Development of new precursors for asymmetric preparation of α-[11C]methyl amino acids for PET
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Aims and outline of the Thesis

The main aims of the work presented in this thesis are:

• to increase stereochemical output of alkylation of the chiral nickel complexes derived from amino acids in order to avoid or at least simplify separation of diastereomeric products of alkylation;
• to develop a new approach to creation of quaternary asymmetric centre via alkylation of a chiral tertiary carbanion by $^{11}$CH$_3$I or $^{11}$CH$_3$OTf and evaluate the applicability of metallocomplex chiral synthons of $\alpha$-amino acids for asymmetric synthesis of $^{11}$C-labeled $\alpha$-methyl amino acids.

Chapter 1  Introduction:

1.1 Short review on the use and preparation of PET-labelled amino acids. Importance for PET using new $\alpha$-substituted amino acids

1.1.1 Positron emission tomography in oncology
1.1.2 Potential benefits of using AAs for PET
1.1.3 Overview of approaches to $^{11}$C amino acids
1.1.3.1 Oppolzer’s synthon and Seebach’s BMI and BDI
1.1.3.2 Catalytic alkylation of an achiral glycine synthon
1.1.3.3 Enzymatic catalysis
1.1.3.4 Biotechnologic approach
1.1.3.5 Catalytic hydrogenation
1.1.3.6 Side-chain modification
1.1.3.7 $\alpha$-[11C]Methyltryptophan
1.1.4 Importance for PET using new $\alpha$-substituted amino acids
1.2 General aspects on nickel complexes and synthesis of $\alpha$-amino acids
1.2.1 Early development of chiral nickel complexes
1.3 References

Chapter 2  Physical-chemical investigation of chiral nickel complexes and effects of fluorination of dopamine:

2.1 Disclosure of conformations of three model complexes in their CDCl$_3$ solutions. Proximity of ortho-protons of the benzyl group to both the $\alpha$-proton of the proline residue and substituents in $\alpha$-position of the amino acid fragment leads to formulation of the first hypothesis about structure of the improved synthon providing higher asymmetric induction. It should carry substituents in ortho-positions of the benzyl group. Collect. Czech. Chem. Commun. 1995, 60, 990. IF 0.88

2.2 Description of the influence of a polar solvent to spin-spin interactions observed in $^{13}$C-NMR spectra of the complex derived from glycine. The high-quality X-ray structure of the complex is presented. MP2 single-point modelling of the complex clearly shows that computers with 1GB RAM are too poor for realistic modelling of the structure of the complex in a vacuum. Transition Metal Chem. 2003, 28, 475. IF 0.92
The same complex is studied, now with experimental synchrotron X-ray measurement of electron density and MP2 modelling followed by topologic analysis. The polarisation of electron density in an aromatic electron cloud of the benzyl group towards positively charged nickel atoms is proved by experiment and could be used for further development of new synthons. The crystallographic data and results of quantum-chemical modelling described in Chapter 2.2 are used. *Acta Crystallogr. A* **2004**, 60, 510. IF 1.68

Further crystallographic and NMR studies of the complexes bearing substituents. Observed influence of two methyl substituents in α-position of the amino acid fragment to spin-spin interactions in a 13C-NMR spectrum and the conformation of the complex in solid state are in good agreement with expectations. The complex with two methyl substituents is a lead compound for synthetic intermediates for preparation of enantiomERICALLY pure α-[11C]methyl amino acids. *Polyhedron* **2007**, 26, 911. IF 1.84

An MP2 investigation of formation of intramolecular hydrogen bonds by the fluorine atom present in 6-fluorodopamine supported the hypothesis on the formation of similar hydrogen bonds between fluorine atoms of 18F-labelled radiopharmaceuticals and biological structures in vivo. *J. Label. Compd. Radiopharm.* **2007**, 50, 528. IF 0.75

**Chapter 3** Creation of new complexes – amino acids synthons for higher stereochemical output of alkylation reactions:

3.1 Description of the preparation of substituted N-benzylprolines, one of which is used for the synthesis of new glycine and alanine synthons. *Chem. Heterocycl. Comp.* **2000**, 36, 544. IF 0.31

3.2 Preparation of new glycine and alanine synthons. Their stereodiscriminative properties are compared with those of previously published structures and found to be superior. Model reactions and spectroscopic analytical methods are suggested aimed to eliminate possible error in determination of the ratio of diastereomers characteristic for HPLC analyses. All measurements of diastereomeric excess (d.e.) were performed by 1H and 13C NMR spectroscopy. *Transition Metal Chem.* **2002**, 27, 884. IF 0.92

3.3 Next eleven new glycine and alanine synthons were prepared and evaluated using the model reactions described in Chapter 3.2. Four complexes exhibited very high level of stereocontrol of methylation under both thermodynamically and kinetically controlled conditions. *Submitted article*

**Chapter 4** Development and evaluation of the complexes for preparation of α-methyl amino acids:

4.1 Description of development of improved procedure for the synthesis of chiral nickel complexes. It significantly decreased amount of nickel ion in waste water and eliminated formation of nickel-contaminated solid waste and thus addressed the environmental dimension of the application of the complexes. This procedure was later used for preparation of [11C]methyltyrosine synthons and for attempts to create a synthon for [11C]methyltryptophan (see Chapters 4.2-4.4). An improved procedure is suggested which allows a significant

4.2 Similar optimisation is done for preparation of a precursor for C^{11}-labelled methyltyrosine. Preparation of a precursor for C^{11}-labelled methyltryptophan failed due to low thermal stability of Boc-protective group applied in the indolyl part of the molecule. *Submitted article*

4.3 The preparation of a tyrosine complex used for assignment of stereochemistry of asymmetric centres is described as well as its mass spectral properties. *J. Mass Spectrom.* 2006, 41, 448. IF 2.95

4.4 A precursor for ^{11}C-labelled methyltryptophan was prepared at lower temperature and employed in a model methylation reaction. Instability of the Boc-protective group during methylation was disclosed using mass-spectrometry. *J. Mass Spectrom.*, DOI: 10.1002/jms.1405. IF 2.95

4.5 Description of the first synthetic steps towards the asymmetric preparation of enantiomerically pure α-[^{11}C]methyl amino acids. *J Label Compd Radiopharm* 2007, 50, 370. IF 0.75

List of abbreviations

5.1 Summary and future perspectives

5.1.1 Perspectives of development of chiral nickel complexes for preparation of radiolabelled α-disubstituted glycines

5.1.2 Perspectives of development of chiral nickel complexes for preparation of radiolabelled α-monosubstituted glycines

5.1.3 Perspectives of physical chemical investigations

5.2 Bibliography

5.3 References