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Why is monoalkylation versus bis-alkylation of the Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and glycine so selective? MP2 modelling and topological QTAIM analysis of chiral metallocomplex synthons of α-amino acids used for the preparation of radiopharmaceuticals for positron emission tomography

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Abstract Chiral Ni(II) complexes are used for the preparation of carbon-11 or fluorine-18 enantiomerically pure α-amino acids for positron emission tomography (PET). They enable the selective monoalkylation of a glycine synthon with high stereoselectivity and the preparation of enantiomerically pure α-amino acids with quarternary α-carbon. Molecular modelling of non-, mono- and di-substituted complexes using quantum theory of atoms-in-molecule (QTAIM) topological analysis of electron density allowed us to formulate a new theory explaining the reasons for highly selective monomethylation of the complexes. In the non-substituted complex (GK), the α-carbon atom exhibits a higher atomic volume and a more positive charge in comparison with mono- and di-substituted complexes. This unusual behaviour is accompanied by increasing the bond critical point (BCP) ellipticity of the iminic bond in GK explained by the higher mechanical strain. Both phenomena indicate the increased reactivity and probably originate in more compact core of GK where shorter distances in the internal coordination sphere result in the higher strain of its bonds.

Keywords Selective alkylation · Amino acids · Positron emission tomography · Topological analysis of electron density · Quantum theory of atoms-in-molecule

Introduction

Since their introduction in 1982 [1], chiral Ni(II) complexes-based synthons of α-amino acids gained noticeable popularity as a very simple, robust and cheap tool for the preparation of enantiomerically pure non-coded amino acids and diagnostics of brain tumours and malfunction of dopaminergic neurons by positron emission tomography (PET) [2–12].

An important improvement occurred when the first generation synthons based on substituted 2-aminobenzaldehyde (as biomimetic analogues of pyridoxal-5-phosphate) [13] were overperformed in asymmetric alkylation reactions by derivatives of 2-aminoacetophenone followed by even more efficient derivatives of 2-aminobenzophenone [14]. The second generation synthons delivered a higher selectivity of C19 monomethylation and much higher ratio of diastereomers of alkylated products under thermodynamically controlled conditions when C19 is epimerised in a basic reaction mixture or in a separate epimerisation step carried out in NaOMe/MeOH [15, 16] (Y. N. Belokon, personal communication). For example, equilibrium ratio of diastereomers of the alanine complex increased from 15% *d.e.* for the first generation to 82% *d.e.*

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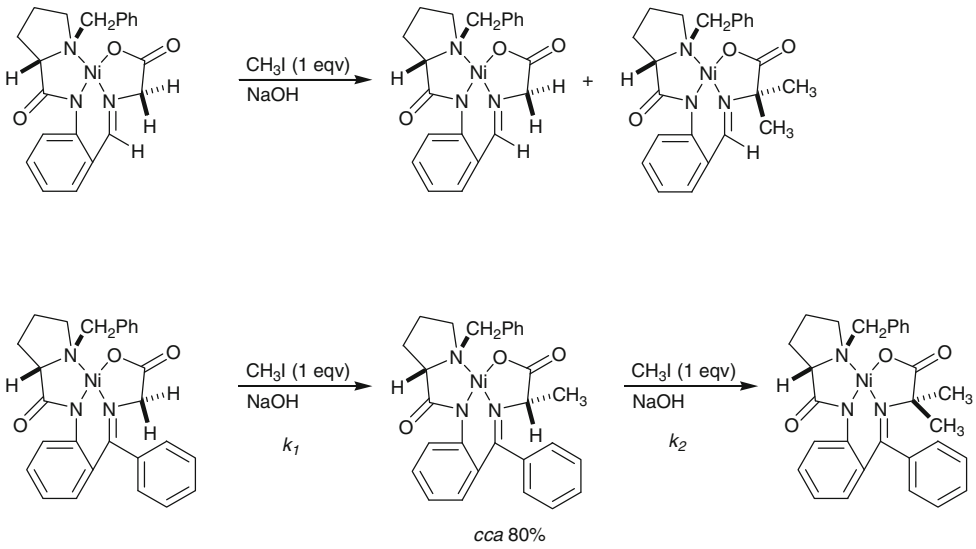
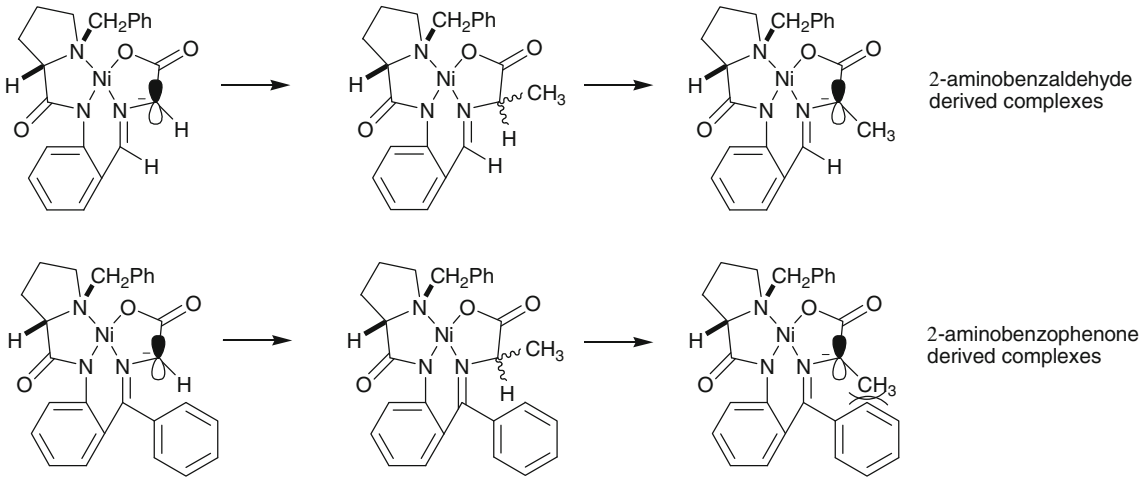


Scheme 1 Selective monomethylation of the second-generation synthon. For the 2-aminobenzophenone-derived complex (GK) a bulkier electrofile can be used in the second alkylation step for the preparation of enantiomerically pure α-methyl amino acids



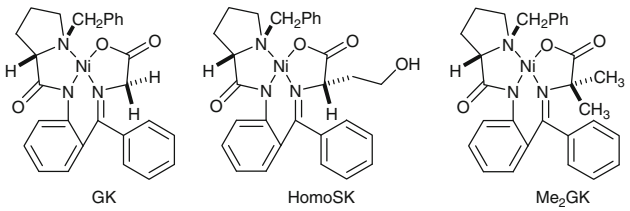
Scheme 2 Steric repulsion leading to the distortion of the sterically hindered monomethylated carbanion

for the second generation [15]. New synthons enabled the preparation of enantiomerically pure α-methyl amino acids by sequential monomethylation of the glycine complex followed by the introduction of a bulkier second C19 substituent (Scheme 1) [17].

This high selectivity was explained by the destabilisation of a carbanion generated from the monomethylated product due to intramolecular steric repulsion, when compared to the carbanion generated from the starting non-substituted complex (Scheme 2) [18]. Such a distortion leads to a non-planar destabilised carbanion (Scheme 2). In this article we present a complementary explanation based on the disclosure of a non-trivial bond strain in the least sterically hindered Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and glycine (GK) when compared with its α-carbon (C19) monoalkylated (HomoSK) and dimethylated (Me_2GK) derivatives (see Scheme 3 and Fig. 1).

Results and discussion

Recently achieved breakthrough in the reduction of the environmental impact of a high-scale production of α-amino acids via Ni(II) complexes [19, 20] and a substantial improvement of the diastereoselectivity of the alkylation reaction [16, 21–25] made the complexes a tool of choice for the preparation of carbon-11 or fluorine-18 enantiomerically pure α-amino acids for PET. In order to achieve simple work-up of the reaction mixture after the alkylation reaction, and easy, cheap and environment-friendly purification of the desired diastereomer of the alkylated complex by the crystallization or simple purification of the reaction mixture in the remote-controlled preparation of labelled α-amino acids for PET, it is important to understand and use the factors determining the high ratio of GK alkylation rates k_1/k_2 (Scheme 1). During the course of our development of the approaches to



Scheme 3 Non-, mono- and di-substituted complexes derived from 2-aminobenzophenone

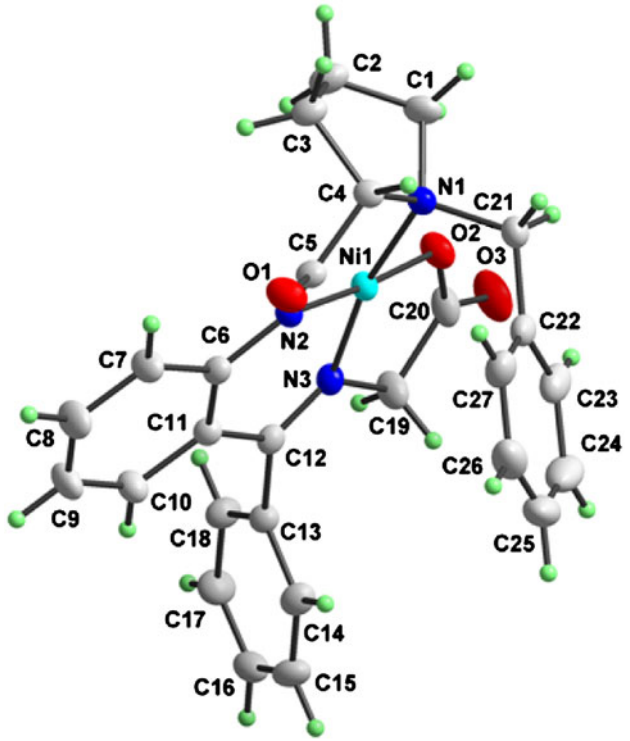


Fig. 1 Numbering scheme for GK (From ref. [26])

carbon-11 labelled α-methyl amino acids and to a strategy of fluorine-18 labelling of peptides, we prepared a number of single crystals of nickel (II) complexes and performed ab initio MP2 quantum-chemical modelling of these structures. In this work we describe the quantum theory of atoms-in-molecules (QTAIM) analysis of the atoms and bonds of interest based on MP2 single-point calculations of the non-, mono- and di-substituted complexes, X-ray structures of which we have published previously (Scheme 3) [26–28]. QTAIM analysis based on MP2 calculations using double-ζ basis sets is considered to be an adequate approach for modelling the large systems where π–π and σ–π interactions play an important role [29]. Initially we expected that the introduction of substituents into the α-position (C-19) of the complexes should subsequently increase the steric hindrance in these complexes. In reality, the atomic volume of C-19 in the non-substituted GK is the highest one among the three complexes (Table 1). As a rule, atomic volumes increase with higher electron density at the corresponding atoms (more negative or less positive atomic charges) in analogous structures [30, 31] otherwise an increasing reactivity at these atoms is indicated. In GK, O2 atom exhibits a lower atomic volume and a more negative charge whereas C19 atom exhibits a higher volume and a more positive charge in comparison with HomoSK and Me_2GK complexes (Table 1). This unusual behaviour is accompanied by the increased BCP ellipticities of Ni–O2, O3–C20 and C19–N3 bonds of GK in comparison with the remaining complexes (Table 2) which may be explained by the mechanical strain. The increased mechanical strain at O2 and C19 atoms indicates the higher reactivity at these sites of GK [30, 31] in comparison with HomoSK and Me_2GK complexes. Significantly stronger O2–C20 bond and weaker C19–N3 bond in GK in comparison with the remaining compounds (Table 2) confirm the observed differences in their electronic structure as well. The atomic volumes of the iminic N3 bonded to C19 follow the similar pattern—they are the biggest in the least substituted GK (Table 1). We hypothesised that such an unexpected behaviour originates in the more compact core of GK where the shorter distances in the internal coordination sphere result in the higher strain of these bonds. Monoalkylated (e.g. monomethylated) complexes derived

Table 1 Atomic charges and volumes of selected atoms in the systems under study (see Scheme 3 and Fig. 1)

Atoms	Charges			Volumes ($Bohr^3$)		
	GK	HomoSK	Me_2GK	GK	HomoSK	Me_2GK
Ni	+1.29	+0.98	+0.98	71.7	87.6	87.0
O2	−1.19	−0.97	−1.03	103.9	109.9	107.2
C20	+1.49	+1.25	+1.27	37.6	42.8	41.5
C19	+0.48	+0.29	+0.24	47.0	44.9	41.2
N3	−1.17	−0.94	−0.92	88.0	81.3	81.6
C3	+0.26	+0.19	+0.19	51.8	56.1	54.9

Table 2 BCP electron densities, ρ_{BCP}, and ellipticities, ε_{BCP}, of selected bonds in the systems under study (see Scheme 3 and Fig. 1)

Bonds	ρ_{BCP} ($e/Bohr^3$)			ε_{BCP}		
	GK	HomoSK	Me_2GK	GK	HomoSK	Me_2GK
Ni–O2	0.101	0.116	0.114	0.424	0.072	0.085
O2–C20	0.327	0.223	0.215	0.089	0.015	0.016
C20–C19	0.249	0.237	0.230	0.064	0.067	0.068
C19–N3	0.234	0.297	0.318	0.048	0.014	0.005
Ni–N3	0.119	0.105	0.111	0.215	0.147	0.157
C2–C3	0.232	0.215	0.226	0.018	0.020	0.018
C3–C4	0.225	0.207	0.215	0.032	0.034	0.034

from 2-aminobenzophenone, where the distances between the nickel atom and the heteroatoms are longer, keep a lower strain and thus they are more stable. In the complexes derived from 2-aminobenzaldehyde, the differences are probably not so profound due to a lower steric hindrance, and so there is a little or no energetic benefit of the monosubstitution in such complexes.

Experimental

The electronic structure of the complexes under study is evaluated at MP2 level of theory using triple-ζ valence (TZV) basis for Ni [32] and double-ζ valence (DZV) basis sets for the remaining atoms [33]. Firefly software package is used for single-point calculations of experimental geometries [34].

The electronic structure of the species under study is investigated using QTAIM topological analysis of electron density [33, 34]. The results are evaluated in terms of atomic volumes V and atomic charges q obtained using the electron density integrated over atomic basins (up to 0.001 e/Bohr^3 level). Bond characteristics are evaluated in terms of electron density ρ (proportional to bond strength) and bond ellipticity ε

$$\varepsilon = \lambda_1/\lambda_2 - 1 \quad (1)$$

at bond critical points (BCP) where $\lambda_1 < \lambda_2 < 0 < \lambda_3$ are the eigenvalues of the Hessian of the BCP electron density. AIM2000 [35] software package is utilized for QTAIM analysis (http://www.aim2000.de/).

Conclusions

We have disclosed an important factor giving rise to the high selectivity of the monoalkylation of nickel (II) complex of the Schiff base of BPB and glycine—the higher strain of the bonds of this non-substituted complex when compared to its mono- and di-substituted analogues. Further MP2/QTAIM analyses of similar less sterically hindered complexes are desirable to verify our findings.

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