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Communication

Evolutionary principles for generating protein mimetics: Directed assembly of peptide loops on topological templates★

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A novel methodology for the reversible competitive condensation of peptide loops to chemoreactive topological templates is presented.

The use of topological templates proves to be a versatile concept in protein design [1] and mimicry [2, 3]. By separating the structural and functional part of a protein receptor, the attachment of ligand binding peptide loops to regioselectively addressable template molecules leads to protein mimetics (template-assembled synthetic peptides, Tasp) exhibiting essential features of native receptors [4].

Here, we present a novel methodology for the reversible competitive condensation of peptide loops to chemoreactive topological templates, applying principles of combinatorial chemistry.

RESULTS AND DISCUSSION

Based on the design of a metal binding Tasp, a cyclic decapeptide (**T**) as template featuring two aromatic aldehydes for chemoselective ligation and two carboxyl groups as complexing sites was prepared by a convergent strategy (Fig. 1).

N- and C-terminally functionalized linear peptides as prototypes for protein loops (**L1**, **L2**) were reversibly assembled to template **T** *via* imine bond formation (Fig. 2).

To assess the effect of ligand directed template assembly, peptide **L2** featuring two His side chains for metal complexation were com-

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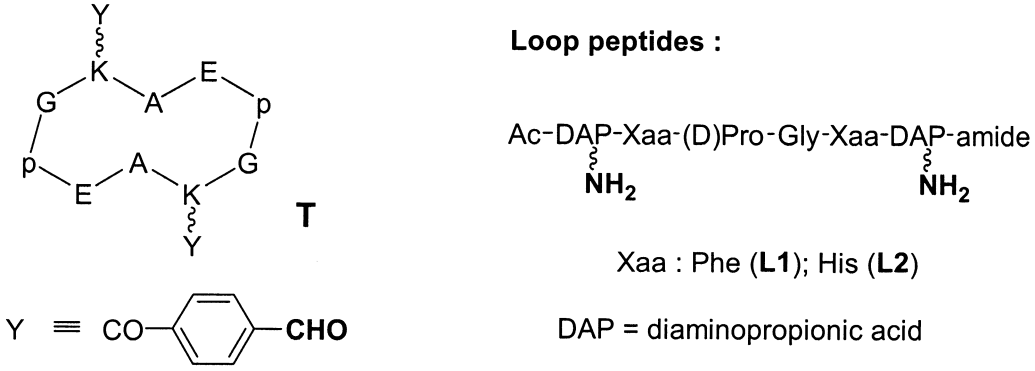

Figure 1

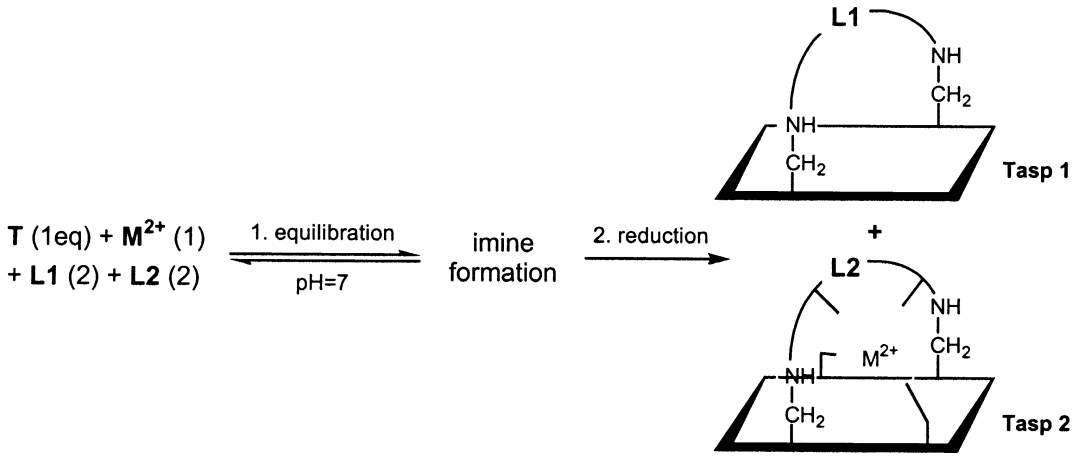

Figure 2

Table 1. Yields (%) of Tasp molecules after competitive ligand (M^{2+}, 1eq) induced assembly of peptide loops L1, L2 (2eq) on a topological template (T, 1eq)

M^{2+}	Tasp 1	Tasp 2	Induction factor (IF)
–	47	53	1.00
Co^{2+}	20	80	3.55
Zn^{2+}	30	70	2.07
Ni^{2+}	47	53	1.00

petitively reacted with **L1** (exhibiting no complexing site) in the presence of various metal ions. After equilibration (step 1) the reaction was quenched with $NaBH_3CN$ (step 2) and the resulting Tasp molecules were analysed by HPLC-MS.

In the absence of metal ions, **Tasp 1** and **2** are obtained in about equal amounts pointing to comparable chemical reactivities of **L1** and **L2.** In contrast, a significant preference for **Tasp 2** is observed in the presence of M^{2+}, with the metal selectivity (corresponding to the induction factor IF) Co > Zn >> Ni (IF = 0).

In conclusion, the elaborated strategy represents a first step in applying evolutionary principles in Tasp design. In particular, the ligand directed assembly of peptide libraries on topological templates opens interesting perspectives in protein mimicry.

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