

Local and Global Chirality Measures of Natural Amino Acids

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Abstract. The electron density cloud of each molecule contains the complete information about the molecule, including information about potential chirality effects, and in the case of a molecule undergoing a conformational or reaction process, also on chirality changes. In chemical reactions, including racemization processes of chiral amino acids, such as Aspartic Acid, the local and global electron density clouds undergo different degrees of shape changes, providing important information, which can be monitored and studied by the tools of mathematical chemistry and computational quantum chemistry. Based on this background, two specific studies have been initiated: Study 1. Demonstration that neither the complete, global electron density cloud, nor any of the local ranges of this electron density cloud can ever become achiral in any actual L to D transformation of amino acids, including the specific case of Aspartic Acid in the *in vivo* conditions of the human eye, where such L to D chirality changes have been implicated as causing cataract.

Study 2. Finding correlations between the gradually increasing size of well-defined chiral surroundings and the surroundings-induced chirality effects on inherently achiral molecules.

Keywords: Chirality of Electron Density Clouds, Chirality Measures, L-to-D Transformations of Amino Acids, Aspartic Acid Racemization and Cataract Formation, The Role of Chiral Surroundings in Racemization

Subject of the Report:

Invited Research Visit of Prof. Paul G. Mezey, Canada Research Chair in Scientific Modelling and Simulation, Memorial University, St. John's, NL CANADA

Invitation by the Kyoto University International Research Unit of Advanced Future Studies, for a one-month visit as Distinguished Research Professor, in charge of "Local and Global Chirality Measures of Natural Amino Acids", to be carried out in the Research Group of Professor Noriko Fujii, at the Research Reactor Institute of Kyoto University, Osaka, Japan, July 9 – Aug 8, 2016.

1. Introduction

Motivated by the advances by Professor Noriko Fujii in the study of Aspartic Acid racemization in the process of cataract formation in the eye (see, for example, Fujii 2012, Sakaue 2015, and Sakaue 2017, and references therein), at the invitation of the International Research Unit of Advanced Future Studies of Kyoto University in the period of 2016 July 9 to Aug 8, the research project on "Local and Global Chirality Measures of Natural Amino Acids" has been initiated. The early results already obtained during that one-month period have served as the basis of two journal publications already nearly complete and soon ready for submission. The two main topics of the Research Project are the following:

Topic 1. Exclusion Rule for Locally or Globally Achiral Structures of "in vivo" L to D Transformation of Aspartic Acid in a Process of Cataract Development in the Human Eye.

Demonstration that neither the complete, global electron density cloud, nor any of the local ranges of this electron density cloud can ever become achiral during any actual L to D transformation of Aspartic Acid in the human eye, in a process that is causing cataract.

Topic 2. Studies on the Effects of Chiral Surroundings on the Local and Global Shapes of Inherently Achiral Molecules.

Finding correlations between the size of well-defined chiral surroundings and the surroundings-induced chirality effects on inherently achiral molecules, as monitored by local shape analysis of electron density clouds.

The location of the research invitation for the project "Local and Global Chirality Measures of Natural Amino Acids" has been the welcoming environment of the Research Group of Prof. Noriko Fujii, at the Research Reactor Institute, Kyoto University, Sennan-gun, Kumatori-cho, Osaka 590-0494, Japan.

2. Related Lecture Presentations:

During this one-month visit, three lectures have been presented by P.G. Mezey.

Lecture 1. During the first week of this invitation, at the location Research Reactor Institute, Kyoto University, Sennan-gun, Kumatori-cho, Osaka 590-0494, Japan, of the Research Group of Prof. Noriko Fujii, some of the initial ideas concerning the two research topics, Topic 1 and Topic 2, have been presented by a lecture by

P.G. Mezey, "General Shape and Chirality Studies of Molecular Electron Densities",

Lecture 2. An additional lecture presentation on these initiatives has been given by P.G. Mezey at the Conference of the Japanese Society for Cataract Research, Iwate Koryu Center, Morioka, Japan July 29-31, 2016,

Paul G. Mezey: "When molecules of the eye turn into their mirror images and become misfits: Right hands in left gloves".

Lecture 3. A somewhat more general, but strongly related lecture by P.G. Mezey has been presented at the International Symposium on “Chemical, Physical and Mathematical Foundations of Complex Phenomena”, organized by the International Research Unit of Advanced Future Studies, Kyoto University, at the invitation of Prof. Masatoshi Murase, Yukawa Institute for Theoretical Physics Kyoto, University, Kyoto 606-8502, August 5, 2016,

Paul G. Mezey: “Imperfect Symmetries, Symmetry Deficiency Measures, and Chirality Measures in Biochemical Processes and Their Role in Some Diseases”.

3. Initial Research Progress with Topic 1 :

Exclusion Rule for Locally or Globally Achiral Structures of “in vivo” L to D Transformation of Aspartic Acid in a Process of Cataract Development in the Human Eye.

Motivated by the earlier findings by the Fujii Research Group concerning the likely transition structure of an actual L to D transformation of Aspartic Acid in the human eye, as described in (Fujii, 2012), (Sakaue, 2015), and (Sakaue, 2017), and references therein, a rather general principle has been found concerning the in vivo L to D chirality changes, also applicable to the case of Aspartic Acid transformations. Based on earlier electron density approaches to molecular shape and molecular chirality characterization (Mezey, 1993, 1996, 1998, 2014), involving both global and local representations of the electron density clouds of molecules, the so-called Holographic Electron Density Theorem (Mezey 1999a, 1999b, 2011, 2012) provides a basis for the interrelations between local and global chirality. This theorem states that in the electronic ground states, any small but positive volume part of the electron density cloud contains the complete molecular information. When applied to the chirality of amino acids, in particular, to Aspartic acid, assumed to be surrounded by some *in vivo* environment, one can derive certain corollaries concerning racemization processes. After the clarification of some of the relevant principles, as applied to chiral and achiral molecular electron density clouds of amino acids and their local fragments, the initial research work leading to some exclusion principles has been already completed during the visit to Research Reactor Institute, Kyoto University, Sennan-gun, Kumatori-cho, Osaka 590-0494, Japan, of the Research Group of Prof. Noriko Fujii. Some additional developments have been also completed after the visit, and now the manuscript of one planned publication is in the stage of being finalized.

Coauthors and tentative title of manuscript 1 in preparation:

Noriko Fujii and Paul G. Mezey: An Exclusion Rule for Locally or Globally Achiral Structures in the Process of “*in vivo*” L to D Transformation of Aspartic Acid Involved in a Process of Cataract Development in the Human Eye.

4. Initial Research Progress with Topic 2 :

Studies on the Effects of Chiral Surroundings on the Local and Global Shapes of Inherently Achiral Molecules.

One may regard this Topic 2 as a natural “counterpart” of Topic 1, since here the tests of actual calculations of electron density shape measures are aimed at describing the “chirality inducing” effects, and their degree and influence on electron density shape properties, when the original, single molecules themselves are achiral, hence a “pure” effect of the chirality inducing efficiency of the surrounding can be studied, without any inherent chirality that may mask, or “blur” the influence of the surroundings. If the chirality inducing effects of the surroundings are better understood, then the influences on inherently chiral molecules, such as most amino acids, can also be better understood. The results are expected to serve novel indications, what changes, potentially, intentionally introduced artificial changes in the surroundings can provide enhancement or hindrance for the L to D transformations of amino acids, including Aspartic Acid. Such studies might contribute to a better understanding of the processes involved, and, potentially, even to some novel means suitable to influence such transformations. Ideally, the ultimate goal in this area could be to find some chemical means to modify the influences of chiral surroundings thereby to hinder the L to D transformations of Aspartic Acid, potentially reducing the chances for cataract formation.

One manuscript is in preparation, describing the method and actual applications of finding correlations between the variations of the size of a well-defined type of *in vivo* chiral surroundings and the surroundings-induced chirality effects on inherently achiral molecules, as monitored by local shape analysis of electron density clouds. Details of the shape analysis methodology can be found in (Mezey, 1993).

Coauthors and tentative title of manuscript 2 in preparation:

Noriko Fujii, Zoltan Antal, and Paul G. Mezey: Size-Dependent Induced Chirality Effects of Chiral Surroundings on the Local and Global Shapes of Inherently Achiral Molecules.

5. References

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