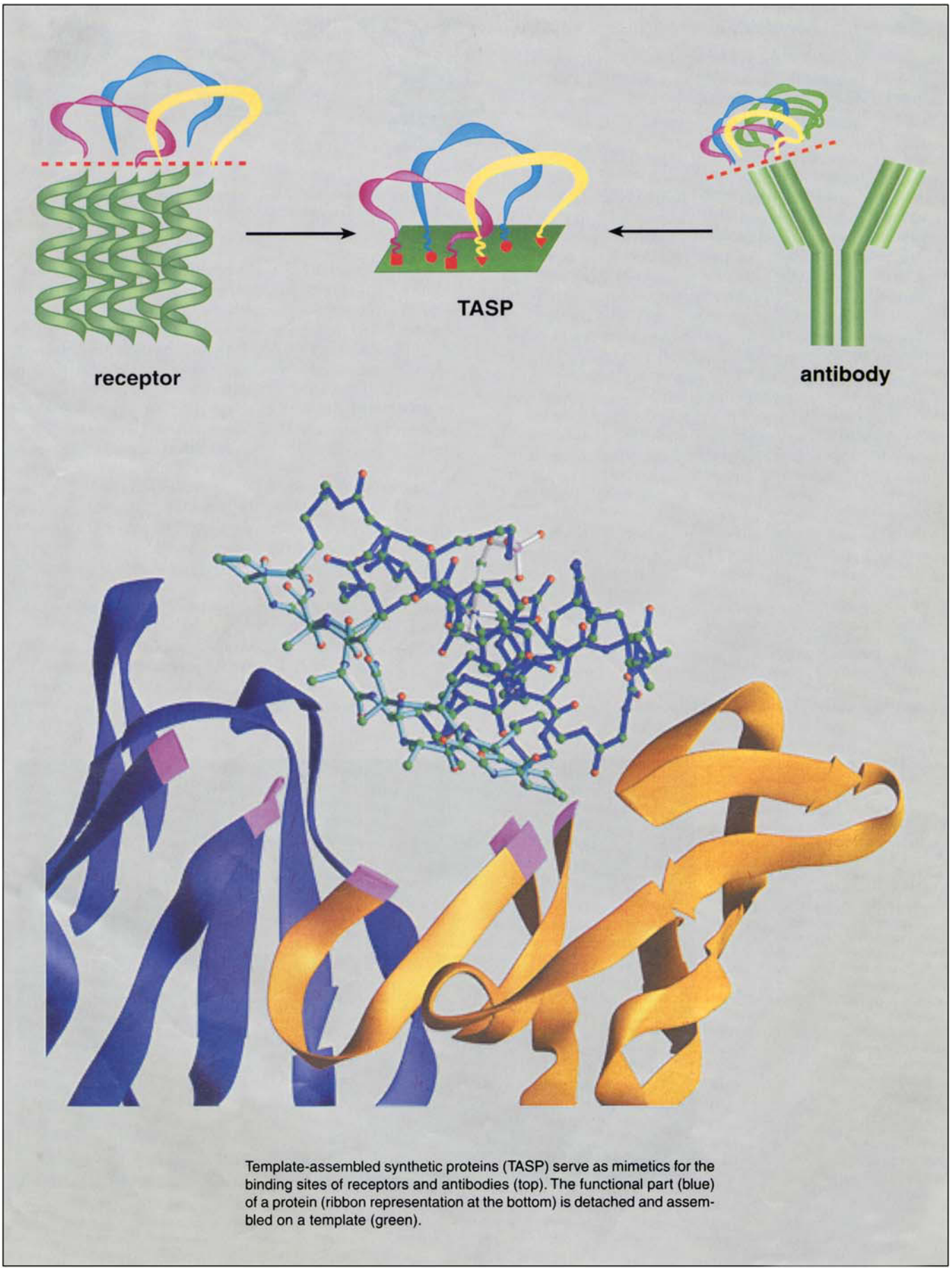


Template-assembled synthetic proteins (TASP) serve as mimetics for the binding sites of receptors and antibodies (top). The functional part (blue) of a protein (ribbon representation at the bottom) is detached and assembled on a template (green).

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# Template Assembled Synthetic Proteins (TASP) as Functional Mimetics of Proteins**

Manfred Mutter,* Pascal Dumy, Patrick Garrouste, Christian Lehmann, Marc Mathieu, Cristina Peggion, Stéphane Peluso, Alain Razaname, and Gabriele Tuchscherer

The use of peptidomimetics and topological templates has become an important tool in protein design and mimicry.[1-4] By introducing these elements in the design process, the synthetic chemist aims to unravel the complex interplay between protein structure and function. In order to avoid the well-known protein folding problem, we have introduced the concept of template assembled synthetic proteins (TASP); here, templates serve as built-in devices for directing the intramolecular assembly of covalently attached peptide blocks into characteristic folding topologies.[5-8] So far, problems with the synthesis have prevented the development of the full potential of this approach.[5] According to the TASP approach, the functional part of a protein, for example the antigen binding site of an antibody or the ligand binding site of a receptor, is detached from the rest of the molecule and assembled on a topological template, which mimics the loop supporting structural framework of the native protein (Fig. 1). Here, we elaborate the methodologies for the synthesis of this novel generation of functional TASP compounds.

The approach comprises two key elements: 1) peptide sequences (loops) containing C- and N-terminal functional-

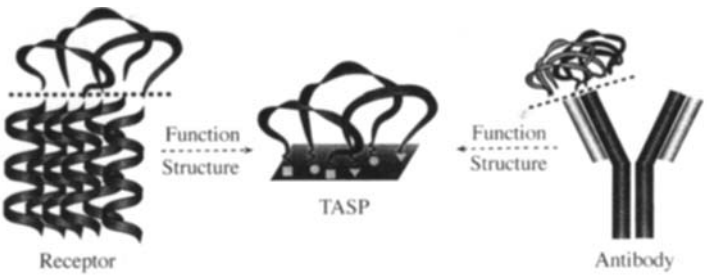


Fig. 1. Concept of template assembled synthetic proteins as mimetics of the binding region of receptors and antibodies.

groups (sticky ends) for chemoselective ligation[9-12] and 2) topological templates for the regioselective assembly of the loops. A prototype template consists of two antiparallel $\beta$-sheet peptides linked through $\beta$-turn-inducing dipeptides or nonpeptidic $\beta$-turn mimetics.[13-15] NMR spectroscopic investigations and molecular dynamics calculations confirm the preferred conformations of the TASP templates shown in Figures 2a and b; the attachment sites, for example the $\varepsilon$-amino groups of the lysine side chains, are all directed to one side of the $\beta$-sheet plane.Choosing from a variety of orthogonal protecting groups for peptide synthesis, we have developed a set of cyclic peptides as templates for the selective attachment of loop sequences.[13-15] In tailoring the flexibility of the backbone and side chains, this template motif may dispose any desired number and geometry of attachment sites.

The stepwise condensation of peptide sequences (loops, $\mathbf{L}^i$) onto these topological templates $\mathbf{T}^i$ (Table 1) is achieved by amide, oxime, and thioether formation[9-12] or combinations thereof.

In strategy A (Scheme 1), the C-terminally activated (step 1) fully protected loop $\mathbf{L}^i$ is fixed to the template $\mathbf{T}$, which contains one single reactive attachment site after removal of the protecting group $Y^i$ (step 2, amide 1). Selective deprotection of the

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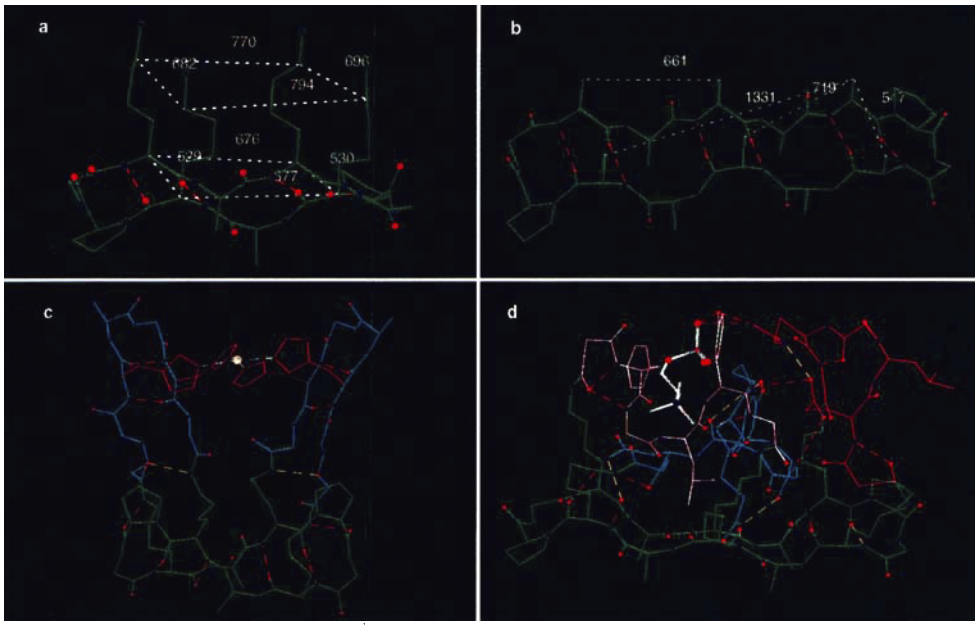



Fig. 2. Design of TASP compounds as functional protein mimetics. a) A cyclic $(ProGlyLysAlaLys)_2$ $\beta$-sheet mimetic (template $\mathbf{T}^2$) generated as a full structure from a regularized protein C$\alpha$-trace by using the program MOLOC [23,24]. Recent NMR/RMD investigations [15] reveal that the cyclopeptide adopts an antiparallel $\beta$-sheet structure spanned between two $\beta$-turns of type II. The given idealized $C_\alpha$–$C_\alpha$ distances [pm] indicate that the mean longitudinal distances are approximately 1.4 Å larger than the transannular ones, whereas the distances on the level of the attachment sites $C_\varepsilon$–$C_\varepsilon$ may adjust through a type of "crankshaft" motion along the $C_\gamma$–$C_\delta$ bond into distances suitable to accommodate a structural unit as exemplified below [25]. b) The extension of the chain of a cyclic peptide to a 14-mer unit $(ProGlyLysAlaLysAlaLys)_2$ ($\mathbf{T}^1$) increases the number of potential attachment sites and range of accessible distances. Thus larger distances become accessible to span functional loops that may even mimic an enzymatic binding cavity. c) Two-loop TASP **TASP II** with a square-planar metal binding site that is formed by condensation of two identical HisAlaGlyHisGly sequences on an 10-mer template ($\mathbf{T}^2$). The conformation was optimized by MAB force field calculations [24]; the metal binding geometry was deduced by weighted superposition of the histidine side chains onto the X-ray crystal structure of tetrakis(imidazole)copper(II) sulfate [26]. d) Representation of one of the eight possible directional isomers of a three-loop TASP as a mimetic for the antigen binding site of the phosphorylcholine specific antibody McPC603 [18,19]. In this model selected side chains were considered to be flexible; zero-distance and weak hydrogen bond constraints are sufficient to retain the shape of the binding cavity to enable it to host the amphiphilic zwitterionic species.

Table 1. Template $\mathbf{T}^i$ and loop sequences $\mathbf{L}^i$ for the synthesis of TASP compounds [a].

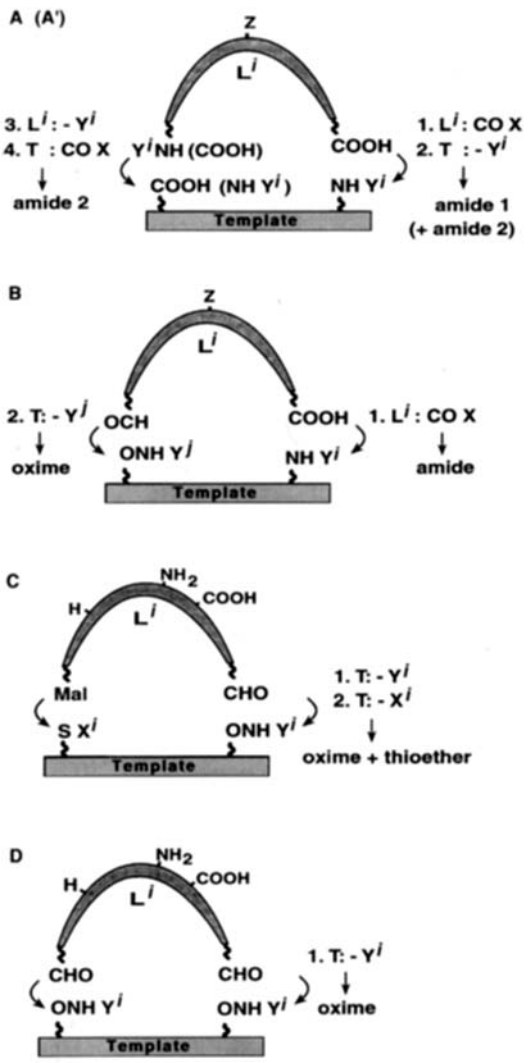
$\mathbf{T}^1$: c[K($Y^1$)C(Acm)K($Y^1$)PGK($Y^2$)AK($Y^2$)AK($Y^3$)PGK($Y^3$)A]
$\mathbf{T}^2$: c[K($Y^4$)PGK($Y^1$)AK($Y^2$)PGK($Y^3$)A]
$\mathbf{T}^3$: c[K($Y^5$)PGK($Y^6$)AK($Y^2$)PGK($Y^3$)A]
$\mathbf{T}^4$: c[K($Y^6$)PGCDRKK($Y^6$)PGFACA]

$\mathbf{L}^1$: Suc-K(Boc)GY(*t*Bu)NG-OH
$\mathbf{L}^2$: Suc-FGLY(*t*Bu)G-OH
$\mathbf{L}^3$: Suc-E(*t*Bu)LGR(Pmc)G-OH
$\mathbf{L}^4$: Boc-S(*t*Bu)H(Trt)AGH(Trt)G-OH
$\mathbf{L}^5$: Alloc-S(*t*Bu)H(Trt)AGH(Trt)G-OH
$\mathbf{L}^6$: $X^1$-HPGHK($X^2$)G-$NH_2$
$\mathbf{L}^7$: $X^2$-FSRSDELTRHIRIHTGK($X^2$)G-OH

[a] Abbreviations: $Y^1$: Boc = *tert*-butoxycarbonyl; $Y^2$: Dde = 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl; $Y^3$: Alloc = allyloxycarbonyl; $Y^4$: Fmoc = 9-fluorenylmethoxycarbonyl; $Y^5$: $COCH_2CH_2S$-Trt; $Y^6$: $H_2NOCH_2CO$; Suc: $HOOC(CH_2)_2CO$; $X^1$: maleoyl-$\beta$-Ala; $X^2$: OCHCO; A: Ala; C: Cys; D: Asp; E: Glu; F: Phe; G: Gly; H: His; I: Ile; K: Lys; L: Leu; N: Asn; P: Pro; R: Arg; S: Ser; Y: Tyr; Acm: acetamidomethyl; Trt: trityl; Pmc: 2,2,5,7,8-pentamethylchroman-6-sulfonyl.

N-terminal amino group of the loop $\mathbf{L}^i$ (step 3) and activation of the carboxyl group on the template (step 4) completes the cyclization of the loop (amide 2). Alternatively, the selective attachment of the N-terminal end may proceed by the formation of an oxime bond after the aminooxy group on the template has been deprotected (step 2 in strategy B). The condensation of peptides containing the same functional groups at both chain ends (for example carboxyl or aldehyde groups, strategies A′ and D, respectively) proceeds in one step and results in a mixture of two isomers with differently oriented loops. These strategies are very suitable for preparing TASP compound libraries for functional screening.[16] Chemoselective ligation procedures[9–12] allow for the condensation of completely unprotected peptides in aqueous solution or solvent mixtures (strategies C and D). Here, the regioselective attachment of a loop peptide to the template in one single condensation step (strategy C) can be achieved by the combination of two orthogonal ligation techniques (e.g. oxime and thioether formation).

The individual strategies (Scheme 1) were evaluated by fixing peptide loops $\mathbf{L}^i$ of different chain length and sequence to cyclic peptides (see Fig. 2a and b) as regioselectively addressable templates $\mathbf{T}^i$ (Table 1). The kinetics of the reaction were monitored by analytical HPLC (Fig. 3) and the target molecules were characterized mainly by ES mass spectrometry, amino acid analysis, and NMR spectroscopy. Typically, the condensation proceeds




Scheme 1. Strategies A - D for the attachment of peptide loop sequences ($\mathbf{L}^i$) to topological templates $\mathbf{T}^i$ (Table 1); $Y^i$ and $Y^j$: amino protecting groups of the attachment sites; Z: side chain protecting groups of $\mathbf{L}^i$. A/A′: $\mathbf{L}^1$–$\mathbf{L}^3$, $\mathbf{T}^1$; B: $\mathbf{L}^4$, $\mathbf{L}^5$, $\mathbf{T}^2$; C: $\mathbf{L}^6$, $\mathbf{T}^3$; D: $\mathbf{L}^7$, $\mathbf{T}^4$.

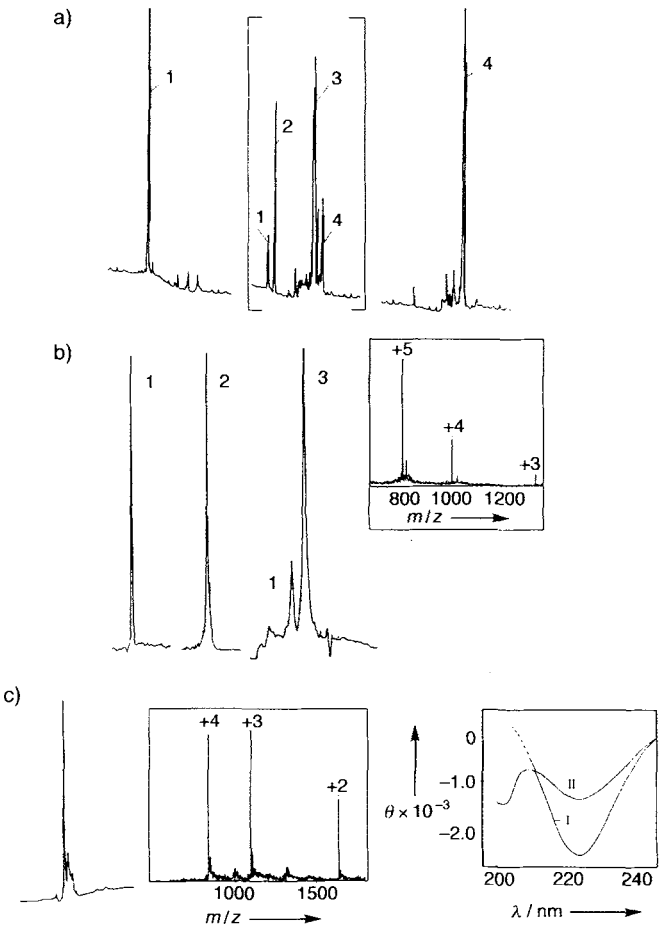
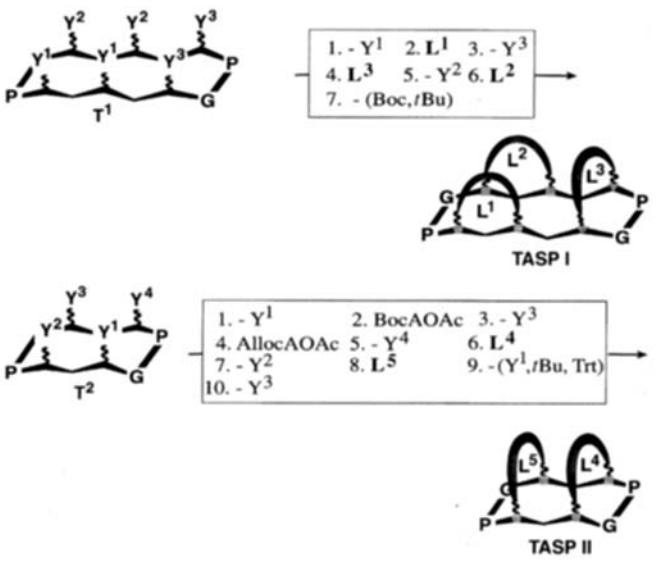



Fig. 3. a) Typical HPL chromatograms of a loop condensation reaction according to strategy A′. 1: $\mathbf{T}^1$ after removal of $Y^i$ (Table 1); 2: PyBop; 3: Noncyclized product after fixation of one chain end (only observed by in situ activation of $\mathbf{L}^1$ at high dilution); 4: Crude product (two isomers) after ligation of $\mathbf{L}^1$ to $\mathbf{T}^1$ (reaction time: 1 h). b) HPL chromatogram of the condensation reaction of the 18-mer peptide $\mathbf{L}^7$ with $\mathbf{T}^4$ (strategy D). 1: $\mathbf{T}^4$; 2: $\mathbf{L}^7$; 3: Crude ligation product (two isomers; reaction time 1 h); insert: ES-MS ($m/z_{calcd}$: 4003 [$M^+$]. c) Synthesis of **TASP 1**. Left: HPL chromatogram of crude product; middle: ES-MS ($m/z_{calcd}$: 3280 [$M^+$]); right: CD spectra in trifluoroethanol (TFE) (I) and TFE/$H_2O$ (1/1) (II); $c = 1$ mg mL$^{-1}$

to completion within less than two hours by applying equimolar amounts of $\mathbf{L}^i$ and $\mathbf{T}$ (Fig. 3a, b). In strategy A′ and D, the reaction between $\mathbf{L}^i$ and $\mathbf{T}$ is performed at high dilution ($<10^{-3}$ M) in order to enhance intramolecular loop cyclization. Under these conditions, we observe a pronounced difference in the reaction kinetics of the first and second attachment step: after fixation of one chain end of the loop $\mathbf{L}^i$ to the template, the loop cyclization reaction proceeds very fast, as indicated by the absence of the intermediate noncyclized molecule. Apart from the selective fixation of the C- and N-terminal end of a loop $\mathbf{L}^i$ as in strategies A–C, the noncyclic intermediate (Fig. 3a in brackets) is only detected when the cyclization is sterically hindered due to the presence of several loops on the template. However, even the condensation of a designed 18-mer peptide to a bifunctional template by oxime bond formation ($\mathbf{L}^7$, strategy D) proceeded without detectable amounts of the intermediate species (Fig. 3b). The increased tendency for loop cyclization on topological templates compared to the regular head-to-tail cyclization reactions is in accord with the theory of peptide macrocyclization.[17]

Starting from a pool of $n$ orthogonal amino or carboxyl protecting groups, up to $n$ different loops can be selectively fixed according to the individual strategies depicted in Scheme 1. By extending the palette of orthogonal protecting groups and by combining various ligation techniques, TASP compounds of higher structural and functional complexity (including TASP compound libraries) become accessible.

As a first example of a potentially ligand (metal, substrate, antigen, transition state analogue) binding TASP compound, peptides derived from the CDR (complementarity-determining region) loop sequences of the phosphorylcholine binding monoclonal antibody McPC603[18, 19] were covalently attached to a topological template (Fig. 2d, **TASP I** in Scheme 2). Starting from a cyclic peptide with pairs of selectively addressable reactive sites, the stepwise condensation of three peptides ($\mathbf{L}^1-\mathbf{L}^3$) by amide bond formation according to strategy A′ provided **TASP I** in high yield and purity (Fig. 3c, left). It is noteworthy that even in the presence of two loops on the template, the condensation of the third loop proceeded smoothly as shown by the HPL chromatogram. Interestingly, the isomers (exhibiting the same molecular mass, Fig. 3c, center) with differently oriented loops were obtained in nonequimolar amounts, indicating an energetic nonequivalence of the different loop orientations. The CD spectra (Fig. 3c, right) show the characteristic features of a loop cluster conformation.[15, 20]




Scheme 2 Synthetic strategies for the assembly of **TASP I** (Fig. 2d) and **TASP II** (Fig. 2c). **TASP I**: $\mathbf{L}^1-\mathbf{L}^3$, $\mathbf{T}^1$; **TASP II**: $\mathbf{L}^4$, $\mathbf{L}^5$, $\mathbf{T}^2$ (Table 1).

The regioselective fixation of loops (strategy B) for TASP compounds with defined chain topology was illustrated by the design and synthesis of a potentially metal binding 2-loop TASP (Fig. 2c, **TASP II** in Scheme 2). To this end, two amino groups of the template $\mathbf{T}^2$ were transformed into aminooxy groups as chemoselectively addressable attachment sites (steps 2 and 4 in Scheme 2). Subsequently, two peptides, each containing two histidine residues as metal binding sites ($\mathbf{L}^5$, $\mathbf{L}^6$), were fixed step by step by C-terminal amide and N-terminal oxime bond formation according to strategy B.

These prototype TASP compounds proved to be readily soluble in aqueous buffer solutions and polar organic solvents, and thus allowed a variety of biochemical investigations of the structure. Preliminary investigations on the conformational and binding properties support the hypothetical structures of $\mathbf{T}^2$ suggested by molecular modeling studies (Fig. 2c, d).[21]

In summary, the presented strategies provide a synthetic entry to a new generation of TASP compounds, thereby extending the template concept[5] in protein design and mimicry. Most notably, the stepwise condensation of peptide loops to regioselectively addressable templates may be performed in aqueous solution and proceeds to completion within hours. The envisaged reattachment of the topological templates to the solid support will further simplify the multistep synthesis of differential loop cyclizations for generating TASP compound libraries. The state-of-the-art in chemoselective ligation and orthogonal protecting techniques determines the number of selectively attachable loops and thus the complexity of the TASP compounds. However, by exploiting the immense repertoire of synthetic organic chemistry for the incorporation of functional groups (sticky ends) into peptide chains, the scope of the present approach will be rapidly expanded. For example, ligand-directed assembly of helices, $\beta$-sheets, and loops onto tailor-made templates represents a new tool for studying supramolecular assembly and molecular recognition processes. Furthermore, this novel concept opens the way for a new generation of functional protein mimetics with a pivotal role in drug design.

## *Experimental Procedure*

The templates and loop sequences (Table 1) were synthesized according to standard procedures in solid-phase peptide synthesis [22] by using orthogonally protected Lys, Glu, and Cys residues in the template sequence **T** as selectively addressable attachment sites for the loops. The N-terminal carboxyl group of $\mathbf{L}^1-\mathbf{L}^3$ was introduced by treating the resin-bound peptide with succinic anhydride. The aminooxyacetyl group ($Y^6$ in $\mathbf{T}^4$) was introduced by coupling $Y^iHNOCH_2COOH$ to the $\varepsilon$-$NH_2$ group of the lysine residue [9,11]. The aldehyde function in the loop sequences (**L**) was generated by mild oxidation ($NaIO_4$) of a serine residue attached either at the N-terminus ($\mathbf{L}^4$, $\mathbf{L}^5$, strategy B) or at the side chain of a lysine residue ($\mathbf{L}^6$, $\mathbf{L}^7$, strategies C, D). Coupling of maleoyl-$\beta$-alanine (Mal) with PyBop (PyBop = benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate) at the N-terminus ($\mathbf{L}^6$) provided the functional group Mal applied in strategy C [12]. For the condensation of the loops $\mathbf{L}^i$ to the templates $\mathbf{T}^i$, 1.1 equivalents of $\mathbf{L}^i$ were added to a 1 mM solution of $\mathbf{T}^i$. Amide bond formation (A, B) was achieved by using PyBop as coupling reagent in DMF, oxime formation in acetate buffer, pH 4.5 (C,D), and thioether formation in buffer pH 7 (in combination with oxime pH 4; C). In general, the condensation reaction proceeded to completion within less than two hours at room temperature.

**TASP I** was synthesized by sequential removal of the Boc (TFA), Alloc ($[(Ph_3P)_2PdCl_2]/Bu_3SnH$), and Dde (2% $H_2NNH_2\cdot H_2O$ in DMF) amino protecting groups in the template $\mathbf{T}^1$ and subsequent ligation of $\mathbf{L}^1-\mathbf{L}^3$ in DMF through the activated N- and C-terminal carboxyl groups (1 equiv PyBop; strategy A′). After the final deprotection step (TFA), the target molecules were purified by reversed-phase HPLC (Vydac, C18) and characterized by ES-MS (Fig. 3c).

For the synthesis of **TASP II** (Scheme 2), the Boc amino protecting group in the template $\mathbf{T}^2$ was removed (TFA) and the amine coupled with $BocHNOCH_2COOH$ (PyBop, DMF). In the second step, the Alloc group of $\mathbf{T}^2$ was removed with

[$(Ph_3P)_2PdCl_2$]/$Bu_3SnH$] and $AllocHNOCH_2COOH$ coupled to the $\varepsilon$-$NH_2$ group of the lysine residue (PyBop, DMF). After removal of the Fmoc group with 20% piperidine in DMF, $L^4$ was ligated through its C-terminal carboxyl group to the free $\varepsilon$-$NH_2$ group of lysine in $T^2$ (PyBop, 1 equiv); after removal of the Dde protecting group with 2% $H_2NNH_2 \cdot H_2O$ in DMF, $L^5$ was attached in the same manner. Subsequently, all acid-labile protecting groups were removed with TFA, the N-terminal serine residue in $L^4$ was oxidized with $NaIO_4$, and the first oxime bond was formed. Finally, Aloc was cleaved with [$(Ph_3P)_2PdCl_2$]/$Bu_3SnH$ and the N-terminal serine residue in $L^5$ transformed to an aldehyde ($NaIO_4$), which readily formed the second oxime bond. The target molecules were characterized by ES-MS and amino acid analysis.

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# Synthesis, Crystal Structure, and Magnetic Properties of an Octanuclear Nickel(II) Complex with a *hexahedro*-$Ni_8$ Core**

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There is currently great interest in polynuclear complexes of transition metals, a large and structurally diverse class of compounds.[1] Polynuclear high-spin nickel(II) complexes have been isolated with a large number of ligands, and much attention has been devoted to the study of their magnetic properties.[2] Most of them are dinuclear, but several trinuclear and cubane-like tetranuclear species have been studied.[2–4] Complexes of higher nuclearity are very scarce, although a few pentanuclear aggregates are known.[5] Very recently, a undecanuclear and a cyclic dodecanuclear species have been characterized.[4, 6]

The violurate anion $H_2vi^-$ ($H_3vi$ = violuric acid or 5-(hydroxyimino)-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione) is a strong-field, bidentate ligand, which coordinates to transition metal ions through the oxime-N atom and the O atom of a vicinal carbonyl group to form a five-membered chelate ring (Fig. 1).[7] Potentially, $H_2vi^-$ is an ambidentate ligand, since it might bind the metal ions through the oxime-O atom and the O atom of the other vicinal carbonyl group to form in this case a six-membered chelate ring; it therefore might also be a bis(bidentate) bridging ligand (Fig. 1). However, these coordination modes have not been characterized up to now.

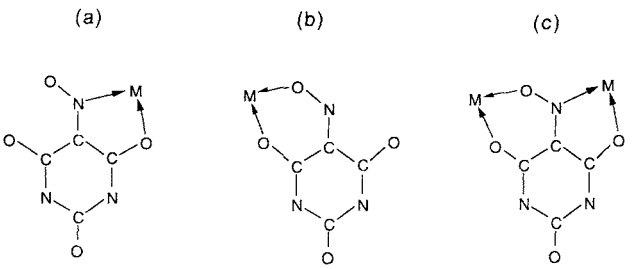


Fig. 1. Possible coordination modes of the violurato ligand (hydrogen atoms are not shown): a) bidentate-*N*,*O*; b) bidentate-*O*,*O* (unknown); c) bis(bidentate), bridging (this work).

Metal ion coordination increases the acidity of $H_2vi^-$ considerably, which undergoes deprotonation much more easily than as a free acid.[8] The resulting $Hvi^{2-}$ anion should exhibit a greater tendency to act as a bridging ligand, but although the deprotonation of some violurato complexes was investigated,[8] no polynuclear species is known.

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