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The absolute configuration of simple aliphatic alcohols through a chemical/computational approach: triarylether derivatives of (+)-*endo*-2-norborneol as a case study

Giuseppe Mazzeo, Patrizia Scafato, Stefano Superchi, Carlo Rosini *

Dipartimento di Chimica, Università della Basilicata, Via Nazario Sauro 85, 85100 Potenza, Italy

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This paper is dedicated to Professor Antonio M. Tamburro (1939–2009), an outstanding researcher and an unforgettable colleague

ABSTRACT

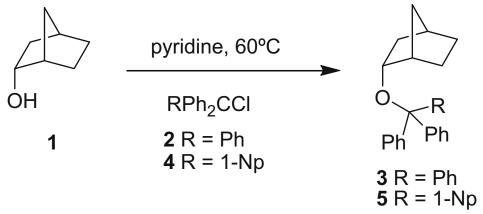
The reliable determination of the absolute configuration of (+)-*endo*-2-norborneol **1**, chosen as a representative case of simple aliphatic UV–vis transparent alcohols, was obtained by transforming this compound in its 1-naphthyl-diphenylmethyl ether **5** whose ECD spectrum displays several, low-lying, intense Cotton effects, which can be satisfactorily simulated in position, sign, and intensity by TDDFT/B3LYP/6-31G* calculations. This result represents a possible, general, new approach to the absolute configuration of aliphatic alcohols.

1. Introduction

The recent progress in computational chemistry has made available powerful ab initio methods for the simulation[1] of electronic chiroptical properties such as specific rotation, and electronic circular dichroism (ECD)[2] which, in principle, allows a reliable assignment of the molecular absolute configuration. As a matter of fact, these methods are increasingly used by experimental organic chemists to assign the absolute configuration of new synthetic and natural compounds.[3] However, some problems still remain, such as the treatment of flexible and transparent molecules. In fact, a large number of conformers and the presence of only high-energy Cotton effects, require the intervention of high-level calculations which, in turn, require powerful computational resources. Such an approach can even become impracticable for large molecules. To provide a solution to this problem, we developed a chemical/computational approach, which requires the transformation of flexible and transparent compounds in chromophoric, conformationally defined derivatives: the analysis of the electronic chiroptical properties of the latter systems is then more simple and reliable, guaranteeing a safe absolute configuration assignment.[4,5] Recently, we faced the absolute configuration determination of aliphatic diols through this approach.[6] By chemical transformation of these flexible and transparent molecules we obtained more rigid derivatives with low-energy, intense Cotton effects, and then higher specific rotation values. This allowed us to use computational methods at low-levels of theory, arriving to a safe absolute configuration assignment with only modest computational efforts. Prompted by these data, we herein report our attempts at extending the same chemical/computational approach to the case of flexible transparent *monofunctional* compounds such as simple aliphatic alcohols, choosing (+)-*endo*-2-norborneol **1**, as a benchmark molecule. This task could also be achieved by transforming the alcohol in a derivative bearing one or more chromophores and displaying, in principle, a low number of conformers. A derivatization which, at first glance seemed to fulfill all the requisite was the triphenylmethylether (trityl) derivatization, one of the most widely used protecting groups for alcohol functionalities.[7,8]

2. Results and discussion

The triphenylmethylether **3** of (+)-*endo*-2-norborneol[9] was easily prepared by a standard procedure (Scheme 1)[10] and its specific rotation values were compared with those of the parent alcohol **1**. Alcohol **1** presents $[\alpha]_D$ numbers which are low in absolute value but independent of the solvent: +1 (*c* 1, chloroform); +7 (*c* 0.97, methanol); +2 (*c* 1.02, *n*-hexane). In the triphenylether **3**, we observed specific rotation values almost an order of magnitude high-



Scheme 1.

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* Corresponding author. Tel.: +39 0971 202241; fax: +39 0971 202232.
E-mail address: carlo.rosini@unibas.it (C. Rosini).

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er, but still quite small in absolute value, $[\alpha]_D = -14$ (*c* 0.90, chloroform) and −14 (*c* 0.96, *n*-hexane).

The ECD[11] spectrum of **3** (acetonitrile) is shown in Figure 1. From this spectrum it can be seen that due to the introduction of the trityl chromophoric system, Cotton effects can be measured in the 250–200 nm spectral range whilst aliphatic alcohols absorb below 200 nm.[12] However, the ECD bands remain weak and we did not observe a significant increase in the specific rotation values on passing from **1** to **3**. So the simulation of the chiroptical properties of **3** with the aim at arriving at a safe assessment of the absolute configuration of **1** remains a difficult task. These discouraging results could depend on the mobility of the trityl group, which can present several conformers having different relative dispositions of the three phenyl rings. Therefore, we decided to look for a less mobile derivatizing agent and we thought to substitute one of the phenyl rings of trityl chloride with a 1-naphthyl group, in order to obtain alcohol derivatives as 1-naphthyl-diphenylmethyl ethers. In fact, the introduction of the 1-naphthyl chromophore should give rise to two advantages: (a) the α-substitution provides derivatives characterized by reduced conformational mobility due to the presence of the steric effect of the *peri* hydrogen in 1-naphthyl-substituted compounds; (b) the naphthyl chromophore possesses two intense electrically allowed transitions at 280 nm (^1L_a, ε 4000 ca.) and at 220 nm (^1B_b, ε 95000 ca.). Therefore clear Cotton effects should appear in the ECD spectra of their alkyl ethers. The new triaryl derivatizing agent **4**[13] was prepared by reacting 1-naphthylmagnesium bromide with benzophenone to give the corresponding alcohol, (87% yield), which was transformed in the required chloride by acetyl chloride[14] in refluxing toluene (40% yield). Reaction of **4** with alcohol **1** in the presence of pyridine provided derivative **5**[15] in a satisfactory yield (60%) (Scheme 1). Compound **5** shows $[\alpha]_D = +26$ (*c* 1, $CHCl_3$) which is about thirty times higher than that of **1**, however its absolute value is still too small to attempt a reliable DFT calculation of the specific rotation.[16] On the other hand, the ECD spectrum of **5** (Fig. 2) is much more intense than that of **3**, presenting at least four strong Cotton effects with different signs. Such a spectrum can be safely reproduced, even by our 'approximate' (i.e., TDDFT/B3LYP/6-31G* or smaller basis sets) computational approach,[6] thus allowing us to determine the absolute configuration.

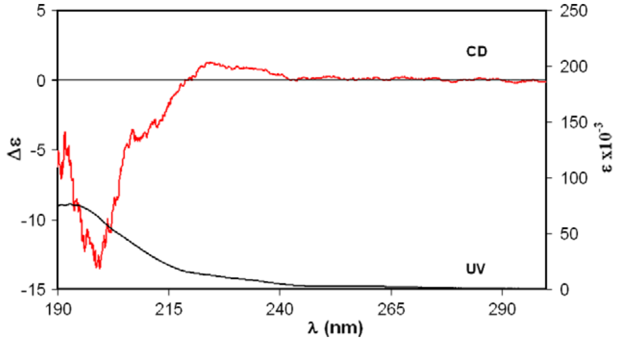

Figure 1. Absorption (UV curve) and ECD (CD curve) spectra of **3** in acetonitrile.

The calculation of the ECD spectrum of **5** was then performed as follows. The input structures were provided by some SPARTAN02[17] calculations: using the MMFF94s force field, seven different conformers were found in the energy range 0–2 kcal/mol. Each of these structures was optimized at the DFT/B3LYP/6-31G* level obtaining the necessary input geometries for the calculations of the chiroptical properties (TDDFT/B3LYP/6-31G* level). It is interesting to note that the three most stable conformers (80% of the total population) present the *peri* hydrogen atom in a free zone of space, thus indicating that this particular geometrical parameter plays an important role in determining the relative conformational stability. In Figure 2, the experimental and calculated (TDDFT/B3LYP/6-31G*, 50 states, velocity formalism, four most stable conformers, almost 90% of the overall population) ECD spectra are reported. The theoretical curve reproduces more than satisfactorily the experimental one: in fact, the sequence of negative, positive, negative, negative, and positive Cotton effects at 265, 240, 220, 205 and 190 nm is correctly reproduced in the sign, position, and intensity (only the intensity of the weak 205 nm band being overestimated[18]), showing that by calculating the ECD spectrum of **5** we can reliably determine the correct absolute configuration of the alcohol **1**. It is noteworthy that all the computational procedure requires 596 h of CPU time on a standard desktop computer: in other words, the possibility of using a low level of theory more than compensates for the difficulty connected with the increase of molecular size on passing from **1** to **5**. Furthermore, the selected chromophore leads to the presence of several Cotton effects, from 300 to 200 nm, their correct simulation of sign, intensity and position is a clear evidence of the correct assignment of absolute configuration. In this way ECD spectroscopy gains the same advantages of VCD spectroscopy, that is, the need of reproducing many CD bands and then a solid guarantee of a correct absolute configuration assignment. Consequently, ECD spectroscopy can be used even alone without a concerted use of the three chiroptical spectroscopies.[19]

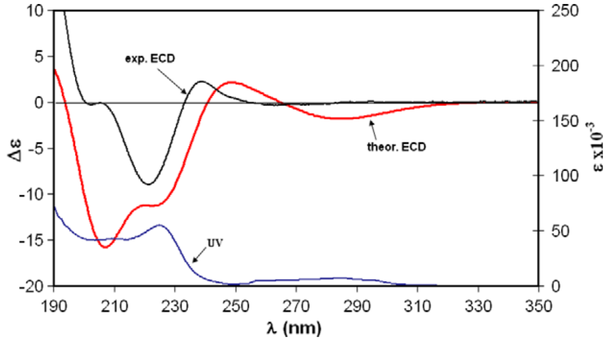

Figure 2. Absorption (UV curve) and ECD (exp. ECD curve) of **5** in acetonitrile. Computed (TDDFT/B3LYP/6-31G* level, 50 states, velocity formalism) ECD spectrum (theor. curve).

3. Conclusions

We believe that these results, even if preliminary, clearly show that the transformation of aliphatic alcohol-triaryl ether could represent a very useful method to arrive at a reliable assessment of the absolute configuration of non chromophoric chiral alcohols. The introduction of such simple chromophoric moieties allows us to observe higher specific rotation values and more intense ECD spectra in the triaryl ethers, then allowing us to make the absolute configuration assignments even employing a low level of theory. In conclusion, coupling experimental organic chemistry with theoretical calculations allows us to solve a problem which is very difficult when using a computational approach only. Work is currently in progress to extend this approach to other simple, more flexible, aliphatic alcohols, even designing new, tailor-made triaryl derivatizing agents. This and a previous paper[6] clearly show how the organic chemistry of the protecting groups can provide significant help to design suitable new groups which are able to both reduce the conformational mobility and introduce chromophoric moieties. These groups can then act as sensitive probes of the absolute stereochemistry of the original molecules, making the computational efforts required for a reliable configurational determination much simpler.

Acknowledgments

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