Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 863–868

TETRAHEDRON: *ASYMMETRY*

Absolute configurational assignment of α-hydroxy acids and α-hydroxy esters from their Cupra A circular dichroism spectra

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Received 23 December 1998; accepted 1 March 1999

Abstract

The in situ formed complexes of cuprammonium solution (Cupra A) with optically active α-hydroxy acids and α-hydroxy esters show circular dichroism spectra suitable for determination of the absolute configuration of both groups of compounds. In the long wavelength spectral region, compounds of *R* configuration at the α carbon atom display a positive Cotton effect of around 600 nm and a negative one at ca. 720 nm, whereas (*S*)-α-hydroxy acids and esters exhibit negative and positive Cotton effects, respectively, in the same spectral range.

1. Introduction

Determination of the absolute configuration of α-hydroxy acids and their derivatives has received increasing attention recently, due to their wide occurrence in nature both in a free form and as their esters or amides. In general, α-hydroxy acid/ester units are present in many anticancer drugs, antibiotics and other bioactive natural products. Among these products are taxol and taxotère — currently considered to be two of the most effective drugs in cancer chemotherapy,[1–3] and a variety of antibiotics, e.g. a newly synthesized bisanthracycline antibiotic WP631[4] or 3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexofuranosyl daunomycinone, an analog of daunomycine.[5] Since it is well-known that α-hydroxy acids are important building blocks in asymmetric synthesis, they can be considered as key intermediates in several synthetic approaches leading to glycols, epoxides, halo esters, amino acids etc. Recently a stereoselective synthesis of the muscarinic receptor starting from (*R*)-(−)-mandelic acid has been described.[6]

The fact that enantiomers may demonstrate several hundredfold variations in pharmaceutical effects, potency at different receptors, as well as significant variations in their rates and pathways of metabolic dispositions, means that the development of methods for the unequivocal determination of the absolute

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0957-4166/99/$ - see front matter
PII: S0957-4166(99)00076-2

configuration of biologically active substances still remains very important. X-Ray diffraction analysis and chemical correlation are the most widely used strategies in this task. However, these methods require either costly instrumentation and crystalline samples or transformation of the compound under investigation into a product of known absolute configuration, often involving a long synthetic route. In this context, circular dichroism (CD) appears to be a fast and very useful technique for stereochemical assignments.

Very recently new strategies for the CD exciton coupling method (ECCD) have been reported for assigning the absolute configuration of α-hydroxy acids.[7,8] In the first, an amidation of the carboxyl group with ethanolamine is followed by derivatization with the hydrophobic 10,15,20-triphenylporphyrinyl-5-benzoyl chromophore to form π,π-bisporphyrin derivatives which undergo intramolecular stacking. The sign of the observed bisignate couplet resulting from this stacking reflects the absolute configuration at the stereogenic center.[7] In the second strategy, derivatization of the carboxylic group of the α-hydroxy acid unit using 9-anthryldiazomethane, and subsequently of the hydroxy group by 2-naphthoyltriazole lead to the bichromophoric system, suitable for ECCD investigations and correlation between stereochemistry and sign of Cotton effects (CEs).[8]

The aim of this paper is to report on a convenient method for determining the absolute configuration of optically active α-hydroxy acids and α-hydroxy esters by in situ generation of chiral complexes with cuprammonium solution (Cupra A). The stereochemical assignment based on the Cupra A CD spectra of a variety of α-hydroxy acids and α-hydroxy esters is described.

2. Results and discussion

CD and visible isotropic absorption (vis) data of in situ formed Cupra A complexes of compounds **1**–**15** are summarized in Table 1. In general, CD spectra of all the compounds studied exhibit similar patterns, characterized by two CD bands of opposite signs in the 400–800 nm spectral range and two other CD bands appearing below 300 nm, mostly also of opposite signs. The presence of aromatic chromophores in compounds **1**, **2**, **8**, **9** and **15** only weakly perturbs this pattern by shifting *d–d* bands, occurring between 400–800 nm, by ca. 40 nm to the red, rather than producing additional bands. For L- and D-tartaric acid as well as for the diisopropyl ester of **5**, a different shape of CD curves in the short wavelengths region is observed. In the 190–300 nm range these compounds exhibit two CD bands of the same sign and of approximately the same magnitude as compared with the remaining compounds. However, the magnitude of their *d–d* bands is ca. twofold higher than in the case of other compounds. This may be explained by the presence of two α-hydroxy acid/ester units in each molecule. According to the additivity principle, contributions stemming from chiral or chirally perturbed chromophores are additive in the resulting CD spectrum. Thus, the higher magnitude of CEs at ca. 600 and 720 nm for **5**, **6** and **12** introduce additional evidence for Cu(II) *d–d* parentage of these transitions. Some representative CD spectra of in situ formed Cupra A chiral complexes are shown in Fig. 1.

The position of the two CD bands in the visible region do not coincide exactly with the isotropic absorption maximum, which appears in between both, and close to the one at shorter wavelength. The vis bands of chiral Cupra A complexes are very broad with a maximum around 625 nm (Table 1). For a 1:1 metal:ligand ratio it is bathochromically shifted by ca. 30 nm in comparison to the visible absorption maximum of Cupra A occurring at 597 nm. No significant differences in the positions of vis maxima were found after changing metal:ligand ratios, e.g. for 1:2 metal:ligand ratio the vis absorption maximum for compounds **3** and **4** appears at 641 and 645 nm, respectively. The shifting of the absorption maxima of copper(II) complexes is generally related to a change in the structure of the coordination polyhedron

Table 1
CD and vis data of in situ formed Cupra A complexes of compounds **1**–**15** determined in 1:1 metal:ligand ratio. Values are given as $[\Theta']^a$ [deg cm^2 dmol^{-1}](λ [nm]) and ε'^a [dm^3 mol^{-1} cm^{-1}](λ [nm])

	CD				Vis
Compound	Band I	Band II	Band III	Band IV	Band A
1 L(+)-Mandelic acid	+2066 (243)	−1350 (279)	−75 (610)	+65 (755)	50 (626)
2 D(−)-Mandelic acid	−2049 (244)	+1564 (281)	+78 (615)	−70 (756)	47 (632)
3 L(−)-Malic acid	+3559 (232)	−836 (288)	−100 (580)	+118 (714)	45 (634)
4 D(+)-Malic acid	−3673 (230)	+1133 (287)	+100 (580)	−120 (715)	46 (635)
5 L(+)-Tartaric acid	+3649 (246)	+1817 (279)	+390 (590)	−592 (743)	42 (645)
6 D(−)-Tartaric acid	−3252 (244)	−1608 (285)	−351 (592)	+600 (744)	50 (641)
7 L(+)-α-hydroxyisovaleric acid	+980 (232)	−675 (291)	−99 (591)	+109 (712)	41 (636)
8 Methyl L(+)-mandalate	+2602 (248)	−2653 (284)	−227 (615)	+194 (761)	41 (623)
9 Methyl D(−)-mandalate	−3552 (249)	+3918 (284)	+240 (612)	−257 (760)	46 (626)
10 Dimethyl L(−)-malate	+2612 (235)	−1586 (271)	−177 (582)	+193 (724)	46 (638)
11 Dimethyl D(+)-malate	−2301 (231)	+1946 (268)	+197 (580)	−217 (715)	51 (639)
12 Diisopropyl L(+)-tartrate	+5970 (267)	+5200 (280)	+630 (594)	−950 (698)	47 (621)
13 Methyl L-(−)lactate	+297 (238)	−412 (290)	−58 (591)	+30 (742)	44 (614)
14 Ethyl L-(−)lactate	+310 (233)	−688 (272)	−83 (586)	+30 (738)	46 (615)
15 Ethyl-(*R*)-2-hydroxy-4-phenylbutyrate	−796 (232)	+404 (280)	+408 (565)	−35 (724)	38 (624)

[a] for explanation of the term [Θ'] and ε' see experimental.

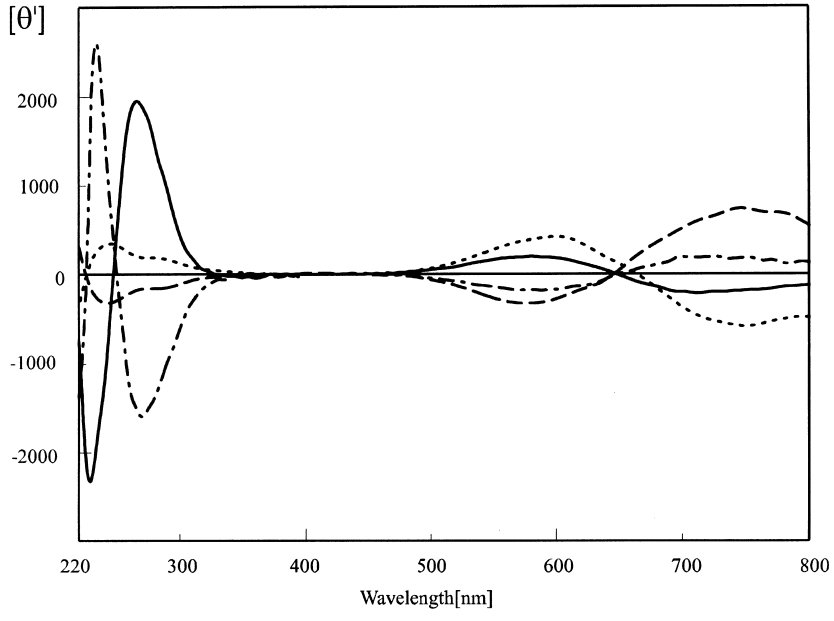

Figure 1. CD spectra of in situ formed Cupra A complexes of **5** (·····), **6** (– – –), **10** (–·–·–), **11** (—)

of the metal ion and/or in coordination of two axial ligands represented mostly by solvent molecules. According to the literature, the absorption maximum at ca. 638 nm is quite characteristic for square planar complexes of the general formula CuL_2H_{-2} or $CuLH_{-2}$ with one or two solvent ligand(s) in the apical positions of the copper(II) ions.[9]

In general, the CD bands at longer wavelengths are better suited for stereochemical correlations than those at shorter ones, because in the former spectral range other chromophores do not absorb. As seen in Table 1, in the 400–800 nm region investigated compounds fall under two different patterns of sign sequence. In the first, a positive CE of around 720 nm follows a negative CE at ca. 600 nm, observed for L-α-hydroxy acids and esters. In the second group, represented by acids and esters from the D series, the opposite relation of sign pattern is observed, i.e. a positive CD band at ca. 600 nm is followed by a negative one at around 720 nm. The observed sign of the CEs for the L-α-hydroxy acids and esters is related to absolute *S* configuration at the stereogenic center, while that for the D-α-hydroxy acids and esters is related to absolute *R* configuration. The exceptional behavior in this context represents only L- and D-tartaric acids (compounds **5** and **6**) and ester **12**, for which L-configurational assignment corresponds to absolute *R* configuration at both stereogenic centers, whereas the D isomer, namely D-tartaric acid, is a 2*S*,3*S* diastereomer. On this basis, it can be concluded that compounds of absolute *R* configuration display two CEs in the long wavelengths spectral region, a positive one at about 600 nm and a negative one at ca. 720 nm. An opposite pattern of signs in this spectral range is characteristic for the *S* isomers of α-hydroxy acids and esters. This statement is in agreement with the previously published data,[10–12] reported for various ligands e.g. copper(II)-gluconic acid, -glucose and -galactosamine systems with copper perchlorate as a stock solution. In all these cases the same CEs signs relation versus absolute configuration was found.

The CD spectra were measured at a 1:1 metal:ligand ratio. However, for compounds **5**, **7**, **8** and **12**, CD spectra with 2:1 and 1:2 metal:ligand ratios were additionally recorded. No significant differences in the shape of CD curves, positions of CD maxima or their amplitudes were found. This independence on concentration gives evidence for the presence of only one species in the solutions studied. This fact agrees with the literature statement that at low metal:ligand ratios, exclusively monomeric complexes of the general formula CuL_2H_{-2} are formed,[13] which could also be predicted on the basis of the visible spectra.[9] As the maximal stabilities of Cupra A chiral complexes were observed in the pH range between 11.1 and 11.4,[14,15] the spectra were recorded at pH value of 11.2. Under these conditions the metal-promoted deprotonation of the alcoholic hydroxy groups leading to formation of CuL_2H_{-2} complexes may easily occur.

The similar shape of CD curves as well as comparable positions of absorption maxima in the visible region for α-hydroxy acids and α-hydroxy esters suggest the same complexation mode for both groups of compounds. Since β-hydroxy acids as well as β-hydroxy esters do not induce CEs with Cupra A solution,[16] it can be concluded that the α-OH group plays a fundamental role in the coordination to the metal core. Very recently, Burger et al. proposed the structure of the Cu(II) complex of D-gluconate.[13] They indicated that the ligand coordination to copper(II) occurs through both acidic and alcoholic OH groups present in the molecule. An application of such a complexation mode to in situ Cupra A complexes would suggest that both α-hydroxy acids and α-hydroxy esters act as bidentate ligands. On the other hand, Kerek and Snatzke pointed out that the amino group in α-amino esters acts as a monodentate ligand in $[Cu(im)_2(am)_2]$ complexes.[10] In our case, no CEs could be found with Cupra A and monohydroxy alcohols e.g. (*R*)- and (*S*)-2-methylbutanol at various metal:ligand ratios. Also optically active esters do not induce CEs in the presence of Cupra A. Since esters do not possess any free hydroxy group and carboxylates as monodentate ligands bind to the copper(II) through their carboxylic hydroxy group,[17] it is reasonable that esters cannot coordinate to the Cu(II) core. The question of a complexation mode of

chiral Cupra A complexes discussed here, especially in the case of α-hydroxy esters, remains open at the moment. However, a square planar arrangement of the α-hydroxy acid molecules in the complex can be assumed to be the most probable as being in line with the literature data.[13] In such a case, the rest of the ligand, i.e. a substituent at the α-carbon atom, must stick out from the complex plane. Depending on the position of the rest of the ligand with respect to this plane, a positive or a negative CE is induced within *d–d* copper bands. Taking into account the similar pattern of sign sequence in the CDs of α-hydroxy acids and α-hydroxy esters and comparable positions of their vis absorption maxima, one can assume the same type of structure of their Cu(II) complexes with both groups of compounds acting as bidentate ligands.

Though on the basis of the chiroptical results alone we are not able to solve the problem of the structure of the complexes formed in the Cupra A solution, this fact is of no relevance for the operating experimental rule, which correlates the signs of CEs with the stereochemistry of α-hydroxy acids and α-hydroxy esters. On the grounds of the aforementioned results, regardless of the complexation mode, the signs of the CE exclusively are required for determination of the absolute configuration.

3. Conclusion

Results of this study have shown that the in situ Cupra A method is a very useful tool for stereochemical assignment of α-hydroxy acids and esters. It was found, that α-hydroxy acids and α-hydroxy esters of the absolute *S* configuration at C(2) give a negative CE around 600 nm and a positive one near 720 nm with Cupra A. On the contrary, the α-hydroxy acids and α-hydroxy esters with absolute *R* configuration at C(2) display an opposite pattern of signs in this spectral range in the presence of Cupra A. Thus, the signs of the CEs directly reflect the stereochemistry at the α carbon atom and can be used for determination of the absolute configuration of α-hydroxy acids and α-hydroxy esters from their CD spectra with Cupra A.

The great advantage of the in situ method is that it is not necessary to synthesize, isolate and purify any derivatives, as required in the above mentioned exciton coupled method.[7,8] Moreover, in comparison to the ECCD method, the application of Cupra A complexes allows determination of the absolute configuration not only of α-hydroxy acids but also of α-hydroxy esters. If only very small amounts of substances are available, the in situ method enables experiments to be carried out directly in the cell. An additional advantage of this in situ method is that the induced CD bands occur in a spectral range in which other chromophores do not absorb.

4. Experimental

All reagents used as a ligand were Fluka products and were used without further purification.

Visible spectra were run on a Cary 1E spectrophotometer over the range 350–900 nm in a 1 cm cell. CD spectra were recorded at 25°C on a Jasco J-720 spectropolarimeter. All spectra were measured over the range of 190–800 nm, using 1 and 0.1 cm cells. Ligand and Cupra A concentrations were 10^{-2} mol dm^{-3} and the pH value of solutions studied was 11.2. In general, samples with 1:1 metal:ligand ratios were used. In some cases (see text), the samples with 2:1 and 1:2 metal:ligand ratios were also measured.

As the true concentrations of the individual optically active complexes present in solution are not known, apparent $[\Theta']$ and ε' values, calculated for the total ligand concentration and assuming 100% complexation, are given.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) and the Polish Academy of Sciences (PAN), grant no. POL 436-113-88.

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