Absolute configuration of *in situ* transition metal complexes of ligating natural products from circular dichroism

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Abstract - Cottonogenic in situ derivatives of potential ligands with different transition metal complexes containing 2 or 3 metal atoms have been used for the purpose of 1) obtaining CD-bands from non-absorbing compounds, and 2) to force flexible molecules into one preferred conformation. Natural products whose stereochemistry can be investigated in this way are e.g. acids, glycols, amines, aminoalcohols, diamines, peptides and nucleoside derivatives. From the Cotton effects the absolute conformations or even absolute configurations can be obtained with the help of empirical rules.

Several transition metal complexes can in situ exchange their (achiral) ligands against chiral ones and give then rise to Circular Dichroism within the d-d - bands. This method has frequently been used in the past especially for the investigation of the stereochemistry of such molecules which contain no easily accessible chromophore, as e.g. diols, acids, amino alcohols, etc. (Ref. 1). We have recently found, that $[Mo_2(O_2CCH_3)_4]$ $(\overline{1})$, its Rh-analogue 2, and $[Ru_2(O_2CC_3H_7)_4]$ Cl (3) can also be used for that purpose (Refs. 2-5), and some of our results are summarized in a recent review (Ref. 6).

We are, however, interested in such complexes also from a more fundamental point of view: in general any chiroptical method can only give **either** the absolute configuration **or** the conformation of a molecule, but not both at the same time. A correlation between these two needs an additional information, which only in very rare cases comes also from CD-measurements. Mainly one will use NMR, IR, or X-ray diffraction data for this purpose, or simple conformational analysis. We can with other words express this fact by stating that chiroptical data give solely the **absolute conformation** of a molecule. If a flexible molecule is now bond to a metal cluster then its conformational freedom is very much restricted, or it is even completely fixed, and by this the determination of the absolute configuration should then become possible from the chiroptical data alone. Some applications to natural products and their derivatives are reviewed in the following.

A. COMPLEXES CONTAINING TWO METAL ATOMS

GENERAL CONSIDERATIONS

There is ample evidence available from X-ray diffraction data (Ref. 7) that complexes like 1, 2, or 3 have practically ideal D_{4h}-symmetry (Fig. 1) and even in case of chiral acylate ligands only a very small twist is introduced along the metal-metal bond (Ref. 8). These two metal atoms are connected by a quadruple bond in case of 1, a single bond for the rhodium analogue, and formally by a "two-and-half" bond in the mixed-valence compound 3. These complexes are completely stable in the crystalline state, and even in solution they are not quickly decomposed by oxygen or water. 1 and 3 are kinetically quite labile and exchange, therefore, in solution their

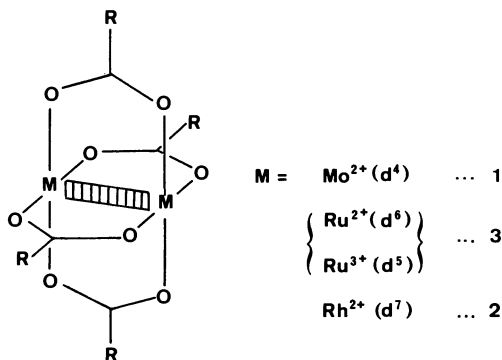M = $Mo^{2+}(d^4)$ ⋯ 1

$\left\{ \begin{array}{c} Ru^{2+}(d^6) \\ Ru^{3+}(d^5) \end{array} \right\}$ ⋯ 3

$Rh^{2+}(d^7)$ ⋯ 2

Fig. 1 Geometry and d-electrons involved for complexes 1, 2, and 3.

ligands very quickly, whereas with **2** heating for several hours is necessary. If an optically active acid is present in solution such a ligand exchange leads then to a chiral complex and several Cotton effects can be observed within the metal cluster absorptions. Such an <u>in-situ</u> generation of optically active complexes has the advantage that one must not isolate and purify these deriva- tives, on the other hand one does not know their concentrations nor their structure(s); since by successive ligand exchange 5 chiral species can in principal be envisaged the actual CD-curve depends, of course, on the conditions of the measurement. If these are kept constant one gets, however, reproducible results, and for the determination of the absolute stereochemistry anyway only the signs and not the magnitudes of the Cotton effects have to be known. For that reason "ficticious" $\Delta\varepsilon$'-values have to be given instead of the usual $\Delta\varepsilon$-values, which we calculate on the basis of the concentration of the ligand.
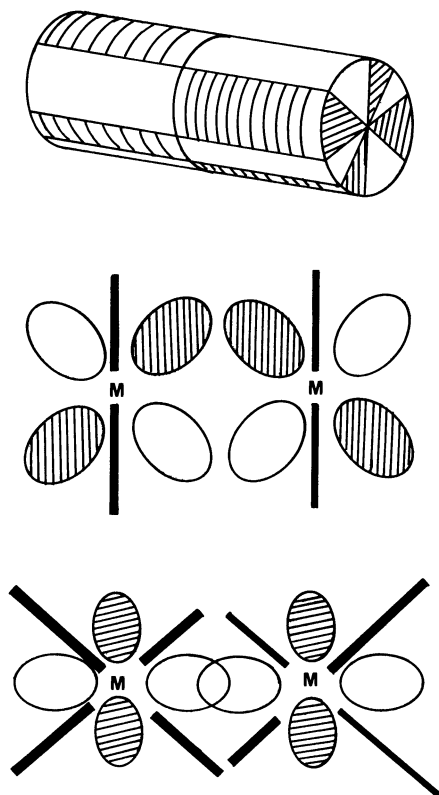

Fig. 2. Nodal planes in sector rules for complexes of **1**, **2**, and **3** with chiral acylate ligands. TOP: Symmetry-determined hexadecant rule. Contributions to Cotton effects of atoms positioned in differently marked sectors have opposite signs. MIDDLE: Additional MO-determined nodal planes, when π - or π*-MOs are involved in a transition. BOTTOM: Additional MO-determined nodal planes, when σ - or σ*-MOs are involved.

As the skeleton of such complexes remains practically achiral the signs of the individual Cotton effects will be determined by sector rules, and the simplest one can be built up from the mirror planes of the molecule (Ref. 9). 5 are present for a complex of this type and a hexadecant rule is thus obtained (Fig. 2). If, however, in a given transition such MOs are involved which contain additional nodal surfaces, then these also have to be taken into account (Ref. 10), leading by this to more complex sector rules (<u>cf.</u> Fig. 2). For stereochemical correlations one should rather concentrate on such Cotton effects, which follow the hexadecant rule, because otherwise too many contributions of opposite signs had to be taken into account. From experience we know that (at least for complex **1**) the Cotton effects between 420 to 280 nm can in general very well be correlated with the absolute configuration, whereas those at longer wavelengths depend also on the individual structure of the acid.

The best solvent for the molybdenum complex **1** is dimethyl sulfoxide, whereas **2** and **3** dissolve also easily in acetonitril or ethanol. For more polar compounds as <u>e.g.</u> nucleosides or nucleotides we had also sometimes to use dimethyl sulfoxide (without or with a few percent of water). In those cases where complex formation needs either heating or addition of base, one must, of course, make sure by control experiments that under these conditions no change of the potential ligand itself is caused by such a procedure.

ACIDS

In presence of optically active acids complex **1** develops at least 5 Cotton effects. The most characteristic ones are those two between 400 and 300 nm, which have opposite signs (Refs. 2, 6). Assuming similar preferred conformations for the acids in these complexes as have been found (for their dimers) in many crystals we have tentatively put in signs into these sectors (Ref. 6): groups positioned in hatched sectors of Fig. 2 should contribute positively to the 400 and negatively to the 300 nm Cotton effect. A comparison of the crystal structure conformations of the leucine (Ref. 11) and the mandelic acid complex (Ref. 8) has revealed, however, that the contributing substituents (at least in the crystal) lie in sectors of opposite signs, but nevertheless the Cotton effects have the same signs for compounds from the same steric series (Ref. 2). The pragmatic rule holds, however, for all investigated α-amino acids (even including proline, **4**), that the in-situ complexes of **1** with amino acids from the L-series have a negative 400 nm and a positive 300 nm Cotton effect (Ref. 6). Fig. 3 shows one more example (norleucine, **5**), and together with it the CD-curves of two dipeptides **6** and **7** in presence of **1**. The rule just mentioned for the amino acids can also successfully be applied to these dipeptides, if one assumes that the most preferred conformation is the one where the longest chain is in an antiperiplanar arrangement; the position of the group sticking out from this plane determines then the signs of the two most characteristic Cotton effects around 400 and 300 nm.
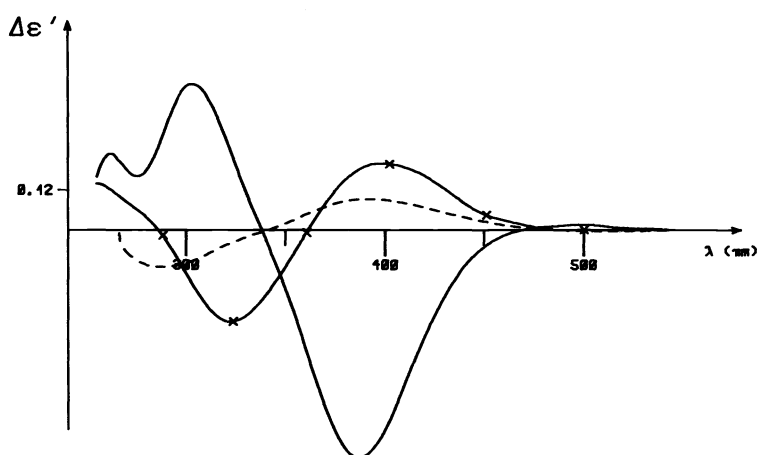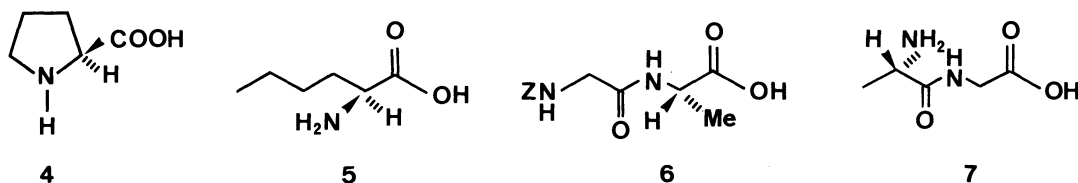

Fig. 3. CD of **5** (————), **6** (- - - - - - -), and **7** (—X—X—) in presence of **1** in DMSO-solution.

4   **5**   **6**   **7**

The rhodium complex **2** is not so suitable for the determination of the stereochemistry of acids since ligand exchange is very slow and needs several hours of heating. On the other hand **3** is also kinetically labile and the Cotton effects developed are in general even larger than those with **1** (Ref. 6). No systematic studies have, however, as yet been done with **2** and **3**.

DIOLS

1 reacts also immediately with chiral 1,2- and 1,3-glycols with formation of optically active in-situ complexes (Refs. 2, 6, 12). Hitherto we have no proof whether the glycol ligates here in a "parallel" or "perpendicular" mode (Fig. 4), in any of these two cases the distance between the oxygen atoms is, however, such that a 1,2-glycol can span it only in a conformation with a torsional angle of approximately 60°. Besides some other minor Cotton effects two larger ones can be observed around 400 and 300 nm, which in general have the same signs, and in between a third Cotton effect of opposite sign can sometimes very distinctly be detected. The investigation of many such examples with rigid structure has shown (Ref. 12), that the sign of the torsional angle O-C-C-O is always the same as that of the 300 nm CD-band (Fig. 4), and it does not matter whether both OH-groups are equatorial (as e.g. in 2α,3β-cholestanediol) or one is axial

(e.g. 2β,3β-cholestanediol, Ref. 6). In the pyranoside series it is furthermore characteristic that the 350 nm Cotton effect shows up only then very pronouncedly when there is no axial RO-group next to this glycol moiety (cf. Fig. 5, glycol 8). This rule holds, however, only for sec,sec-glycols; sec,tert-glycols like 9 may show completely different Cotton effects (Fig. 5).
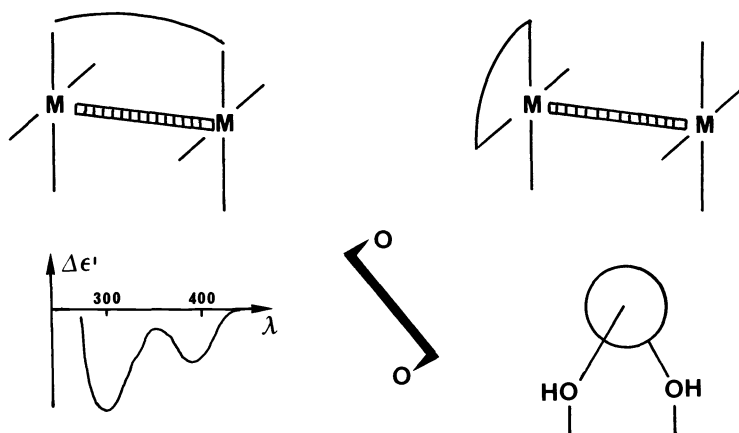

Fig. 4. Helicity rule for glycols. TOP: The two most probable geometries for bidentate ligation of a 1,2-glycol onto 1. BOTTOM: General appearance of CD between 400 and 300 nm for a negative torsional angle O-C-C-O (magnitude appr. -60°, as sketched out.)
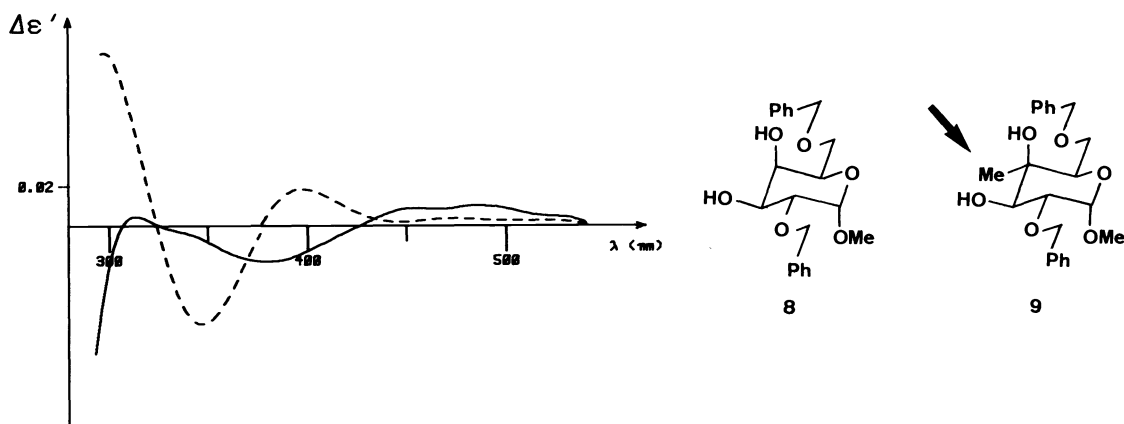
Fig. 5. CD of the sec,sec-glycol 8 (- - - - - - -) and of analogous sec,tert-glycol 9 (————————) in presence of 1 in DMSO-solution.

This same rule could be extended to open-chain vic-glycols (Ref. 4) and here one gets the correct CD-signs if one forces the glycol into such a conformation that each O-C-C-R moiety of a sec,sec-glycol like e.g. 10 adopts an antiperiplanar conformation (Fig. 6). This seems indeed very reasonable because only in such a conformation the bigger group R avoids steric interaction with the still present acetate ligands. Even for a prim,sec-glycol like propane-1,2-diol (11) one gets the correct sign for the 300 nm Cotton effect by this same rule (Fig. 7), in such a case the 400 nm Cotton effect is, however, barely observable.
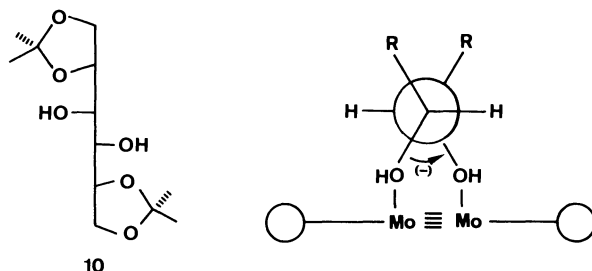
Fig. 6. Preferred conformation of an aliphatic 1,2-diol (as e.g. 10) when complexed onto 1 (only "parallel" bidentate ligation indicated).

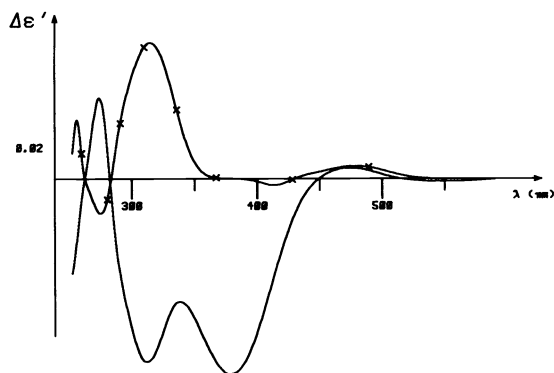Fig. 7. CD of aliphatic 1,2-diols **10** (————)
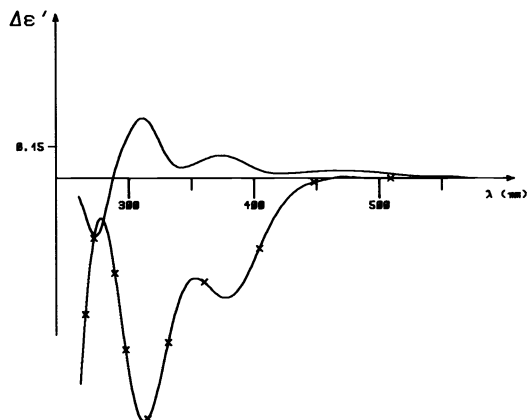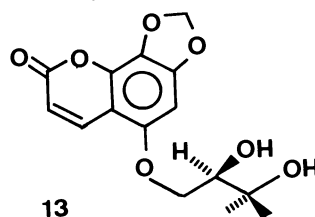and **11** (—X——X—) in presence of **1** in DMSO-
solution.
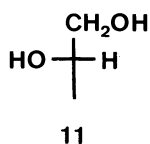

Fig. 8. CD of chimyl alcohol (**12**, ————)
and the coumarin **13** (—X——X—) in presence
of **1** in DMSO-solution.

11

12

13
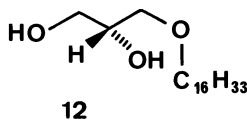
We have also applied this same rule to lipids with 1-monosubstituted glycerol structure (**12**, Ref.
4, Fig. 8). Large Cotton effects of the same type are also obtained, if both hydrogens of the
HOCH$_2$ group are substituted by methyl groups; the absolute configuration of the coumarin de-
rivative **13** could be determined in this way with appr. 1 mg of substance. It is also worthwhile
to note that the absolute configuration of chimyl alcohol (**12**) can in this way unequivocally be
obtained with not more than 0.2 mg.

(R,R) ... **14**

(S,S) ... **15**
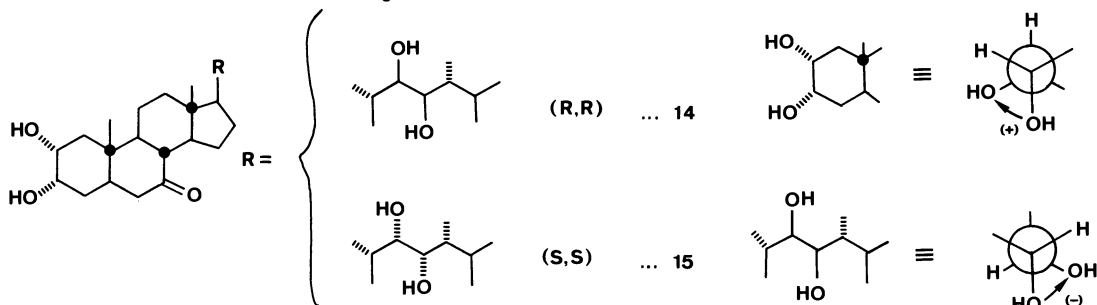
Even if two not interfering glycol groups are present in the same molecule this method can be
applied successfully: Anastasia and coll. (Ref. 14) have prepared the diastereomeric ketotetrols
14 and **15** and determined the stereochemistry in the sidechain by conventional procedures. In the
in-situ complexes with **1** the torsional angle of the glycol moiety on ring A is always positive,
whereas it should be negative in the (R,R)-stereomer **14**, but positive for its (S,S)-isomer **15**. In
the sum-curve of the two CD-spectra the contributions from the sidechain complex should thus
cancel each other, whereas in the difference spectrum **14** - **15** twice the Cotton effects of the
(R,R)-stereoisomer should remain. This is indeed the case (Fig. 9), and even the 7-keto group
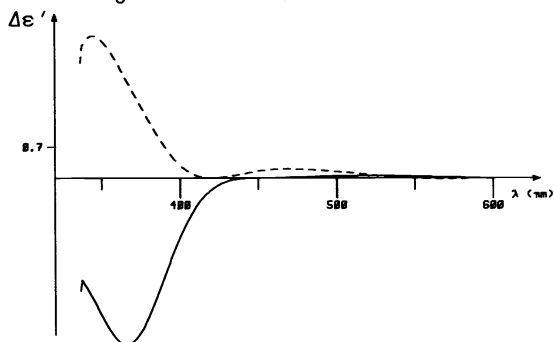does not give difficulties.

Fig. 9. Sum (**14** + **15**, - - - - - - -) and difference
(**14** - **15**, ————) of CD-curves of steroidal
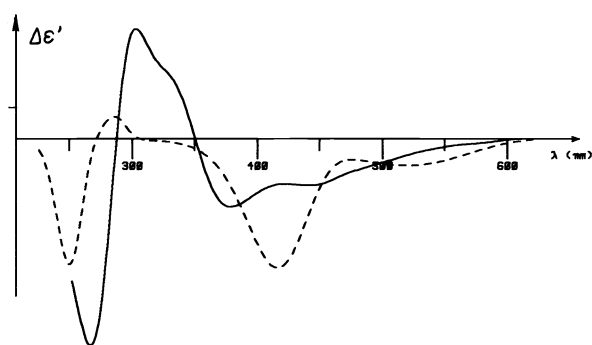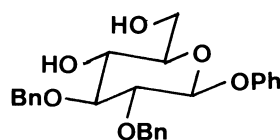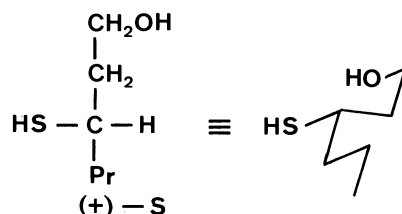bis-glycols in presence of **1** in DMSO-solution.

Fig. 10. CD of the pyranoside 1,3-glycol **16** (--------)
and of the monothio-1,3- glycol **17** in presence of **1** in
DMSO-solution. Curve for **16** enlarged by a factor of 4.

Pyranoside derivatives with free hydroxygroups at C-4 and C-6 give also several Cotton effects in the presence of **1**, but the shape of the CD-curve differs appreciably from that of the vic-glycols (**16**, Ref. 12, Fig. 10). The (S)-monothioglycol **17** could complex in a similar fashion with **1** (Fig. 10), and although the presence of an HS-group will definitely influence the electronic transitions, for the same absolute conformation (cf. Ref. 15) yet an overall similar shape of the CD-curves was observed (Fig. 10).

Hitherto we have not yet found conditions under which **2** gives such optically active in-situ complexes with glycols; **3** reacts, but only after several hours of heating.

AMINES, AMINO ALCOHOLS AND DIAMINES

Whereas monoalcohols and most monoamines (exception: phenylethylamine, Ref. 2) do not give optically active in-situ complexes with **1**, vic-amino alcohols do so (Refs. 3, 6). Fig. 11 shows two examples (**18, 19**), and in these cases the 300 nm Cotton effect is followed by a stronger one of opposite sign around 260 nm, which fact might be the reason that this first, otherwise more characteristic CD-band is quite small in such spectra. The 400 nm Cotton effect has in these cases opposite sign to that at 300 nm, and the Cotton effect in between is much more pronounced than for most glycols, but also of opposite sign to that of the 300 nm CD. If the same steric restriction holds as for the prim,sec-diols then the sign of the 300 nm Cotton effect is again the same as the sign of the torsional angle O-C-C-N. Corresponding diamines give in presence of **1** CD-curves similar to those of the complexes with amino alcohols of same absolute configuration (cf. **20**, Fig. 11, Ref. 16). Some heavily substituted ephedrine derivatives (**21-23**), which did not react with the often used CUPRA-reagent (Ref. 17) gave small but well interpretable CD-curves with complex **1** (Ref. 3).
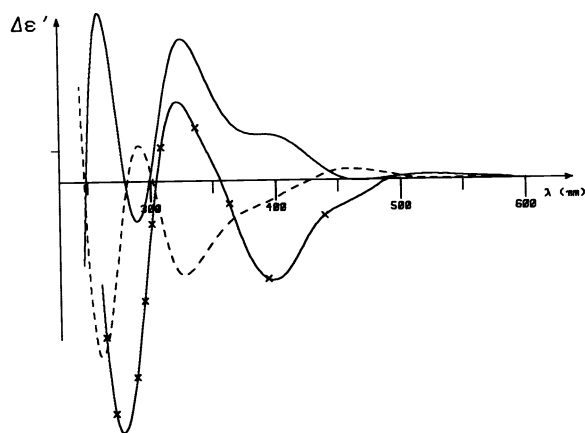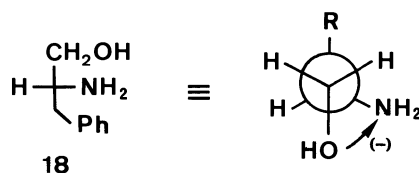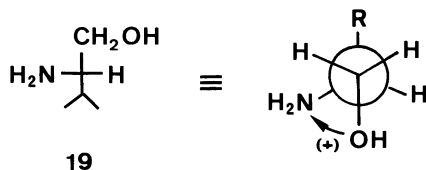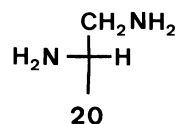

Fig. 11. CD of the 1,2-aminols **18** (————) and
19 (--------), and of the 1,2-diamine **20** (—X—X—)
in presence of **1** in DMSO-solution.

Contrary to **1** the analogous complexes **2** and **3** react immediately with many optically active monoamines and develop several Cotton effects (Ref. 6). Since these latter two complexes usually crystallize with additional ligands or solvent molecules in the axial positions of the metal cluster (Ref. 7) it seems very probable that monoamines complex in solution in the same way. This would also explain why **2**, which does not exchange its ligands against other acylates at room temperature, reacts immediately with amino acids in presence of a base (but not anymore as the Zwitter-ion!) under formation of optically active complexes; **2** does also not give Cotton effects in presence of the salts of optically active amines. Such "axial" complexation can furthermore easily explain the difference in behaviour of amino acids towards **1** and **2**: L-proline (**4**) gives a completely different CD-spectrum to that of all the other amino acids in presence of **2** (Fig. 12). If our assumption is correct then prolonged heating of such a solution should result in the formation of another optically active complex (ligation through the carboxylate moiety). Fig. 13 shows that this is indeed the case: after 16 hours of reflux two large Cotton effects below 420 nm are developed e.g. for L-alanine (**24**), which are not observable in the CD-spectrum obtained immediately after dissolving the amino acid in the stock solution of **2**.
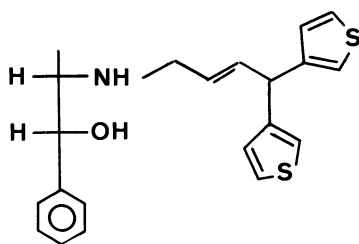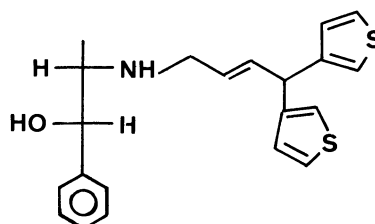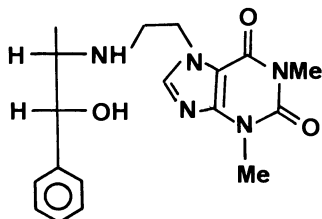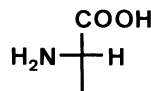

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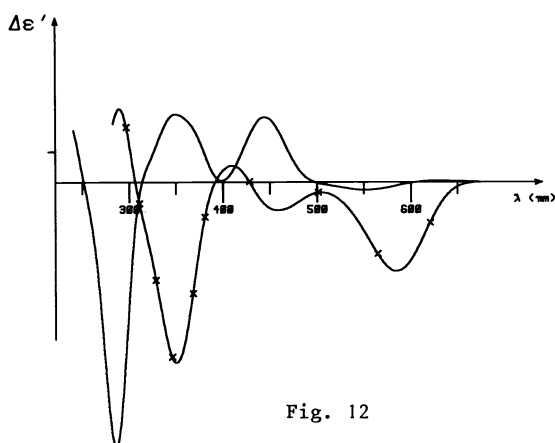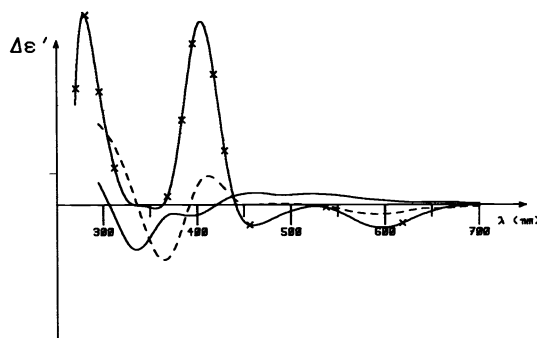

22

23

24

Fig. 12

Fig. 13

Fig. 12. CD of L-Pro (**4**, ————) and L-Phe (—X—X—) in presence of **2** in aqueous ethanol-solution.

Fig. 13. CD of L-Ala (**24**) in 88% aqueous ethanol + KOH in presence of **2** immediately after preparation of the solution (————), after 24 hours standing at room temperature (--------), and after 16 hours reflux, but without addition of KOH (—X—X—). The third curve is reduced by a factor of 2.4.
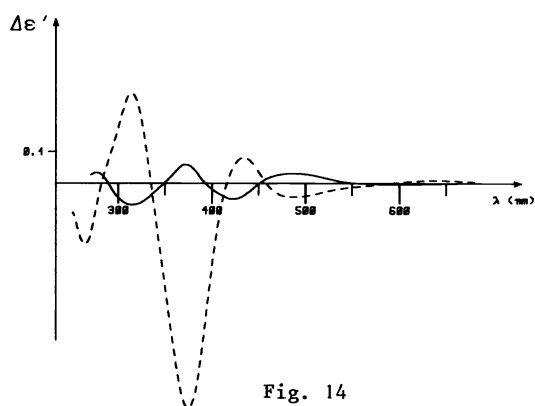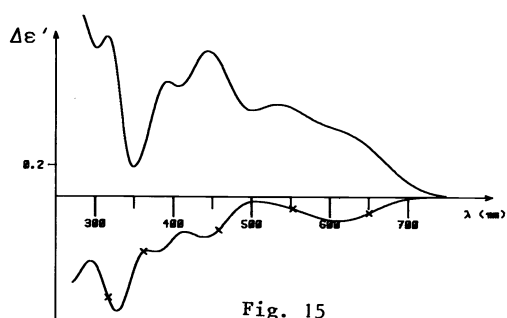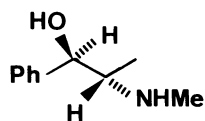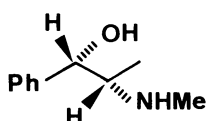
Fig. 14

Fig. 15

Fig. 14. CD of (-)-ephedrine (**25**, ————————) and (+)-pseudo-ephedrine (**26**,------)
in presence of **2** in ethanol-solution.

Fig. 15. CD of (-)-ephedrine (**25**, —X—X—) and (+)-pseudo-ephedrine (**26**,
————————) in presence of **3** in ethanol-solution.

25

26

With this in mind it is difficult to say whether 1,2-amino alcohols give (axial) unidentate or
bidentate complexes with **2** or **3**; experimentally we see great differences between a threo- and
its corresponding erythro-stereoisomer with identical configuration at the centre of chirality
connected to the nitrogen. Thus the signs of the individual Cotton effects of (-)-ephedrine (**25**)
and (+)-pseudo-ephedrine (**26**) are opposite with both complex **2** (Fig. 14) or complex **3** (Fig.
15), and in the first case some CD-bands differ also appreciably in magnitude. This enantiomorphic
behaviour of the CD-curves resembles that of the complexes of 1,2-diols with **1**, but does not
necessarily exclude axial unidentation. Exchange of the N-methyl-group for another, much larger
substituent (**21 - 23**) changes somewhat the Cotton effects at longer wavelengths and reduces the
magnitudes of the individual CD-bands, does, however, not change the signs of the Cotton effects
below 420 nm (Ref. 18, Fig. 16 for complexes with **2**). For these compounds the complexes **2**
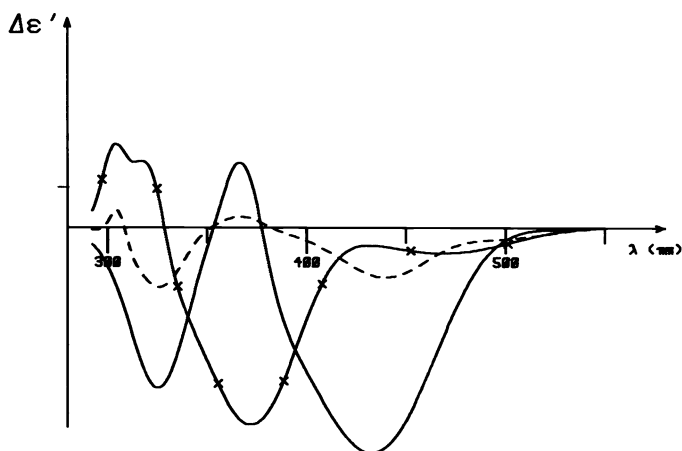and **3** are much more suitable than is **1**.

Fig. 16. CD of L-erythro-Tinofedrine (**21**, ————————), D-threo-Tinofedrine (**22**,
—X—X—), and Cafedrine (**23**, --------) in presence of **2** in ethanol-solution (+
water for **23**). The third curve is enlarged by a factor of 2.

NUCLEOSIDES

As expected on the basis of the aforementioned results, nucleosides give optically active <u>in-situ</u> complexes with **1** only if they contain ribose with its 1,2-glycol moiety (Ref. 6). The only <u>excep-</u> tion to this are phosphates and their esters, but they also may complex axially, in a similar way as we have found for simple optically active esters of phosphoric acid (Ref. 5). Fig. 17 shows
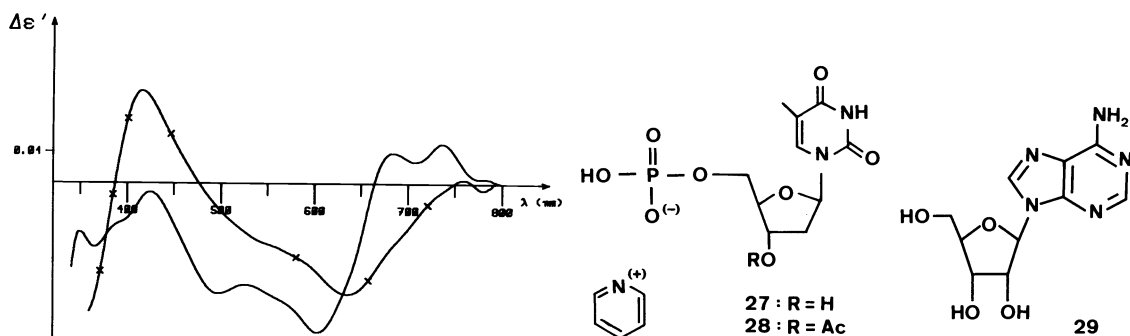

Fig. 17. CD of the nucleotide **27** (————) and its acetate **28** (—✕——✕—) in presence of **1** in DMSO-solution.

27 : R = H
28 : R = Ac
29

the Cotton effects obtained with deoxythymidine phosphate (pyridinium salt, **27**) and of its O-ace- tate **28**. With such very small effects and relatively large noise baseline shifts are not always avoidable, and thus <u>e.g.</u> a positive maximum in one curve may correspond to a negative minimum in the other. In these cases it is advisable to compare also the first derivatives of the CD-curves (cf. Fig. 18). Inspection and comparison of both types of curves helps appreciably to find common features.

On the contrary, **2** and **3** react also with deoxyribosides, but even here heating and/or addition of 2 to 3 equivalents of KOH is necessary to produce Cotton effects. We are well aware of the danger that under these conditions (especially when for solubility reasons dimethylsulfoxide has to be used as the solvent) chemical changes of the nucleoside may be possible, on the other hand in general we got reproducible results even when working under somewhat different conditions. Fig. 19 shows the changes obtained in the CD-spectrum of adenosine (**29**) in presence of **2** and KOH before and after heating. The shapes of the finally recorded CD-spectra were practically indepen- dent on the way how these solutions were prepared.

The CD-curves of such <u>in-situ</u> complexes with nucleosides and nucleotides depend very much on the type of the base <u>present</u>, so that applications of these complexes also in the analysis of their derivatives seem possible.
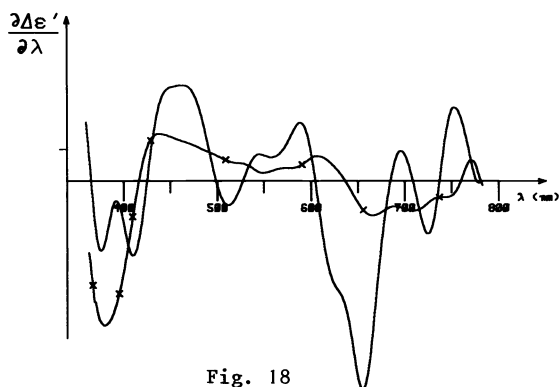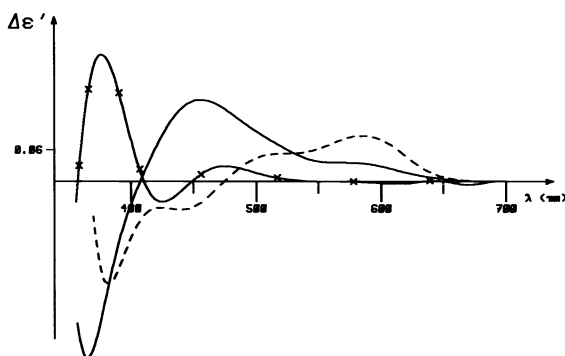

Fig. 18

Fig. 19

Fig. 18. First derivatives of the CD-curves of **27** (————) and **28** (—✕——✕—) of Fig. 17.

Fig. 19. CD of adenosine (**29**) in presence of **2** and KOH in DMSO-solution: immediately after preparation of the solution (————), adenosine-solution kept 1 hour at 60°C and then **2** added (--------), and final CD-curve developed after additional 1.5 hours standing at 60°C (—✕——✕—).

B. COMPLEXES CONTAINING THREE METAL ATOMS

In the foregoing chapters it was shown that even very similar transition metal complexes are of different usefulness for the purpose of determining the absolute stereochemistry of diverse liga-ting molecules from CD. We are, therefore, testing also other ones than those described above, and quite recently we have found (Ref. 19) that complexes of such a type as given in Fig. 20 (cf. e.g. Ref. 20), which contain three metal atoms tied together by a central oxygen and several acylate rests (octahedral arrangement around each metal atom) can also serve to generate Cotton effects in presence of chiral ligands. From general considerations follows (Refs. 9, 10) that the simplest symmetry-determined sector rule should consist for these complexes of 12 sectors. A more systematic study is in progress, and a few examples are given here for illustration. The achiral complexes used hitherto were three, in which the metal is iron, differing only in the ligand L (Fig. 20, L = water or pyridine), and one with ruthenium. Here again we found different complexing behaviour against diverse uni- or (potentially) bidentate ligands.
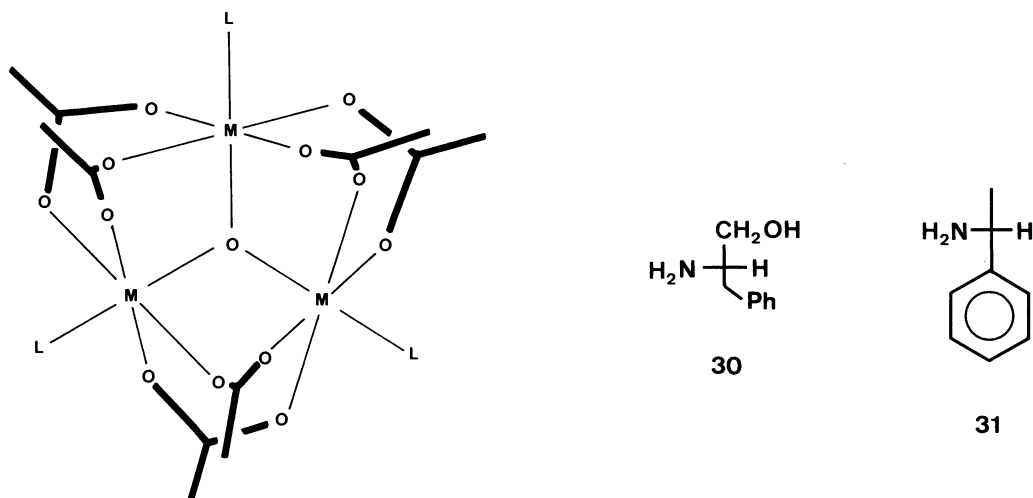

Fig. 20. Trinuclear complexes used for the generation of Cotton effects of chiral acids, amines, glycols, etc. M may be Fe or Ru, L is water or pyridine.

Aminoalcohols like D-phenylalaninol (**18**) or its L-enantiomer **30** give in presence of the iron-complex containing water als further ligand at least 4 well defined Cotton effects; Fig. 21 shows the enantiomorphous CD-curves for these two in situ complexes. Also the three (pseudo-) ephe-drine derivatives **21** - **23** give very pronounced Cotton effects in presence of several of these complexes. The CD-curves of two other such complexes (propane-1,2-diol **11** with the iron-complex containing pyridine as further ligand, and phenylethylamine **31** in presence of the ruthenium com-plex) are presented in Fig. 22.
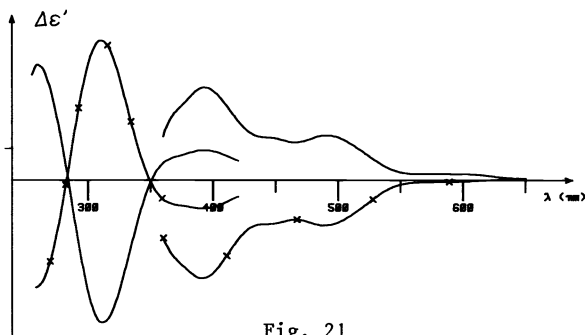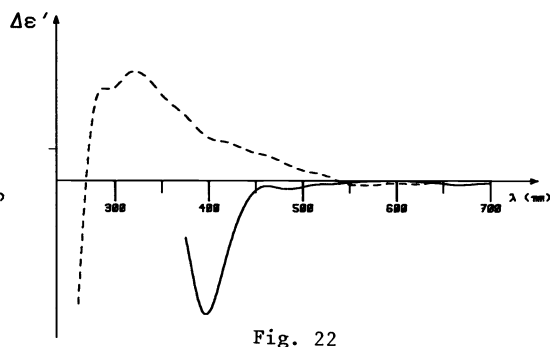

Fig. 21

Fig. 22

Fig. 21. CD of phenylalaninols **18** (————) and **30** (—×——×—) in presence of the Fe-complex of Fig. 20 (L = water).

Fig. 22. CD of propane-1,2-diol (**11**, ————) in presence of the Fe-complex of Fig. 20 (L = pyridine) in acetonitril-solution, and of phenylethylamine (**31**) in presence of the Ru-complex of Fig. 20 (L = water) in ethanol-solution.

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