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Synthesis, Conformation, and Electrochemical Studies of Dap Homo-Peptides and their Ferrocenyl-Conjugates

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Introduction

Electron transfer processes in proteins depend primarily on the distance between the centres involved but are heavily mediated by the nature of the amino acid side chains, by backbone conformations and H-bonds [1-3]. In particular, the macrodipole moment generated by ordered structures (*e.g.*, helices) appears to play a relevant role. In this contribution we report synthesis and analyses of new ferrocenyl-peptide systems (Figure 1), characterized by helical homo-peptide spacers (Dap), with pendant ferrocenyl (Fc) moieties [4].

Z-[L-Dap(Boc)]$_n$-NH-*i*Pr	*n = 1-4*
Fc-CO-[L-Dap(Boc)]$_n$-NH-*i*Pr	*n = 1-4*
Z-[L-Dap(Boc)]$_n$-NH-Fc	*n = 1-4*
Bz-[L-Dap(Boc)]$_n$-NH-Fc	*n = 1-4*
Fc-CO-[L-Dap(Boc)]$_n$-NH-Fc	*n = 1-4*

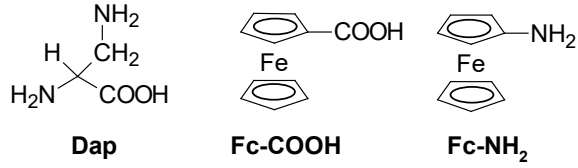

Fig. 1. Chemical structures of the Fc-peptide conjugates synthesized and studied in this work.

Results and Discussion

Synthesis and conformation

All syntheses were performed in solution as previously reported [5,6]. SPPS is feasible [7], but we chose the stepwise solution synthesis as it allowed us to study peptides of intermediate length as well. Our peptides adopt β-turn/3_{10}-helical conformations both in solution and in the crystal state. In particular, we solved the X-ray crystal structures for Fc-CO-[L-Dap(Boc)]$_2$-NH-Fc [8] and for Bz-[L-Dap(Boc)]$_2$-NH-Fc (Figure 2, left) [4]. Both dipeptides maintain the same conformation in chloroform solution, as assessed by 2D NMR techniques [4,8]. In particular, they form a β-turn, stabilized by an intramolecular H-bond. In addition, two *intraresidue* H-bonds are observed: they connect the side-chain CO of each Dap residue to its α-NH. The FT-IR analysis as well [4,8] points to the formation of helical structures in the same solvent of the NMR measurements.

Cyclic Voltammetry

In a 3_{10}- or α-helix, the carbonyl groups generate a macrodipole, with the positive pole oriented towards the *N*-terminus, that strongly affects the oxidation potential of the metal group. By elongating the peptide chain, oxidation in the Fc-CO-[L-Dap(Boc)]$_n$-NH-*i*Pr series becomes more difficult, whereas in the Z-[L-Dap(Boc)]$_n$-NH-Fc becomes easier (Figure 2, right) [4]. This effect is due to the peptide macrodipole, thus confirming the helical conformation.

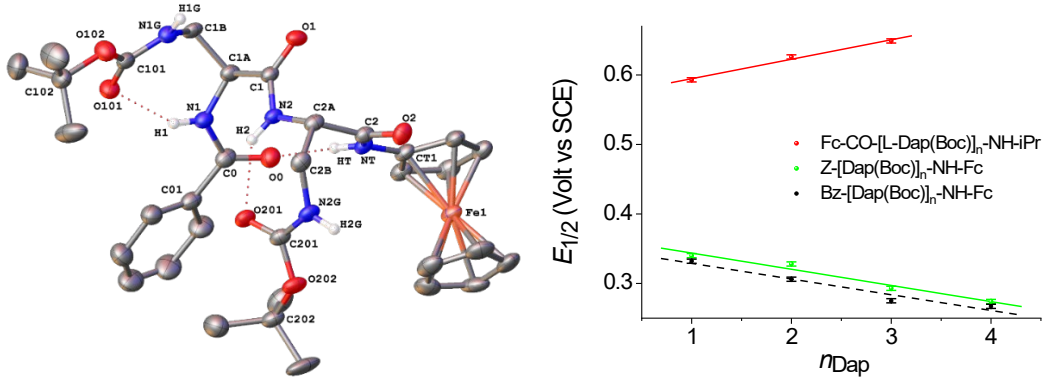

Fig. 2. ***Left****: X-Ray diffraction structure of Bz-[L-Dap(Boc)]$_2$-NH-Fc, with atom numbering (from ref. 4, with permission). H-atoms of the ferrocene unit, aliphatic carbon atoms and benzyl ring are omitted for clarity. H-bonds are indicated by dotted red lines.* ***Right****: variation in oxidation potentials of Z-[L-Dap (Boc)]$_n$-NH-Fc (n = 1-4), Bz-[L-Dap(Boc)]$_n$-NH-Fc (n = 1-4), and Fc-CO-[L-Dap (Boc)]$_n$-NH-iPr (n = 1-3). Each potential is obtained as the mean value of manifold measures (error bars ± 3 mV) (from ref. 4, with permission).*

Conclusions

Conformational studies in solution (^{1}H NMR, IR, and CD) and in the crystal state (X-ray diffraction) revealed the tendency of side-chain protected, Dap homo-peptides to adopt β-turn or helical conformations. Our cyclic voltammetry and spectroscopic (UV-Vis variations upon oxidation, not shown) analyses, [4,8] performed to map the peptide-mediated charge transfer, highlighted the influence of the molecular skeleton on the redox and optical properties of the molecules.

Acknowledgments

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