this method. Evidently the bulky *t*-Bu group hinders the effective association of *t*-BuOH with Ni(acac)<sub>2</sub>, so that a 1:1 mixture of *t*-BuOH and CCl<sub>4</sub> is still a suitable solvent. Acetone and acetonitrile, although somewhat inferior to *t*-BuOH, can also be used in this manner.

It was also found that d-d transitions could be used for diagnostic purposes as well (Figure 1 in ref 1 and Table I). Usage of this region has the advantage of usually being free of absorptions due to the substrate compound. Note that the broad transition at ca. 615

(1) J. Dillon and K. Nakanishi, *J. Amer. Chem. Soc.*, **96**, 4057 (1974).