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# A New Case of Induced Helical Chirality in a Bichromophoric System: Absolute Configuration of Transparent and Flexible Diols from the Analysis of the Electronic Circular Dichroism Spectra of the Corresponding Di(1-naphthyl)ketals

**Sabina Tartaglia, Francesca Pace, Patrizia Scafato, and Carlo Rosini***

*Dipartimento di Chimica, Università della Basilicata, via N. Sauro 85,*
*85100 Potenza, Italy*

*carlo.rosini@unibas.it*

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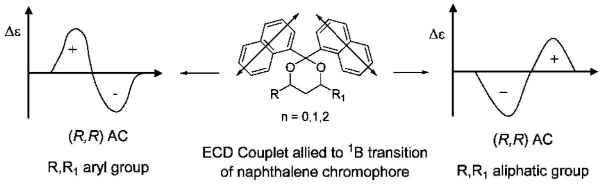
## ABSTRACT



**Di(1-naphthyl)ketals of 1,*n*-diols show couplet effects allied to the $^1$B naphthalene transition in their CD spectra. This means that they assume a conformation with a prevailing sense of twist of the naphthalene rings, imposed by the absolute configuration (AC) of the starting diols and by the nature of the R$_1$ groups. A positive couplet for aliphatic diols is a probe of (*R,R*), AC while the opposite sign is found for (*R,R*) aromatic diols.**

Nowadays, the analysis of the chiroptical properties (optical rotation (OR), electronic circular dichroism (ECD), vibrational circular dicroism (VCD)) carried out by nonempirical methods such as the exciton model[1,2] or the use of ab initio techniques[2,3] can provide a safe assignment of the molecular absolute configuration (AC). However, in spite of these significant progresses, some problems still remain: in particular, the treatment of the electronic chiroptical properties of all those compounds showing small $[\alpha]_D$ and/or weak ECD signals, such as aliphatic alcohols, diols, ethers, amines, and so on. In fact, such compounds are species without typical UV−vis chromophores which, in addition, present a large conformational flexibility so that many conformers showing different (even opposite) OR values and/or ECD spectra are simultaneously present, leading to a weighted average value which is small. This fact constitutes then the main obstacle to a straightforward analysis of the chiroptical data and then

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(3) For a general discussion of the ab initio calculation of chiroptical properties: (a) Polavarapu, P. L *Chirality* **2002**, *14*, 768–781. (b) Pecul, M.; Ruud, K. *Adv. Quantum Chem.* **2006**, *50*, 185–227. (c) Crawford, T. D. *Theor. Chem. Acc.* **2006**, *115*, 227–245. (d) Polavarapu, P. L. *Chem Record* **2007**, *7*, 125–136. (e) Crawford, T. D.; Tam, M. C.; Abrams, M. L. *J. Phys. Chem. A* **2007**, *111*, 12057–12068. (f) Stephens, P. J. In *Computational Medicinal Chemistry for Drug Discovery*; Bultinck, P.,; de Winter, H.,; Langenaecker, W.,; Tollenaere, J., Eds.; Dekker: NY, 2003; Chapter 26, pp 699−725.

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to a reliable AC determination. For a few years we have been involved in a research project aimed at providing some solutions to this difficult problem. Thus we decided to transform the flexible, transparent compounds in chromophoric, conformationally defined derivatives: the analysis of the electronic chiroptical properties of these systems should result as more simple and reliable, guaranteeing a safe AC assignment.[4] The same kind of approach has been recently used by Stephens and co-workers[5] to facilitate the analysis of the VCD spectra of (−)-borneol. The flexible, transparent aliphatic molecules we treated were mainly 1,*n*-diols,[4b] and we present herein a new type of chemical derivatization of some transparent 1,*n*-diols (compounds **1**) in the corresponding conformationally defined di(1-naphthyl)ketals, **2**. The reasons of the above derivatization are as follows: these compounds are easily synthesized from di(1-naphthyl)ketone and the corresponding 1,*n*-diol. In this way, on passing from the starting, *acyclic* 1,*n*-diols **1** to the *cyclic* compounds **2**, we certainly will have a reduction of the conformational freedom. The introduction of the naphthyl chromophore gives two remarkable advantages: (a) the α-substitution provides derivatives characterized by reduced conformational mobility owing to the presence of the steric effect of the *peri* hydrogen in 1-naphthyl-substituted compounds; (b) the naphthyl chromophore possesses the electrically allowed transition ${}^1B_b$ at 220 nm, with high $\varepsilon$ value (90 000 ca.) and with known (long-axis) polarization direction.[6] So, clear Cotton effects should appear in the ECD spectra of **1**. In particular, we expect that the derivatives **2** will assume a conformation where the two naphthyl chromophores are twisted with respect each other, with a preferential sense of twist dictated by the stereogenic center of the optically active diol: i.e., we expect that in these systems a transfer of chirality from the diol (central chirality) to a preferential sense of twist of the two naphthyl rings (helical chirality) will occur. It is noteworthy that, as reported in some previous instances, the aryl rings were directly linked,[4b,7–9] while in the present case, they *are linked to the same carbon atom but not directly. From this point of view the method should constitute a completely new example of central to helical chirality transfer*. Then, the presence of two twisted naphthalene chromophores should guarantee, in the ECD spectrum, the appearance of an exciton couplet, linked to the naphthalene ${}^1B_b$ transition at 220 nm. Then, by knowing the molecular conformation and the polarization direction of this transition, it should be possible to assign the AC of the starting diols by means of the Harada-Nakanishi rule.[1a]

Ketals **2** were easily synthesized by reaction of dimethyl acetal of di(1-naphthyl)ketone with the optically active diols **1a**−**h** (Figure 1), traces of *p*-TsOH, and 4 Å activated molecular sieves. Purification by chromatography column afforded ketals **2a**−**h** (Scheme 1), in 50−60% yield, as foamy white solids. The experimental UV spectra of **2a**−**h** present similar features, typical of the naphthalene chromophore:[6] an absorption band at ~283 nm ($\varepsilon \sim 12000$) due to ${}^1L_a$ transition, followed by a more intense absorption band at ~224 nm ($\varepsilon \sim 79000$) allied to ${}^1B_b$ transition. The CD spectra show weak Cotton effects at about 280 nm, followed by clear couplet effects centered at 220 nm, with A values between 45 and 650.

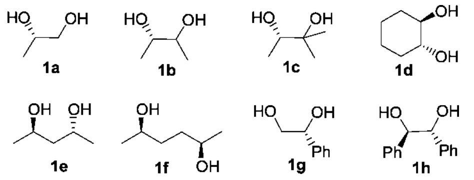
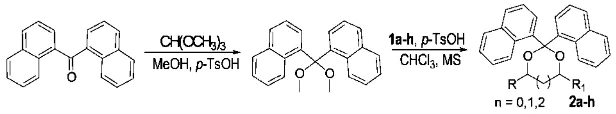


**Figure 1.** Structures of 1,*n*-diols **1a**−**h**.

**Scheme 1.** Preparation of Ketals **2a**−**h**



In Figure 2 are reported the spectra of **2b**, while in Figure 3 are reported the data of **2f**, as representative examples.

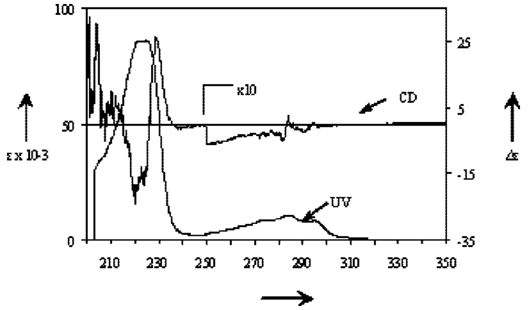


**Figure 2.** Absorption and ECD spectra of **2b** in THF.

The analysis of the ECD spectra of ketals **2a**−**h** reveals that we can indeed observe the expected exciton couplet allied to the electrically allowed (intense) ${}^1B_b$ transition.

*We can then state that in these systems the aromatic groups are twisted, making possible the degenerate exciton*

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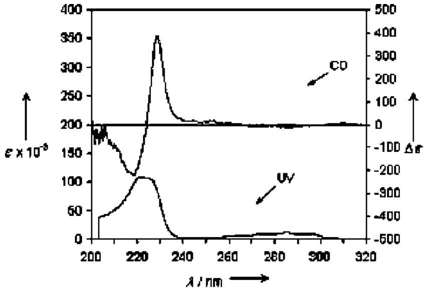

**Figure 3.** Absorption and ECD spectra of **2f** in THF.

*coupling between the naphthalene $^1$B transition (220 nm).* In other words, fixed, for example, the absolute configuration (*R*) (or (*R*,*R*)) of optically active diols, the aromatic groups of **2**, in principle, can assume *P* or *M* torsion. In solution, two diastereoisomers in equilibrium between them $(R,M) \rightleftarrows (R,P)$ will be present. Since the couplet effect is clearly observable, this means that one diastereoisomer (the most stable one) is prevailing in solution: a transfer of chirality from the stereogenic center(s) of optically active diols to the sense of twist of the two naphthalene groups occurs. The sign of the couplet reflects the chirality defined by the $^1$B transition dipole moments. Since the polarization direction of the $^1$B transition within the naphthalene ring is known, the AC of the stereogenic centers of the diols can be determined, once the conformation of the most stable diastereoisomer has been established.

It is also noteworthy that (*R*) (or (*R*,*R*)) aliphatic diols give rise to positive couplets at 220 nm while (*R*) (or (*R*,*R*)) aromatic diols give rise to negative couplets at 220 nm. It is known[4a] that the most stable conformation of dimethyl dioxolanes derived from aliphatic or aromatic diols presents the aliphatic (or aromatic) groups in a gauche disposition, while the hydrogen atoms are in axial situation. We can use this information to build the two possible conformers of a generic (*R*) (or (*R*,*R*)) diol (Figure 4).

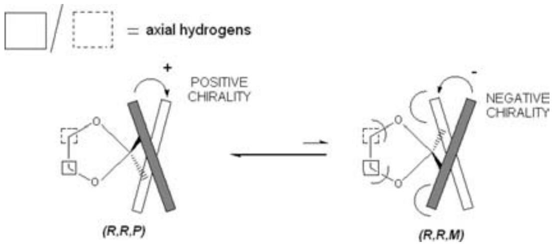

**Figure 4.** Conformational diastereoisomers of (*R*,*R*)-**2b**. The solid square represents a hydrogen atom pointing above the dioxolane ring, while the dashed square represents a hydrogen atom below the same ring. The rectangles represent naphthalene rings: the dark one is placed above the dioxolane ring, and the white one is placed below the same ring.

In these two structures, the two naphthalene rings place the *peri* hydrogens in a free region of space, and they differ in energy because in the (*R*,*R*,*P*) conformer repulsive interactions between the aromatic rings and the axial hydrogens linked to the stereogenic centers are completely absent. Therefore the conformer (*R*,*R*,*P*) possessing positive chirality is the most stable one; i.e., the above equilibrium will be shifted toward the (*R*,*R*,*P*) diastereoisomer and hence a positive couplet should be present in its ECD spectrum, as experimentally found. This means that when *a positive couplet is observed in the ECD spectrum of a di(1-naphthyl)ketal derived from an aliphatic diol, such a diol will have (R) (or (R,R))* AC. As observed previously, in the case of (*R*) (or (*R*,*R*)) aromatic diols, we have the opposite correlation: the reason for that can be appreciated looking at Figure 5 where the conformational diastereoisomers of the di(1-naphthyl)ketal of (*R*,*R*)-1,2-diphenylethane-1,2-diol are reported.

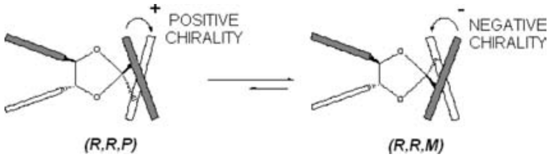

**Figure 5.** Conformational diastereoisomers of (*R*,*R*)-**2h**. The rectangles linked to the stereogenic centers represent benzene groups, while those linked to the same carbon atom of the dioxolane ring represent naphthalene groups: the darker ones are placed above the dioxolane ring, and the clearer ones are placed below the same ring. In (*R*,*R*,*M*), stabilizing edge/face electronic interactions between the aryl rings are possible: a couple (darker rectangles) above the dioxolane ring and the others (clearer rectangles) below the same ring.

It results quite clearly from Figure 5 that for the (*R*,*R*,*M*) conformer two possible face/edge electronic interactions are possible: the former one between the rings above the dioxolane plane and the latter one between the rings below the same plane. It is generally accepted that interactions of this type play an important role in some fundamental chemical and biochemical processes,[10] and a rough quantitative estimate of this interaction is of the order of about 2 kcal/mol,[10] i.e., a number sufficient to overcome steric repulsions and so shift the (*R*,*R*,*P*)/(*R*,*R*,*M*) equilibrium toward the (*R*,*R*,*M*) conformer. To put the above-described results on a more quantitative basis, a conformational analysis of compounds **2b** and **2h**, chosen as representative examples, has been carried out by means of molecular mechanics (MMFF94s force field of SPARTAN02),[11] and the structures so obtained were used to simulate the experimental ECD spectra by means of DeVoe calculations.[1b–e] In the case of **2b**, two different conformers having positive and negative torsion of the naphthalene rings have been found with populations of 88% and 12%, respectively. Using the

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[10] Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2001**, *124*, 104–112.

[11] *SPARTAN '02*Wavefunction Inc,: 18401 Von Karman Av. Suite 370, Irvine, CA 92612, 2002, http://www.wavefun.com/.

**Table 1.** Observed and Predicted Helicity of Ketals **2a**−**h**

| compd | observed exciton couplet amplitude, A | helicity and exciton chirality of the most stable conformer | predicted population of the most stable conformer and predicted (De Voe) A value | predicted AC |
|---|---|---|---|---|
| (*S*)-**2a** | −45 | *M*, negative | – | (*S*) |
| (*R*,*R*)-**2b** | +45 | *P*, positive | *P* (58%), +90 | (*R*,*R*) |
| (*S*)-**2c** | −55 | *M*, negative | – | (*S*) |
| (*R*,*R*)-**2d** | +70 | *P*, positive | – | (*R*,*R*) |
| (*R*,*R*)-**2e** | +650 | *P*, positive | – | (*R*,*R*) |
| (*R*)-**2f** | +650 | *P*, positive | – | (*R*) |
| (*R*)-**2g** | −70 | *M*, negative | – | (*R*) |
| (*R*,*R*)-**2h** | −600 | *M*, negative | *M* (100%), −500 | (*R*,*R*) |

geometrical parameters of these structures, the known direction of the $^1$B transition dipole moment within the chromophore, and standard spectroscopic parameters[6] for this transition ($\lambda_{\max}$ 220 nm, $D = 40$ D,[2] $\Gamma = 3$kK), a positive couplet (in agreement with experiment but ten times more intense than the experimental one) has been found. Optimizing the geometries at the DFT/B3LYP/6-31G* level,[12] the populations become 58% and 42%,[13] respectively, and therefore the weighted average ECD spectrum is still a positive couplet but with intensity only twice the experimental one, i.e., in good agreement with experiment and with our previous qualitative predictions. In the case of **2h**, the molecular mechanics calculations provided only one conformer where the edge-to-face disposition of the benzene rings with respect to naphthalene groups is clearly present and where the $^1$B transition dipoles define a negative chirality (Figure 6), in total agreement with our qualitative predictions. The ECD DeVoe calculations provide a negative couplet having intensity very similar to that experimentally found (Figure 15 of Supporting Information).

In the following Table 1 are collected observed and predicted exciton couplet amplitudes and helical chirality of **2a**−**h**: it results immediately that the true ACs of compounds **2** can be correctly obtained.

The main conclusions of this investigation are as follows: first, the transformation of aliphatic 1,*n*-diols in the corresponding di(1-naphthyl)ketals guarantees a strong reduction of the number of conformers; i.e., the ketals exist as 1 or 2 conformers. These compounds present strong chromophoric groups (the naphthalene rings), and owing to the presence of the stereogenic centers of the diol moieties, the two chromophores are twisted with respect to each other, with a prevailing sense of twist leading to the observation, in the ECD spectra of ketals **2**, of significant couplet effects from the analysis of which (even to a qualitative level) it is possible to obtain the AC of the starting diols. Therefore, we can state that a *simple, new method for assigning the AC of aliphatic diols has been set up*. Interestingly, this method has been tested also with diols where the two functional groups are well far away (compound **1h**); i.e., compounds diffuse in natural product chemistry, and therefore it can find several applications in this field. The method is based on the observation of exciton couplet effects which, in turn, are a consequence of the prevailing sense of twist of the naphthalene planes. *This represents a new case of helicity induction in a bichromophoric system*, different from those described previously, because the two chromophores are not linked directly.

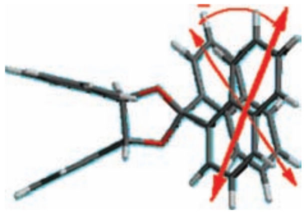

**Figure 6.** Only conformer of **2h**, provided by molecular mechanics calculations. Edge-to-face disposition of the benzene rings with respect to the naphthalene ones is evident. The electric dipole moments of the $^1$B transition define negative chirality.

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**Supporting Information Available:** Experimental data: NMR, absorption and CD spectra of compounds **2a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] These populations have been obtained using the $\Delta G$ value of 0.18 kcal/mol, provided by the DFT calculations. With this energy difference, the populations become 66 and 33% at −133° C, in excellent agreement with some variable-temperature NMR measurements (see Figure 16 of Supporting Information). The same analysis provides an energy of activation for the P/M interconversion of about 9 kcal/mol (see Figure 16 of Supporting Information).