Tetrahedron. Vol. 26, pp. 3653 to 3659 Pergamon Press 1970. Printed in Great Britain

CIRCULAR DICHROISM STUDIES ON CUPRAMMONIUM COMPLEXES OF DIOLS AND AMINO-ALCOHOLS*

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(*Received in the UK* 26 *January* 1970; *Accepted for publication* 3 *March* 1970)

Abstract--A method for the stereochemical study of cyclic 1,2-diols and 1,2-amino-alcohols by measurement of the CD spectra of their solutions in cuprammonium is described. The use of the method is demonstrated by the determination of the absolute configuration of (+) and (−)-*trans*-2-methylamino- and 2-dimethylaminocyclohexanol, and of (+)-*trans*-cyclo-octane-1,2-diol.

DURING the late 1940's and the early 1950's Reeves[1] developed the complexing of vicinal diols with cuprammonium as a useful tool for structural studies on such systems. Whether or not complexing had occurred was determined by measurement of rotational shift at 436 nm ($\Delta[M]_{Cupra}$), § or by measurement of changes in conductivity. It was shown that the sign of the rotational shift was related to the sign (as defined by Reeves[1]) of the dihedral angle between the two C—O bonds, and therefore to the absolute configuration of the diol. From a study of a series of rigid diols it was shown[1] that complex formation only occurred if the dihedral angle was between 0 and $\pm 60°$. It was also shown that five-membered chelate rings were favoured and that the complex had[2] a copper:diol ratio of 1:1. The observed results were correlated with the ease of formation of isopropylidene acetals, and with rates of periodate oxidation.[1] Reeves, however, used the technique for studying systems of known absolute configuration, namely glycopyranosides and their derivatives, and was thus able to determine the conformation of the sugar ring in the complex. These studies led to a considerable advance in the knowledge of the preferred conformations of such molecules. Later, the method was used in the determination of the absolute configuration of several carbohydrate antibiotics.[3-5]

Work on amino-alcohols[6,7] and N-methylated amino-alcohols[8] showed that the methods developed by Reeves could be applied with equal confidence to systems containing these groupings. The method was used to confirm the absolute configuration of kanamycin. During the course of these studies it was shown[7] that tetra-amino-copper sulphate solutions (TACu) would complex with amino-alcohols, but not with diols.

Throughout the above work the emphasis was on the conformation of the ligand and no regard was paid to the chelate ring conformation. Much work has been carried out on the stereochemistry of chelate rings in metal complexes,[10] most studies being concerned with diamine complexes, a few with amino-alcohols and none with diols. The rotational shift observed in the above studies with cuprammonium must arise from the asymmetric perturbations of the copper transitions by the

* For a preliminary report of part of this work see *Chem. Commun.* 1580 (1968)

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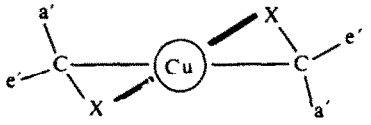
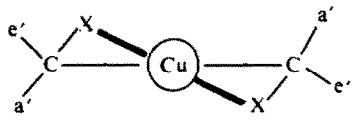
§ $\Delta[M]_{Cupra} = [M]_{Cupra} - [M]_{H_2O}$.

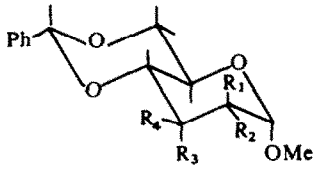
chirality of the chelate ring formed with the diol or amino-alcohol, and thus it would be expected that investigation of the CD spectra of cuprammonium complexes would lead to information on the chelate conformation. Two conformations, I and II, are possible for a five-membered chelate ring; these correspond to Reeves' negative and positive dihedral angles respectively. Corey and Bailar[11] designated these two conformations in an unambiguous way as k and k', respectively. Unfortunately, a rather arbitrary use of k and k' based on a trivial diagrammatic error as well as the introduction of several other symbols of identical meaning has unnecessarily confused the k, k' nomenclature.[12] To avoid this confusion we use the symbols λ and δ respectively for I and II, as proposed by Douglas.[13]



I λ



II δ



III

Use of conformationally rigid ligands such as system III enables the sign of Cotton effects to be assigned to particular chelate conformations. The CD spectra were determined for several diols (1–6) and amino-alcohols (7–13) based on system III in which the dihedral angle was + or −60°. Two bands were observed, always of opposite sign. Typical spectra for diols are shown in Fig 1 and for amino-alcohols in Fig 2. It will be seen that in *all cases* a δ chelate conformation was associated with a positive effect at about 580–600 nm, and a λ conformation with a negative effect in that region. Details of the long wavelength bands are given in Tables 1 and 2. Reeves[1] has already demonstrated that a diol monomethyl ether will not complex. We have now synthesised[9] methyl 3-amino-4,6-O-benzylidene-3-deoxy-2-O-methyl-α-D-glucopyranoside (III, $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = NH_2$) and shown that its cuprammonium solution gave no observable CD bands.

Reeves had shown that compounds of system III having the reactive groups in diaxial positions, (*i.e.* 180° dihedral angle) gave only low rotational shifts and this was interpreted as being due to the absence of complex formation. Investigation of the CD spectra of cuprammonium solutions of such compounds (Table 3) gave no *observable* bands.

Further, amino-alcohols (but not diols), gave two bands with TACu solution (cf. lit.[7]). It was therefore assumed that a detectable CD band implies chelate formation. Since one is dealing with an equilibrium, the measurement of $[\theta]$ is not meaningful as the amount of complex present will depend on concentration, and the precise stereochemistry of the ligand. The values found for $[\theta]$ were generally in the range 300–700

for the long wavelength band. The dimethylamino-hydroxy system in compound 13, however, gave a value well outside this range. Similar results have been obtained with other compounds containing this grouping[14] (see below).

Triol systems, such as compounds 19 and 20 in which there is competitive complexing (cf. lit.[1]) showed very weak Cotton effects (Table 4).

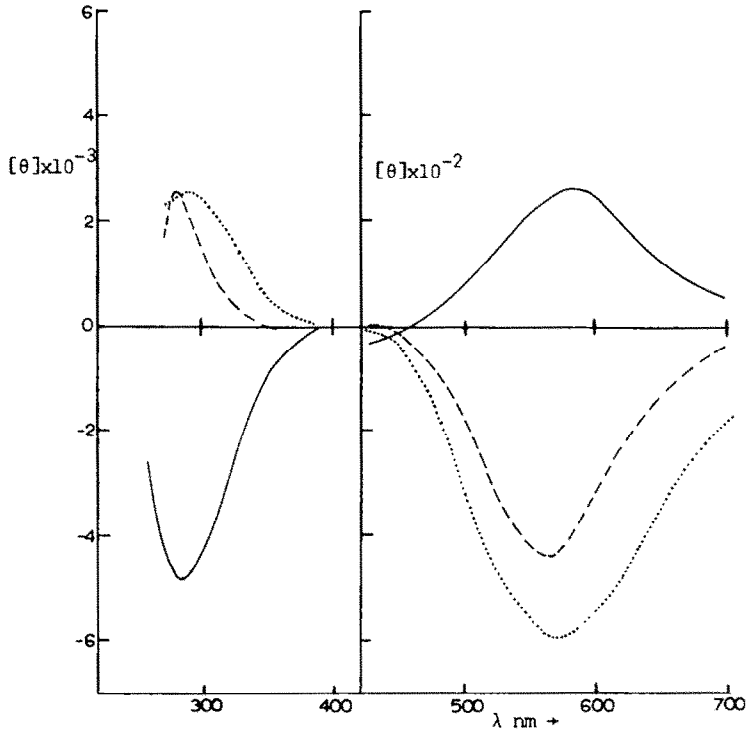


FIG. 1 CD spectra of methyl 4,6-O-benzylidene-α-D-glucopyranoside (————), methyl 4,6-O-benzylidene-α-D-allopyranoside (- - - - - - - -), and methyl 4,6-O-benzylidene-α-D-mannopyranoside (.....), in Cupra A solution.

The CD technique for assessing cuprammonium complexing has clear advantages over the previously used single wavelength method. Small amounts of material are required (2–8 mg) and also Cupra A[1] is more easy to work with than is Cupra B.[1] The material under investigation can be recovered if necessary. The general applicability of this technique has been shown in its use in the determination of the structure of a naturally-occurring diol, rishitin,[15] in the investigation of the conformation of furanoside rings,[16] and in structural studies on the components of carbohydrate antibiotics.[14]

The usefulness of the technique will be further illustrated by the following two examples.

Kay and Robinson[17] have described the resolution of (±)*trans*-2-methylaminocyclohexanol and the N-methylation of the enantiomers to give (+) and (−)-*trans*-2-dimethylaminocyclohexanol. The absolute configuration of the above four compounds was inferred (though not proved) by consideration of the ORD spectra of their benzoate methiodide salts. Dr. Robinson kindly provided us with samples of the

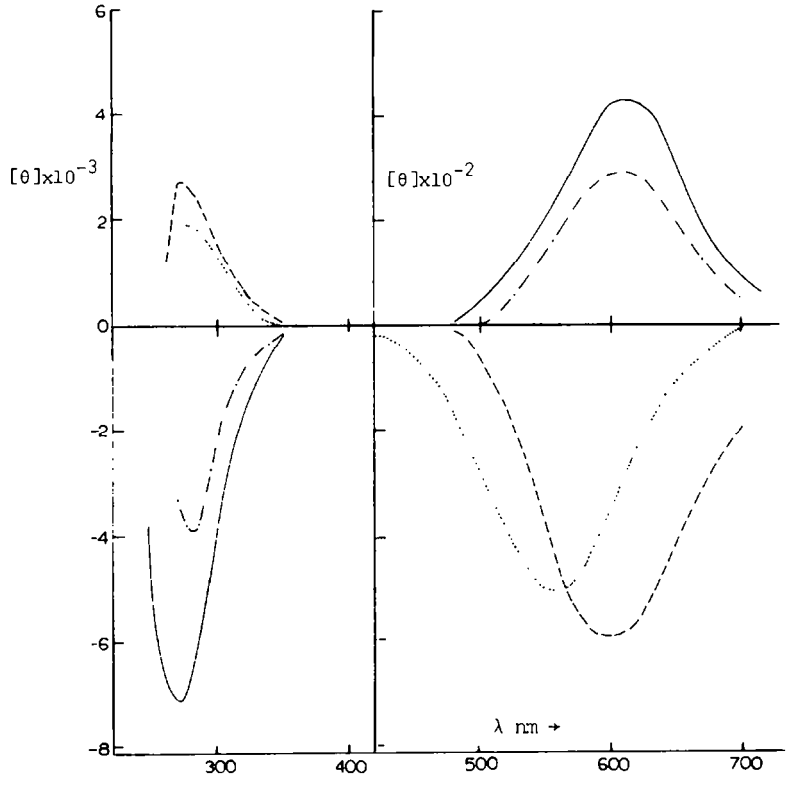


FIG. 2. CD spectra of methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-glucoside (————), methyl 2-amino-4,6-O-benzylidene-2-deoxy-α-D-glucoside (-·-·-·-·-·-), methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-alloside (.....) and methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-mannoside (----------) in Cupra A solution.

TABLE 1. CD SPECTRA (LONG WAVELENGTH BAND) OF 4,6-O-ACETALS OF METHYL D-ALDOHEXOPYRANOSIDES

No.	Compound	Chelate Conformation[a]	$\Delta[M]^{\circ}_{Cupra}$	$[\theta]$	λ_{max} (nm)
1	4,6-O-benzylidene-α-glucoside[e]	δ	−2160[b]	+250	580
2	4,6-O-benzylidene-β-glucoside	δ	−2230[b]	+420	580–590
3	4,6-O-benzylidene-α-mannoside[f]	λ	+819[c]	−580	560
4	4,6-O-benzylidene-β-mannoside	λ	+1080[d]	−490	570–580
5	4,6-O-benzylidene-α-alloside[g]	λ	+1795[c]	−430	560
6	4,6-O-ethylidene-β-glucoside	δ	−1970[b]	+410	580–590

[a] Chelate ring conformation predicted from the known conformation of the ligand.
[b] Lit.[1]
[c] Lit.[2]
[d] C. B. Barlow and R. D. Guthrie, unpublished work.
[e] (III) $R^1 = H = R^3$; $R^2 = OH = R^4$.
[f] (III) $R^2 = H = R^3$; $R^1 = OH = R^4$.
[g] (III) $R^1 = H = R^4$; $R^2 = OH = R^3$.

TABLE 2. CD SPECTRA (LONG WAVELENGTH BAND) OF AMINO-SUGARS DERIVED FROM METHYL 4,6-O-BENZYLIDENE-α-D-ALDOHEXOPYRANOSIDES

No.	Compound	System III				Chelate Conformation[a]	$\Delta[M]^{\circ}_{Cupra}$	$[\theta]$	λ_{max} (nm)
		R^1	R^2	R^3	R^4				
7	3-amino-3-deoxy-glucoside	H	OH	H	NH_2	δ	−1111[b]	+420	610–620
8	2-amino-2-deoxy-glucoside	H	NH_2	H	OH	δ	−979[b]	+285	610–620
9	3-amino-3-deoxy-mannoside	OH	H	H	NH_2	λ	+455[b]	−590	600
10	2-amino-2-deoxy-mannoside	NH_2	H	H	OH	λ	+70[b]	−417	580
11	3-amino-3-deoxy-alloside	H	OH	NH_2	H	λ	+849[b]	−510	550
12	3-methylamino-3-deoxy-glucoside	H	OH	H	NHMe	δ	−1363[c]	+285	610
13	3-dimethylamino-3-deoxy-glucoside	H	OH	H	NMe_2	δ	−1574[c]	+195	550

[a] Chelate conformation predicted from known conformation of ligand.
[b] Lit.[6]
[c] Lit.[8]

four compounds so that we might study the CD of their cuprammonium complexes. The (−) compounds (see Table 5) formed a complex with a λ chelate ring and the (+) compounds a δ chelate. Thus, the (−) compounds have the (1R, 2R) configuration and the (+) the (1S, 2S), in agreement with the suggestion of Kay and Robinson,[17] and their own more recent results.[18] Our findings are also in agreement with the assignment by Umezawa and his co-workers[7] of the (1R, 2R) and (1S, 2S) configurations to (−) and (+)*trans*-2-aminocyclohexanol, using the single wavelength method for studying copper complexes.

The second example is the determination of the absolute configuration of (+)-*trans*-cyclo-octane-1,2-diol, which in cuprammonium solution showed a positive CD band at 540 nm (θ = 100) showing the presence of a δ chelate. Such a chirality can be incorporated into a crown structure for the cyclooctane ring with the 1S, 2S diol stereochemistry. Since this diol is related to (−)-*trans*-cyclooctene[19,20] it confirms the R absolute configuration assigned to the latter compound through chemical correlation[20] and the use of ORD and CD techniques.[21]

Some preliminary measurements of the CD of cuprammonium solutions of acyclic diols and amino-alcohols have been made, but these will be discussed in a later paper.

In summary, the CD method outlined above provides a rapid method for structural studies of diols and amino-alcohols that is an improvement on the earlier single wavelength technique. The method is of course limited to those diols or amino-alcohols with C—O or C—N bonds at a projected dihedral angle in the ±60° range thus allowing chelate ring formation. Since the method does not involve isolation or knowledge of the properties of a 1:1 complex further discussion of the more detailed stereochemistry of these complexes will be deferred until studies with other diol-metal chelates have been completed. A supplementary CD method has recently been developed for these systems making use of the chiralities of the derived osmate esters[22] or thionocarbonates[23] and of the dibenzoate chromophore.[24]

TABLE 3. METHYL 4,6-O-BENZYLIDENE-α-D-ALTROPYRANOSIDES THAT GAVE NO OBSERVABLE CD BANDS (180° dihedral angle)

No.	Compound	System III R^1	R^2	R^3	R^4	$\Delta[M]^{\circ}_{Cupra}$
14	2,3-diol	OH	H	OH	H	−34[a]
15	2-amino-2-deoxy	NH_2	H	OH	H	−27[b]
16	3-amino-3-deoxy	OH	H	NH_2	H	−42[b]
17	3-methylamino-3-deoxy	OH	H	NHMe	H	+1[c]
18	3-dimethylamino-3-deoxy	OH	H	NMe_2	H	+21[c]

[a] Lit.[1]
[b] Lit.[6]
[c] Lit.[8]

TABLE 4. CD SPECTRA (LONG WAVELENGTH BAND) OF METHYL GLUCOPYRANOSIDES (compensating complexes)

No.	Compound	$\Delta[M]^{\circ}_{Cupra}$	$[\theta]$	λ_{max} (nm)
19	α-anomer	+244[a]	−29	580
20	β-anomer	+250[a]	−25	580

[a] Lit.[1]

TABLE 5. CD SPECTRA (LONG WAVELENGTH BAND) OF 2-AMINOCYCLOHEXANOL DERIVATIVES

Compound	$[\theta]$	λ_{max} (nm)	Chelate Conformation
(+) N-methyl	+247	550	δ
(−) N-methyl	−248	550	λ
(+) N,N-dimethyl	+76	580	δ
(−) N,N-dimethyl	−72	580	λ

EXPERIMENTAL

Methyl 2-amino-4,6-O-benzylidene-2-deoxy-α-D-mannopyranoside. This compd has previously been described as a glass.[6] In a prep for these studies it spontaneously crystallised and was recrystallised from water to give the product, m.p. 109–110°, $[\alpha]_D^{25}$ +40° (*C* 0·79, $CHCl_3$) (lit.[6] + 43°). (Found: C, 59·8; H, 6·9. Calc for $C_{14}H_{19}NO_5$: C, 59·8; H, 6·8%).

Circular dichroism measurements. Spectra were measured at 20–25° on a JASCO UV/ORD/5 instrument fitted with a CD attachment. Solutions were in Cupra A,[1] such that the diol or amino-alcohol to copper ratio was 1:1.

Acknowledgements—We thank the S.R.C. for financial support and for the award of a studentship to A.D.W. Gifts of compounds from Professor E. J. Corey and Drs. P. Garegg and P. Robinson are gratefully acknowledged.

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