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Circular Dichroism Determination of the Conformation of Optically Pure 1-(1-Naphthyl)ethylamino-Substituted 1,3,5-Triazine Derivatives

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CD data of the optically pure 2-ethoxy-4-hexylamino-6-[1-(1-naphthyl)ethylamino]-1,3,5-triazine, 2-chloro-4,6-bis[1-(1-naphthyl)ethylamino]-1,3,5-triazine, and 2,4,6-tris[1-(1-naphthyl)ethylamino]-1,3,5-triazine are presented. The analysis of the CD spectra has afforded the conformational characterization of the three 1,3,5-triazine derivatives. A detailed definition of the stereochemistry of these compounds has been obtained by a computing DeVoe approach, using NMR information for the assumed conformation.

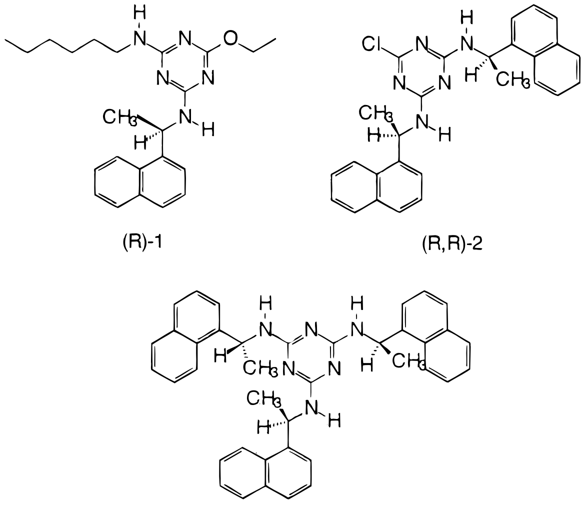
Introduction

2,4,6-Trichloro-1,3,5-triazine (s-trichlorotriazine) is a heteroaromatic compound having a high reactivity toward nucleophilic reagents. This characteristic has been exploited to obtain different s-triazine derivatives, which have been employed as drugs,[1] agrochemicals,[2] dyes,[3] or synthetic receptors.[4] Through the reaction of s-trichlorotriazine or a dichlorotriazine derivative with optically active 1-(1-naphthyl)ethylamine as nucleophile, a series of chiral derivatives have been prepared and used as selectors for the HPLC separation of enantiomers, after being linked to silica gel.[5]

We have recently found the optically active 1-(1-naphthyl)ethylamino-substituted 1,3,5-triazine derivatives **1**−**3** (Chart 1) can be successfully used as chiral solvating agents (CSAs) for the NMR determination of the enantiomeric composition of chiral compounds, the derivative **3** being the most efficient and versatile chiral auxiliary.[6]

To gain some insight on the origin of their different stereodifferentiating capability, we have been prompted to establish the conformational features of the three chiral triazine derivatives.

Chart 1



(R)-1

(R,R)-2

(R,R,R)-3

The circular dichroism (CD) spectroscopy appears highly suitable because compounds **1**−**3** possess two chromophores, naphthalene and s-triazine, having electrically allowed well-characterized electronic transitions.[7,8]

Electrically dipole-allowed transitions located in a chiral system can interact between themselves giving rise, in the CD spectrum, to a characteristic bisignate curve named exciton couplet. The sign and the intensity of the couplet depend on the overall chemical structures of the compounds. This approach has been used for the nonempirical assignment of the absolute configuration of compounds which possess either the suitable chromophores in their structure or introduce them by derivatization of adequate functional groups present in the molecule.[9] The electrically dipole-allowed transitions of

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[5] (a) Oi, N.; Nagase, M.; Sawada, Y. *J. Chromatogr. A* **1984**, *292*, 427. (b) Iuliano, A.; Pieroni, E.; Salvadori, P. *J. Chromatogr. A* **1997**, *786*, 355. (c) Lin, C. E.; Li, F. K.; Lin, C. H. *J. Chromatogr. A* **1996**, *722*, 211. (d) Lin, C. E.; Li, F. K.; Lin, C. H. *J. Chromatogr. A*, **1996**, *722*, 189.

[6] (a) Uccello-Barretta, G.; Iuliano, A.; Menicagli, R.; Peluso, P.; Pieroni, E.; Salvadori, P. *Chirality*, **1997**, *9*, 113. (b) Uccello-Barretta, G.; Iuliano, A.; Franchi, E.; Balzano, F; Salvadori, P. *J. Org. Chem.* **1998**, in press.

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[9] Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy, Exciton coupling in Organic Stereochemistry*; University Science Books: Oxford, 1980.

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Table 1. UV and CD Data (Acetonitrile Solutions) for Compounds 1−4

	ϵ		$\Delta\epsilon$				
compd	$\lambda = 280$ nm	$\lambda = 220$ nm	$\lambda = 280$ nm	$\lambda = 225$ nm	$\lambda = 217$ nm	$\lambda = 210$ nm	$\Delta\epsilon$ (210)−$\Delta\epsilon$ (225)
(*R*)−**1**	5 000	78 000	5	−100	0	70	170
(*R*,*R*)−**2**	20 000	135 000	25	−200	0	150	350
(*R*,*R*,*R*)−**3**	15 000	153 000	17	−270	0	191	461
(*R*,*R*,*S*)−**4**	14 000	141 000	5	−87	0	63	150

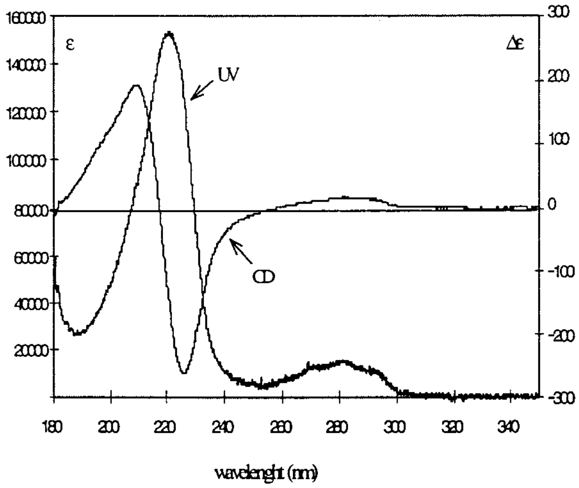

Figure 1. Absorption and CD spectra (acetonitrile solution) of 2,4,6-tris[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**3**).

the compounds **1**−**3** can give rise to exciton couplets, whose sign and intensity reflect the stereochemistry of the molecules. Since the absolute configuration of the 1-(1-naphthyl)ethylamino moieties is known, the presence of an exciton couplet can be used to determine the conformation of the compounds.

Therefore, the aim of this work is to show how a CD-based approach allows us to define the stereochemical features of compounds **1**−**3**.

Results and Discussion

The s-triazine derivatives **1**−**3** possess two chromophores, naphthalene and s-triazine. The former shows an intense absorption band at 220 nm ($\epsilon = 104\,000$), assigned to the electrically allowed ^1B_b transition polarized along the long axis of the naphthalene, and a band at 280 nm ($\epsilon = 5700$), assigned to the ^1L_a transition, polarized along its short axis.[7] The 1,3,5-triazine chromophore shows a strong absorption band at about 210−220 nm ($\epsilon = 45\,000$), assigned to an electrically allowed doubly degenerate transition whose two components are polarized in the plane of the s-triazine ring.[8]

The UV spectrum of **3** (Figure 1) shows an absorption band at 280 nm ($\epsilon = 15\,000$) attributable to the ^1L_a transition of the naphthalene chromophores and a very strong band at 220 nm ($\epsilon = 153\,000$) due to the ^1B_b transition of the naphthalene chromophores and to the electrically allowed doubly degenerate transition of the triazine ring. In the CD spectrum (Figure 1), a positive Cotton effect at 280 nm ($\Delta\epsilon = 17$) and two strong bands at 225 nm ($\Delta\epsilon = -270$) and at 210 nm ($\Delta\epsilon = 191$) are present, which are reasonably the two components of an exciton couplet centered at 217 nm ($\Delta\epsilon = 0$) arising from the coupling of the electrically allowed transitions of the naphthalene and s-triazine chromophores.

To have an exciton couplet in the CD spectrum of a compound, the involved chromophores have to assume a statistically definite reciprocal orientation: in particular, in this case, taking into account the polarization direction of the ^1B_b transition dipole moments, the 1-naphthyl groups are not free to rotate, because free rotation of each group would prevent the coupling with the other transitions, owing to the innumerable orientations that the transition dipole moment can assume.[9]

Therefore, the first information afforded by the CD spectrum of **3** (Figure 1) is the highly reduced conformational freedom of the 1-naphthyl groups.

In principle, an exciton couplet in the CD spectrum of **3** could be originated by the coupling of the naphthalene transitions with the transition of the triazine or of the naphthalene transitions each other or by a combination of the two possibilities. The analysis of the CD spectra of **1** and **2** can help us in the interpretation of the CD spectrum of **3**. Both of these compounds show CD spectra quite similar to the spectrum of **3** as far as position, shape, and sign of the bands are concerned: the only difference is the intensity of the bands, which, practically, doubles going from **1** to **2** and triples going from **1** to **3** (Table 1). Given that only one 1-(1-naphthyl)ethylamino moiety is present in **1**, the exciton couplet in the CD spectrum of this compound is certainly attributable to a coupling between the ^1B_b transition of the naphthalene chromophore and the electrically allowed transition of the triazine ring. The similarity of the spectra and their additivity suggest that also in the case of **2** and **3** pairwise interactions occur between the triazine transition and the ^1B_b transition of each naphthalene chromophore. Furthermore, the orientation of each 1-(1-naphthyl)ethylamino moiety with respect to the triazine ring must be almost the same in **1**, **2**, and **3**: in fact, it is well-known that the amplitude of the split-type Cotton effects in systems whose chromophores are exciton-coupled depends on the dihedral angle between the transition dipole moment vectors of the two coupled chromophores.[9] The same reciprocal orientation of the triazine and naphthalene chromophores in compounds **1**−**3** suggests that the conformation assumed by each 1-(1-naphthyl)ethylamino moiety is almost the same in each compound; therefore, it does not depend on the nature of the other substituents on the triazine ring, but it is attributable to the conformational control arising only from the 1-(1-naphthyl)-ethylamino group linked to the triazine nucleus. To confirm this interpretation, the UV and CD spectra (Table 1) of 2,4-bis[(*R*)-1-(1-naphthyl)ethylamino]-6-[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**4**), the epimer of **3**, were recorded: if the conformation assumed by each 1-(1-naphthyl)ethylamino moiety in respect to the triazine ring depends only on its own conformational control, the contributions to the CD spectrum of the two groups having opposite absolute configuration will be mutually canceled. The CD spectrum of **4** is quite similar to the CD spectrum of **1** as far as shape, position, intensity, and sign of the bands are concerned: therefore, the CD spectrum of **4** looks like a CD spectrum of a mono 1-(1-naphthyl)ethylamino-substituted 1,3,5-triazine having

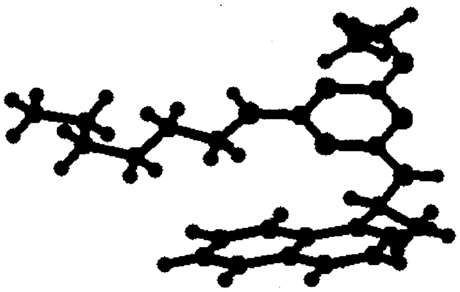

Figure 2. Minimum energy conformation of 2-ethoxy-4-hexylamino-6-[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**1**).

Table 2. Comparison between Experimental and Calculated CD Data for Compounds 1−3

	ϵ		$\Delta\epsilon$					
	$\lambda = 220$ nm		$\lambda = 225$ nm		$\lambda = 217$ nm		$\lambda = 210$ nm	
compd	exptl	calcd	exptl	calcd	exptl	calcd	exptl	calcd
(*S*)−**1**	78 000	70 000	100	100	0	0	−70	−100
(*S*,*S*)−**2**	135 000	125 000	200	220	0	0	−150	−240
(*S*,*S*,*S*)−**3**	153 000	158 000	270	320	0	0	−191	−320

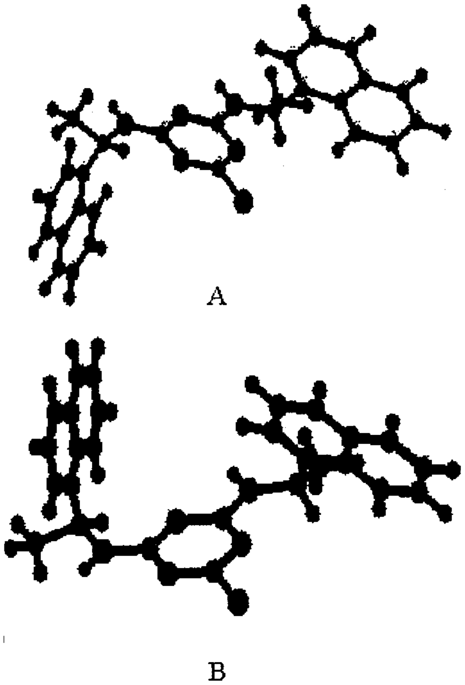

Figure 3. Minimum energy conformation of the C_2-symmetric conformer (A) and of the nonsymmetric one (B) of 2-chloro-4,6-bis[(S)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**2**).

(R) absolute configuration, the contributions of the two moieties having opposite absolute configuration being mutually canceled, confirming the above interpretation of the CD spectra of **2** and **3**.

Although the information afforded by the analysis of the CD spectra of **1**−**3** has given us a picture of some structural characteristics of these compounds, the conformation assumed by the molecules must be better defined. A suitable approach is the coupled oscillator calculations using the DeVoe model.[10]

According to this model each allowed transition is represented in terms of experimental data such as polarization direction and dipolar strength, using the ultraviolet spectra of suitable model compounds.[11]

As starting geometries, for carrying out these calculations, minimum energy conformations, obtained by means of the program PC MODEL (MMX force field), were employed. The minimum energy conformations of the three derivatives were obtained placing restrictions coming from the NMR investigation. This afforded the conformation of each single 1-(1-naphthyl)ethylamino moiety which has been found very similar for the three derivatives. The determination of the inter NOEs by 2D ROESY analysis allowed us to establish that, as expected, the C*−H bond is nearly coplanar to the naphthyl plane and transoid to the NH bond.[12] This has been also fully confirmed by correlating the vicinal coupling constants N−H/C*−H to the involved dihedral angle.[13] In fact this last has been calculated as 140°, corresponding to the coupling value of 7.4 Hz.

At the beginning we have calculated the CD spectrum of **1**, using the minimum energy conformation depicted in Figure 2: the excellent agreement (Table 2) between the experimental and the calculated CD values confirm that the minimum energy conformation used for the calculation is the prevailing one assumed in solution by compound **1,** as far as the relative disposition of the 1-(1-naphthyl)ethylamino moiety and the s-triazine ring is concerned. Taking into consideration the additivity of the CD spectra and, therefore, placing the second 1-(1-naphthyl)ethylamino moiety so that it has the same conformation of the first moiety, we have obtained the starting geometry for compound **2**. Its ^{1}H NMR spectrum, recorded in DMSO-d_6 as a solvent at room temperature, shows two sets of signals for each proton or group of equivalent protons, having relative intensities of 2:1. These corresponded to two conformers, a C_2-symmetric one and a nonsymmetric one, which are slowly exchanging at room temperature. In Figure 3 are depicted the minimum energy conformations corresponding to the two conformers: we have performed DeVoe calculations for each conformer, and the mean value of the CD calculated spectra, taking into consideration the relative populations of the two isomers, is in good agreement with the experimental data (Table 2). It is noteworthy that using CD spectroscopy, flanked by DeVoe calculations, we can attribute to the C_2-symmetric conformer of **2** the conformation A depicted in Figure 3, given that starting from the other C_2 conformation, in which the two NH protons are directed toward the chlorine atom, a calculated CD spectrum in agreement with the experimental one is not obtained.

As far as compound **3** is concerned, we recorded CD spectra at low temperatures, until −40 °C (Figure 4). On lowering the temperature, only small differences in the relative intensities of the CD spectra are observed,

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[10] Rosini, C.; Zandomeneghi, M.; Salvadori, P. *Tetrahedron: Asymmetry* **1993**, 2261.

[11] The ^1B_b transition was described by means of a single dipole, located in the center of the naphthalene system and directed along the long axis of this chromophore; a dipolar strength of 49 D,[2] centered at 220 nm was attributed to it, according to the intensity of this transition.[7] Two dipoles located in the center of the triazine nucleus and directed perpendicularly to one another were used to describe the electrically allowed doubly degenerate transition of the triazine chromophore: a dipolar strength of 25 D^2 centered at 220 nm was attributed to it, on the basis of the UV spectrum of the 2,4,6-tris-[(*S*)-1-cyclohexylethyl]-1,3,5-triazine,[14] used as a model compound.

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

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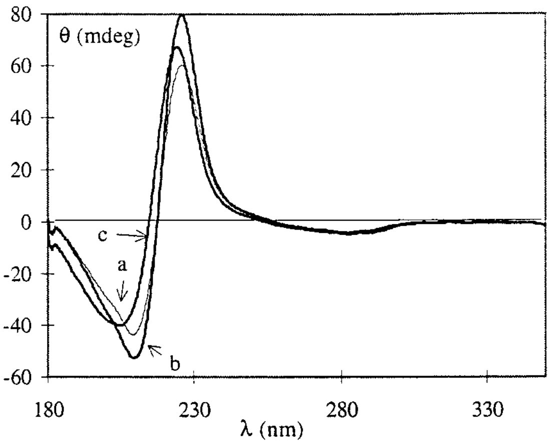

Figure 4. CD spectra (acetonitrile solutions) of 2,4,6-tris[(*S*)-1-(1-naphthyl) ethylamino]-1,3,5-triazine (**3**) at (a) room temperature, (b) −20 °C, and (c) −40 °C.

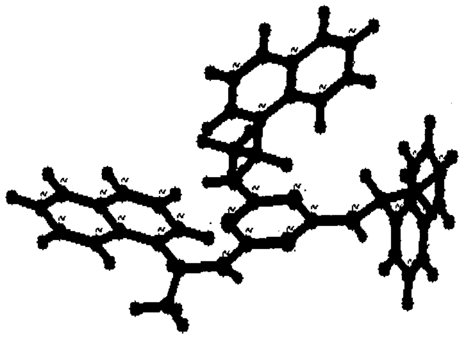

Figure 5. Minimum energy conformation of 2,4,6-tris[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**3**).

probably due only to slower molecular motions and to a change in the viscosity of the medium: therefore, we can conclude that **3** is present, at room temperature, as a largely prevalent isomer.[15] This is confirmed by the NMR measurements which show this compound is present, at room temperature, as a single isomer having two 1-(1-naphthyl)ethylamino moieties fully equivalent, differentiated by the third. This information allows us to exclude for **3** a conformation where each NH proton is directed toward the NH nitrogen of the other 1-(1-naphthyl)-ethylamino moiety; however, whereas it is according to a conformation where two 1-(1-naphthyl)ethylamino moieties place their NH protons toward each other. Therefore, taking into account this information and starting from the minimum conformation of **2** we have obtained, for compound **3**, the minimum energy conformation depicted in Figure 5, whose calculated CD spectrum is in keeping with the experimental one[16] (Table 2).

In conclusion, this approach has shown the great potentiality of CD spectroscopy for establishing, in a nonempirical way, the stereochemical features of the 1-(1-naphthyl)ethylamino-substituted 1,3,5-triazine derivatives also in the presence of a high degree of symmetry.

Experimental Section

NMR measurements were performed on a spectrometer operating at 300 MHz for ^{1}H, equipped with a temperature control unity (±0.1 °C). The 2D NMR spectra were obtained using standard sequences. The double quantum filtered DQF−COSY experiments were recorded with a spectral width of 3000 Hz; 512 increments of 8 scans and 2K data points were acquired. The relaxation delay was 5 s. The data were zero-filled to 2K × 1K, and a Gaussian function was applied for processing in both dimension. The phase-sensitive 2D ROESY spectra were acquired with a spectral width of 2000−3000 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 dimensions.

Circular dichroic spectra were obtained on a recording spectropolarimeter using a 0.1-mm path length cell and spectropolarimetric grade acetonitrile as a solvent, at 25 °C, unless otherwise specified. Sample concentration for CD analysis were typically (6−9) × 10^{-4} M. UV−vis absorption spectra were obtained using a 0.1-mm path length cell and spectrophotometric grade acetonitrile as a solvent, at 25 °C. Sample concentration of UV−vis analysis were typically (6−9) × 10^{-4}M.

Materials. All the optically pure 1-(1-naphthyl)ethylamino-substituted 1,3,5-triazine derivatives were prepared as previously described[6] and matched the reported characteristics.[6]

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[15] Salvadori, P.; Lardicci, L.; Menicagli, R.; Bertucci, C. *J. Am. Chem. Soc.* **1972**, *94*, 8598.

[16] In light of the conformations obtained by means of DeVoe calculations of the CD spectra, the explanation for the absence of naphthyl−naphthyl coupling in the di- and trisubstituted triazine derivatives is the nearly perpendicular relationship of the transition dipole moments of the naphthalene chromophores, which results in the disappearance of the exciton coupling, that could be expected taking into account the interchromophoric distance and the intensity of the transitions.