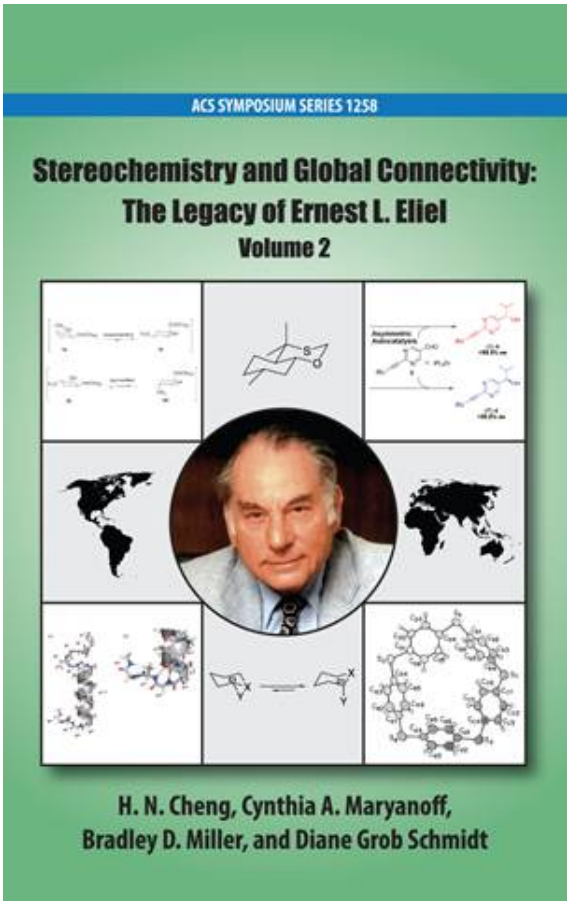
ACS SYMPOSIUM SERIES 1258
Stereochemistry and Global Connectivity:
The Legacy of Ernest L. Eliel
Volume 2
H. N. Cheng, Cynthia A. Maryanoff,
Bradley D. Miller, and Diane Grob Schmidt

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Stereochemistry and Global Connectivity: The Legacy of Ernest L. Eliel

Volume 2

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ACS SYMPOSIUM SERIES **1258**

Stereochemistry and Global Connectivity: The Legacy of Ernest L. Eliel

Volume 2

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Foreword

The ACS Symposium Series was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of the series is to publish timely, comprehensive books developed from the ACS sponsored symposia based on current scientific research. Occasionally, books are developed from symposia sponsored by other organizations when the topic is of keen interest to the chemistry audience.

Before agreeing to publish a book, the proposed table of contents is reviewed for appropriate and comprehensive coverage and for interest to the audience. Some papers may be excluded to better focus the book; others may be added to provide comprehensiveness. When appropriate, overview or introductory chapters are added. Drafts of chapters are peer-reviewed prior to final acceptance or rejection, and manuscripts are prepared in camera-ready format.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previous published papers are not accepted.

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Foreword

A major strength of American Chemical Society (ACS) is the large number of volunteers who help to grow and sustain the organization, from local sections to technical divisions, from regional to national meetings, from task forces to national committees, and from conducting research to writing and reviewing manuscripts for journals. Some of them spend literally thousands of hours on behalf of ACS and the global chemistry enterprise, helping students or fellow scientists, organizing meetings and symposia, reaching out to the local communities, publicizing the benefits of science, and connecting with global colleagues and partners.

One of the people who excelled in these efforts was the late Prof. Ernest L. Eliel. For many years he taught at the University of Notre Dame and the University of North Carolina and was an acknowledged leader in organic stereochemistry and conformational analysis. He was also a leader at ACS, serving as ACS President in 1992 and Chair of ACS Board of Directors in 1987-89. He initiated several international activities, particularly with respect to Latin America. I had worked with him on many occasions, and he was always courteous, judicious, analytical, and thoughtful.

Unfortunately Prof. Eliel left us in 2008. As ACS Immediate Past President in 2016, it was my pleasure to be associated with a symposium organized by Dr. Cynthia Maryanoff and me at the ACS National Meeting in Philadelphia in honor of Prof. Eliel. Because of the success of the symposium, Dr. Maryanoff and I decided to team up with Dr. H. N. Cheng and Dr. Bradley Miller to edit a book highlighting stereochemistry and global connectivity, which represented two of the key legacies of Prof. Eliel. We were very pleased that so many of our academic colleagues were willing to participate in this project in honor of Prof. Eliel. Thanks are due to all of the authors and my co-editors for their wonderful efforts.

Because stereochemistry is a fundamental chemistry concept, ongoing research is carried out in different subfields of chemistry (such as organic, medicinal, carbohydrates, polymers), using various analytical techniques (such as NMR, X-ray crystallography, and circular dichroism). The two volumes of this book contain many research papers that represent cutting-edge research in all the above areas. Because chemistry is now a world-wide enterprise, global connectivity is important to chemistry practitioners, and the chapters on international activities should be of great interest as well. Hopefully the readers will find these two book volumes useful to them in their research or professional work, and the example of Prof. Eliel will motivate them to volunteer their time and talent to ACS and the global chemistry enterprise!

Diane Grob Schmidt
2015 ACS President

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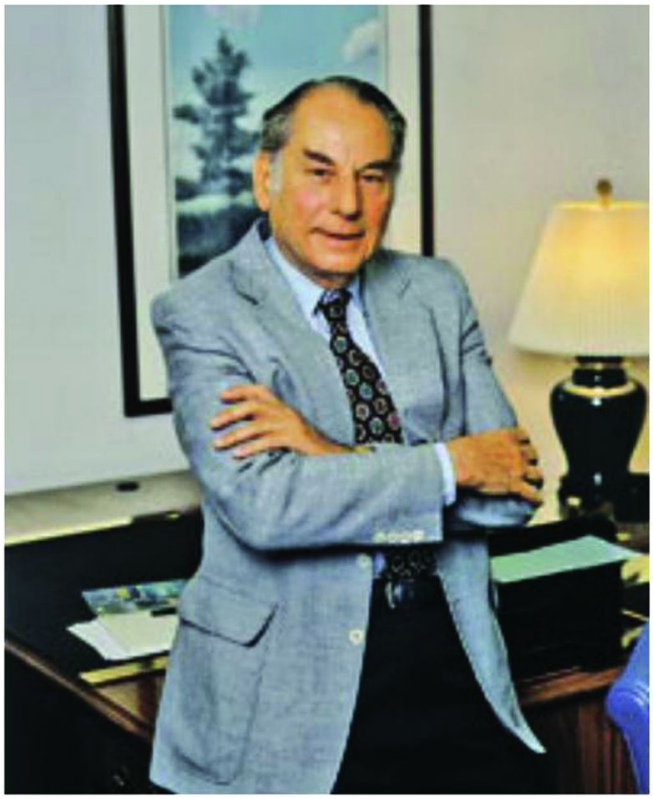
In Memory of Ernest Eliel



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Ernest Ludwig Eliel was an eminent organic chemist known for his seminal contributions to organic stereochemistry and conformational analysis. He was born in Cologne, Germany and moved to Scotland, then Canada, then Cuba. He received his B.S. from the University of Havana in 1946. He moved to the USA in 1946 and obtained his PhD at the University of Illinois in two years with eight publications that resulted from his work. He taught at the University of Notre Dame in 1948-1972 and then moved to the University of North Carolina at Chapel Hill. He was well-known as an outstanding teacher and researcher. He died in Chapel Hill in 2008.

Eliel was active in the ACS and served in numerous capacities. He was Chair of the ACS Board of Directors in 1987-89 and ACS President in 1992. His scientific contributions and professional involvements were widely recognized. Among his awards and recognition were membership of the National Academy of Sciences (NAS) (1972), the George C. Pimentel Award in Chemical Education

(1995), the ACS Priestley Medal (1996) and the NAS Award for Chemistry in Service to Society (1997). We dedicate this book to the memory of his contributions to chemistry and his efforts to connect scientists worldwide through its practice.

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Preface

The two volumes of this book are partially based on a symposium held at the ACS Fall National Meeting in Philadelphia in August 2016 on Connectivity and the Global Reach of Chemistry: Honoring the Life and Scientific Contributions of Ernest L. Eliel. The symposium speakers consisted of friends and former colleagues of Prof. Eliel, and they provided reminiscences of Eliel as well as updates of their own research work in honor of Eliel. The symposium was well-received and encouraged us to edit this two-volume symposium book. In addition to the symposium speakers, we also invited several other colleagues in the global chemistry enterprise to contribute papers related to stereochemistry and global connectivity.

Prof. Eliel was well-known scientifically for his work on organic stereochemistry and conformational analysis. His book, *Stereochemistry of Carbon Compounds*, was a classic that had a profound influence on the field. He was also active in the ACS and served as Chair of the ACS Board of Directors in 1987-89 and ACS President in 1992. As an ACS leader, he recognized the importance of global connectivity and promoted the strengthening of international activities in chemistry. He started several valuable programs that facilitated international exchange, particularly those that related to Cuba, Mexico and the rest of Latin America. In view of Prof. Eliels outstanding contributions to chemistry and its global practice, we are featuring two topics in this book that reflect his legacy: stereochemistry and global connectivity.

Thus, the aim of this book is to recognize the contributions of Prof. Eliel and to highlight the latest developments in stereochemistry and global connectivity so that younger people who may not know Eliel can benefit from the information given in the chapters of this book.

A total of 22 chapters are included in the two volumes of this book. Volume 1 consists of 10 chapters, including an overview (Chapter 1), two chapters on Tribute to Ernest Eliel, three chapters on Global Connectivity, and four chapters on Carbohydrates.

In this volume (Volume 2), 12 chapters are gathered and grouped in two sections:

1) Stereochemistry of Organic Compounds
2) NMR Applications

All 12 chapters (including those under NMR Applications) involve stereochemistry in various organic, inorganic, biochemical, and polymer systems

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and are excellent examples of the importance of stereochemistry to the practice of chemistry today.

This book is targeted to all chemists and chemical engineers, particularly those with an interest in stereochemistry or international relations. Since stereochemistry is an important basic concept for chemistry, biochemistry, polymer science, and other related areas, hopefully many chemistry professionals and students find the chapters useful. Moreover, the chemistry enterprise is becoming increasingly globalized. Thus, global connectivity and networking may be of interest as well. This book is also suitable as a reference work for libraries.

We appreciate the efforts of the authors who took time to prepare their manuscripts and the reviewers for their cooperation during the peer review process. We also thank Arlene Furman, Tracey Glazener, Elizabeth Hernandez and their colleagues at ACS Books for their patient and effective handling of the manuscripts.

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Chapter 7

Solvent Effects on Electronic Circular Dichroism Spectra

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The Electronic Circular Dichroism Spectrum (ECD) is a valuable tool to study the unknown absolute configuration of an optically active molecule. And the comparison between experimental data and theoretical computational calculations has been a successful strategy for this study. However, the ECD spectrum is very sensitive to solvent effects that significantly change the character of the results obtained. This chapter is focused on the study of the solvent effects and their application in both experimental and computational chemistry of ECD of the compound 3,3′-dibromo-1,1′-bi-2-naphthol.

Introduction

The study of the chiroptical properties has as one of the challenges the elucidation of the absolute conformation of a molecule. And the comparison of the results obtained experimentally with those derived from computational calculations has been a successful strategy employed. Another motivation in this area is the determination of the conformation of flexible molecules that can adopt specific conformations when interacting with chiral environments. The chiroptical properties of a molecule are very sensitive to the medium polarity such as, for example, the variation of the dielectric constant of the medium in the presence

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of a solvent or local polarity and conformational changes at the active site of proteins. This phenomenon occurs in the experiments of optical rotation (OR), electronic or magnetic circular dichroism (ECD or MCD), vibrational CD (VCR), and Raman optical activity (ROA). From this point of view, understanding the effects of the medium where the molecule is located is of fundamental importance for the calculation and experimental determination of chiroptical properties.

In the present chapter, we present some experimental and computational simulation results in order to understand the influence of the solvent on the chiroptic properties of the enantiomeric pair (R)-(+)-3,3′-dibromo-1,1′-bi-2-naphthol and (S)-(−)-3,3′-dibromo-1,1′-bi-2-naphthol. Next, we will present some methodologies used in the elaboration of models for the study of the effect of the solvent on chiroptic properties. A detailed discussion of the effects on optical rotation and electronic circular dichroism can be found in the works of Pecul et al. (*1*, *2*), and Pescitelli et al. (*3*). These studies present a more elaborate discussion on the subject and should be consulted for a greater understanding on the part of the readers. Another interesting study by Polavarapu et al. (*4*) on the conformational sensitivity of 6,6′-dibromo-1,1′-bi-2-naphtol predicted that the electronic absorption and ECD spectra do not show significant variations for different conformations of the hydroxyl group present in the molecule. Although the extensive study on this topic is found in the literature, we have not found a study, both experimental and theoretical, on the influence of the solvent on the chiroptic properties of the enantiomeric pair of 3,3′-dibromo-1,1′-bi-2-naphthol. We also present some considerations about the phenomenon of chirality and atropisomerism in the context of its importance in obtaining the absolute conformation of molecules of interest.

Chirality and Atropisomerism

The omnipresence of molecules that constitute the living matter and which have as the major characteristics to differ from each other only by the three-dimensional arrangements of their constituent elements can be thought of as a medium that evolution “chose” to increase the levels of differentiation of matter. In others words, the formation of different substances from the few elements that account for the most of the mass of organic matter, i.e., carbon, hydrogen, oxygen, and nitrogen atoms. It would therefore be reasonable to dispose of the levels of differentiation of matter, starting from the following possible levels:

First: different combinations of protons, neutrons, electrons and other fundamental particles forming different chemical elements;

Second: different combinations in number and types of chemical elements forming different molecules;

Third: same chemical elements in number and types, but different connectivity forming constitutional isomers, and;

Fourth: same elements, same connectivity, but different spatial arrangements forming stereoisomers.

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If we consider that particles, except the electron, are formed by the combination of other subatomic particles, like quarks, and these in turn, formed by different combinations of other elements present in the string theory, we can the raise the hypothesis that all the known matter with their different physical and chemical properties are nothing but expressions of one or a few forming units of the whole and also of quantum vacuum fluctuations. It is therefore no surprise that molecules differing only by the spatial arrangement of the chemical elements may have different chemical properties. Among the molecules that keep the stereoisomeric relationship between them, we highlight those that are non-overlapping mirror images. These are the enantiomers, molecules that exist in pairs in nature, that is, molecules that can be thought as a "right" and "left". As well-established, the condition for a molecule to exist in pairs is the total absence of symmetry in its three-dimensional structure. For organic compounds, the simplest condition for achieving this asymmetry is the existence of a single carbon atom bearing four different substituents, known as chiral or asymmetric carbon. However, the presence of a chiral carbon is not a sufficient or necessary condition, because even in its absence, a molecule may exist in pairs. As an example, we have some biphenyl systems, which will the object of the present chapter. This phenomenon is known as atropisomerism, and takes place when the energetic barrier for rotation around the single bond that connects the aryl groups is sufficiently high, leading to enantiomeric conformations sufficiently stable to be isolated. The word atropos comes from the Greek and means "a" (not) and "tropos" (rotation), that is, impeded rotation in the axial axis that joins the aryl groups. The first molecule synthesized and exhibiting this characteristic was 6,6′-dinitro-2-2′-diphenyl acid obtained by Christie and Kenner in 1922 (*5*). These are biaryl systems where the presence of substituents in the ortho position prevents the free rotation around the single bond and, consequently, the non-interconversion of one enantiomer into the other.

Computational Models for Solvent

The solvent can be considered, from the standpoint of computational modeling, in distinct ways: 1) the solvent is considered as a source of potential around the molecule, and in this case the molecule is treated from a quantum mechanical point of view and the solvent can be modeled as a homogeneous and isotropic continuous dielectric model, the polarizable continuum model (PCM) is commonly used method in computational chemistry to model these effects, or as a collection of discrete charges, and 2) the solvent and the molecule are treated at the same level of calculation. In the PCM model the molecule of interest is placed in a cavity in the continuous medium and the interactions are described by the inclusion of a term describing these interactions in the wave equation. The shape of the cavity may vary depending on the model chosen, and may be a sphere or have a more complex shape. The cavity model developed in the research group of Professor Tomasi is one of the most used and the cavity is formed by spheres

centered in the solute´s nucleus and the surface of the same is divided into charge finite elements (*6*, *7*).

Another approach used is 3) to consider the solvent in an explicit manner, together with the molecule of interest forming a super molecule, where the solute molecule and the solvent molecules are treated at the same level of theory. The effect of the solvent molecules is obtained from the difference between the results obtained with the molecular complex and those obtained with the isolated molecule. This approach uses a combination of quantum-mechanical and molecular mechanics methods (QM/MM) where the most important part of the system is treated by *ab initio* methods and the effect of the environment is treated using MM (*8*).

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Basic Theory for Solvated Systems

The theory involved in the Polarizable Continuum Model in the study of solvent effect in the spectrum of electronic circular dichroism was developed by Tomasi et al.

The effects of the solvent are incorporated into a version of the integral equation formalism (IEF). In the formulation of a theory for the effect of the solvent we must take into account the quantum mechanical methodology used and the model chosen for the solvent. One of the most used methodologies that lead to results with more precision is the Density Functional Theory (DFT) and in relation to the solvent model one of the choices is to use a continuous atomistic model for the solvent.

The complete Hamiltonian for the solute molecule can be written as (*9*):

$$H = H_0 + V_{MS} + V'(t) \qquad (1)$$

where H_0 is the Hamiltonian in vacuum and $V'(t)$ is the time-dependent perturbation. In this formulation a surface charge density was introduced which represents the response of the solvent to the external field after the creation of the solute cavity in the solvent. The surface charge density was partitioned into small portions called "tesserae" of area equal to k. The equation for $V'(t)$ describes the time-dependent perturbation in the solute molecule in terms of the external electric field and from this equation we can calculate the effective polarizability of the molecule.

Approximate solutions from the effective Hamiltonian can be obtained from a procedure analogous to that obtained for isolated molecules. The modification that must be made is in the Fock operator which must now include the effects of the solvent in the presence of an oscillating field. It has been shown (9) that the orbitals and their energies are modified in comparison to the isolated molecule. This modification was represented as:

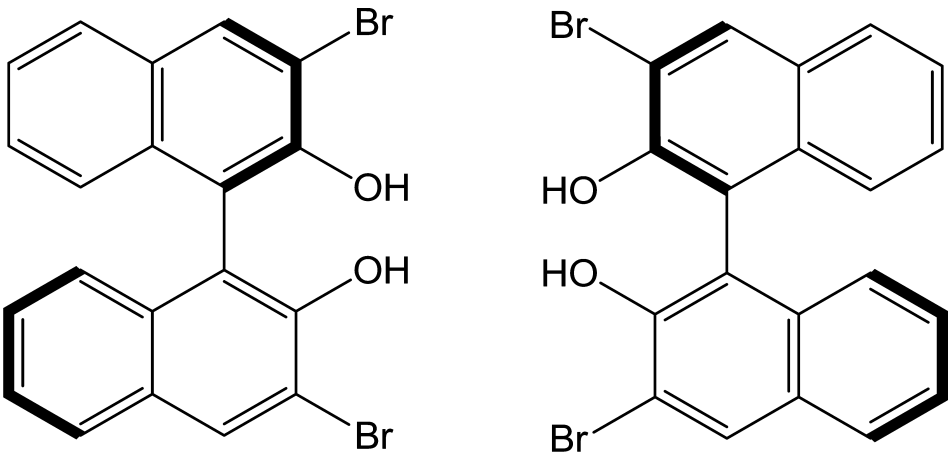
$$\mathbf{q_{bj}} = - \mathbf{Q}(\varepsilon)\mathbf{V_{bj}} \qquad (2)$$

where Q is the dielectric matrix that defines the apparent bulk of the solvent and depends on the geometry and the dielectric constant. The PCM model solute-

solvent interactions are of electrostatic nature and due to this fact the correlation between the results obtained in computer simulations are in better agreement with polar solvent than in relation to non-polar solvent. The method derived from the DFT / PCM formalism provides reliable model in relation to electrostatic effects in the solvent chiroptical properties of molecules and also has a dependence on the nature of the solvent (*9*).

Solvent Effects on ECD Spectra

(*R*)-(+)-3,3′-dibromo-1,1′-bi-2-naphthol (**1**) and (*S*)-(−)-3,3′-dibromo-1,1′-bi-2-naphthol (**2**) (Figure 1) were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). Stock solutions of **1** and **2** (10 mM) were prepared in ethyl alcohol. The solvents were of analytical grade. Circular Dichroism (CD) spectra were recorded with a Jasco J-815 spectropolarimeter (Jasco, Japan) equipped with a thermostatically controlled cell holder. The spectra were obtained with 1 nm step resolution, response time of 1 s and scanning speed of 50 nm/min. The spectra were recorded at a bi-naphthol concentration of 15 mM over a wavelength range of 200–350 nm at 20°C. A 3 mL quartz cuvette with a 10 mm path length and a magnetic stirrer were used for the measurements. The baseline (solvents) was subtracted from all measurements.



(**1**) (**2**)

*Figure 1. Chemical Structures of (R)-(+)-3,3'-Dibromo-1,1'-bi-2-naphthol (**1**) and (S)-(−)-3,3'-dibromo-1,1'-bi-2-naphthol (**2**).*

In Figures 2a and 2b we present the ECD spectra of the binaphthols **1** and **2** in different solvents. Although some alteration can be seen depending on the solvent, the (*R*) enantiomer always showed a negative band centered around 240 nm and a positive one around 226 nm. How could be expected, the (*S*) enantiomer presented opposite ECD bands.

Interestingly, a correlation was obtained between the dielectric constants of the solvent and the ECD intensity. The results depicted in Figure 3 show that the increase in the polarity of the solvent provoked a decrease in ECD intensity.

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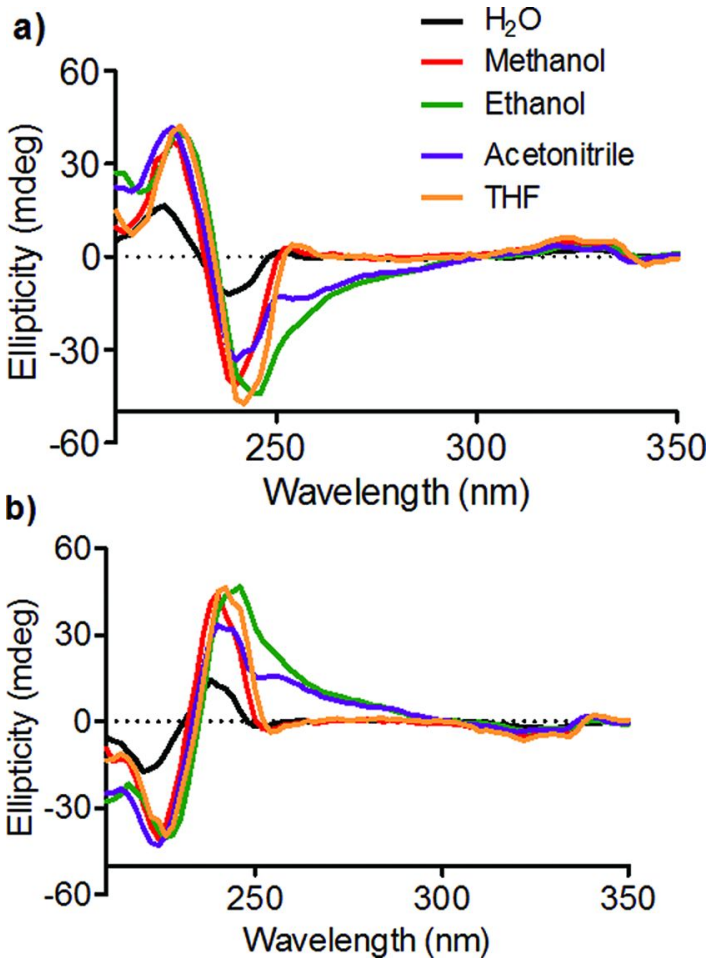

*Figure 2. ECD spectra of binaphthols **1** (a) and **2** (b) in different solvents.*

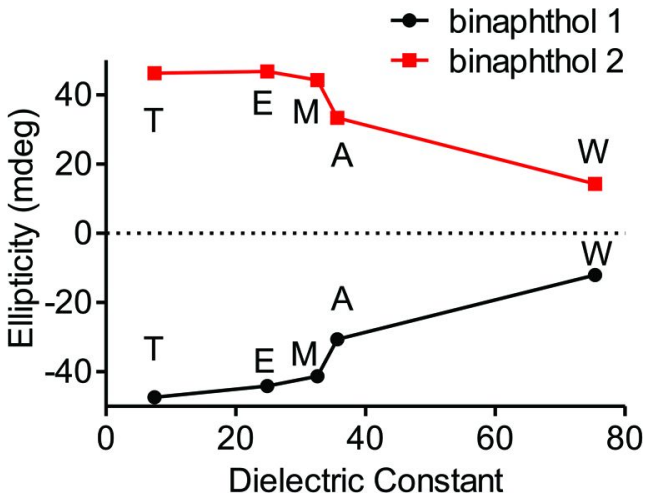

*Figure 3. Dielectric constant effects on ECD intensity of binaphthols **1** and **2**. The solvents used were: tetrahydrofuran (T), ethanol (E), methanol (M), acetonitrile (A) and water (W).*

Computational Methodology

The torsional potential energy curves of the stereoisomers (R,S) -3,3′-dibromo-1,1′-bi-2-naphthol (BiNaphthol) were obtained at the *ab initio* level in a time dependent Density Functional Theory approach in search to obtain reliable results as compared with the experimental ones. The search for the most stable conformation adopted by BiNaphthol, in the solvent phase was performed in a relaxed scan of δ1 dihedral angle, 0 – 360(30°), at B3LYP/6-31G (d,p) level of theory (Figure 4). In Figure 4 the Carbon, Hydrogen, Bromide and Oxygen atoms are represented by colors brown, white, purple and red, respectively.

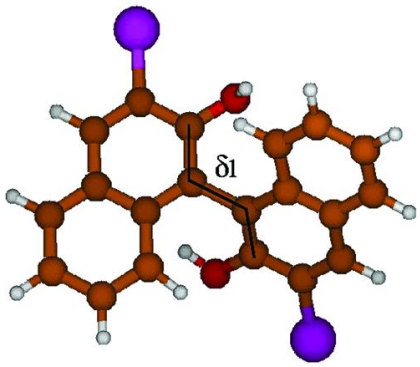

Figure 4. Definition of the torsional angle δ_1.

Figure 5 shows two minimum energy conformations of BiNaphthol using water and ethanol described by PCM solvation model. This procedure was applied to the others solvents: methanol, acetonitrile and tetrahydrofuran. On the basis of the low energy conformers, the stationary points for each curve were confirmed by the frequency analysis minima with all real frequencies. As we can observe in the Figure 5 the energetic barrier at 180 degrees for the R-S interconversion of BiNaphthol is much higher than the thermal energy, kT, at 25°C (0.59 kcal/mol). This barrier is more pronounced in the presence of water as solvent than with ethanol; this behavior can be explained due to the higher value of the dielectric constant of water as compared with ethanol. Another interesting result is the same value for the minimum of the torsion angle of BiNaphthol in both solvents. According to the Figure 5 we can infer that the molecule can adopt two stable conformations at the torsion angle of approximately 90 and 270 degrees.

The excited-state behavior in the Franck–Condon (FC) region of the BiNaphthol was investigated in different solvents by means of time-dependent Density Functional Calculations, including solvent effects (Water, Methanol, Ethanol, Acetonitrile, and Tetrahydrofuran) by the Polarizable Continuum Model and using the CAM-B3LYP functional and 6-311++G(2df,p) basis sets at molecular geometry obtained employing B3LYP/6-31G(d,p). The ECD spectra obtained are shown at Figures 6 and 7. All calculations were performed using the Gaussian09 program (*10*).

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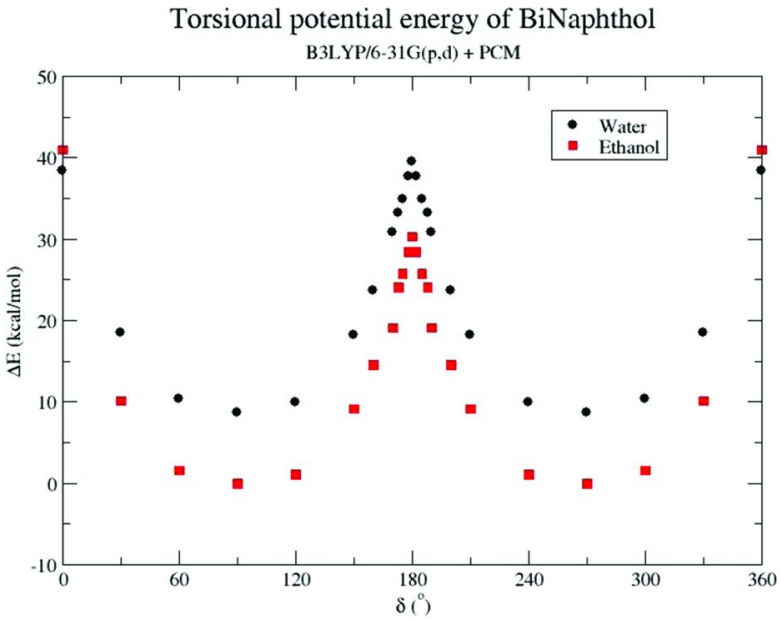

Figure 5. Potential Energy Surface for BiNaphthol at B3LYP/6-31G(d,p) + PCM.

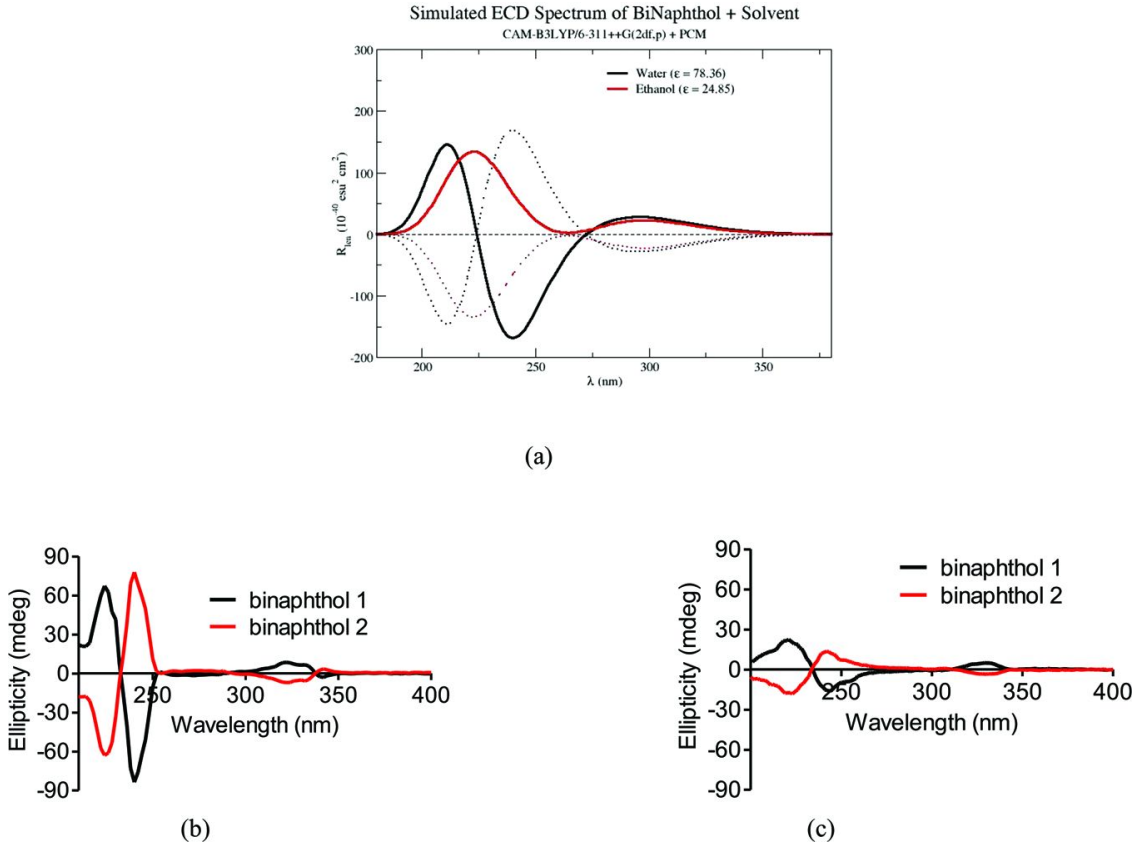

Figure 6. Calculated ECD spectra of (R,S) BiNaphthol in Water and Ethanol at the CAM-B3LYP/6-311+G(2df,p)//B3LYP/6–31G(d,p) level (a), and its experimental ECD results (b) Ethanol and (c) Water.

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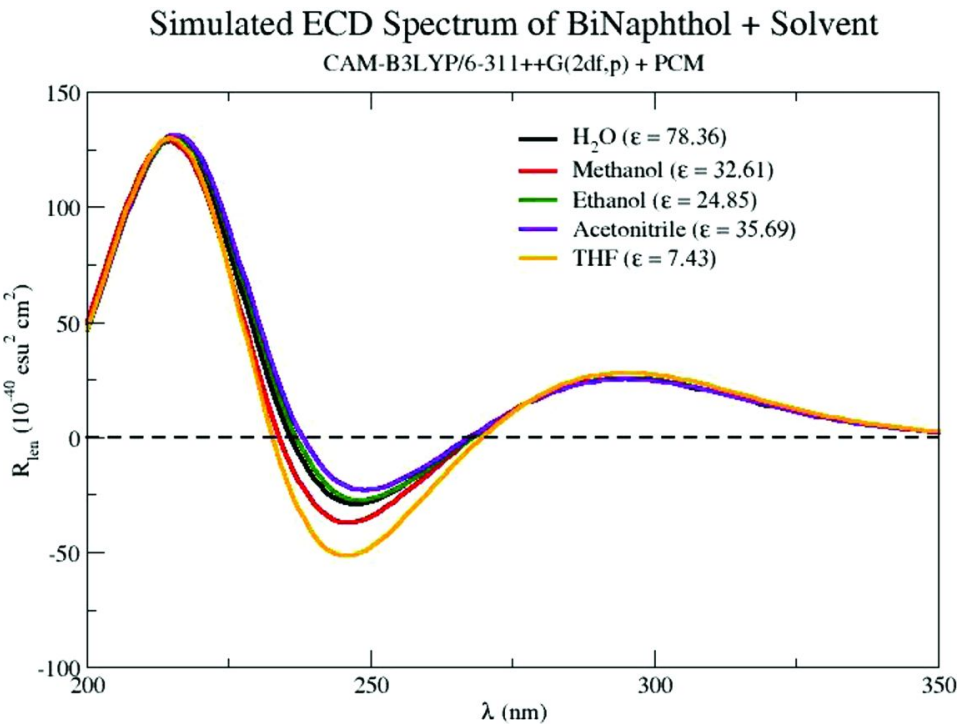

Figure 7. Simulated ECD spectra of BiNaphthol in Water, Methanol, Ethanol, Acetonitrile, and Tetrahydrofuran at the CAM-B3LYP/6-311+G(2df,p)//B3LYP/6–31G(d,p) level.

In Figure 6 (a) we present the results for BiNaphthol two solvents: water and ethanol. The red line symbolizes the R-isomer and the black line the S-isomer. We can observe that there is an inversion of the ECD signal to the antipodes R-S as observed experimentally. We also observed that the ECD spectrum consists of three bands and in the case of the R isomer we have two positive bands around 212 and 300 nm and a negative one around 240 nm. In Figure 6 (b) and 6 (c) we can observe a good agreement for both computed spectra. We can observe that the three bands in the indicated regions and also the shift to the lower energy region for the ethanol solvent when compared to the solvent water. The second positive band, around 300 nm, does not have its position modified when comparing the two solvents used.

In Figure 7 we present the spectrum of ECD for the BiNaphthol molecule in the studied solvents: water, methanol, ethanol, acetonitrile and tetrahydrofuran. We can observe the presence of three bands: two positive around 212 and 300 nm and one negative around 240 nm. The highest intensity is verified for the band at 212 nm followed by the band at 240, and the lowest intensity located at around 300 nm. The effect of the solvent is more pronounced for the band located around 240 nm (the negative band), and the other two bands do not show a significant variation with the solvent change. This result can also be verified experimentally when compared with the experimental results presented in Figure 3 unless for the water solvent which shows a significant variation also for the band located around 212 nm; this effect was not verified in the calculations.

The band located around 240 nm shows the following order of decreasing value for the intensities: $I_{Acetonitrile} < I_{Ethanol} < I_{water} < I_{methanol} < I_{THF}$. The intensities,

relative to the solvents acetonitrile, ethanol, and THF, of the calculated negative band are in good agreement with the values obtained experimentally and presented in Figure 3. The results for the solvents water, and methanol, however, are in not agreement with the experimental results. Further calculations are been carried out to overcome these findings as, for example, the elaboration of a model with explicit solvent molecules around the solute.

Concluding Remarks

The effects of the solvent on the ECD spectrum are an important research area due to the possibility of obtaining information on the absolute conformation of a molecule of interest. The PCM model is applicable in the study of solvent effect for those with low and high polarity, and for the case of solvents were hydrogen bonds play a role this methodology is not yet extensively applicable, however, some results are quite close to those obtained experimentally. The molecule under study has a solvent-dependent ECD spectrum with a pronounced negative band around 240 nm and has the following decreasing order for the intensity value: $I_{Acetonitrile} < I_{Ethanol} < I_{water} < I_{methanol} < I_{THF}$. Complementary studies are being carried out using the supermolecule methodology with explicit solvent molecules in order to investigate the possible contribution of the formation of hydrogen bonds in the ECD spectrum as a function of the variation of solvent polarity.

Acknowledgments

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