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CIRCULAR DICHROISM—LXIX[1]

CORRELATION BETWEEN THE STEREOCHEMISTRY OF AMINO STEROIDS AND CHIROPTICAL PROPERTIES OF THEIR UNIDENTATE COPPER(II) SUCCINIMIDATE COMPLEXES

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Abstract—The complexes of formula [$\mathrm{CuSu_2Am^*_2}$] formed *in situ* from amino steroids ($\mathrm{Am^*}$) and a methylene chloride solution of the complex [$\mathrm{CuSu_2Pr_2}$] (Su: succinimidate; Pr: isopropyl amine) show in the range of the d–d bands two Cotton effects at approx. 700 (Band I) and 600 nm (Band II), whose signs are correlated with the preferred torsion angle of the $\mathrm{H_2N{-}Cu}$ moiety: a positive torsion angle leads to a positive CD-band I and to a negative CD-band II. These complexes form useful Cottonogenic derivatives of primary amino compounds.

Recently we[2] described some properties of square-planar neutral copper(II) complexes of general formula [$\mathrm{CuIm_2Am_2}$] (Im: imidate, e.g. Su: succinimidate, Pht: phthalimidate; Am: achiral amine, $\mathrm{Am^*}$: chiral amine) in non-aqueous solutions in which the amine acts as a unidentate ligand. In solution the imidate rings are coplanar with the ($\mathrm{CuN_4}$)-plane.[2] In the case of achiral amine ligands Cotton effects are induced within the copper d–d transitions leading to CD-bands at 730–680 nm (CD-band I) and 620–570 nm (CD-band II) of opposite signs. Their rotational strengths change somewhat with concentrations because of dissociation according to

$$[\mathrm{CuSu_2Am^*_2}] \rightleftharpoons [\mathrm{CuSu_2Am^*}] + \mathrm{Am^*}$$

(different solvations[3] are not considered here). $\Delta\epsilon$-values are therefore not suitable quantitative measures of the rotational strengths. The high kinetic lability of these complexes allows their *in situ* preparation by simply dissolving the respective optically active amine $\mathrm{Am^*}$ in a solution in methylene chloride of an optically inactive complex of the same type which is easily accessable, e.g. [$\mathrm{CuSu_2Pr_2}$] (Pr: isopropyl amine). These complexes are, therefore, very suitable Cottonogenic derivatives[4] of chiral amines obtainable in milligram scale and not necessitating the isolation of the reaction products, as e.g. in case of salicylidene derivatives.[5-7] Recently the use of lanthanide shift reagents has been proposed for a similar purpose;[8] in this case the induced Cotton effect at approx. 300 nm has to be utilized, i.e. in a wavelength range where the complex shows very intense absorption. An even more severe disadvantage is the fact that the sign of this Cotton effect depends on the ratio of concentrations of amine to metal in a not easily predictable way.

For the complexes [$\mathrm{CuSu_2Am^*_2}$] we similarly observed strong Cotton effects in this wavelengths region which were, however, not evaluated for the same reasons. On the contrary, the anisotropy parameter $g' = \Delta\epsilon/\epsilon$ is much more favourable in the visible region ($g' \approx 3 \times 10^{-3}$) where furthermore ligand-, charge transfer- and solvent-absorption bands are absent. We have observed that the signs of the CD-bands I and II do not depend at all on the conditions of the measurements, e.g. choice of solvent, concentration, ratio of [Cu]:[$\mathrm{Am^*}$], type of achiral imidate, etc. for a chiral amine $\mathrm{Am^*}$ of given absolute configuration, and can thus always be determined unequivocally.

Table 1 summarizes our results obtained for a series of amino steroids **1–9** (see also Fig. 1). Except for the 5α-amino compound **4** they all show the two CD-bands mentioned above of opposite signs. A rationalization of these sign patterns can be given in a pragmatic way by applying to these complexes the same principles which proved to be so useful for many other chromophores. According to this treatment[9] the whole molecule is devided into "spheres" commencing with the chromophore, which forms the first one. The second sphere is composed of the ring, into which the chromophore is incorporated, the third sphere consists of rings or substituents connected with the second sphere, etc. If the chromophore is not part of a ring the torsion angle around the bond connecting the chromophore with the next atom is an equivalent for the second sphere.[11,12] That chiral sphere which is nearest to the chromophore determines then in general the signs of the Cotton effects. For the d–d transitions in a complex [$\mathrm{CuSu_2Am^*_2}$] the chromophore consists of the electrons around the copper atom, i.e. of the moiety ($\mathrm{CuN_4}$) and the π-system of the imidate parts (Fig. 2). As second sphere functions the torsion angle around the Cu–N bond between the copper and the amine nitrogen. Only when these two spheres are achiral do we have to resort to Ruch's theorem[13] on the general form of the chirality functions

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Table 1. CD-bands in the visible region of the [CuSu$_2$Am$^*_2$] complexes prepared "*in situ*"

Amino steroid	[Am*]: [Cu] molar ratio	CD-band I		CD-band II		$(\omega)^a$
		λ_{max}	$\Delta\varepsilon$	λ_{max}	$\Delta\varepsilon$	
1	1.2	697	−0.10	577	+0.165	−60°
2	2.0	706	+0.450	615	−0.700	+60°
3	2.0	705	+0.360	615	−0.570	+60°
5	1.1	703	+0.120	580	−0.175	+60°
6	1.6	694	+0.109	577	−0.146	+60°
7	0.55	678	+0.175	539	−0.510	+60°
8	2.0	710	+0.410	605	−0.540	+60°
9	2.0	675	+0.031	550	−0.030	+60° & −60°
10	2.0	705	−0.150	606	+0.550	−60°
11	2.0	670	−0.225	590	+0.450	−60°

a) approximate torsion angle of most preferred conformation of the H_2N–Cu moiety, according to Fig. 3

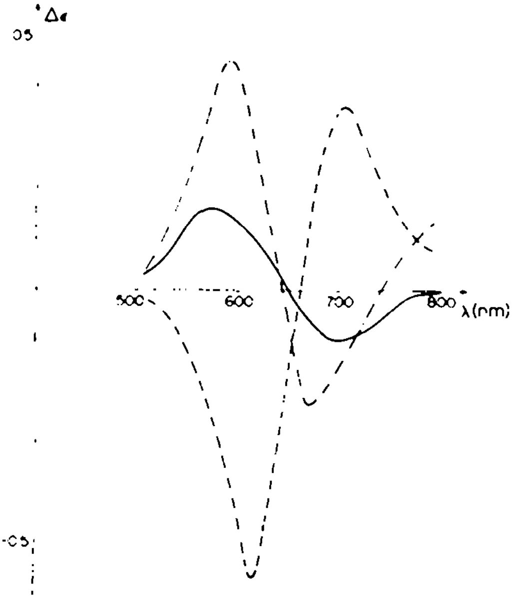


Fig. 1. CD-curves of the *in situ* complexes between [CuSu$_2$Pr$_2$] and steroid amines **1** (——), **3** (– – – –), and **11** (-·-·-·-).

in order to learn whether a sector rule may be applicable for third-sphere contributions, or not. Our treatment of the chiroptical properties of these complexes [CuSu$_2$Am$^*_2$] differs thus somewhat from that of Wellman *et al.*[14] of square-planar bidentate copper/amino acid complexes.

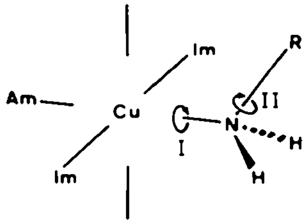
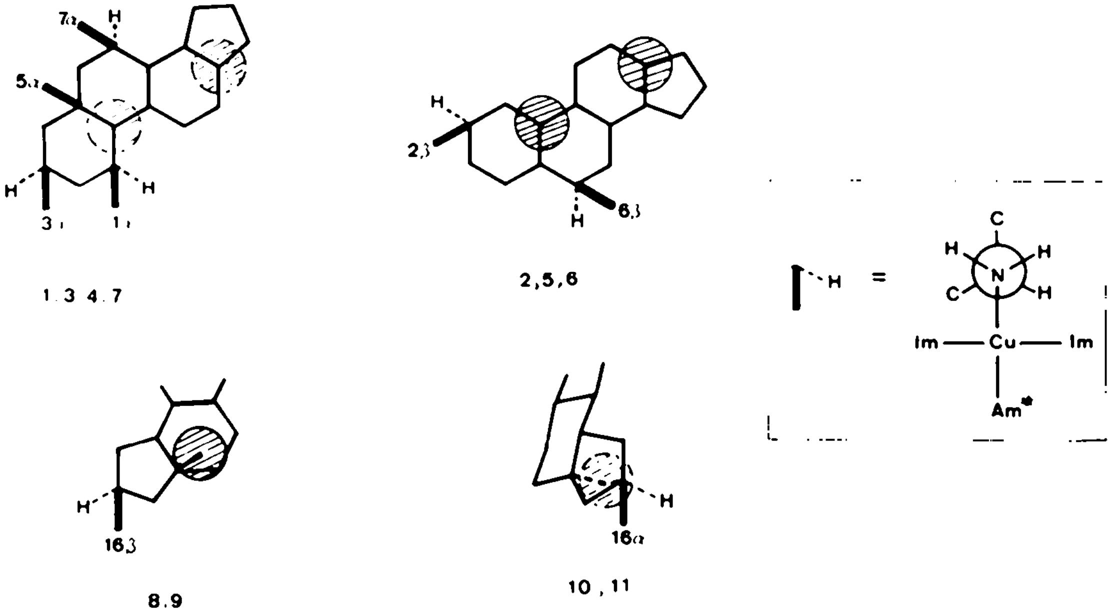


Fig. 2. Perspective schematic drawing of a complex [CuIM$_2$·Am$_2$]. The alkyl rest R sticks out from the (CuN$_4$)-plane and is periplanar to the two axial positions around the Cu. The chromophore consists of the electrons around the Cu-atom and the π-electrons of the imidate moieties Im. A twist around the Cu–N bond to the amine part (I) is a measure of the chirality of the second sphere, a torsion around the N–C$_\alpha$-bond (II) will determine the distribution of the other atoms over different octants (third-sphere chirality).

From molecular models it is obvious that the N–C$_\alpha$ bond of the amine ligand tends to protrude from the (CuN$_4$)-plane as much as possible regardless what be the torsion angle around the Cu–N bond to the imidate moieties. The N–C$_\alpha$ bond is in such a conformation periplanar to the axial positions (Fig. 2). Neglecting for the moment the ligand chirality, the symmetry of the skeleton of the complexes, including this N–C$_\alpha$-bond (at least on time average), is thus C_2, if the two alkyl substituents bound to the amine nitrogens point to the same side of this plane, or C_{2h} if they are on opposite sides. In both cases we are dealing with achiral first spheres. Regardless of whether the two alkyl substituents are on the same or on opposite sides of this

(CuN_4) plane, for each chiral half of the complex the same correlation between the Cotton effect and the stereochemistry must hold.[2] The question of additivity of the contributions of these two halves was discussed in detail in Ref. 2b; as long as we are interested only in the signs of the Cotton effects we can neglect vicinal effects (in a general sense).

The preferred torsion angles around the N–C_α bond of the amine ligands can also be estimated from molecular models. The situation is similar to that of salicylidene derivatives of amino steroids, where we were able to correlate the sign of the CD-bands with this torsion angle around the same N–C_α bond,[7] for nitro steroids,[11] where an analogous correlation holds, or for nitryloxy steroids,[12] in which case we had, however, at hand mainly esters of equatorially arranged hydroxy compounds. Treating the Cu–N bond like any other σ-bond the preferred conformation of the H_2NCu moiety will be staggered with respect to the respective ring atoms of the steroid skeleton. Figure 3 summarizes schematically



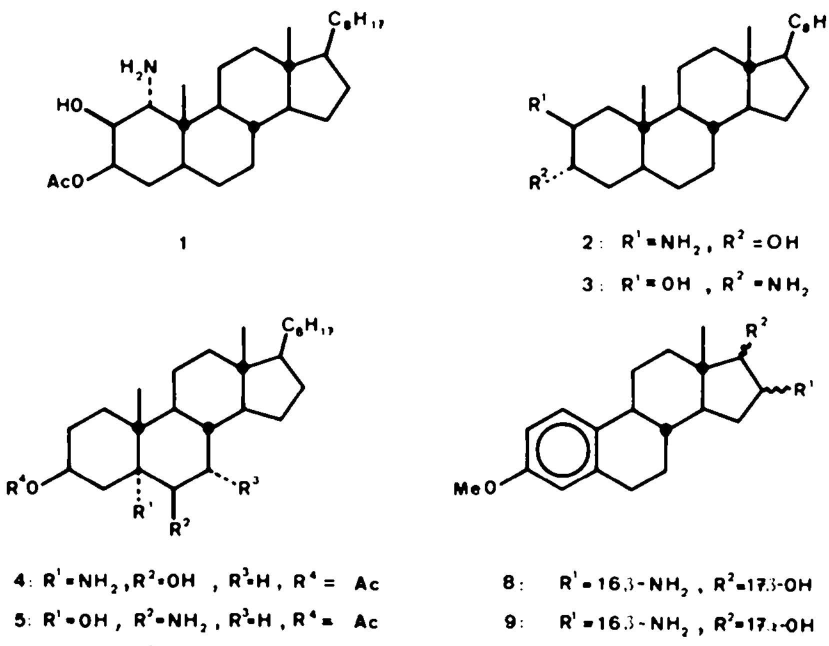
1 3 4 7

2,5,6

8,9

10, 11

Fig. 3. Schematic projections of $[CuSu_2Am^*_2]$ complexes along the N-R bond (see Fig. 2). The thick bar represents the N–Cu-bond (*cf.* insertion on the right), the hatched circles the angular methyl groups. Only hydrogens geminal to the nitrogen atoms are indicted, the stereochemistry of the complexing NH_2-group is indicated in these schematic formulae in the usual way.



1

2: $R^1 = NH_2$, $R^2 = OH$

3: $R^1 = OH$, $R^2 = NH_2$

4: $R^1 = NH_2$, $R^2 = OH$, $R^3 = H$, $R^4 = Ac$

5: $R^1 = OH$, $R^2 = NH_2$, $R^3 = H$, $R^4 = Ac$

6: $R^1 = H$, $R^2 = NH_2$, $R^3 = OH$, $R^4 = Ac$

7: $R^1 = H$, $R^2 = OH$, $R^3 = NH_2$, $R^4 = H$

8: $R^1 = 16\beta\text{-}NH_2$, $R^2 = 17\beta\text{-}OH$

9: $R^1 = 16\beta\text{-}NH_2$, $R^2 = 17\alpha\text{-}OH$

10: $R^1 = 16\alpha\text{-}NH_2$, $R^2 = 17\beta\text{-}OH$

11: $R^1 = 16\alpha\text{-}NH_2$, $R^2 = 17\alpha\text{-}OH$

Fig. 4.

these preferred conformations as deduced from models. For this estimation we consider that conformation impossible for which the N–Cu-bond points "into" the ring; of the two others remaining because of the interaction with the two imidate moieties this one seems to be energetically favoured where the second and third rings are most distant from the copper. For the amino steroids containing a geminal hydrogen to the NH_2 group we use the same notation for these conformations as in similar earlier cases,[7,11] and this is also given in Table 1.

There exists a good correlation between the sign of this torsion angle and the signs of the CD-bands I and II for the complexes of amino steroids with a geminal hydrogen atom: a positive torsion angle leads to a positive CD-band I and a negative CD-band II, and *vice versa*. Interestingly enough this correlation is the same as for the salicylidene derivatives of the same amines[7] though the conformational analysis is somewhat different there. This "torsion-angle-rule" is actually in this case identical with an octant rule as required by the D_{2h}-symmetry of the chromophore.

Some compounds deserve special consideration. **4** did not show measurable Cotton effects, and two reasons may be offered for this; firstly the 5-amino group is sterically severely hindered, which will impede complex formation, secondly the second and third spheres are achiral for this molecule, as can be inferred from Fig. 3. Compound **9** gives only very small rotational strengths and we ascribe this to the fact that besides the sterically favoured (+60°)-conformer, the (−60°)-conformer is also present, because there can exist an internal hydrogen bond to one of the imidate moieties, thus leading to a great deal of compensation for the CD. Compound **11** gives three distinct CD-bands, and the additional one may be attributed to the presence of another type of complex where the 17α-OH cis to the 16α-NH_2 (but this time not hindered by a nearby methyl as in case of **8**) participates in complex formation, e.g. either by ligating in an axial position with the copper, or by forming a hydrogen bond to the H_2N group or one of the carbonyls of the neighbouring imidate moieties. With the exception of the amine **4**, which failed to give induced CD-bands, for all other amino steroids investigated this correlation between the sign of the CD-bands and the preferred conformation of the complexed amino group holds thus nicely. We recommend, therefore, this simple new chiroptical method for the determination of the stereochemistry of primary amino groups in amino steroids.

EXPERIMENTAL

All CD-spectra were recorded at room temperature in cells of path lengths of 0.5–2.0 cm with the Dichrograph III (Jobin-Yvon). Formal Δε-values were calculated on the basis of the copper concentration and not considering dissociation. Measurements were done on *in situ* preparations of the complexes obtained in the following way: 3–10 mg of amino steroid were added to 2.5–8 cm³ of a 0.005 M solution of $[CuSu_2Pr_2]$ in methylene chloride. This complex was prepared according to the original procedure;[14] the solvent was previously dried over molecular sieve 4 Å (Riedel de Haen) and distilled. The synthesis of the amino steroids is described in Ref. 17.

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