Synthesis of rhodium complexes with amino acids and their structure determination by using chiroptical methods

Theses of the Ph.D. dissertation

Gábor Szilvágyi

M.Sc. in chemistry

Supervisors:

Dr. Miklós Hollósi, professor emeritus, D.Sc., full member of HAS

Dr. Zsuzsanna Majer, associate professor, Ph.D.

Consultant:

Dr. Elemér Vass, associate professor, Ph.D.

Eötvös Loránd University, Doctoral School of Chemistry

Director: *Dr. György Inzelt, full professor, D.Sc.*

Synthetic Chemistry, Materials Science, Biomolecular Chemistry PhD Programme

Director: *Dr. András Perczel, full professor, D.Sc., corresponding member of HAS*

Eötvös Loránd University, Institute of Chemistry, Department of Organic Chemistry

Laboratory for Chiroptical Structure Analysis

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1. Introduction

In the last few decades the dinuclear rhodium complexes have attracted considerable attention because of their specific structure and catalytic activity[1]. So far the main application of these metal complexes is the catalysis which spread from basic to pharmaceutical research[2].

Usually asymmetric catalytic reactions take place in the solution phase, hence it is imperative to know the exact „active" steric structure of the metal complexes in this phase, since the activity and selectivity of the complexes depend on its stereochemistry[3]. NMR spectroscopy and X-ray diffraction are powerful tools to determine the steric structure of transition metal complexes. The X-ray measurements require a single crystal of the sample with suitable size and quality that is frequently difficult to obtain, furthermore the X-ray diffraction gives information exclusively on the solid-state structure. To study a flexible molecule by NMR is not a simple route, because its use for conformation analysis is rather limited. In recent years, chiroptical methods – primarily ECD and VCD spectroscopy – combined with DFT calculations have been applied increasingly for the determination of the stereochemistry of transition metal complexes[4].

2. Objectives

During my doctoral studies several dirhodium complexes were synthesized from amino acids and their derivatives. Our further goal was to demonstrate that the parallel application of vibrational and electronic circular dichroism spectroscopy – as complementary techniques – and combined with DFT calculations can be a powerful method for the elucidation of the stereochemical properties of metal complexes as well. I do believe that my doctoral study will enhance the place of chiroptical spectroscopy in the arsenal of the structure determination methods.

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[1] D. J. Timmons, M. P. Doyle in Multiple bonds between metal atoms (Eds: F. A. Cotton, A. C. Murillo, A. R. Walton), Springer, New York, **2005**, vol. *13*, p. 591.
[2] a) M. El-Deftar, F.G. Adly, M. G. Gardiner, A. Ghanem *Curr. Org. Chem.,* **2012**, *16*, 1808–1836. b) H. M. L. Davies, J. R. Manning *Nature*, **2008**, *451*, 417–424.
[3] H. M. L. Davies, D. Morton *Chem. Soc. Rev.*, **2011**, *40*, 1857–1869.
[4] T. Wu, X-Z. You, P. Bouř *Coord. Chem. Rev.,* **2015**, *284*, 1–18.

3. Experimental methods

Chiroptical methods: the absolute configuration and conformation were determined by vibrational and electronic circular dichroism spectroscopy (VCD and ECD, respectively)

Analytical methods: Fourier transform infrared spectroscopy (FTIR), high-performance liquid chromatography (HPLC) and mass spectrometry (MS)

Applied quantum chemistry: calculations were performed at DFT level of theory by using Gaussian software package.

4. New scientific results (theses)

1. Several substituted dirhodium complexes were successfully synthesized from Z- and Ac-protected phenylalanine. Additionally, reversed-phase HPLC protocols were developed for their purification, subsequently, these methods were successfully applied for the purification of the other complexes, as well.
2. Pioneering in the literature, these substituted dirhodium complexes of Z- and Ac-phenylalanine were identified by ECD spectroscopy. I have established that the degree of the substitution does not affect for the shape of the ECD curves, while there is difference in their amplitude. In the case of monosubstituted complexes, beside ECD measurements, VCD spectra were recorded as well. Additionally, DFT calculations were performed in order to support the spectroscopic data. Thus, by using the combination of three independent methods, I could identify the conformational relationship of the synthesized dirhodium complexes in solution.
3. However, in the case of monosubstituted complexes, it was possible to elucidate their probable supramolecular structure from the experimental IR and VCD spectra and their temperature and solvent dependence, without any theoretical calculations.
4. Several dirhodium complexes were synthesized from non-protected amino acids, it was found that they have a twisted paddlewheel structure and C_2 symmetry. In all cases the complexes have two equivalent amino carboxylate ligands.

5. I have realized, that the above mentioned complexes (thesis 4.) are inherently chiral (Up to now, there is no record for this in the literature). According to experimental data chirality of the amino acid ligands are able to predetermine the chirality of the forming metal centre. Applying optical active ligands the reactions were diastereoselective. Pioneering in the literature I have established a rule between the chirality of ligands and the forming metal centre. In the case of optically inactive ligands the lack of chiral induction resulted in a racemic mixture. In only one case, the racemic mixture was separated by chiral HPLC.
6. The absolute configuration of the coordinated N atom was determined by ECD spectroscopy. In the ECD spectra, the Cotton effect around 400 nm is in unambiguous relation with the absolute configuration of the coordinated N atom. Based on this observation, I have suggested an empirical chiroptical rule which creates a connection between the sign of the Cotton effect and the absolute configuration of the N atom. These experimental results were confirmed by using DFT calculations.
7. Beside ECD spectroscopy, VCD spectroscopy – as a complementary technique – was applied which gave the opportunity to determine the absolute configuration of the forming metal centre. The VCD spectra do not depend on the absolute configuration of the N atom. Based on the coupled vibrational modes of the carboxylate groups of the ligands there is a possibility to apply exciton-coupled VCD. In the VCD spectra of the complexes an exciton couplet can be observed at around 1660 cm^{-1} which is in unambiguous relation with the absolute configuration of the metal centre. The experimental observations were confirmed by DFT calculations. Based on these observation, I have suggested an exciton chiroptical rule which creates a connection between the sign of the exciton couplet and absolute configuration of the metal centre. The experimental results were confirmed by using DFT calculations. By using this simple chiroptical rule and given the strength of related vibrational exciton couplet in the experimental VCD spectrum it was possible to identify the absolute configuration of such dinuclear rodium complexes quickly and easily, even from diluted solutions.

5. Publications, presentations and posters related to the dissertation

Publications

1. **Gábor Szilvágyi**, Miklós Hollósi, László Tölgyesi, Jadwiga Frelek, Zsuzsa Majer, Dirhodium complexes of amino acid derivatives: separation and characterization by circular dichroism spectroscopy, *Tetrahedron: Asymmetry*, **2008**, *19*, 2594−2599.
   IF: 2,796

2. **Gábor Szilvágyi**, Zsuzsa Majer, Elemér Vass, Miklós Hollósi, Conformational Studies on Chiral Rhodium Complexes by ECD and VCD Spectroscopy, *Chirality,* **2011**, *23*, 294−299. IF: 2,35

3. Hollósi Miklós, Knapp Krisztina, Majer Zsuzsa, **Szilvágyi Gábor**, Vass Elemér, A VCD-spektroszkópia alkalmazása peptidek, peptidmimetikumok és királis átmenetifém-komplexek térszerkezetének felderítésében, *Magyar Kémiai Folyóirat*, **2012**, *118*, 145−150. IF: 0

4. Zsuzsa Majer, **Gábor Szilvágyi**, László Benedek, Antal Csámpai, Miklós Hollósi, Elemér Vass, Chelate Structure of Dirhodium-Amino Acid Complex Indentified by Chiroptical Spectroscopy and NMR, *European Journal of Inorganic Chemistry*, **2013**, 3020−3027. IF: 2,965

5. **Gábor Szilvágyi**, Balázs Brém, Gábor Báti, László Tölgyesi Miklós Hollósi, Elemér Vass, Dirhodium complexes: determination of absolute configuration by exciton chirality method using VCD spectroscopy, *Dalton Transactions*, **2013**, *42*, 13137−13144.
   IF: 4,097

Presentations

1. **Gábor Szilvágyi**, Elemér Vass, Zsuzsa Majer, Miklós Hollósi,
   Structure Analysis of Chiral Dirhodium Complexes by ECD and VCD Spectroscopy,
   XVI. Nemzetközi Vegyészkonferencia (2010), Kolozsvár, Románia

2. **Gábor Szilvágyi**, Elemér Vass, Miklós Hollósi, Zsuzsa Majer,
   Chiroptical studies on chiral dinuclear rhodium complexes,
   Magyar Spektrokémiai Vándorgyűlés — XIV. Hungarian–Italian Symposium on Spectrochemistry (2011), Sümeg

3. **Szilvágyi Gábor**, Vass Elemér, Csámpai Antal, Hollósi Miklós, Majer Zsuzsa,
   Új ródiumkomplexek: szerkezetvizsgálat kiroptikai spektroszkópiával,
   XVII. Nemzetközi Vegyészkonferencia (2011), Kolozsvár, Románia

4. **Szilvágyi Gábor**, Brém Balázs, Báti Gábor, Vass Elemér, Hollósi Miklós, Majer Zsuzsa, Eredendően királis diródium komplexek – indukált kiralitás,
   XVIII. Nemzetközi Vegyészkonferencia (2012), Kolozsvár, Románia

5. **Szilvágyi Gábor**, Majer Zsuzsa, Hollósi Miklós, Vass Elemér,
   Fémkomplexek szerkezetének nyomában kiroptikai módszerekkel,
   MTA Koordinációs Kémiai Munkabizottság & Peptidkémiai Munkabizottság (2013 október 28.), Budapest

6. **Szilvágyi Gábor**, Hollósi Miklós, Vass Elemér,
   VCD spektroszkópia alkalmazása fémkomplexek abszolút térszerkezetének meghatározására, XIX. Nemzetközi Vegyészkonferencia (2013), Nagybánya, Románia

Posters

1. Benedek László, **Szilvágyi Gábor**, Hollósi Miklós, Jadwiga Frelek, Majer Zsuzsa,
   Kétmagvú átmenetifém komplexek: diródium-aminosav komplexek elválasztása és kiroptikai jellemzése,
   Vegyészkonferencia (2008), Hajdúszoboszló

2. Zsuzsa Majer, **Gábor Szilvágyi**, Miklós Hollósi, Jadwiga Frelek,
   Dinuclear Transition Metal Complexes: Separation and Characterisation of Dirhodium-Amino Acid Complexes, 38th International Conference on Coordination Chemistry (ICCC38, 2008), Israel

3. László Bendek, **Gábor Szilvágyi**, Miklós Hollósi, László Tölgyesi, Zsuzsa Majer,
   Effect of the stucture of chiral ligands on the ECD of dinuclear complexes,
   10th International Symposium on Applied Bioinorganic Chemistry, (ISABC10, 2009), Debrecen

4. **Gábor Szilvágyi**, Zsuzsa Majer, Elemér Vass, Andrea Bodor, László Benedek, Miklós Hollósi, Spectroscopic studies on the chiral dinuclear rhodium complexes,
   12th International Conference on Circular Dichroism (2009), Brescia, Olaszország

5. **Gábor Szilvágyi**, Balázs Brém, Gábor Báti, Elemér Vass, Miklós Hollósi, Zsuzsa Majer, Twisted chiral paddlewheel structure: synthesis and structure determination of dirhodium complexes by chiroptical spectroscopy,
   4th EuCheMS Chemistry Congress (2012), Prague, Czech Republic

6. Szabó Márk, **Szilvágyi Gábor**, Vass Elemér, Hollósi Miklós, Majer Zsuzsa, Eredendően királis diródiumkomplexek: szerkezet és katalitikus aktivitás,
   XVIII. Nemzetközi Vegyészkonferencia (2012), Kolozsvár, Románia

7. Kleineisel Márk, **Szilvágyi Gábor**, Hollósi Miklós, Vass Elemér,

N-fenil-α-aminosavakkal képzett diródium-aminosav komplexek előállítása és szerkezetvizsgálata, XIX. Nemzetközi Vegyészkonferencia (2013), Nagybánya, Románia

8. **Szilvágyi Gábor**, Szabó Márk, Kleineisel Márk, Csámpai Antal, Hollósi Miklós, Vass Elemér, Twisted dirhodium complexes of natural and modified amino acids: synthesis and structure determination using chiroptical methods (ECD, VCD),
   International Conference on Organic Synthesis, ICOS-20 (2014), Budapest

9. Márk Szabó, **Gábor Szilvágyi**, Elemér Vass, Antal Csámpai, Miklós Hollósi Predetermination of chirality by *N*-alkylated amino acids − Investigation of stereochemistry of the coordinated amino group in rhodium complexes,
   26th International Symposium on Chiral Discrimination, ISCD-26, Prague, Czech Republic

10. Márk Kleineisel, **Gábor Szilvágyi**, Elemér Vass, Antal Csámpai, Miklós Hollósi, Synthesis and structure determination of twisted chiral rhodium complexes from *N*-phenyl-α-amino acids,
    26th International Symposium on Chiral Discrimination, ISCD-26, Prague, Czech Republic

11. **Gábor Szilvágyi**, Márk Szabó, Márk Kleineisel, Elemér Vass, Antal Csámpai, Miklós Hollósi, AC determination of twisted rhodium complexes: can the coordinated amino group be chiral?
    26th International Symposium on Chiral Discrimination, ISCD-26, Prague, Czech Republic

6. Further publications, presentations and posters

Publications

1. **Gábor Szilvágyi**, Gábor Varga
   A kátrány, mint nyersanyag a római kori Pannóniában, infravörös spektroszkópiai (FT-IR) azonosítása és összehasonlítása (Birch bark pitch identified in Roman Age Pannonia) *Communicationes Archaeologicae Hungariae*, **2007**, 165−174. IF:0

2. E. Vass, U. Strijowski, K. Wollschläger, I. M. Mándity, **G. Szilvágyi**, M. Jewgiński, K. Gaus, S. Royo, Z. Majer, N. Sewald, M. Hollósi
   VCD studies on cyclic peptides assembled from L-alpha-amino acids and a *trans*-2-aminocyclopentane- or *trans*-2-aminocyclohexane carboxylic acid
   Journal of Peptide Science, **2010**, *16*, 613−620. IF: 1,954

3. Miklós Hollósi, Elemér Vass, **Gábor Szilvágyi**, Anrea Jakas, Ilona Laczkó
   Structure analysis of proteins, peptides and metal complexes by vibrational circular dichroism
   ARKIVOC, **2012**, *5*, 291−300. IF: 1,057

4. Zsuzsa Majer, Szilvia Bősze, Ildikó Szabó, Viktor G. Mihucz, Anikó Gaál, **Gábor Szilvágyi**, Giancarlo Pepponi, Florian Meirer, Peter Wobrauschek, Norbert Szoboszlai, Dieter Ingerle, Christina Streli
   Study of dinuclear Rh(II) complexes of phenylalanine derivatives as potential anticancer agents by using X-ray fluorescence and X-ray absorption,
   Microchemical Journal, **2015**, *120*, 51−57. IF: 2,746 (2014)

Presentations

1. Ignace Hanssens, Ann Vanhooren, Bart Devreese, Kris De Vriendt, Zsuzsa Majer, Eszter Illyés, **Gábor Szilvágyi**
   Tryptophan-mediated photolysis of disulfide bonds in proteins and peptides,
   International Congress of Radiation Research (ICRR, 2007), CA, USA

2. **Szilvágyi Gábor**, Illyés Eszter, Ignace Hanssens, Majer Zsuzsa
   A triptofán szerepe a ciklopeptidek diszulfidhídjainak fotolízisében,
   XXX. Kémiai Előadói Napok (KEN, 2007), Szeged

Posters

1. **Szilvágyi Gábor**, Illyés Eszter, Ignace Hanssens, Majer Zsuzsa
   Triptofán-tartalmú modellpeptidek tervezése, szintézise és fluoreszcencia tulajdonságainak vizsgálata
   XI. Nemzetközi Vegyészkonferencia (2005), Kolozsvár, Románia

2. **Gábor Szilvágyi**, Eszter Illyés, Kata Horváti, Ignace Hanssens, Zsuzsa Majer
   Modeling and Synthesis: Tryptophan-mediated photolysis by near-UV light
   1st European Chemistry Congress (2006), Budapest

3. **Szilvágyi Gábor**, Illyés Eszter, Ignace Hanssens, Majer Zsuzsa
   UV fény hatása a Triptofán-tartalmú modellpeptidekre
   Centenáriumi Vegyészkonferencia (2007), Sopron

4. Domonkos Celesztina, **Szilvágyi Gábor**, Bősze Szilvia, Vass Elemér, Tobias Bogner, Benedek László, Harmat Veronika, Majer Zsuzsa
   Kétmagvú átmenetifém komplexek szerkezetvizsgálata és *in vitro* funkcionális hatása
   Vegyészkonferencia (2010), Hajdúszoboszló

5. Szabó Márk, **Szilvágyi Gábor**, Rábai József, Hollósi Miklós, Vass Elemér
   2-(fluoralkil)-alkoxi-2-fenilecetsav észterek ródiumkatalizált aszimmetrikus szintézise
   XIX. Nemzetközi Vegyészkonferencia (2013), Nagybánya, Románia