Zinc Porphyrin Tweezer in Host−Guest Complexation: Determination of Absolute Configurations of Diamines, Amino Acids, and Amino Alcohols by Circular Dichroism

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Received October 9, 1997

We describe a microscale method based on exciton-coupled CD which does not require chromophoric derivatizations. The achiral chromophoric host porphyrin tweezer **1** binds to an acyclic chiral diamine through nitrogen/zinc coordination to form a macrocyclic host−guest complex; the CD of which reflects the absolute configuration of the diamine. This method can be extended to amino acids and amino alcohols after simple chemical modifications.

The absolute configuration of amines has been determined by the exciton-coupled CD method, a microscale approach widely applied to a variety of compounds containing two or more chromophores.[1] This CD method results from through-space interaction of isolated chromophores which can be preexisting within the parent molecule or introduced by derivatization of −OH, $-NH_2$, etc. Examples for its application in determining absolute configuration of amines include Schiff base formation with aromatic aldehyde chromophores,[2] quaternary ammonium salts of tertiary amines,[3] and intramolecular bisporphyrin chiral stacking induced by derivatized acyclic diamines with single stereogenic centers.[4] The absolute configuration of amines has also been investigated by the benzene chirality rule (sector rule)[5] and by induced CD using indan-1-carboxylic acids[6] and polyacetylene carboxylic acid helices.[7]

Induced CD in host−guest complexes has been used for *enantiomeric differentiation* in calixarenes,[8] cyclic resorcinol tetramers,[9] and sugar sensing molecular receptors based on mono- and bifunctional boronic acid derivatives[10a] including fluorescent receptors.[10b] Porphyrins have also been used in the design of artificial chromophoric hosts to discriminate between enantiomeric amino acids, diamines and carbohydrates.[11] Linker bridged bisporphyrin derivatives which accommodate various achiral amines[12] and linear array formed from amino acid bridged zinc porphyrin dimers and ethylenediamine have been reported.[13]

In the following we extend the use of porphyrins for determining the *absolute configuration* of diamines with single stereogenic centers by using porphyrin tweezer **1** connected by a pentanediol spacer. The zinc porphyrin was chosen because of its facile coordination to amines and the square pyramidal ligand arrangement of the zinc atom.[14] The porphyrin tweezer **1** was synthesized by coupling pentanediol with 5-(*p*-carboxyphenyl)-10,15,20-triphenylporphyrin[15] followed by metal insertion with $Zn(OAc)_2$ (60% overall yield, λ_{max} 419 nm, ϵ 890 000 (in CH_2Cl_2)).

The powerful porphyrin chromophore, with the effective electric transition moment running in the 5−15 direction,[16] can couple over a distance of ∼50 Å.[17] Binding of the diamine to porphyrin tweezer **1** leads to a unique arrangement of the effective electric transition moments which gives rise to a coupled CD. The absolute sense of twist is rationalized as follows. As shown in Figure 1 for (*R*)-1,2-diaminopropane (**2**) and tweezer **1**, the substrate is sandwiched between the two porphyrin planes P-1 and P-2 leading to either conformer **I** where the larger group (L) projects out and the smaller group (S) is clamped between P-1/P-2 or conformer **II** where the situation is reversed. For steric reasons, conformer **I** associated with a negative CD couplet should be energetically favored, which was observed experimentally (Figure 1), λ_{ext} 435 nm ($\Delta\epsilon$ −93) and 426 nm ($\Delta\epsilon$ +76), A −169.

The flexibility of the pentanediol linker between the two porphyrins in tweezer **1** allows it to accommodate diamines of variable lengths and L groups. Table 1 lists the CD data for the coordination of tweezer **1** with diamines **2**−**11**. Compounds **2**−**9** represent 1,2-, 1,3-, 1,4-, and 1,5- diamines containing primary amino groups at both positions with various L groups including methyl, *N*-methylcarboxamide, methoxy carbonyl, hydroxymethyl, acetoxymethyl, and *N*-benzylcarboxamide. In all cases but one, the predicted CD sign is in agreement with the observed CD couplet of the diamines/tweezer **1** complex. The exception is L-lysinol (**7**) which gave a complicated CD curve;[19] this can be solved by protecting the hydroxyl group as an acetate (compound **8**). Two amino groups are required for complexation with tweezer **1** to form a macrocyclic complex. Thus, neither *R*-(−)-1-cyclohexylethylamine nor mono-Boc-protected L-lysine methyl ester (protected in the ϵ- or α-position) produced exciton-coupled CD spectra with porphyrin tweezer **1**. The same holds for compounds **10** and **11**, which showed no characteristic CD possibly due to the lack of coordination between zinc and the weakly nucleophilic nitrogen lone pair electrons in the indole group of **10** and the amide group of **11**. The stereochemistry of 1,3- and 1,4-diamines with methoxy carbonyl as L groups could not be determined due to the facile lactam formation of these compounds under the experimental conditions.

This approach can be extended, after simple high yield chemical modifications, to amino acids (Table 2) and amino alcohols (Table 3) which have a primary amino group directly attached to the

(1) (a) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy−Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983. (b) Nakanishi, K.; Berova, N. *The Exciton Chirality Method*; Nakanishi, K., Berova, N., Eds.; VCH Publishers: New York, 1994; p 361.

(2) Gargiulo, D.; Ikemoto, N.; Odingo, J.; Bozhkova, N.; Iwashita, T.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1994**, *116*, 3760.

(3) Zhao, N.; Kumar, N.; Neuenschwander, K.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **1995**, *117*, 7844.

(4) Matile, S.; Berova, N.; Nakanishi, K. *Enantiomer* **1996**, *1*, 1.

(5) Smith, H. E.; Neergaard, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 116.

(6) Takenaka, S.; Koden, M. *J. Chem. Soc, Chem. Commun.* **1978**, 830.

(7) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6345.

(8) Takeshita, M.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1088.

(9) Kikuchi, Y.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 217.

(10) (a) James, T.; Sandanayake, K. R. A. S.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1910 and references therein. (b) James, T. J.; Linnane, P.; Shinkai, S. *J. Chem. Soc. Chem. Commun.* **1996**, 281 and references therein.

(11) (a) Takeuchi, M.; Imada, T.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 10658. (b) Takeuchi, M.; Kijima, H.; Hamachi, I.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 699. (c) Mizutani, T.; Ema, T.; Ogoshi, H. *Tetrahedron* **1995**, *51*, 473. (d) Mizutani, T.; Kurahashi, T.; Mukakami, T.; Matsumi, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *117*, 88991. (e) Konishi, K.; Yahara, K.; Toshishige, H.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1994**, *116*, 1337. (f) Crossley, M. J.; Mackay, L. G.; Try, A. C. *J. Chem. Soc., Chem. Commun.* **1995**, 1925. (g) Arimori, S.; Takeuchi, M.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 245. (h) Imai, H.; Nakagawa, S.; Kyuno, E. *J. Am. Chem. Soc.* **1992**, *114*, 6719.

(12) (a) Danks, I. P.; Lane, T. G.; Sutherland, I. O.; Yap, M. *Tetrahedron* **1992**, *48*, 7679 and references therein. (b) Hunter, C. A.; Meah, M. N.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5773. (c) Schneider, H.-J.; Wang, M. *J. Org. Chem.* **1994**, *59*, 7464.

(13) Liu, H.; Huang, J.; Tian, X.; Jiao, X.; Luo, G.; Ji, L. *J. Chem. Soc. Chem. Commun.* **1997**, 1575−1576.

(14) Buchler, J. W. *Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. I, Chapter 10, p 425.

(15) Matile, S.; Berova, N.; Nakanishi, K.; Novkova, S.; Philipova, I.; Blagoev, B. *J. Am. Chem. Soc.* **1995**, *117*, 7021.

(16) Matile, S.; Berova, N.; Nakanishi, K.; Fleischhauer, J.; Woody, R. *J. Am. Chem. Soc.* **1996**, *118*, 5198.

(17) Matile, S.; Berova, N.; Nakanishi, K. *Chem. Biol*. **1996**, *3*, 379.

(18) *n*-Hexane is the solvent of choice since it always afforded a bisignate CD curve that was in agreement with the predicted sign. However, with methylene chloride, chloroform, benzene, toluene, and acetonitrile, the signs of CD were not always in accord with prediction showing that factors other than steric bulkiness can be overriding.

(19) However at −8 °C, **7** with tweezer **1** gave a weak exciton CD couplet with the predicted sign (λ_{ext} 435 nm ($\Delta\epsilon$ − 6.7) and 421 nm ($\Delta\epsilon$ + 5.3)).

S0002-7863(97)03539-7 CCC: $15.00
Published on Web 06/06/1998

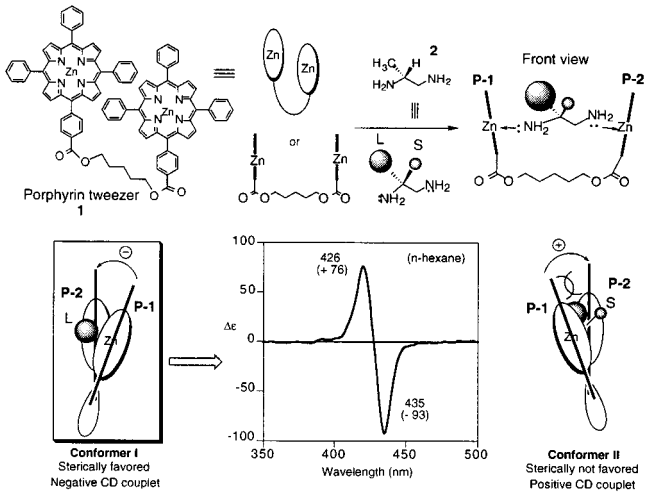
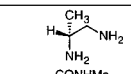
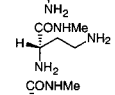
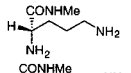
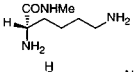
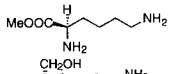
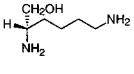
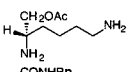
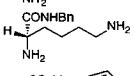
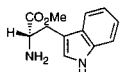
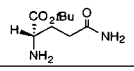


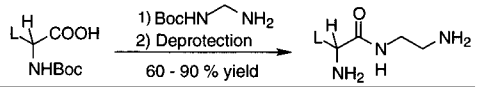
Figure 1. Adduct formed between porphyrin tweezer **1** and (*R*)-1,2-diaminopropane **2**. Complexation of **1** with **2** can adopt two conformations: (**I**) with the L group projecting out of the sandwich and (**II**) with the S group projecting out of the sandwich. The negative sign of the couplet is in agreement with the energetically favored conformer **I**.

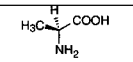
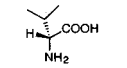
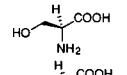
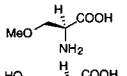
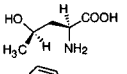
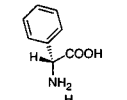
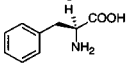
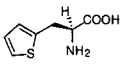
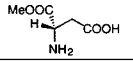
Table 1. CD Data of Diamines Coordinated to **1** in *n*-Hexane[18]

Compound	Diamines	Predicted Sign	1 st λ(Δε) 2 nd λ(Δε)	A
2[a]		(-)	435 (- 93) 421 (+ 76)	- 169
3		(-)	435 (- 23) 420 (+ 16)	- 39
4		(-)	432 (- 15) 421 (+ 17)	- 32
5		(-)	433 (- 103) 423 (+ 90)	- 193
6[a]		(+)	433 (+ 205) 423 (- 177)	+ 382
7		(-)	434 (- 23) 427 (+ 27) 420 (+ 6)	
8		(-)	434 (- 45) 423 (+ 21)	- 66
9		(-)	433 (- 84) 423 (+ 76)	- 160
[10]		(-)	n.d.	
[11]		(-)	n.d.	

[a] The enantiomer of which showed mirror image CD spectra. n.d. no distinctive CD.

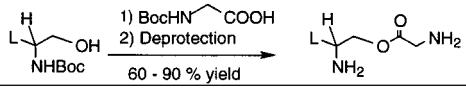
Table 2. CD Data of Derivatized Amino Acids with **1** in *n*-Hexane

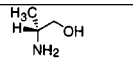
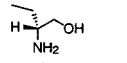
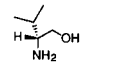
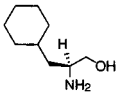
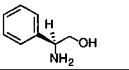


Compound	Parent Amino Acids	Predicted Sign	1 st λ(Δε) 2 nd λ(Δε)	A
12		(+)	432 (+ 59) 422 (- 48)	+ 107
13[a]		(-)	433 (- 200) 422 (+ 162)	- 362
14		(+)	432 (+ 17) 422 (- 14)	+ 31
15		(+)	432 (+ 33) 422 (- 26)	+ 59
16		(+)	432 (+ 39) 423 (- 39)	+ 78
17		(-)	433 (- 53) 423 (+ 42)	- 95
18		(+)	435 (+ 27) 427 (- 15)	+ 42
19		(+)	432 (+ 32) 423 (- 27)	+ 59
20		(-)	431 (- 45) 421 (+ 38)	- 83

[a] The enantiomer of which showed mirror image CD spectra.

Table 3. CD Data of Derivatized Amino Alcohols with **1** in *n*-Hexane



Compound	Parent Amino Alcohols	Predicted Sign	1 st λ(Δε) 2 nd λ(Δε)	A
21		(-)	430 (- 105) 422 (+ 90)	- 195
22		(-)	431 (- 206) 422 (+ 178)	- 384
23		(-)	431 (- 220) 422 (+ 177)	- 397
24		(+)	431 (+ 296) 422 (- 250)	+ 546
25		(+)	431 (+ 84) 422 (- 70)	+ 154

stereogenic center. It could also possibly be applied to functional groups other than carboxyls and hydroxyls.

α-Amino acids **12**−**19** with various L groups were derivatized with ethylenediamine to yield diamines. Complexation of these diamines with tweezer **1** gives rise to exciton-coupled CD spectra with the signs reflecting the absolute configurations of these compounds (Table 2). The absolute configuration of *β*-amino acid **20** was determined as in the case with α-amino acids.

The absolute configuration of α-amino alcohols **21**−**25** could also be determined by applying the same methodology described above after derivatization with glycine (Table 3). The CD amplitudes seem to be governed by the size of the S and L groups (compound **21**−**24**), i.e., larger disparity in size leads to larger CD amplitudes.

The present paper demonstrates the utility of porphyrin tweezer **1** for determining the absolute configurations of chiral diamines, amino acids, and alcohols through host−guest complexes. In this method, the CD of the substrate complex is measured directly without derivatization, and the sample can be readily recovered; moreover, it requires only about 1−2 *μ*g of tweezer **1** and several micrograms of diamine. It can be extended to amino acids and α-amino alcohols after simple derivatizations. Further extensions of this method are in progress.

Acknowledgment. We are grateful for NIH grant GM 34509.

Supporting Information Available: Experimental procedures for synthesis of porphyrin tweezer **1**, synthesis **3**, **5**, **7**, **8**, and **9**, derivatizations of compound **12** to **25**, and general procedures for CD measurements (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA973539E