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Control of helicity in C_3-symmetric systems by peptide-like β-turns

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Abstract

Cyclic imidazole-containing hexapeptides with three arms bound to the peptide scaffold via the secondary nitrogen atoms of the imidazoles are presented; these arms, together with a part of the macrocycle, form peptide-like β-turns making their helicity predeterminable and allowing the diastereoselective synthesis of Λ-metal complexes.

Keywords: Chirality; Imidazoles; Peptides; Peptidic β-turns

C_3-Symmetric systems have been studied extensively for the last decade[1] as they can be used as catalysts[2] in organic syntheses, ligands[3] for metal complexes, supramolecular hosts[4] or nanoscale devices.[5] For the control of the helicity of C_3-symmetric systems, chiral centers and chiral axes are predominantly used and the stereochemical information is passed on by repulsive interactions.[6] It would, however, be of interest to provide systems wherein the helicity is additionally or alternatively predetermined by conformation-controlling hydrogen bonds, like peptidic or peptide-like β-turns. Herein, we present the synthesis of a system in which the helicity is controlled by three peptide-like β-turns (**1** shown in Fig. 1). The system consists of an imidazole-containing cyclic hexapeptide as a scaffold to which are attached three flexible arms via the secondary nitrogen atoms of the imidazole units. The hydrogen atoms of the amide bond of the arms should be able to form hydrogen bonds with the carbonyl groups of the peptidic scaffold.

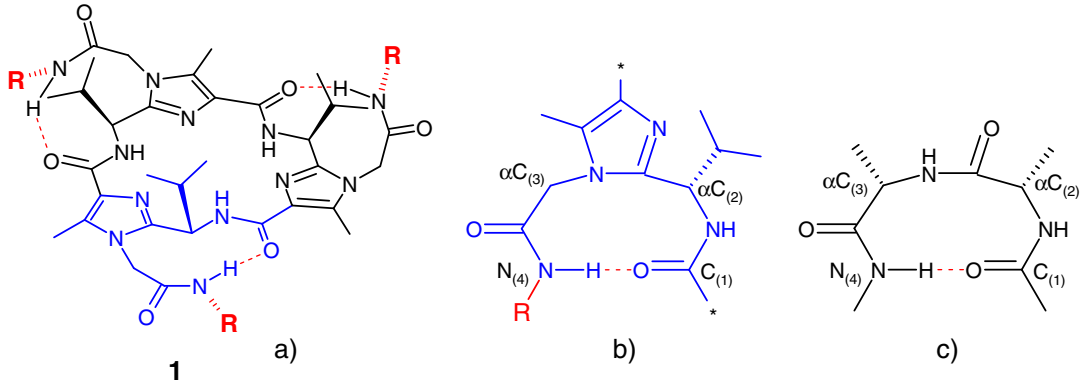

Fig. 1. (a) Cyclic hexapeptide **1** with the control of helicity via three peptide-like β-turns; (b) peptide-like β-turns motif of **1**; and (c) peptidic β-turn.

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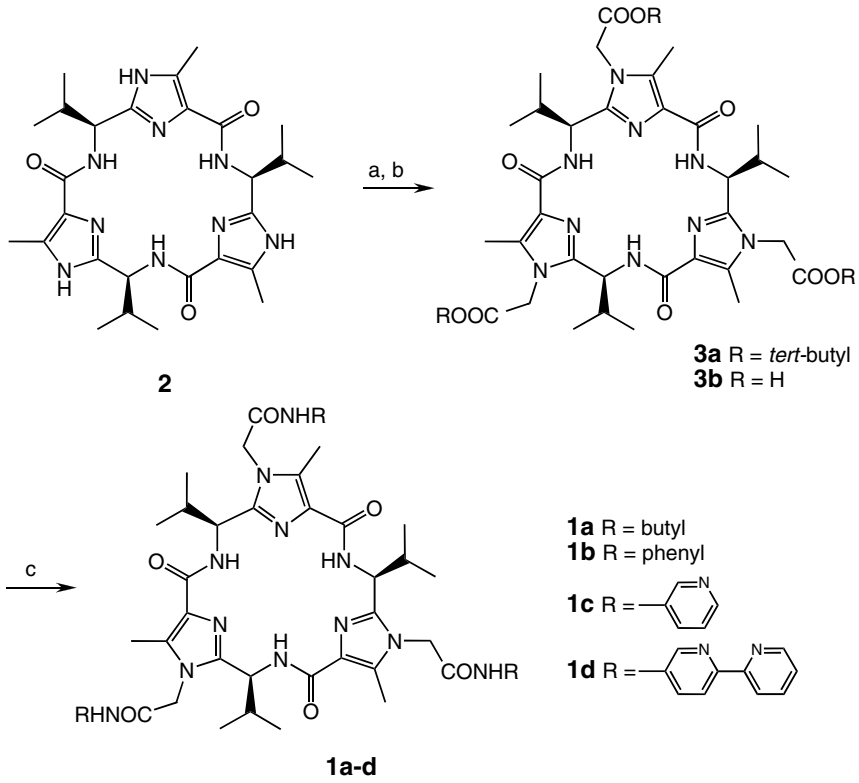

Scheme 1. Reagents and conditions: (a) K_2CO_3, $BrCH_2COO$*tert*-Bu, CH_3CN, Δ, 90%; (b) TFA, DCM, quant.; (c) DMC, RNH_2, Et_3N, DCM, 0 °C→rt, 35–90%.

The three formed spatially arranged units resemble in their form peptide β-turns, the central amide bond of which is incorporated into an imidazole (Formula 1). The spatial orientation of the three arms is determined by the chirality of the macrocycle. Accordingly, the helicity of the total system is unambiguously predetermined by the formation of peptide-like β-turns composed of a part of the cyclic scaffold and the flexible arms.

The synthesis of compounds **1** starts from the backbone-modified cyclic peptide **2**[7] (Scheme 1). This can be prepared in only a few steps and in large quantities from L-valine and a simple amino ketone. Threefold alkylation of the secondary nitrogen atoms of the imidazoles with *tert*-butyl bromoacetate affords triester **3a**, which can subsequently be converted with trifluoroacetic acid into triacid **3b**. The amide formation is carried out by reaction with the desired amine in the presence of 2-chloro-1,3-dimethylimidazolidinium chloride (DMC)[8] as the coupling agent and triethylamine in dichloromethane. By this pathway, we could synthesize several helical systems of type **1** (Scheme 1).

To investigate the formation of the peptide-like β-turns in **1**, molecular-modeling calculations were carried out for **1b**. The energies of the conformers of **1b** were determined with the DFT method (B3LYP) using the 6-31G* basis set.[9] The results show that the two types of β-turns can be present in **1b**. More precisely, a dihedral angle $C_{(1)}$–α$C_{(2)}$–α$C_{(3)}$–$N_{(4)}$ of either 5° or 85° can be taken (Fig. 1).[10] If all three loops have a dihedral angle of 5°, all three arms point into the same direction and are helically arranged (**1bA** shown in Fig. 2). In total, the system has *M*-helicity, which is induced by the turn formation. If, however, all three loops have a dihedral angle of 85°, the arms are arranged in one plane (**1bB** shown in Fig. 2).

The energy difference between these two conformers was calculated to be 19.8 kJ mol^{-1}, the helical conformer **1bA** being energetically more favored. If only one of the three loops takes a dihedral angle of 85°, the remaining two taking the more advantageous angle of 5°, the energy difference to **1bA** amounts to only 3.5 kJ mol^{-1}. If two of the loops take the dihedral angle of 85°, the energy difference to **1bA** amounts to 11.8 kJ mol^{-1}. Apart from the C_3-symmetric conformers **1bA** and **1bB**, an energetic minimum for a further C_3-symmetric conformer (**1bC**) of **1b** was found.

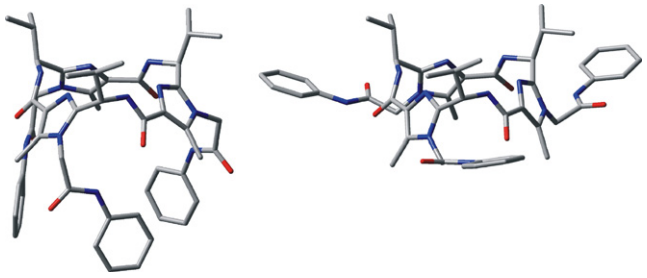

Fig. 2. Molecular structures of **1bA** and **1bB** calculated with B3LYP/6-31G*. All hydrogen atoms were omitted for clarity.

In this case, the three arms point into the same direction as the isopropyl groups, and the total system has also *M*-helicity. However, this conformation is not stabilized by hydrogen bonds, and, accordingly, **1bC** is destabilized by 43.7 kJ mol^{-1} vis-à-vis **1bA**. An energy minimum for a conformation where the three arms are oriented in a *P*-helix could not be found with B3LYP/6-31G*. This is in accordance with the hypothesis that the peptide-like β-turns have a conformation-stabilizing effect, since in *P*-helices no advantageous hydrogen bonds can be formed.

For a further confirmation of the hypothesis that in molecule **1** three peptide-like β-turns are formed, we carried out ^{1}H NMR investigations with **1b**. As expected, the ^{1}H NMR spectrum of **1b** in $CDCl_3$ (10 mM) shows a broad signal for the NH-amide hydrogens of the anilide units having a mean value of 10.3 ppm, which indicates strong hydrogen bonds: this can be deduced from the comparison with acetanilide, which has an amide signal at (only) 7.2 ppm in $CDCl_3$ (30 mM). The assumption that the hydrogen bonds are primarily intramolecular hydrogen bonds can be confirmed by two further experiments:[11] firstly, the anilide signal in the ^{1}H NMR spectrum of **1b** remains at a mean value of 10.2 ppm even at 10 times lower concentration of **1b** (1 mM)—in the case of intermolecular hydrogen bonds, a significant shift of the signal would have been expected. Secondly, amide proton–deuterium exchange rates were assessed to provide a further supporting evidence for the role of the anilide in generating stable intramolecular hydrogen-bonds. Exchange rates with deuterated methanol, with a 1:2 $CD_3OD/CDCl_3$ solution of **1b**, demonstrated the exceptional stability of the anilide NH hydrogen bond, as its NMR signal was still present after 2 h, whereas the anilide protons of the reference system (acetanilide) under equivalent conditions exchanged with deuterium instantly. This shows that the anilide hydrogen atoms of **1b** can be reached only difficultly by the solvent molecules, which indicates the presence of strong intramolecular hydrogen bonds.

The predetermination of the helicity caused by the loop-like arrangement of the arms can best be proven by the diastereoselective synthesis of helix-like metal complexes. Thus, ligands with an *M*-helix-like arrangement of the arms should selectively form the corresponding Λ-metal complexes. For verifying this assumption, ligand **1d** was reacted with various divalent metal salts and the respective UV, CD, and high resolution ESI mass spectra were recorded. The mass spectra of the solution indicate the formation of 1:1 complexes. For all metal complexes and independently from the used solvent, a positive Cotton effect can be observed at 320–330 nm and a negative Cotton effect at 300 nm (Fig. 3 and Table 1). These two effects are typical for Λ-trisbipyridyl metal complexes.[12,13] To our knowledge, this is the first description of a diastereoselective preparation of Ca, Cu, and Mn trisbipyridyl complexes. The extent of the energetic favorization of the Λ-complexes vis-à-vis the Δ-complexes was determined by DFT calculations. According to B3LYP/6-31G* calculation of **1d**·Zn^{2+}, the energy difference between the Λ-isomer with the lowest energy and the Δ-isomer with the lowest energy is more than 118.1 kJ mol^{-1}. Although the transfer of results calculated in the gas phase to the situation in the condensed phase has to be made with precaution, such a large energy difference nevertheless allows the conclusion that only the Λ-isomer is present in solution.

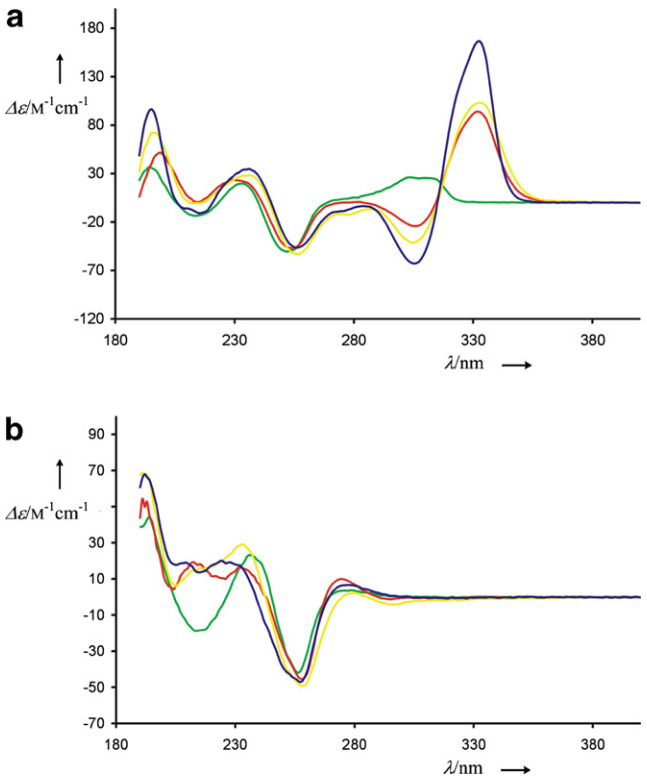

Fig. 3. CD spectra of the receptors (a) **1d** (green) and (b) **1c** (green) with $Ni(NO_3)_2$ (red), $Cu(CF_3SO_3)_2$ (yellow) and $Zn(CF_3SO_3)_2$ (blue) in CH_3CN.

Table 1
CD spectra of the complexes of receptors **1c** and **1d** with metal ions ([**1**] = 2.0×10^{-4} mM and **1**:M^{n+} = 1:1)

	M^{n+}	Δε/M^{-1} cm^{-1} (wave length/nm)
1c[a]	—	23.3 (236), −41.8 (256), 3.6 (279)
1c[a]	Ni^{2+}	16.3 (232), −45.0 (257), 9.9 (274), −1.3 (295)
1c[a]	Cu^{2+}	29.2 (233), −49.2 (258), 2.2 (280), −4.2 (296)
1c[a]	Zn^{2+}	−47.0 (257), 6.6 (278)
1d[a]	—	19.6 (233), −50.6 (252), 26.0 (303), 25.3 (309)
1d[a]	Ca^{2+}	38.8 (234), −48.0 (255), 2.4 (287), −13.4 (298), 57.8 (320)
1d[a]	Mn^{2+}	10.6 (236), −65.2 (254), 13.7 (280), −37.1 (304), 143.4 (331)
1d[b]	Fe^{2+}	24.6 (238), −50.4 (259), −67.2 (302), 114.5 (324), −2.03 (393), 5.33 (481), −9.81 (550)
1d[a]	Co^{2+}	15.5 (235), −53.1 (255), 3.4 (283), −16.6 (303), 93.1 (328)
1d[a]	Ni^{2+}	−47.0 (254), 0.6 (282), −24.3 (306), 93.9 (332)
1d[a]	Cu^{2+}	28.3 (236), −53.2 (256), −41.3 (305), 103.0 (333)
1d[a]	Zn^{2+}	34.8 (236), −46.5 (256), −62.7 (305), 166.4 (332)
1d[b]	Zn^{2+}	41.5 (237), −62.2 (257), −39.6 (304), 124.8 (333)
1d[c]	Zn^{2+}	100.0 (243), −76.3 (263), −56.1 (299), 150.1 (324)

[a] In CH_3CN.
[b] In MeOH.
[c] In MeOH/H_2O (1:9).

In the case of the tridentate ligand **1c**, too, the reaction with metal salts leads to a diastereoselective complex formation (Fig. 3 and Table 1). The three pyridine arms are arranged propeller-like around the metal center. Such a helically controlled propeller-like arrangement in labile coordination complexes has been observed in only a few systems up to date.[14] According to B3LYP/6-31G* calculations, the energy difference between the Λ-isomer of **1c**·$\mathbf{Zn}^{2+}$ and the Δ-isomer amounts to 33.3 kJ mol^{-1}.

In summary, we could show that three arms can be fixed on an imidazole-containing hexapeptide, the conformation of which is controlled via three peptide-like β-turns. The helicity of the arms thus can be predicted, which allows the diastereoselective synthesis of various—even kinetically labile—octahedral metal complexes. This concept of using peptide-like β-turns for the structure formation in C_3-symmetric systems should be applicable to other systems, too.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.065.

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