The *s*-Triazine Chromophore as a Probe for the Absolute Configuration Determination of (+)-1-(9-Anthryl)ethylamine by Circular Dichroism

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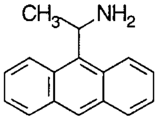
The absolute configuration of (+)-1-(9-anthryl)ethylamine was determined in nonempirical way by circular dichroism using *s*-triazine as suitable chromophore to give rise to an exciton coupling reflecting the stereochemistry of the amine.

Introduction

Optically active 1-arylethylamines are widely used chiral auxiliaries. In fact, for many years they have been used as resolving agents for racemic acids[1] and for the preparation of Pt(II) complexes, useful tools to separate simple alkenes.[2] In more recent years, this kind of compound has been employed, sometimes after simple derivatizations, to prepare chiral stationary phases (CSPs) for HPLC[3] or as chiral solvating agents[4] (CSAs) and chiral derivatizing agents for NMR spectroscopy.[4,5] In particular, optically active 1-(9-anthryl)ethylamine (**1**) (ANTEA) (Chart 1) has been recently synthesized and used as CSA for the NMR determination of the enantiomeric composition of carboxylic acids.[6] However, despite the usefulness and the potential of this compound in the field of the chiral recognition, to the best of our knowledge, its absolute configuration has never been reported.

The problem of the determination of the absolute configuration of the enantiomers of ANTEA can be nicely solved by circular dichroism (CD) spectroscopy, after a suitable modification of its structure. Indeed **1** possesses a chromophore, the anthracene, the electronic transitions of which are well characterized:[7] in particular, its UV spectrum shows, in addition to an absorption band of medium intensity at 360 nm ($\epsilon = 7600$) with complex vibrational structure assigned to the ^1L_a transition polarized along the short axis of the chromophore, a very intense absorption band at 252 nm ($\epsilon = 204\,000$) assigned to the ^1B_b transition polarized along the long axis of the anthracene[7] (Chart 2). By introducing in **1** a second chromophore having well-defined electrically allowed transitions, exciton coupling effects could be observed by CD spectroscopy.[8] As it is well-known, the analysis of the exciton coupling affords a simple and reliable nonempirical way for assigning absolute configurations.[8]

Chart 1



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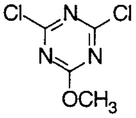

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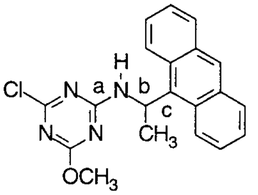

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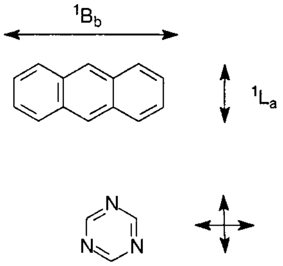
Chart 2



In this case we decided to introduce the second chromophore necessary for the exciton coupling by reacting **1** with the dichloro-*s*-triazine derivative **2**, obtaining a stable ANTEA-substituted *s*-triazine derivative (Chart 1) having the same absolute stereochemistry of **1**, since the nucleophilic displacement of the chlorine atom does not involve the stereogenic center of **1**. The UV spectrum of the *s*-triazine chromophore shows an absorption band at about 220 nm ($\epsilon = 45\,000$) assigned to an electrically

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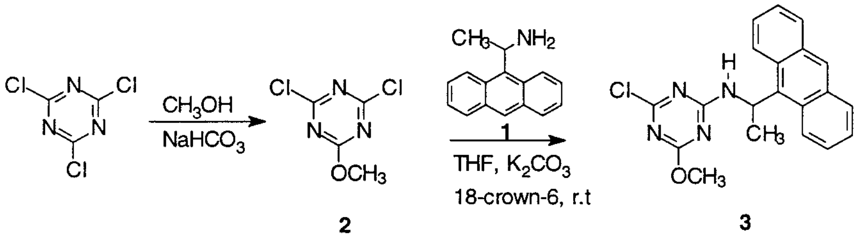
Scheme 1



allowed doubly degenerate transition whose components are polarized in the plane of the chromophore[9] (Chart 2). This transition can be used for the stereochemical assignment of **1**: in fact, the analogous 1-(1-naphthyl)-ethylamino derivative shows in the CD spectrum an exciton couplet due to the coupling of the electrically allowed transitions of the naphthalene and *s*-triazine chromophores.[10]

Results and Discussion

(+)-1-(9-Anthryl)ethylamine **1**, having an enantiomeric purity of >98%, was prepared according to the Khun and Buddrus method.[6] The derivative **3** was obtained starting from *s*-trichlorotriazine, following the reaction sequence reported in the scheme.

The first reaction was carried out in a methanol−water mixture employing NaHCO$_3$ as a base, according to the Dudley[11] et al. procedure. The displacement of the second chlorine atom was performed using phase-transfer catalysis conditions: THF as solvent, an equivalent of K$_2$CO$_3$ as base, and 18-crown-6 as phase-transfer catalyst.[12] The reaction, monitored by TLC, required 4 days of stirring at room temperature to be completed: the crude product, obtained after filtration of the mixture and evaporation of the solvent, was purified by column chromatography, affording pure **3** in 75% yield (Scheme 1). Structural assignments were carried out by NMR spectroscopy. The ^{1}H NMR spectrum of **3** shows, at room temperature, two sets of signals for each proton or group of protons, which coalesce at about 120 °C. They are attributable to the presence of two conformers, which are slowly exchanging at room temperature, due to the restricted rotation around the a, b, and c bonds of **3** (Chart 1). These isomers are in a 70/30 ratio, as evaluated on the basis of the integral values, and are differentiated by the distance between the methoxy and the anthryl groups. Such a distance is higher in the less-populated conformer, as deducible on the basis of the chemical shift values: in fact, the methoxy protons belonging to the less populated conformer are deshielded in respect to the same protons of the more populated conformer, because they feel the diamagnetic anisotropy of the anthryl moiety to a minor extent. On the basis of the coupling constant of the NH and CH, the dihedral angle between the NH and CH bonds has been calculated to be 130° or 40°, using a modified Karplus correlation for the NH−CH moiety.[13] The definitive assessment of the 130° value to this angle was performed on the basis of the inter NOE effect[14] (see spectra recorded in DMSO-d_6 in the Supporting Information), which shows the NH and CH protons are far from each other.

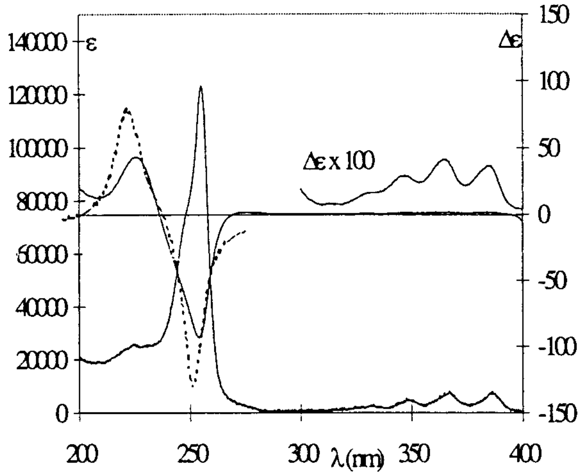


Figure 1. UV and CD spectra (solid lines) and CD calculated spectrum (dashed line) of (+)-2-[-1-(9-anthryl)ethylamino]-4-chloro-6-methoxy-1,3,5-triazine (**3**).

The UV spectrum of **3** (Figure 1) shows an absorption band, having a complex vibrational structure, at 360 nm ($\epsilon = 9000$) and a strong absorption band at 255 nm ($\epsilon =$ 150 000) attributable respectively, on the basis of the previous discussion, to the ^1L_a and ^1B_b transitions of the anthracene chromophore and an absorption at 225 nm (ϵ = 25 000) assignable[9] to the electrically allowed transition of the *s*-triazine chromophore. The CD spectrum shows a positive band at 360 nm, having a complex vibrational structure, attributable to the asymmetrically perturbed ^1L_a transition and two Cotton effects having opposite sign, the first one at 255 nm ($\Delta\epsilon = -95$) and the second one at 225 nm ($\Delta\epsilon = 45$). These are likely the two components of an exciton couplet centered at 230 nm ($\Delta\epsilon = 0$) due to the coupling of the electrically allowed transitions of the anthracene and *s*-triazine chromophores.[15]

To carry out a spectrum−stereochemistry relationship, we needed to know the prevailing conformations of **3**, which were obtained by means of the program PC-MODEL (MMX force field), after imposing structural

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[14] Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect*; VCH Publishers: New York, 1989.

[15] The CD spectrum of tris[(*S*)-1-cyclohexylethylamino]-1,3,5-triazine, used as model compound for the asymmetrically perturbed *s*-triazine chromophore, shows a positive Cotton effect at 240 nm ($\Delta\epsilon$ = 1) and a negative one at 215 nm ($\Delta\epsilon = -5$) (see Supporting Information).

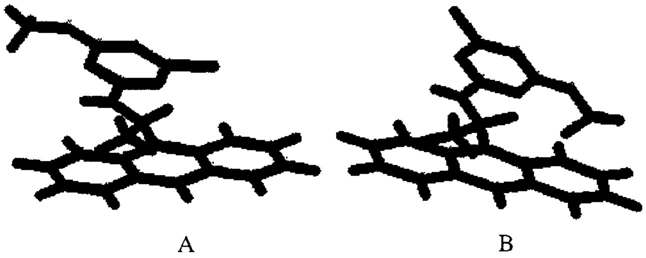

Figure 2. Minimum energy conformers (A and B) of (*R*)-2-[-1-(9-anthryl)ethylamino]-4-chloro-6-methoxy-1,3,5-triazine (**3**).

restrictions on the basis of the information coming from the previously discussed NMR results, and assuming the *R* absolute configuration for the stereogenic center of **3**. Two energy minima were obtained, corresponding to the two structures depicted in Figure 2. The absolute configuration of **3** can be now determined by means of coupled oscillator calculations of the CD spectrum, according to the DeVoe model.[16] The DeVoe calculations require two sets of input parameters: the geometry of the aggregate of chromophores and the description of the spectroscopic characteristics of the same chromophores. Therefore, the minimum energy conformations depicted in Figure 2 were used as starting geometries, while the electrically allowed transitions were represented as follows. The ^1B_b transition of the anthracene chromophore was described by means of a single dipole located in the center of the anthracene and directed along its long axis: a dipolar strength of 87 D^2 was attributed to it, according to the intensity of its UV absorption band.[7] Two dipoles located in the center of the triazine ring and directed perpendicularly to each other were used to describe the electrically allowed transition of this chromophore: a dipolar strength of 25 D^2 was attributed to this transition, on the basis of the UV spectrum of a suitable model compound.[10]

In Figure 1 is depicted the CD calculated spectrum which is the mean value of the CD-calculated spectra of the two conformers, taking into account their relative population. The agreement between the experimental spectrum and the calculated one allows us to conclude that the absolute configuration at the stereogenic center of **3** is *R*. Therefore, given that the nucleophilic displacement of the chlorine atom of **2** does not involve the stereogenic center of **1**, the *R* absolute configuration can be also assigned to (+)-1-(9-anthryl)ethylamine showing a positive sign of the optical rotation at 589 nm.

Thus, **3** resulted a suitable compound for the absolute configuration assignment of (+)-ANTEA by CD spectroscopy. Therefore the *s*-triazine chromophore could be a probe for the exciton-coupling circular dichroism assignment of the absolute configuration of amines possessing a suitable aryl chromophore in their structure.

Experimental Section

Melting points were taken using a Reichart Termovar apparatus and are uncorrected. Optical rotations were measured on digital polarimeter in 1-dm tube. TLC analysis were performed using silica gel plates (Si 60). Flash chromatography was performed using silica gel (230−400 mesh). Elemental analyses were performed by the Microanalytical Laboratory of University of Pisa.

NMR measurements were performed on a spectrometer, operating at 300 MHz for ^{1}H, equipped with a temperature control unity (±0.1 °C). Signal position are reported in ppm downfield from tetramethylsilane as an external standard; the number of protons, multiplicity, and proton assignments are indicated in parentheses. The phase-sensitive 2D ROESY spectrum was acquired with a spectral width of 3500 Hz in 2K data points using 8 scans for each of 512 t_1 increments. The spin-lock time was set to 300 ms. The data were zero-filled to 2K × 1K, and a Gaussian function was applied for processing in both dimension.

Circular dichroic spectra were obtained on a spectropolarimeter using a 0.1-mm path length cell and spectropolarimetric grade acetonitrile as a solvent. Sample concentration for CD analysis were typically (6−9) × 10^{-4} M. UV−vis absorption spectra were obtained on a spectrophotometer using a 0.1-mm path length cell and spectrophotometric grade acetonitrile as a solvent. Sample concentration of UV−vis analysis were typically (6−9) × 10^{-4} M.

Materials. Tetrahydrofuran (THF) was distilled from Na/K alloy, methanol was distilled from magnesium. 2,4,6-trichloro-1,3,5-triazine was recristallized from CCl_4. (+)-1-(9-Anthryl)-ethylamine[6] and 2,4-dichloro-6-methoxy-1,3,5-triazine[11] were prepared as previously described and matched the reported characteristics.

(+)-2-[1-(9-Anthryl)ethylamino]-4-chloro-6-methoxy-1,3,5-triazine (3). To a solution of 2,4-dichloro-6-methoxy-1,3,5-triazine (0.16 g, 0.889 mmol) in dry THF (7 mL) were added K_2CO_3 (0.13 g, 0.889 mmol) and a catalytic amount of 18-crown-6. To this mixture, a solution of (+)-1-(9-anthryl)-ethylamine (0.2 g, 0.905 mmol) in dry THF (10 mL) was added dropwise at room temperature. After 4 days of stirring at room temperature and monitoring the reaction by TLC (SiO_2; hexanes−ethyl acetate 6:4), the mixture was filtered on a pad of silica gel, and the solvent was removed at reduced pressure. The crude product was purified by column chromatography (SiO_2; hexane−ethyl acetate 6:4), affording 0.227 g (75% yield) of chemically pure **3**: mp 169−171 °C; $[\alpha]_D^{25} = 4.35$ ($c = 1.04$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm) 8.31 (m, 3H, aromatics), 7.95 (d, 2H, aromatics), 7.38 (m, 4H, aromatics), 6.62 (q, 1H, CH), 6.54 (q, 1H, CH), 6.47 (d, 1H, NH), 6.43 (d, 1H, NH), 3.78 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 1.96 (d, 3H, CH_3); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm) 9.84 (d, 1H, NH, J 5.2 Hz), 9.68 (d, 1H, NH, J 5.2 Hz), 8.69 (d, 1H, H peri), 8.52 (s,1H), 8.22 (m, 1H), 8.08 (d,1H, H peri), 7.93 (m,1H), 7.51 (m,-4H), 6.46 (m, 1H, CH), 3.81 (s, 3H, OCH_3), 3.05 (s, 3H, OCH_3), 1.87 (d, 3H, CH_3), 1.82 (d, 3H, CH_3). Anal. Calcd: C, 65.84; H, 4.70; Cl, 9.72; N, 15.36. Found: C, 65.92; H, 4.70; Cl, 9.71; N, 15.34.

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Supporting Information Available: UV and CD spectra, 2D ROESY spectrum, and ^{1}H NMR spectrum (in DMSO-d_6 and $CDCl_3$). This material is available free of charge via the Internet at http://pubs.acs.org.

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