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Absolute Configurations of *N*,*N*-Dialkyl α-Amino Acids and *β*-Amino Alcohols from Exciton-Coupled Circular Dichroism Spectra of Cu(II) Complexes

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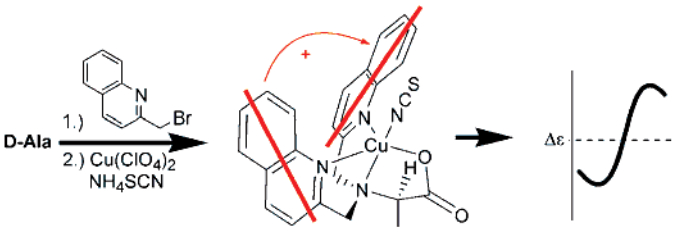
ABSTRACT



A circular dichroism technique has been applied to the absolute configurational assignment of acyclic α-amino acids and *β*-amino alcohols with single stereogenic centers via a one-step derivitization procedure requiring microgram quantities of material. Metal ions fix the geometrical relationship of two chromophores, affording CD spectra that agree with theory on the basis of the expected conformation of the ligands in the metal complexes.

The assignment of absolute configuration of acyclic molecules with single stereogenic centers remains a difficult problem. The Bijvoet method,[1] used widely in X-ray crystallography, is applicable to many compounds in the solid state. Circular dichroism methods have been used extensively for solutions.[2] The most successful CD method, exciton-coupled circular dichroism (ECCD), has been applied successfully to the direct configurational assignment of difunctional compounds such as diols, diamines, α-hydroxy carboxylic acids, and some α-amino acids by attachment of chromophores to two different atoms.[3−6] We have undertaken an approach in which (1) two chromophores are attached to a single nitrogen atom of an amine, and (2) the geometry of the chromophores is fixed by complexation to a metal ion, generating ECCD spectra. This approach may offer greater scope for the configurational analysis of amines than previously reported methods, especially for acyclic compounds due to the additional geometric definition offered by metal complexation. In this paper, we report intitial studies of derivatives of α-amino acids and *β*-amino alcohols, which show a consistent and theoretically reasonable relationship between the sign of the ECCD couplet and the absolute configuration of the amine. We suggest that this behavior may be useful in the microgram-scale determination of absolute configurations of primary amines.

We reported previously the synthesis and chiroptical properties of metal ion complexes of a series of tripodal,

(1) Bijvoet, J. M.; Peerman, A. F., van Bamel, A. I. *Nature* **1951**, *168*, 271.

(2) (a) Smith, H. E.; Neergaard, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 116. (b) Takenaka, S.; Koden, M. *J. Chem. Soc., Chem. Commun.* **1978**, 830. (c) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6345.

(3) Nakanishi, K.; Berova, N. In *Circular Dichroism: Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers: New York, 1994; p 361.

(4) (a) Huang, X.; Rickman, B. H.; Borhan, B.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1998**, *120*, 6185. (b) Gariulo, D.; Ikemoto, N.; Odingo, J.; Bozhkova, N.; Iwashita, T.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1995**, *117*, 7844. (c) Matile, S.; Berova, N.; Nakanishi, K. *Enantiomer* **1996**, *1*, 1. (d) Hoer, K.; Gimple, O.; Schreier, P. and Humpf, H.-U. *J. Org. Chem.* **1998**, *63*, 322.

(5) Carroll, K. M.; Schwartz, J.; Ho, D. M. *Inorg. Chem.* **1994**, *33*, 2707.

(6) Fujii, S.; Isago, T.; Sano, M.; Yanagibushi, N.; Hirasawa, S.; Takahashi, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3509

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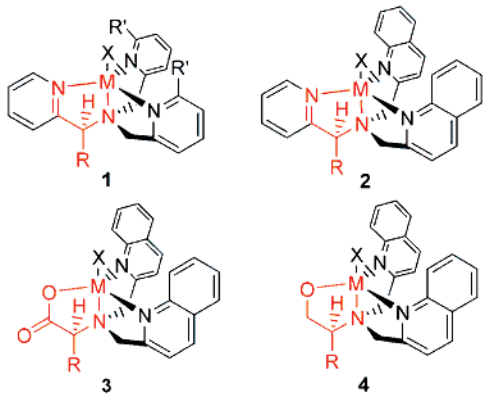
tetradentate ligands.[7] The compounds studied were derivatives of chiral 2-pyridylalkylamines (e.g., **1**). Several com-



pounds were examined, varying the nature of the alkyl group and the achiral arms, using solid state, solution, and computational methods.[8] The conformational behavior of the compounds was surprisingly consistent and predictable, with Zn(II) and Cu(II) complexes of the ligand adopting a propeller-like twist with axial chirality dictated by the absolute configuration of the asymmetric carbon atom. The circular dichroism spectra of bis-quinaldyl derivatives **2** displayed exciton coupling,[9] and yielded to assignment of the solution orientation of the quinoline rings in agreement with the predicted conformation of the ligand in the coordination complex as well as crystallographic data. Given that the twist of the tripod ligand is determined by the chirality of the carbon atom in the five-membered ring chelate (red portion of **1**), it was anticipated that derivatives of other amines that form similar chelates should display analogous conformational behavior, and therefore exhibit ECCD spectra. Geometry optimization calculations (SPARTAN-PM3)[10] of several Cu(L)(SCN) complexes of *N*,*N*-bis-(2-quinolylmethyl) amino acid and amino alcohol derivatives **3** and **4** supported this hypothesis, showing **3** and **4** to represent the lowest energy minima that could be found by manually entering several possible conformations. For example, in the case of the alanine derivative (**3**, R═CH_3), the conformation indicated in **3** gave the lowest energy, with several additional conformations identified within 3 kcal/mol. Approximately half of these displayed the same sense of orientation of the chromophore dipoles as **3**, and these tended to be the lower energy conformers.

Commercially obtained amino acids and β-amino alcohols were easily derivatized by reaction with 2 equiv each of 2-(bromomethyl)quinoline and base in ethanol. Extractive isolation and evaporation yielded the ligand, which was characterized by ^{1}H NMR and mass spectrometry.[11] Dissolution in methanol with an equivalent each of $Cu(ClO_4)_2$ and NH_4SCN produced solutions that gave CD spectra with characteristics recorded in Tables 1 and 2.[12] The compound

Table 1.

amino acid [a]	CE 1 (mdeg)	inflection point, nm	CE 2 (mdeg)
L-histidine	239 nm (−52)	230	226 nm (+12)
L-valine	239 nm (−52)	232	228 nm (+15)
L-tryptophan	239 nm (−125)	233	231 nm (+72)
L-cysteine	239 nm (−50)	232	228 nm (+28)
L-tyrosine	240 nm (−71)	234	231 nm (+12)
S-phenylglycine	240 nm (−33)	232	225 nm (+10)
L-arginine	239 nm (−28)	233	231 nm (+12)
L-leucine	239 nm (−90)	232	230 nm (+24)
L-alanine	239 nm (−81)	232	228 nm (+12)
L-isoleucine	239 nm (−75)	232	228 nm (+35)
L-methionine	239 nm (−33)	232	229 nm (+15)
L-serine	240 nm (−25)	233	227 nm (+17)
L-aspartic acid	240 nm (−45)	232	227 nm (+37)
L-lysine	239 nm (−30)	232	228 nm (+11)
L-phenylalanine	240 nm (−64)	231	229 nm (+23)
L-glutamic acid	240 nm (−27)	232	228 nm (+21)
L-asparagine	239 nm (−38)	233	228 nm (+21)
L-glutamine	240 nm (−29)	232	226 nm (+12)
L-alanine methyl ester	239 nm (−95)	231	228 nm (+10)
S-phenylglycine methyl ester	240 nm (−35)	232	228 nm (+11)

[a] Enantiomers of all compounds gave mirror image CD spectra.

D-tryptophan served as an example for the small scale required for the reaction. Figure 1 shows a spectrum obtained from 3 μg of D-tryptophan. The bulk of the compounds that were tested for this study were prepared on 50−85 mg scale.

Among the variety of metal ion salts that were investigated, $Zn(ClO_4)_2$ and $Cu(ClO_4)_2$ gave consistent results in many cases. However, the combination of $Cu(ClO_4)_2$ and NH_4SCN,

(7) Canary, J. W.; Allen, C. S.; Castagnetto, J. M.; Wang, Y. *J. Am. Chem. Soc.* **1995**, *117*, 8484.
(8) Canary, J. W.; Allen, C. S.; Castagnetto, J. M.; Chiu, Y.-H.; Toscano, P. J.; Wang, Y *Inorg. Chem.* **1998**, *37*, 6255−62.
(9) Castagnetto, J. M.; Xu, X.; Berova, N.; Canary, J. W. *Chirality* **1997**, *9*, 616.
(10) *Spartan 4.0* is available from Wavefunction, Inc., 18401 Von Karman Ave., Ste. 370, Irvine, CA 92612.
(11) The spectroscopic data were consistent with the desired structures. Some overalkylation of amino acids with nucleophilic side chains (e.g., Lys, Cys) was observed.
(12) Recorded on an AVIV 62A DS instrument. The concentration of the *N*,*N*-bis(2-quinaldyl) derivative was determined by UV−vis.

Table 2.

amino alcohol	CE 1 (mdeg)	inflection point	CE 2 (mdeg)
(*S*)-isoleucinol[a]	240 nm (−109)	233	229 nm (+29)
(*S*)-(+)-2-amino-3-cyclohexyl-1-propanol[a]	240 nm (−150)	233	229 nm (+35)
(*S*)-leucinol	240 nm (−98)	233	229 nm (+30)
(*S*)-phenylglycinol	240 nm (−84)	233	229 nm (+30)
(*S*)-(+)−2-amino-1-propanol	239 nm (−130)	232	228 nm (+36)
(*S*)-(+)-2-amino-3-methyl-1butanol	239 nm (−98)	232	229 nm (+27)
(*S*)-(−)-2-amino-3-phenyl-1-propanol	240 nm (−92)	233	229 nm (+24)
(*S*)-(+)-2-amino-1-butanol	239 nm (−90)	233	228 nm (+28)

[a] The antipodes of these compounds were not studied. Enantiomers of all other compounds gave mirror image CD spectra.

affording [Cu(L)(SCN)](ClO_4), provided by far the best ECCD spectra for all of the chelating compounds studied.[13] The SCN^- ion may influence coordination by potential donors present in the side chain of the amino acids by blocking an electrophilic site on the copper ion. Although suitable crystals for X-ray diffraction are not yet available, key features of the structures of the complexes may be inferred by other spectroscopic data. While we have not been able to identify any structurally characterized five-coordinate $[Cu(L)NCS)]^+$ complexes, the 2078 cm^{-1} band in the infrared spectrum of **3** most resembles N-bonded four- and six-coordinate complexes for which both X-ray and IR spectroscopic data are available.[14,15] The $Cu(ClO_4)_2$ complex of the derivatives generally show d−d transitions at 700−720 nm with a shoulder in the 850−900 nm range. Addition of SCN^- results in a 30−50-nm red shift with diminished intensity and concomitant increase in the intensity of the 900-nm shoulder. This behavior may be consistent with an equilibrium shift in the copper coordination sphere from square-based pyramidal coordination toward predominantly trigonal-bipyramidal arrangement.[16,17] There is also a 3−4-nm red shift in the 234-nm absorbance ($\pi-\pi^*$ quinoline) upon binding Cu(II), as well as the appearance of an absorbance at 400−425 nm corresponding to the LMCT band from coordination of the SCN^- to the Cu(II).

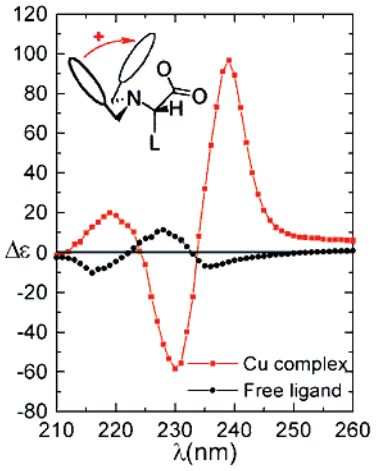
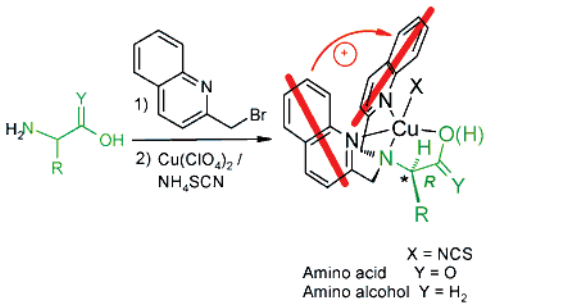


Figure 1. CD of the *N*,*N*-bis(2-quinaldyl) derivative of D-tryptophan and its $Cu(ClO_4)_2$ complex, 0.3 mM in MeOH.

Assay of 17 of the common amino acids[18] plus phenylglycine gave ECCD spectra with the sign of the two Cotton effects corresponding to that predicted by theory,[19] assuming the conformation depicted in **3** and **4**. (Table 1). For each case, the first Cotton effect (CE) was observed at 239−240 nm and the second CE appeared at 229 nm. In every instance, the inflection point corresponded to the λ_{max} observed in the UV−vis spectrum for the longitunal $\pi-\pi^*$ transition of the quinoline arms. The data shown in Tables1 and 2 display varied amplitudes for the ECCD spectra and in some cases, unequal Cotton effect intensities. These differences may arise from several sources, including: (1) subtle differences in orientation of the quinoline dipoles in the lowest energy conformation; (2) differential population of alternate conformations accessible at room temperature; and (3) different yields or side reactions in compounds with nucleophilic side chains.

Employment of the same derivatization method with alanine methyl ester and phenylglycine methyl ester gave CD spectra similar to those of the corresponding amino acids; mass spectrometry data indicate that the methyl group was lost under the conditions of the derivatization reaction. A series of commercially available β-amino alcohols was also investigated (Scheme 1; R = *sec*-butyl, isobutyl, phenyl, methyl, isopropyl, benzyl, ethyl, Y = H_2). In each case, good quality ECCD spectra were obtained. Every compound of

Scheme 1



(13) The free ligands did not yield ECCD spectra, but gave only simple CD spectra of greatly reduced amplitude.

(14) Raymond, K. N.; Basolo, R. *Inorg. Chem.* **1966**, *5*, 1632. (The C−S stretch was not discernible due to overlapping peaks.)

(15) Farago, M. E.; James, J. M. *Inorg. Chem.* **1965**, *4*, 1706.

(16) Zahn, S.; Canary, J. W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 305.

(17) Wei, N.; Murthy, N. N.; Karlin, K. D. *Inorg. Chem.* **1994**, *33*, 6093−6100.

"*S*" absolute configuration gave negative ECCD spectra, in agreement with the expected negative chirality of the two quinolines in the Cu(II) complexes (Table 2). Both the derivatized amino acids and β-amino alcohols follow the conformational model similar to that proposed previously for bisquinaldyl derivatives of 2-pyridylmethylamines,[7] where the "*R*" substituent (Scheme 1) points away from the quinaldyl arms. This feature, and the chelation of the metal, allow the orientation of the quinolines to be dictated by the absolute configuration of the chiral carbon atom.

Since the α-amino acids and β-amino alcohols gave such consistent results, an attempt was made to find some amines that did not work. Thus, chiral primary amines that do not contain additional chelating groups such as 1-naphthylethylamine were derivatized and found surprisingly to give ECCD spectra with $Cu(ClO_4)_2$ in methanol but with opposite sign.[20] The structural basis of the ECCD couplet observed with these complexes is unknown but one possiblility is that the chiral arm adopts a conformation with the largest substituent in the least sterically demanding position, as shown in Figure 2 for (*R*)-1-cyclohexylamine. The orientation of the quinolines is then dictated by the other two substituents. In Scheme 2, conformer B is favored over A, giving a negative orientation and couplet for "*R*" absolute configuration.

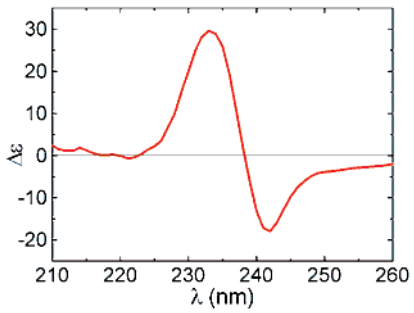
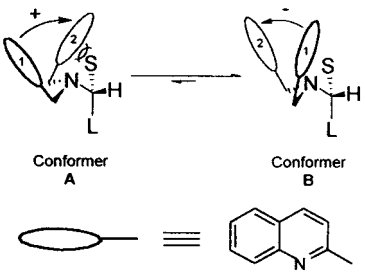


Figure 2. CD of the $Cu(ClO_4)_2$ complex of the *N*,*N*-bis(2-quinaldyl) derivative of (*R*)-1-cyclohexylethylamine, 0.3 mM in methanol.

Scheme 2. Possible Binding Conformations of Amine Derivatives in $Cu(ClO_4)_2$ Complexes



Similar spectra were observed for each antipode of (*S*)-(−)-1-(1-naphthyl)ethylamine (CE 1, inflection point, CE 2, A: 239, 229, 222, (−) 150), (*S*)-(−)-α-methylbenzylamine (241, 238, 232, (−), 35), and (*S*)-(+)-1-cyclohexylethylamine (242, 239, 233, (−), 48). The compound *sec*-butylamine was the only one found that failed to give ECCD spectra.

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Supporting Information Available: Experimental procedures for derivatization reactions and CD measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Glycine and proline were excluded. Threonine gave an ECCD spectrum but with opposite sign, possibly due to the presence of a second chiral center.

(19) Nakanishi, K.; Berova, N. In *Circular Dichroism: Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers: New York, 1994; p 361.

(20) With these compounds, addition of NH_4SCN resulted in extraction of the Cu(II) ion from the ligand, evidenced by loss of amplitude and the ECCD features in the spectra.