(*R*)-(+)- and (*S*)-(−)-1-(9-Phenanthryl)ethylamine: Assignment of Absolute Configuration by CD Tweezer and VCD Methods, and Difficulties Encountered with the CD Exciton Chirality Method

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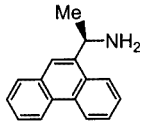
In agreement with predictions from the stereochemical outcome of pyruvate hydrogenation with chiral 1-(9-phenanthryl)ethylamine (**1**), the (+) isomer (as measured in $CHCl_3$) was assigned the (*R*) configuration by use of the Zn–porphyrin host-guest CD exciton chirality method after derivatization with 4-[(Boc-amino)methyl]pyridine-2-carboxylic acid, and also directly on the amine by use of the VCD method. Attempts to use the bis(chromophoric) CD exciton chirality method after derivatization with a naphthimido group happened to be more difficult because of the complex electronic structure of the phenanthryl group, although the naphthimido moiety was the most suitable chromophore in this case. The results are discussed.

Introduction

Since the first use of 1-phenylethylamine for the enantioselective synthesis of spiro[4,4]nonylamine-1 in 1968,[1] enantiopure 1-arylethylamines have become established as useful chiral auxiliaries[2] and have been widely used as chiral shift agents for enantiomeric ratio determinations.[3,4] During work on asymmetric catalytic heterogeneous hydrogenation of α-oxo esters, we became interested in enantiopure 1-(9-phenanthryl)ethylamine (**1**) as a chirality inducer.



(*R*)-α-[9-phenanthryl]-ethyl amine
1

Racemic amine **1** had been prepared[5] (one step and 97% isolated yield) from commercially available phenanthrene-9-carbonitrile and resolved on a preparative scale on a CHIRALCEL OD column.[5] The (+) isomer, with an enantiomeric purity of 99.9%, was obtained in 38.5% yield and was eluted first; the (−) isomer, with 99.5% enantiomeric purity, was obtained in 37.5% yield and was eluted second.[5] Faced with the problem of determining the absolute configuration of **1**, it appeared that CD spectroscopy offered a range of possible solutions.[6]

In the light of a recent report by Salvadori et al.[7] on 1-(9-anthryl)ethylamine, the dichromophoric CD exciton approach[8] appeared also to be promising for compound **1**, which possesses the similar structural features of an aromatic chromophore with strong electric dipole allowed transitions[9] and the easily derivatized amino group, both directly attached to the chiral center. On the other hand, the application of exciton methods to bis(phenanthrene) compounds had proven not to be straightforward, owing to the complex electronic structure of the chromophore,[10] which can give rise to complicated UV/CD profiles. It was therefore an interesting challenge to attempt the configurational assignment of **1** by direct coupling of phenanthrene with a suitable chromophore introduced onto the amino group; however, the interpretation of the experimental CD spectrum of the resulting dichromophoric derivative **2** (Scheme 1) turned out to be difficult. The (+)-(*S*) absolute configuration apparently suggested by CD was inconsistent with the stereochemical outcome of catalytic hydrogenation, which supported the opposite (+)-(*R*) assignment (by

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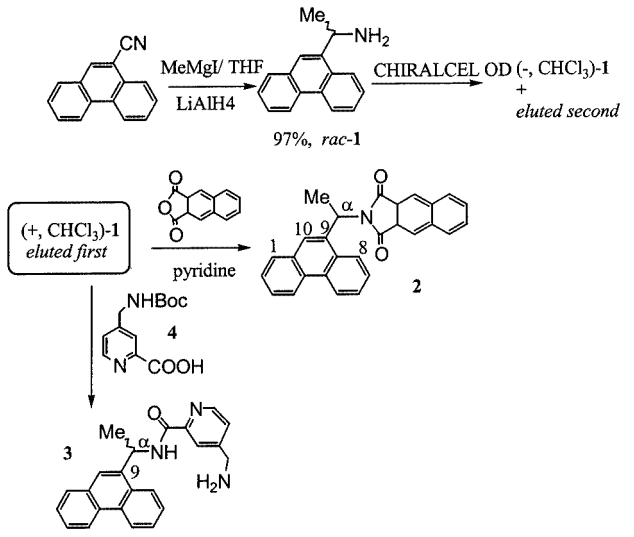
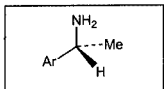


Scheme 1

Table 1. Stereochemical outcome of heterogeneous hydrogenation of pyruvate to lactate in the presence of enantiopure 1-arylethylamines

R – Naphthyl ethyl amine (+, EtOH)	gives	***R*** – Lactate
R – Anthryl ethyl amine (+, $CHCl_3$) [5]	gives	***R*** – Lactate
R(?) – Phenanthryl ethyl amine (+, $CHCl_3$)	gives	***R*** – Lactate



Ar = Naphthyl, Anthryl Phenanthryl

comparison with similar amines, Table 1). Two other methods were thus considered: the CD tweezer[11] method and the vibrational CD[12] (VCD) method.

We present here a discussion of the application of the CD exciton chirality method to derivative **2**, as well as the determination of the absolute configuration of **1** by use of the CD tweezer method on derivative **3**, and directly on amine **1** by the VCD method (Scheme 1).

Results and Discussion

The Dichromophoric Exciton Method[8] on Derivative 2 [Formed from Amine (+)-1]

Compound **2** was prepared according to standard procedures, starting from (+)-**1**.[13] The 2,3-naphthimido chromophore was chosen on the basis of its ease of introduction, suitable symmetry, and electronic properties.[13] The strong electric dipole allowed transition at 256 nm ($\varepsilon \approx$ 72,000 for *N*-methyl-2,3-naphthimide in hexane[14]), which is long-axis polarized, could serve as an ideal spectroscopic probe in the coupling with the strongest transition of phenanthrene, centered at 255 nm in the isolated chromophore and also long-axis polarized.[9]

The conformation was determined by semiempirical (MNDO-PM3) structure optimization[15] and confirmed by ^{1}H NMR NOE experiments. The crucial structural parameter to be investigated was the dihedral angle θ

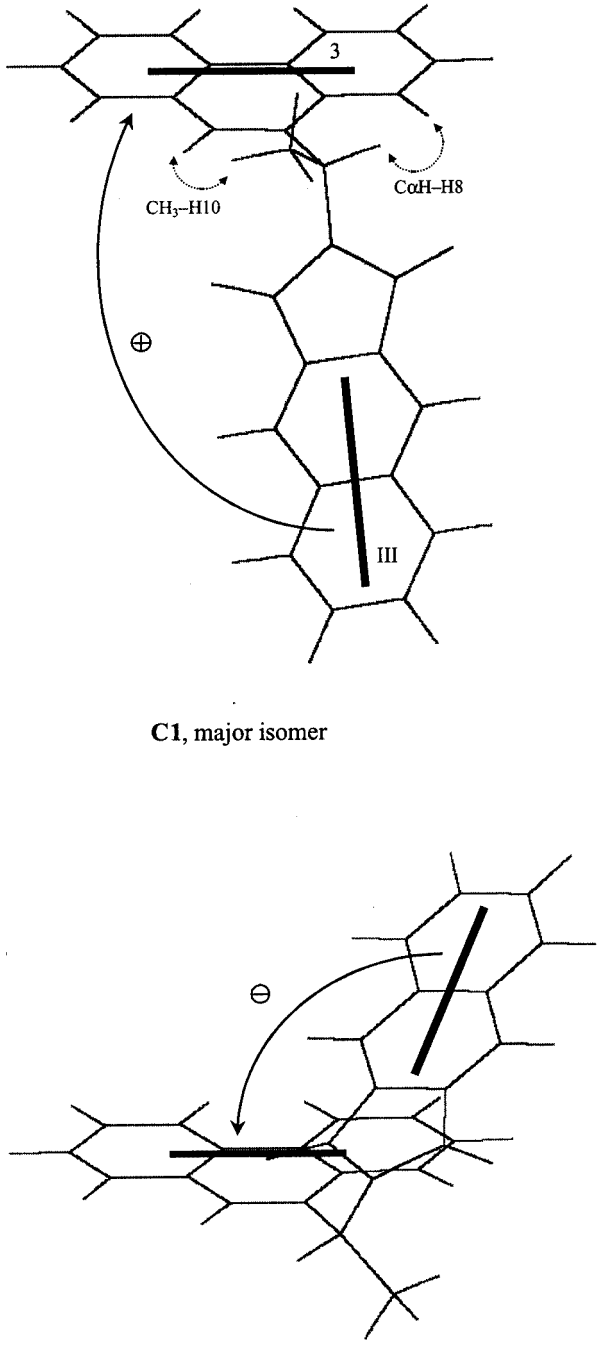
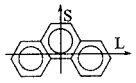
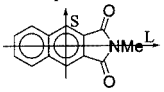


Figure 1. PM3 minimum-energy structures for (*R*)-**2**; solid lines: transition dipoles relative to the two strongest transitions around 250 nm (Bands 3 and III in Table 2); curved dotted double arrows: observed ^{1}H NMR NOEs; curved solid arrows: chirality defined by transitions 3/III

(N−Cα−C9−C10) (Figure 1). MNDO-PM3 calculations on the arbitrarily chosen (*R*) enantiomer found two well-defined minima, for θ = +84° (conformation **C1**) and θ = −105° (conformation **C2**, Figure 1). Conformation **C2** was +4 kcal/mol higher in energy than **C1**, and separated by a barrier of about 9 kcal/mol.[16] The averaged conformation observed by ^{1}H NMR exhibited NOEs of similar intensities

Table 2. Spectral parameters for phenanthrene and *N*-methyl-2,3-naphthimide

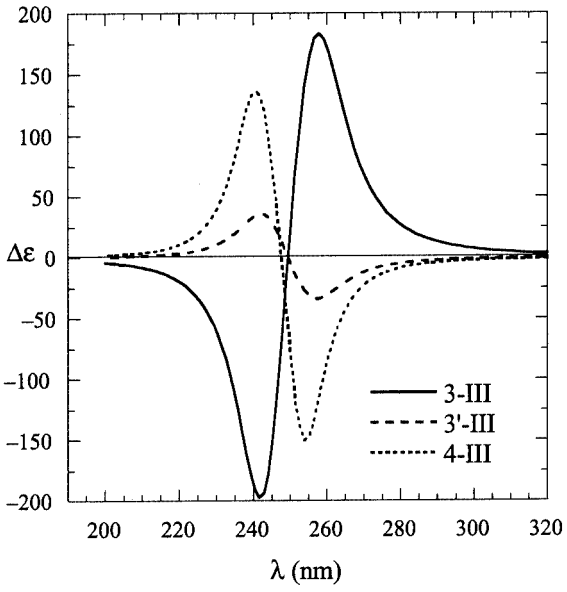
		Calculated[a]			Experimental[b]	
	Band	λ_{max} (nm)	f[c]	Pol.[d]	λ_{max} (nm)	ε_{max}
Phenantrene 	1 (^1L_b)				350	350
	2 (^1L_a)	295	0.14	L	293	16,000
	3 (^1B_b)	256	1.55	L	251	65,000
	4	250	0.66	S		
	5 (^1C_b)	221	0.18	L	212	33,000
	6	206	0.13	L		
Naphthimide 	I	325	0.06	L	352	5,400
	II	283	0.06	S	289	8,000
	III	244	1.83	L	256	70,000
	IV	241	0.34	S		
	V	216	0.21	L	216	23,000

[a] See ref.[17] for details. [b] For phenanthrene in cyclohexane (ref.[9]) and *N*-methyl-2,3-naphthimide in hexane (ref.[14]). [c] Oscillator strength. [d] Transition polarization: L, long axis, S short axis (see diagram)

between CH_3 and H10 and between CαH and H8, with no NOE between CH_3 and H8 or between CαH and H10, in accordance with the most stable conformation (**C1**) found by calculation.

Table 2 shows the most intense electronic transitions calculated for phenanthrene and *N*-methyl-2,3-naphthimide by CNDO-S/CI methods,[17] along with the experimentally measured absorption spectra.[9,14] If one were to follow a conventional exciton chirality approach,[8] one would naturally focus on the two most intense transitions (bands 3 and III in Table 2), both long-axis polarized. In the major conformation (**C1**) of (*R*)-**2**, these transitions define a positive chirality (Figure 1), and so a positive CD couplet with crossover near 255 nm would be expected for the (*R*) configuration. For quantitative CD calculations on exciton-coupled systems, a commonly employed method is DeVoe's.[18,19] In the current case, a positive couplet of moderate amplitude ($A = +360$) was found for the 3/III coupling of (*R*)-**2** (Figure 2, solid line).[20] On the other hand, the presence of several transitions, illustrated in Table 2, was likely to complicate the appearance of the CD spectrum.

Figures 3 and 4 show the UV absorption and CD spectra of compounds (+)-**1** (dotted lines) and **2** (solid lines) in chloroform. The two most intense UV absorptions in acetonitrile occurred at 253 nm for phenanthrene (corresponding to band 3) and at 260 nm for the naphthimide chromophore (corresponding to band III, from subtraction and second derivative of spectra, not shown); only a small red shift was observed for **2** in chloroform (maximum at 258 nm). As expected, the CD spectrum of **2** was composed of many Cotton effects of comparable intensities, most of which could not be safely assigned on the basis of our CNDO data.[21] In particular, no obvious exciton couplet was detected around 255 nm. The sequence (in acetonitrile) of a negative and a positive band at 267 and 259 nm could not be identified as the exciton couplet between transitions 3 and III, because of the very different intensities of the two



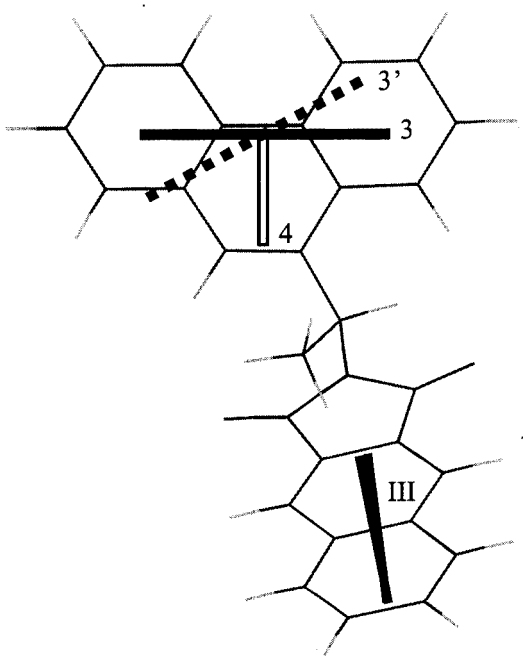


Figure 2. CD couplets calculated by DeVoe's method for (*R*)-**2** (**C1** conformer) and various coupled dipoles; transition dipoles 3 and III: long-axis polarized transitions of phenanthrene and naphthimide chromophores (as in Table 2); 3′: same as 3, but tilted according to Platt's model; 4: short-axis polarized transition predicted by CNDO (Table 2); the possibility of rotation of 4 according to Platt's model has not been taken into account

Cotton effects and a deviation of the positions from what would be expected for a Davydov splitting. A hypobathochromic effect was observed in chloroform (main Cotton effects: 261 nm, $\Delta\varepsilon = +30$; 269 nm, $\Delta\varepsilon = -10$), but the overall appearance of the spectrum was retained well, thus proving the conformational similarity in the two solvents.

Such features cannot therefore be viewed as proof of the (*S*) configuration, which would indeed be in contradiction with the stereochemical outcome of hydrogenation (see

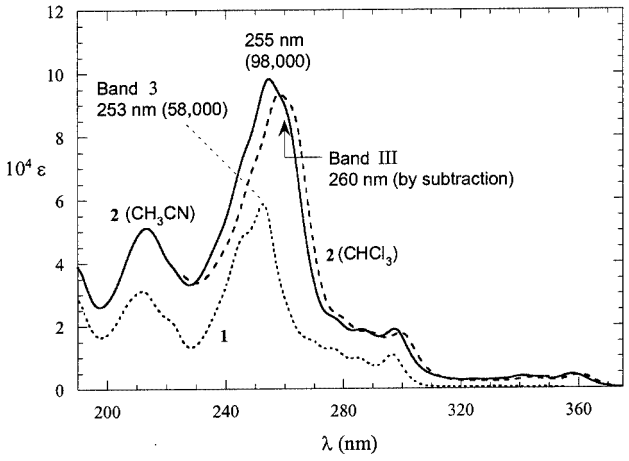


Figure 3. UV spectra of 1.85 mM (*R*)-**2** in CH_3CN (solid line) and in $CHCl_3$ (dashed line), and of 2.20 mM (*R*)-**1** (dotted line) in CH_3CN; path length 0.01 cm; band nomenclature refers to Table 2, and numeric data to the spectra in CH_3CN

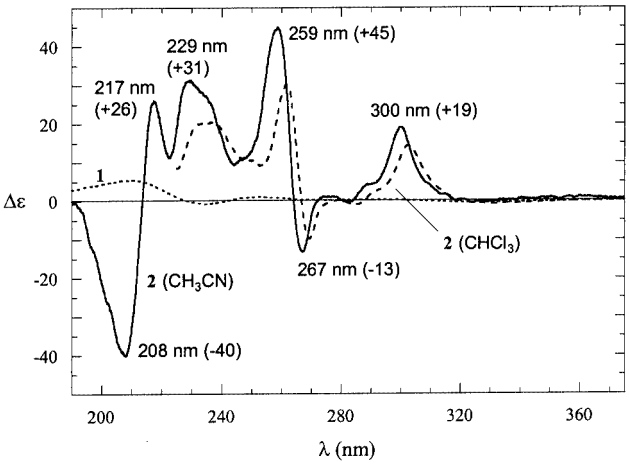


Figure 4. CD spectra of 1.85 mM (*R*)-**2** in CH_3CN (solid line) and in $CHCl_3$ (dashed line), and of 2.20 mM (*R*)-**1** (dotted line) in CH_3CN; path length 0.01 cm; numerical data refer to the spectra in CH_3CN

above) and the results of other spectroscopic methods (see below). It seems that the application of the exciton method was hampered in this case by the innate weakness of the diagnostic couplet and by extensive band overlap. In particular, on the basis of DeVoe's calculations, it can be observed that:[22]

a) As already pointed out by Harada et al.,[10b] the presence of a second transition[23] close in energy and orthogonal to ^1B_b (band 4 in Table 1) is critical. The 4/III coupling (Table 2) gives rise to a moderate *negative* couplet ($A = -280$, DeVoe's method) for (*R*)-**2** (Figure 2, dotted line), which would superimpose and almost cancel the 3/III couplet.

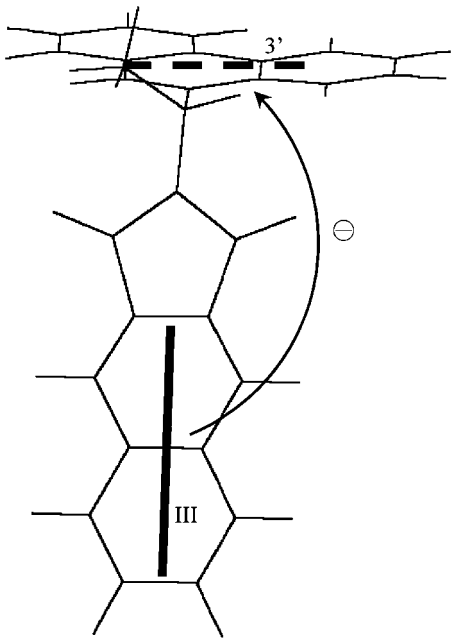
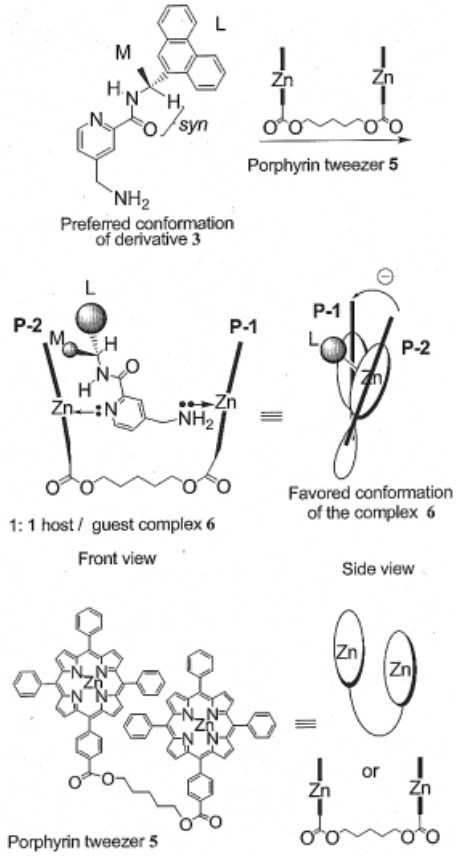


Figure 5. Chirality defined by transition dipoles 3′/III (Table 2 and Figure 4) for the major PM3 conformer (**C1**) of (*R*)-**2**; the orientation of 3′ arises from rotation of the phenanthrene ^1B_b band (transition 3 in Table 2) according to Platt's model

b) The substitution at C9 causes the long axis of the naphthimide chromophore to lie close to the plane of symmetry of phenanthrene (orthogonal to the aromatic plane). In this situation, a small alteration in the orientation of dipole 3 may reverse the sign of the chirality of the transition moments.[24] For example, Platt's vector model[25] predicts a ^1B_b dipole slightly rotated toward the direction perpendicular to the C9−Cα bond, owing to the alkylamino substituent. The extreme situation with 3 rotated as 3′ in Figure 2 corresponds to a negative chirality (Figure 5) and gives rise to a *negative* 3′/III couplet ($A = -70$, dashed line spectrum in Figure 2).

Determination of the Absolute Configuration of Derivative 3 [Formed from Amine (+)-1) by the CD Tweezer Method[11]*]*

Some of us have recently developed the CD tweezer method for absolute configurational assignment of primary amines, by utilization of host/guest complexation between an achiral chromophoric host, bis(zinc−porphyrin) tweezer **5**, and a chiral bidentate ligand formed from a primary amine and the carrier **4**.[11] The absorption of the porphyrin is red-shifted (ca. 420 nm), and so the observed CD of the host/guest complex arises solely from the interaction between the two porphyrins without interference from the preexisting phenanthryl chromophore.[26] By the usual procedure,[11a] a 1:1 host/guest complex **6** was formed through zinc−nitrogen coordination between the zinc porphyrin tweezer **5** and the bidentate derivative **3**, obtained from (+)-**1** and carrier **4** (Scheme 2).[11a]



Scheme 2

In the host/guest complex **6**, the lowest-energy conformation of **3** has the carbonyl oxygen atom *anti* to the pyridine nitrogen atom and *syn* to the methine proton located at the chiral center.[27] The porphyrin (P-2) closer to the chiral center therefore approaches its binding site, the pyridine nitrogen atom, from the less hindered side, that bearing the medium-sized (methyl) group, in order to avoid steric interaction with the large phenanthryl group. If the configuration were (*R*), as shown in the scheme, the approach of P-2 from the methyl side would result in a counterclockwise twist between the two porphyrins (see side view), which would result in a negative exciton CD couplet. A negative CD couplet was observed experimentally for the complex **6** (Figure 6). The absolute configuration of (+)-**1** is therefore assigned as (*R*).

*Determination of the Absolute Configuration of (+)-***1** *by the VCD Method*[12]

Determination of the absolute configuration by the VCD method[12] was carried out on the free amine **1** (no need for any derivatization). The method involves first measuring the IR and VCD spectra of an enantiopure sample (in the neat liquid or solution state), and an ab initio quantum mechanical calculation of the IR and VCD spectra of a particular absolute configuration and conformation of the molecule is then carried out. Comparison between measured

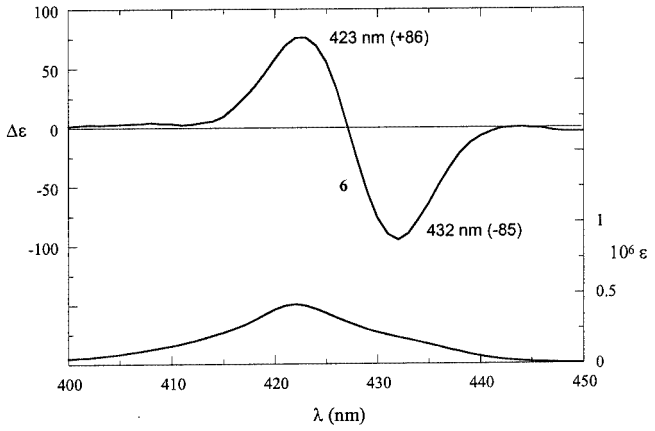


Figure 6. Absorption and CD spectrum of host/guest complex **6** in methylcyclohexane

and calculated spectra with respect to the signs and relative magnitudes of VCD bands then allows assignment of the absolute configuration of the measured sample.[28–34] In comparison of experimental and calculated VCD spectra, the emphasis is placed on the bands of strongest VCD intensity.

IR and VCD spectra of (+)-**1** were measured with a modified [28] chiral IR Fourier transform VCD spectrometer (Bomem/BioTools, Quebec, Canada). The maximum efficiency of polarization modulation of the IR beam was centered at 1400 cm^{-1}. Other instrumental conditions for the collection of the VCD spectra were: 4 cm^{-1} resolution, 12 h total collection time, and two sample concentrations in $CDCl_3$, 12 mg/135μL (0.40 M) in a 0.092-mm path-length BaF_2 cell and 15.5 mg/300μL (0.23 M) in a 0.094-mm path-length BaF_2 cell.

The (*R*) enantiomer of **1** was chosen for calculation of its IR and VCD spectra. The molecular structure was constructed with the aid of the HyperChem program (Hypercube, Inc. Gainsville, Florida, USA). The preferred conformers, calculated by PM3, were found to have the methyl group orthogonal to the phenanthryl plane (consistently with the most stable structure found by PM3 for derivative **2**). The three NH_2 rotamers for the lowest-energy orientation of the ethylamino group were optimized with Gaussian 98 (Gaussian, Inc., Pittsburgh, Pennsylvania, USA) at the DFT (B3LYP/6-31G*) level.[35] The optimized conformations and relative energies are shown in Figure 7. A 180° rotation of the ethylamino group increases the energy of each rotamer by ca. 8 kJ/mol.

The vibrational frequencies and IR and VCD intensities for the three lowest-energy conformers were calculated with Gaussian 98, again at the DFT (B3LYP/6-31G*) level. For comparison with experimental measured values, the calculated frequencies were scaled by 0.97 and the calculated intensities were converted into Lorentzian bands with 4 cm^{-1} halfwidth and plotted with Axum 6 (Mathsoft, Inc., Cambridge, Massachusetts, USA). The calculated spectra are compared to the observed spectra in Figure 8. Boltzmann population-weighted sums (66% Conformer 1, 31% Conformer 2, and 3% Conformer 3) of the calculated spectra

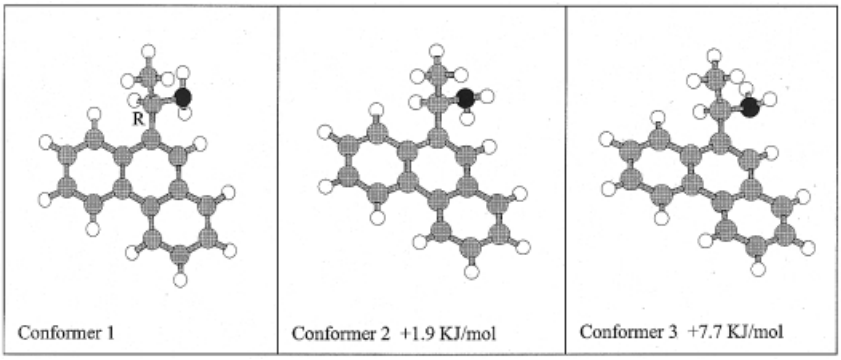


Figure 7. Optimized geometry of the lowest-energy conformers of (*R*)-1-(9-phenanthryl)ethylamine (**1**)

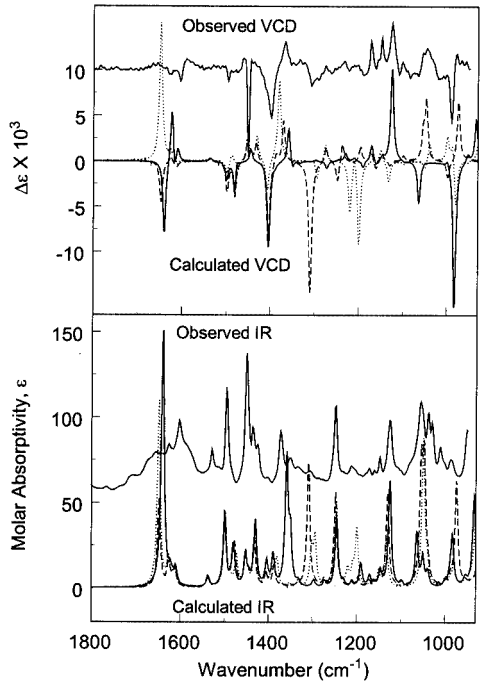


Figure 8. Comparison of IR (lower frame) and VCD (upper frame) spectra observed for (+)-**1** (0.40 M in $CDCl_3$) with those calculated for three conformers (shown in Figure 7) of (*R*)-**1**: (——) Conformer 1; (- - -) Conformer 2; (···) Conformer 3

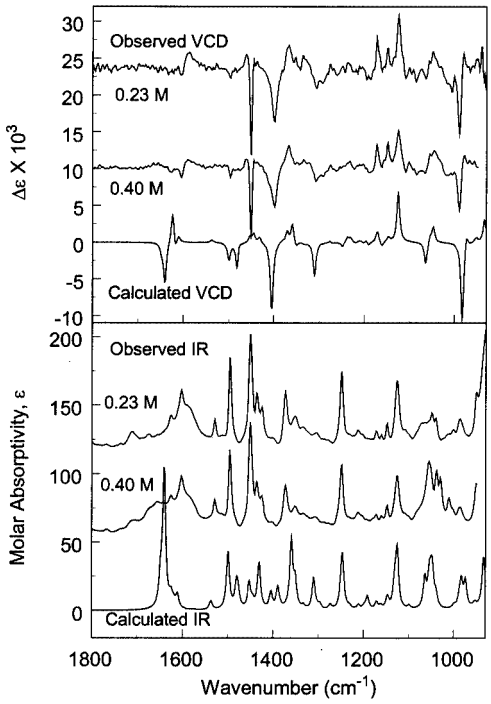


Figure 9. Comparison of observed IR and VCD spectra of (+, $CHCl_3$)-**1** at 0.40 and 0.23 M in $CDCl_2$ with Boltzmann population-weighted sum of spectra of Conformer 1 (66%), Conformer 2 (31%) and Conformer 3 (3%)

are compared to experimental results in Figure 9 for two sample concentrations.

Agreement in sign and relative magnitude between most of the major observed and calculated VCD bands was achieved for the lowest-energy Conformer 1 (Figure 8). Improved agreement was obtained with a Boltzmann population-weighted sum of the calculated spectra (Figure 9). In particular, VCD features near 1300 and 1050 cm^{-1} in the observed VCD spectrum corresponded to a contribution from Conformer 2. No VCD features unique to Conformer 3 were found in the observed spectrum, which was consistent with the small population calculated for this conformer. The correlation of VCD bands was further supported by the corresponding correlation of relative intensities of the calculated and measured IR spectra. The discrepancies between observed and calculated spectra in the 1650 cm^{-1} region (large contributions from NH_2 deformation) may be attributable to NH−N dimer formation or interaction between the amino groups and $CDCl_3$ solvent, which are not included in the calculation and which can give rise to broadening and shifting of bands. Some changes in both the IR and the VCD spectra in this region were observed for a sample measured at half the concentration (Figure 9), confirming the assignment of broad IR features in the 1650 cm^{-1} region to aggregation in $CDCl_3$ solution, and showing agreement between observed and calculated (−/+) VCD couplet patterns in this region at lower concentrations. The intense, sharp VCD feature observed at 1450 cm^{-1} corre-

sponded to methyl antisymmetric deformation coupled to NH_2 scissors motion. This band correlated with the IR band and negative VCD feature calculated at 1483 cm^{-1}. Concentration-dependent bands were also observed in the 970−1070 cm^{-1} region, where NH_2 wag and twist contribute. Despite some differences in frequencies and relative intensities, the observed VCD features all correlated in sign with calculated VCD features, and with this degree of correlation between the measured and the calculated VCD spectra, the assignment of the absolute configuration of (+)-**1** as (*R*) could be made without uncertainty. Calculations for the only alternative, those corresponding to the (*S*) enantiomer, would result in the reversal in sign of all the VCD bands, which would produce very poor agreement with experiment. In addition to the identification of the absolute configuration, the VCD study provided information on the conformations populated in solution.

Conclusion

Two of the independent CD methods used to determine the absolute configuration of 1-(9-phenanthryl)ethylamine (**1**) − the Zn−porphyrin host-guest CD exciton chirality method [11] and the VCD method[12] − resulted in the assignment (+)-(*R*) (in CH_3Cl), in agreement with the observed stereochemical outcome of hydrogenation of α-oxo esters induced by (+)-**1**, Table 1.

The third approach, the dichromophoric exciton chirality method, based on conventional CD exciton coupling between two chromophores, turned out to be unreliable, due to the rather complicated electronic structure of the phenanthrene group. Some previous reports[10] had already demonstrated difficulties in application of the exciton chirality method to phenanthrene, due to the complexity of its electronic structure. Even when phenanthrene interacts with such a relatively simple and symmetric chromophore as the naphthimide, the observed CD is complex and does not allow straightforward configurational assignment. We can therefore conclude that the application of the phenanthrene chromophore to exciton chirality treatments may give rise to unpredictable results and so should in general be discouraged.

Interestingly, this finding also applies to other cases in which the application of the conventional exciton chirality method is structurally hampered either by conformational heterogeneity[36] or by coplanarity of coupled transition moments.[37] Our result stresses that, if the observed CD spectrum looks complicated and the diagnostic features unexpectedly weak, the exciton approach must be applied with caution and possibly checked against an independent assignment.

In contrast, the CD analysis based on the Zn−porphyrin tweezer method and the VCD method provided a straightforward assignment of the absolute configuration of **1**. The Zn−porphyrin tweezer CD method is a powerful new approach to determination of absolute configurations, which (unlike the exciton coupling method) does not require knowledge of the location and direction of transition moments within the molecule under study; in this case the observed CD reflects the induced chiral sense of twist between the two porphyrins in the host-guest complex, dictated by the steric factors in the chiral guest. It can also be used on microgram-quantities of sample or less.

The VCD method can be applied directly with the sample in solution without the need for chemical modification, whenever sufficient material for the acquisition of a high-quality IR spectrum is available. With current sampling techniques, this is usually a few milligrams. The VCD method also provides experimentally verifiable information on the predominant solution conformations of the molecule. The VCD method cannot currently be used with high reliability for molecules so large that the number of basis functions needed for a practical DFT calculation at the level of 6−31G*/B3LYP or higher is exceeded. That limit is currently approximately 1000 basis functions, or molecular weights exceeding approximately 500. Difficulties with the VCD method also arise for molecules with many significantly populated conformations under the experimental measurement conditions. In such cases, many VCD spectra must be averaged together, often with regions possessing a high degree of intensity cancellation, in order to compare calculated spectra to experimental spectra. For the current study, none of these limitations was encountered, and the assignment of absolute configuration, based on fitting of the *entire* observed VCD (and IR) spectrum of the *underivatized* molecule, could be made without any ambiguity or uncertainty.

Experimental Section

1-(9-Phenanthryl)ethylamine (**1**) (racemic and enantiopure) has been described and fully characterized (cf. ref.[5]). Reagents **4** and **5** are well-known and often-used compounds.

(*R*)-*N*-[1-(9′-Phenanthryl)ethyl]-2,3-naphthimide (2): This compound was prepared from **1** (57.2 mg) and 2,3-naphthalenedicarboxylic anhydride,[13] and purified from unchanged **1** by filtration through silica gel (ethyl acetate, R_f = 0.85). The anhydride was prepared from the corresponding diacid[13b] and sublimed at 160 °C/2 Torr before use. ^{1}H NMR (300 MHz): δ = 2.13 (d, *J* = 7.0 Hz, 3H, CH_3), 6.38 (q, *J* = 7.0 Hz, 1H, $C^{\alpha}H$), 7.57−7.66 (m, 6H, H^2, H^3, H^6, H^7, $H^{6'}$), 7.97−8.02 (m, 3H, H^1, $H^{5'}$), 8.24 (s, 2 H, $H^{1'}$), 8.25 (dd, *J* = 6.5, 3.5 Hz, 1 H, H^8), 8.25 (s, 1 H, H^{10}), 8.64 (dd, *J* = 7.0, 1.5 Hz, 1 H, H^4), 8.71 (dd, *J* = 6.5, 3.5 Hz, 1 H, H^5).

Derivative 3: This compound was prepared from compound **1** (3.5 mg) and carrier **4** by a two-step procedure, in 86% combined yield.[11a] ^{1}H NMR (CD_3OD, 300 MHz): δ = 8.83 (dd, *J* = 1.5, 8 Hz, 1 H), 8.72 (d, *J* = 8.0 Hz, 1 H), 8.67 (d, *J* = 5.0 Hz, 1 H), 8.24 (dd, *J* = 1.5, 8 Hz, 1 H), 8.18 (s, 1 H), 7.90 (s, 1 H), 7.87 (dd, *J* = 1.5, 8 Hz, 1 H), 7.52−7.67 (m, 5 H), 6.08 (q, *J* = 7.0 Hz, 1 H), 4.23 (s, 2 H), 1.82 (d, *J* = 7.0 Hz, 3 H). FAB-HRMS: calcd. for $C_{23}H_{22}ON_3$ $[M + 1]^+$ 356.1763; found 356.1785. CD measurement of the host/guest complex **6** formed by zinc porphyrin tweezer **5** and derivative **3** was performed as described previously.[11a]

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[16] To account for the solvent effect, molecular mechanics MMFFs calculations in $CHCl_3$ were also carried out with the GB/SA solvation model implemented in MACROMODEL 7.0, Schrödinger, Inc., Portland, OR. A full relaxed scan around θ with steps of 15° resulted in two minima, which were further optimized to give the absolute minimum at θ = +92° and a relative minimum at −112° (+4 kcal/mol and barrier of 7 kcal/mol).
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[20] DeVoe's calculations were carried out by a computer routine by Hug and co-workers: C. L. Cech, W. Hug, I. Tinoco, Jr., *Biopolymers* **1976**, *15*, 131−152; with the experimental spectral parameters.[9,14] Dipole polarizations were inferred from CNDO calculations (Table 2) as shown in Figures 2 and 3. Dipoles 3 and III were placed in the centers of the C4a−C5a bond,[10a] and of the C9′−C10′ bond, respectively. To take the conformational distribution into account, DeVoe calculations were also carried out for structures obtained by starting from the minimum energy PM3 structure (**C1**) and by variation of the angle θ by ±40° around the value of 84°; the sign of the couplet [positive for (*R*)-**2**] was not found to be affected. The minor isomer (**C2**) in the (*R*) configuration gives rise to a weak negative couplet ($A = -26$, Figure 1 right) and, in view of its negligible population (about 0.1% corresponding to 4 kcal/mol energy difference), should not interfere in the result.
[21] Low-temperature CD spectra recorded in CH_2Cl_2 showed no substantial spectral change down to −75 °C, ruling out the possibility of the existence of multiple minimum-energy conformations.
[22] Even by including all the transitions detected by CNDO in the DeVoe calculations (Table 2), we could in no way entirely reproduce the observed CD spectrum of **2**. Its full interpretation is likely to require mechanisms of optical activity other than only the coupled oscillators to be taken into account, and is beyond the scope of this paper.
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