

Ph.D Thesis

**INVESTIGATION OF INTRA- AND INTERMOLECULAR
CHEMICAL EXCHANGE PROCESSES BY MULTINUCLEAR
SOLUTION AND SOLID-STATE NMR SPECTROSCOPY**

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I. INTRODUCTION

For many years nuclear magnetic resonance (NMR) has been one of the most versatile and useful techniques in the structural study of organic- and organometallic compounds. To get a deeper understanding of the inherent molecular interactions, the NMR structure determination of new compounds is complemented with the identification of exchange pathways and the determination of the corresponding thermodynamic parameters. Exchange NMR provides a unique insight into the coordination chemistry of metal-organic complexes and the molecular dynamics of conformationally flexible organic compounds. For a better understanding of structure-function relations in the field of supramolecular chemistry and organocatalysis, one has to gain a clear picture of the three-dimensional molecular structure and the underlying molecular processes. One important aspect of this research is the characterization of bifunctional catalysts (in the absence of reactants and products) with respect to their self-association phenomena encoded inherently in their structures. I became interested in determining the nature and origin of *intra*- and *intermolecular* exchange processes and identifying the various states (species) of a given molecule in order to obtain a detailed picture of the network of interactions at the atomic level and their effect on conformational dynamics.

From the experimental point of view, it is a challenge to identify individual conformational states for small (<1kDa) molecules because their room temperature NMR spectra contain usually averaged resonances only: under fast exchange conditions the unique NMR parameters (chemical shifts, *J*-coupling constants, relaxation times) of the individual states are not directly accessible. To overcome this, and to exploit the information content of multidimensional spectra, experiments in the slow exchange regime must be performed. The appearance of the NMR spectra is governed by the ratio of the exchange rate *k* and the chemical shift difference $\Delta\nu$ measured in Hertz. There are two possibilities to alter the ratio *k*/ $\Delta\nu$ without introducing new chemical entities into the solution. The two methods involve variable temperature NMR and magnetic field-dependent studies. Lowering the temperature yields slower exchange rates and the resonances of the individual molecular states (conformers, monomeric/dimeric species) become observable in the spectra. This allows us to collect the desired structural information based on *J*-coupling or NOE correlations. A further advantage of working in the slow exchange regime at low temperature in highly viscous solutions is the effective cross-relaxation which is characteristic of biomolecules but is uncommon for small molecules. The initial buildup of the negative nuclear *Overhauser* effect (NOE) yields distance information for proton pairs and allows us to introduce important distance restraints and to determine the three dimensional structure of small molecular systems.

In studying systems undergoing exchange processes there are also several advantages of performing experiments at different magnetic field-strengths. Using different spectrometer frequencies (400 MHz vs. 600 MHz) one may influence the appearance of the NMR spectra without altering the

temperature. In the simplest two site $[A] \leftrightarrow [B]$ exchange model high-field spectrometers shift the system towards the slow exchange regime and the unwanted broadening and magnetization transfer effects of chemical exchange may disappear so that the structural study of the individual molecular states becomes possible. In a more complex system both *intra*- and *intermolecular* exchange processes exist and the slow exchange regime may not be achieved for all processes by cooling the sample. In that case one may exploit the advantages of lower field instruments where chances for temporary sharpening of the resonances may be achieved and one may find the appearance of the spectrum more suitable for analysis.

The aforementioned temperature- and field-dependent solution studies are well supported by solid-state NMR experiments. The crystalline state introduces order and generally restricts the motion of molecules so that the conformation (as governed by the crystal packing) can be studied in a well defined environment. Therefore, the solid-state magic angle spinning (MAS) and cross-polarization (CP)-MAS NMR study of conformationally flexible molecules are important reference points for studying dissolution induced structural changes. In such combined solution- and solid-state NMR studies some information between the solution and solid-state structures are readily available from comparing the values of the isotropic chemical shifts. During my research I preferred the combination of solution- and solid-state NMR techniques and explored systems with both small and large changes in the structure.

II. AIMS

My research involves the structure elucidation of organic- and organometallic samples using the combination of low-temperature solution- and solid-state NMR techniques. In such a method-oriented structural chemistry approach the emphasis was put on the assessment and characterization of new molecular recognition phenomena as well as the identification of the sources of dynamic processes observed in solution. My Thesis is based on a few case studies where the three dimensional molecular structure could only be determined *via* simultaneous studies of the nature of *intra*- and *intermolecular* chemical exchange processes. The underlying equilibrium processes made the NMR spectra dependent on the choice of solvent, concentration, temperature and the applied NMR spectrometer frequency. My aim was to change these parameters deliberately in order to gain information about the individual molecular states (conformations, monomers, dimers etc.) which are generally not accessible from routine room temperature NMR characterizations.

Behind my structural investigations there has been a state-of-the-art chemistry: organocatalysis and supramolecular chemistry. I have been investigating unique molecular systems arising from my research collaborations. With the thiourea modified bifunctional cinchona alkaloids my primary aim was to investigate a *self-association* phenomenon and its structural origins. In the case of

trimethyltin(IV)-tropolonate I was focusing on a *dismutation* reaction which transformed the structure into dimethyltin(IV)-tropolonate and Me₄Sn spontaneously. When investigating a dinuclear gold(I)-complex derived from xantphos my goal was to prove the existence of *metal-metal bonding* affected by an *intramolecular* exchange between the enantiomeric helical conformers of the macrocycle.

III. APPLIED METHODS

The *intra*- and *intermolecular* chemical exchange processes in conformationally flexible and strongly aggregating molecules have been investigated by taking advantage of the following NMR methods:

- The NMR spectra were recorded at 400 and 600 MHz spectrometers.
- Two dimensional through-bond *homo*- and *heteronuclear* correlation experiments (DQFCOSY, TOCSY, HSQC, HMBC) were routinely applied for resonance assignments.
- Multinuclear ¹H-, ¹³C-, ¹⁵N-, ¹⁹F-, ³¹P-, ¹¹⁹Sn-NMR experiments were performed.
- Dissolution induced structural changes have been investigated by the combination of solution and solid-state (MAS and CP/MAS) NMR methods.
- Thermodynamic parameters (*K*, ΔH , ΔS and ΔH^\ddagger , ΔS^\ddagger) were determined by using temperature dependent (179-343K) solution NMR experiments. Dynamic NMR investigations involved lineshape analyses of the NMR spectra and EXSY experiments.
- Spin-system analysis were performed for non-first order multiplets (*AA'BB'*) in ³¹P-NMR.
- Structural problems have been addressed by the analysis of NOESY and ROESY spectra. Three dimensional structures were determined by the assessment of ¹H-¹H distances derived from kinetic NOESY experiments in the negative NOE regime.
- *In situ* ¹H-NMR kinetic experiments have been performed and analysed.
- I have gained experiences with the following software packages: VnmrJ 2.2C, STARS, Origin 8.0, WinDNMR 7.1, HyperChem 8.0, EXSYCalc, WeblabViewer 4.0 és CorelDraw 9.0.

IV. RESULTS

1. A new molecular self-recognition mechanism has been discovered for the bifunctional organocatalyst (3*R*,4*S*,8*S*,9*S*)-9-[(3,5-bis(trifluoromethyl)phenyl)-thiourea](9-deoxy)-*epi-quinine*. The three dimensional structure of the hydrogen-bonded dimeric self-assembly of the catalyst was determined using accurate ¹H-¹H distances derived from kinetic NOE experiments (−80°C, 600 MHz). The study is complemented with a comparison with other members of the bifunctional thiourea/amine organocatalyst family where self-association has been assessed. The acidic N_BH protons of the

3. The decisive role of the quinoline moiety in the molecular recognition process of bifunctional thiourea/amine 9-*epi*-cinchona catalysts was rationalized by the characterization of the intermolecular CH/ π interaction. It has turned out that one of the aromatic α -C-H protons of the quinoline moieties acts as a donor of *intermolecular* hydrogen-bonding towards the π -system of the second quinoline ring within the dimeric assembly.

4. Dissolution induced structural changes of trimethyltin(IV)-tropolonate have been investigated by multinuclear solution and solid-state ^1H -, ^{13}C - and ^{119}Sn -NMR experiments. I have described that trimethyltin(IV)-tropolonate rearranges into dimethyltin(IV)-ditropolonate and tetramethyltin in a spontaneous dismutation reaction. The kinetics of the methyl-migrational process was monitored by ^1H -NMR experiments. It has turned out that the rearrangement occurs faster in liquid and solid-state as compared to dilute solutions of apolar, aprotic solvents.

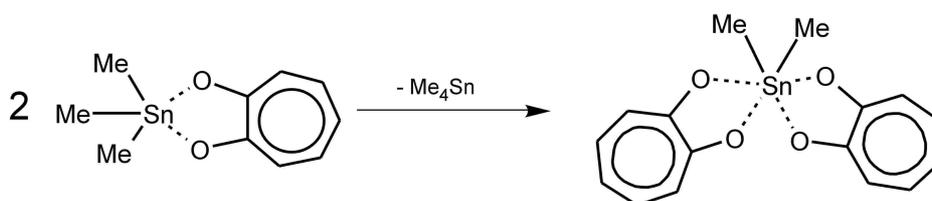


Figure 3. The methyl-migrational dismutation process of trimethyltin(IV)-tropolonate

5. The principal values of the chemical shielding tensor ($\delta_{11}=159,1$ ppm; $\delta_{22}=94,6$ ppm; $\delta_{33}=-71,9$ ppm) have been determined by the analysis of the solid-state ^{119}Sn -MAS NMR spectrum of trimethyltin(IV)-tropolonate. The isotropic chemical shift ($\delta_{\text{iso}}=60,6$ ppm) was compared to the value measured in the apolar, aprotic solvent CDCl_3 . The dynamics of the tropolonate ligand in solution was rationalized by comparing the number of resonances in solution- and solid-state NMR spectra. The coordination number at the central tin(IV) atom as well as the Me-Sn-Me angles were deduced from ^{119}Sn NMR parameters: $\delta_{119\text{Sn}}$ chemical shifts and $^2J_{\text{H},119\text{Sn}}$, $^1J_{\text{C},119\text{Sn}}$ heteronuclear coupling constants. They appeared to be sensitive to the presence of *O*- and *N*-donor solvents which induce dismutation at higher rate than the non-coordinating solvents.

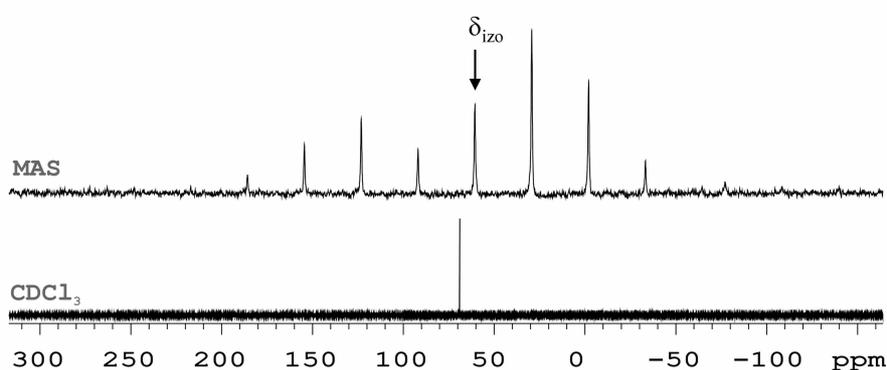


Figure 4. The solution and solid-state ^{119}Sn -NMR (224 MHz) spectra of trimethyltin(IV)-tropolonate

6. The conformational analysis of $[\text{Au}^{\text{I}}_2(\text{xantphos})_2](\text{NO}_3)_2$ complex (*xantphos* = 9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene) has been performed using the information of solvent and temperature dependent two dimensional NMR experiments. Different magnetization transfer pathways (NOE vs. exchange) were distinguished by the identification of the sources of chemical exchange processes (NOESY). The resonance assignment was performed in conjunction with exchange NMR for reasons of molecular symmetry. It appeared that the conformational dynamics of the complex stems from the mutual exchange of the helical enantiomers of the 16-membered ($\text{Au}_2\text{P}_4\text{C}_8\text{O}_2$) macrocyclic structure having a C_2 symmetry. The corresponding thermodynamic parameters of the intramolecular exchange process were determined by lineshape-analysis using variable temperature ^1H - and ^{31}P -NMR spectra. The activation enthalpy of the process was found to be $\Delta H^\ddagger = 48,4 \pm 1 \text{ kJ}\cdot\text{mol}^{-1}$.

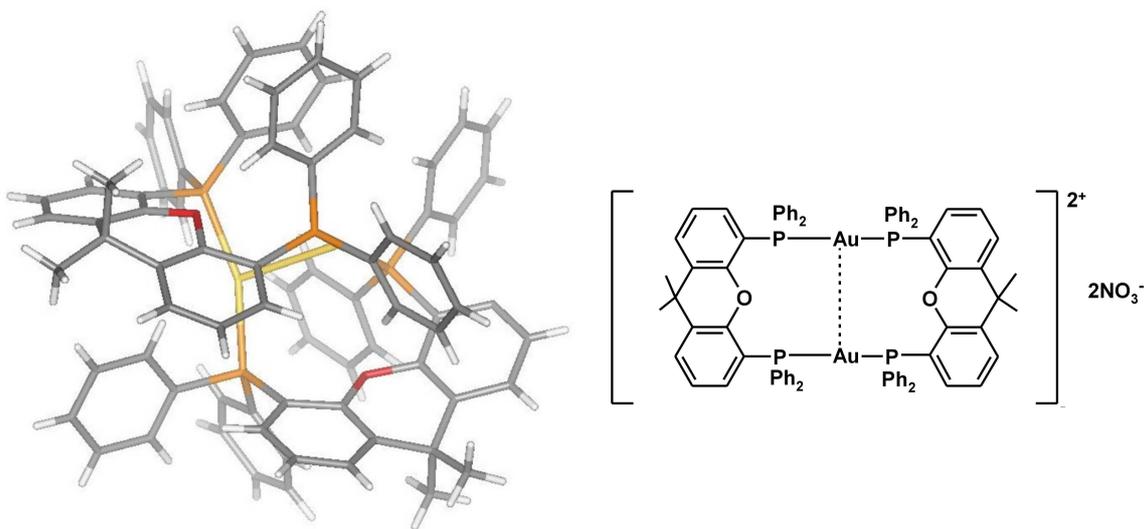


Figure 5. The structure of the $[\text{Au}^{\text{I}}_2(\text{xantphos})_2](\text{NO}_3)_2$ complex

7. I have proven the existence of the aurophilic interaction ($\text{Au}\cdots\text{Au}$) in solution for the dinuclear $[\text{Au}^{\text{I}}_2(\text{xantphos})_2](\text{NO}_3)_2$ complex using dynamic ^{31}P -NMR spectroscopy. It has turned out that the long range homonuclear $^3J_{31\text{P},31\text{P}}$ couplings are mediated by the metal-metal bond in the $\text{P}-\text{Au}\cdots\text{Au}-\text{P}$ moiety. Therefore, in context of the known stereochemistry, the appearance of the ^{31}P $AA'BB'$ spin-system indicates the presence of the aurophilic interaction. Signal doubling effects were found in the solid-state ^{13}C -CP/MAS and ^{31}P -MAS NMR spectra which were interpreted as the consequence of a *head-to-head* and *tail-to-tail* arrangement of the molecules in the crystal lattice.

V. CONCLUSIONS

The NMR spectroscopic investigations of thiourea/amine bifunctional organocatalysts have revealed that the single set of resonances in the room temperature NMR spectra hides an intriguing self-association process that has been further complicated by the conformational dynamics of the molecules. One may conclude that self-association which is an inherent process within the investigated organocatalyst family may influence our thinking when describing the mechanism of catalytic reactions. It is likely that the newly discovered molecular interactions and the underlying chemical exchange processes will also influence the development of future catalyst systems.

My solution- and solid-state NMR investigations of the trimethyltin(IV)-tropolonate complex has established that the dismutation reaction $2\text{Me}_3\text{Sn}(\text{Trp}) \rightarrow \text{Me}_2\text{Sn}(\text{Trp})_2 + \text{Me}_4\text{Sn}$ proceeds faster in polar solvents than in non-coordinating solvents. This suggests that solvent coordination plays an important role in the dismutation process *via* changing the coordination number of the central tin(IV) atom and by inducing structural changes.

Variable temperature and solvent dependent ^1H - and ^{31}P -NMR studies in conjunction with low temperature ^1H -NOESY experiments have confirmed that the dinuclear gold(I)-complex $[\text{Au}^{\text{I}}_2(\text{xantphos})_2](\text{NO}_3)_2$ possesses conformational flexibility in the solution, which arises from the aurophilic interaction and the stereochemistry of the ligand. According to the low-temperature NMR studies the complex adopts a helical conformation exhibiting an $\text{Au}\cdots\text{Au}$ bond, which confirms its macrocyclic structure as it appears in the crystal structure.

In conclusion, the combination of temperature dependent solution as well as solid-state NMR applications provide new perspectives in the study of chemical exchange processes in bifunctional and conformationally flexible small molecular organic systems. The possibility to determine accurate ^1H - ^1H distances from low temperature (-80°C) experiments performed in viscous solutions will further increase the potential of NOESY in small molecular structure determinations.

VI. PUBLICATIONS

Papers

- 1) Andrea Deák, Tünde Megyes, Gábor Tárkányi, **Péter Király**, László Biczók, Gábor Pálincás, Peter J. Stang: „Synthesis and solution- and solid-state characterization of gold(I) rings with short Au•••Au interactions. Spontaneous resolution of a gold(I) complex” *J. Am. Chem. Soc.*, **2006**, 128(39), 12668–12670.
- 2) Gábor Tárkányi, **Péter Király**, Gábor Pálincás, Andrea Deák: „Conformational analysis of a helically distorted gold(I) macrocycle derived from xantphos: evidence for the aurophilic Au•••Au interaction from NMR” *Magn. Reson. Chem.*, **2007**, 45, 917-924.
- 3) Andrea Deák, **Péter Király**, Gábor Tárkányi: „Preparation and structural characterization of trimethyltin(IV) tropolonate. Investigation of a rare methyl-migrational dismutation in the solution, solid and liquids states” *Dalton Trans.*, **2007**, 2, 234-239.
- 4) Gábor Tárkányi, **Péter Király**, Szilárd Varga, Benedek Vakulya, Tibor Soós: „Edge-to-face CH/ π aromatic interaction and molecular self-recognition in *epi*-cinchona based bifunctional thiourea organocatalysis” *Chem. Eur. J.*, **2008**, 14, 6078-6086.
- 5) **Péter Király**, Szilárd Varga, Benedek Vakulya, Tibor Soós, Gábor Tárkányi: „Self-association promoted conformational transition of (3*R*,4*S*,8*R*,9*R*)-9-[(3,5-bis(trifluoromethyl)phenyl)-thiourea](9-deoxy)-*epi*-cinchonine” *Magn. Reson. Chem.*, **2010**, 48, 13-19.

Posters

- 1) **Péter Király**, Gábor Tárkányi, Tünde Tunyogi, Andrea Deák, Gábor Pálincás „Investigation of the Au•••Au aurophilic interaction by NMR”, EUROMAR, July 6-11, **2008** St. Petersburg, Russia (ENG)
- 2) **Péter Király**, Andrea Deák, Tibor Soós, Gábor Pálincás, Tünde Tunyogi, Szilárd Varga, Benedek Vakulya, Gábor Tárkányi „Low temperature NMR spectroscopic investigation of self-assembled systems: differential line broadening effects in NMR of small molecules”, Small Molecules Are Still Hot (SMASH), **2009**. September 20-23. Chamonix, France (ENG)

Presentations

- 1) Tárkányi Gábor, **Király Péter**, Megyes Tünde, Pálincás Gábor, Deák Andrea “Arany makrociklusok szerkezetvizsgálata ¹H-, ¹³C- és ³¹P-NMR spektroszkópiás módszerekkel”, (HUN) MTA KK Kutatóközponti Tudományos Napok, **2006**. május 18-19., Budapest
- 2) **Király Péter** “Arany- és óntartalmú komplexek vizsgálata szilárd fázisú- és dinamikus oldat NMR spektroszkópiával”, (HUN) X. Doktori Iskola, **2007**. május 9., Mátraháza

- 3) **Király Péter**, Tárkányi Gábor, Tunyogi Tünde, Deák Andrea “Szilárd NMR–mérések a szupramolekuláris kémiában”, (HUN) MTA KK Kutatóközponti Tudományos Napok, **2007**. május 22., Budapest
- 4) Tárkányi Gábor, **Király Péter**, Tunyogi Tünde, Pálincás Gábor, Deák Andrea “Arany-makrociklusok szerkezetvizsgálata oldat- és szilárdfázisú NMR spektroszkópiás módszerekkel”, (HUN) Centenárium Vegyészkonferencia, **2007**. május 30., Sopron
- 5) **Király Péter**, Tárkányi Gábor, Varga Szilárd, Vakulya Benedek, Soós Tibor “NMR spektroszkópiai vizsgálatok a bifunkcionális organokatalízisben”, (HUN) MTA KK XI. Doktori Iskola, **2008**. április 21-22., Mátrafüred
- 6) **Király Péter**, Vakulya Benedek, Varga Szilárd, Soós Tibor, Tárkányi Gábor “Tiourea alapú bifunkcionális organokatalizátorok konformációs dinamikájának és asszociációs folyamatainak vizsgálata NMR spektroszkópiával”, (HUN) MTA NMR munkabizottsági ülés, **2008**. november 25., Budapest, Richter Gedeon Nyrt
- 7) **Király Péter**, Soós Tibor, Varga Szilárd, Vakulya Benedek, Tárkányi Gábor “9-tiokarbamid-*epi*-cinkona organokatalizátorok asszociációjának hatása a monomer állapotok konformációs egyensúlyára”, (HUN) MTA KK Kutatóközponti Tudományos Napok, **2009**. november 24-26., Budapest
- 8) **Péter Király**, Tibor Soós, Szilárd Varga, Benedek Vakulya, Gábor Tárkányi: „Self-association promoted conformational transition” (ENG), MTA/MKE NMR Munkabizottsági ülés, Richter Gedeon NyRt., **2009**. december 11., Budapest

VII. PAPERS FORMING THE BASE OF THE DISSERTATION

- 1) Andrea Deák, Tünde Tunyogi, Gábor Tárkányi, **Péter Király** and Gábor Pálincás „Self-assembly of gold(I) with diphosphine and bitopic nitrogen donor linkers in the presence of trifluoroacetate anion: formation of coordination polymer versus discrete macrocycle” *Cryst. Eng. Comm.*, **2007**, 9, 640-643.
- 2) Tünde Tunyogi, Andrea Deák, Gábor Tárkányi, **Péter Király**, Gábor Pálincás „Solvent-assisted spontaneous resolution of a 16-membered ring containing gold(I) showing short Au•••Au aurophilic interaction and a figure-eight conformation” *Inorg. Chem.*, **2008**, 47(6), 2049-2055.
- 3) Imre Miklós Szilágyi, János Madarász, György Pokol, **Péter Király**, Gábor Tárkányi, Sami Saukko, János Mizsei, Attila L. Tóth, András Szabó, Katalin Varga-Josepovits „Stability and Controlled Composition of Hexagonal WO₃” *Chem. Mater.*, **2008**, 20(12), 4116-4125.
- 4) Imre Miklós Szilágyi, István Sajó, **Péter Király**, Gábor Tárkányi, Attila L. Tóth, András Szabó, Katalin Varga-Josepovits, János Madarász, György Pokol „Phase transformations of ammonium tungsten bronzes” *J. Therm. Anal. Calorim.*, **2009**, 98, 707-716.