CHEMIE

Synthesis and Anion Binding Properties of a Cyclic Pseudohexapeptide Containing 1,4-Disubstituted 1,2,3-Triazole Subunits

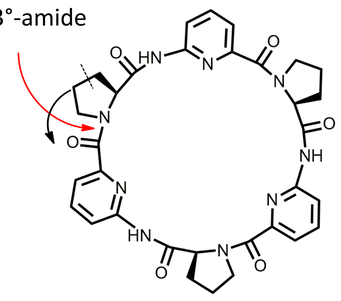
Disha Mungalpara[a], Richard Goddard[b], Stefan Kubik[a]*

[a]Fachbereich Chemie-Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, 67663 Kaiserslautern, Germany, *e-mail: disha@rhrk.uni-kl.de*

[b]Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

Motivation

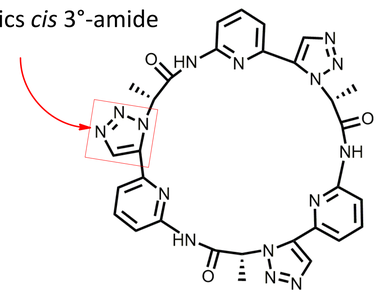
cis 3°-amide



1

Cyclopeptide **1** has strong affinity to inorganic anions.[1] Its preferred conformation features *cis*-conformations at the tertiary amides and a converging arrangement of the NH groups.

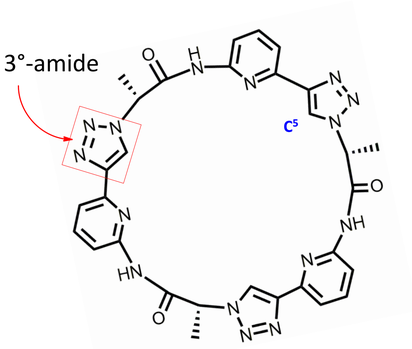
mimics *cis* 3°-amide



2

Pseudopeptide **2** is a structural mimic of **1** with a very similar overall conformation.[2] The 1,5-disubstituted 1,2,3-triazole rings serve as surrogates for the *cis*-amides in **1**.

mimics *trans* 3°-amide

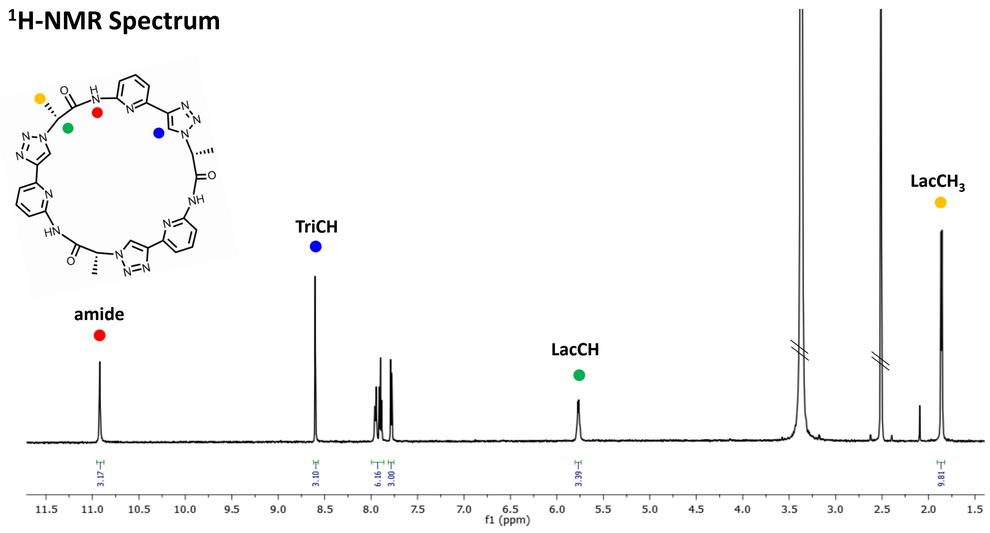


3

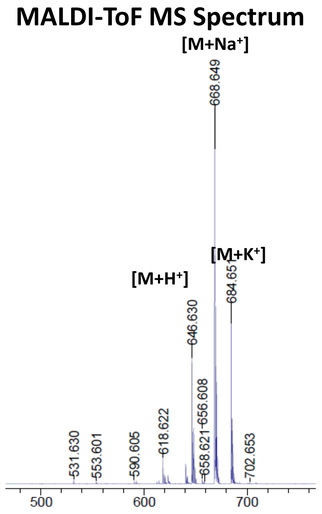
The 1,4-disubstituted 1,2,3-triazole units in **3** should have a profound effect on the overall conformation of this pseudopeptide because they mimic *trans*-amides.[3] They also introduce new hydrogen bond donors along the ring in the form of triazole C^5-H groups.

Characterization

^{1}H-NMR Spectrum



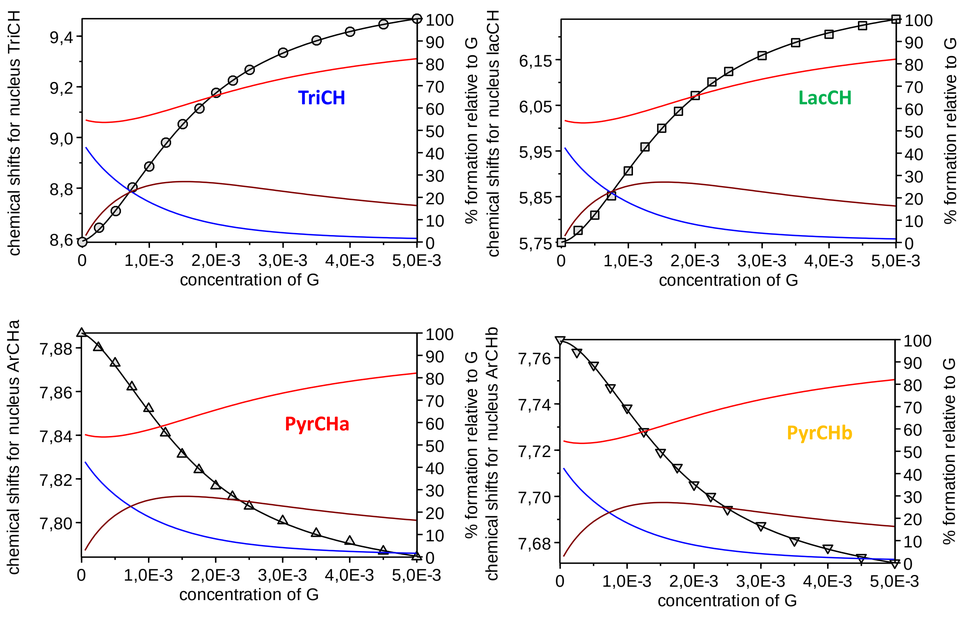
MALDI-ToF MS Spectrum

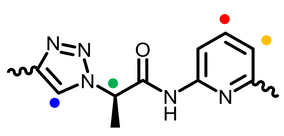


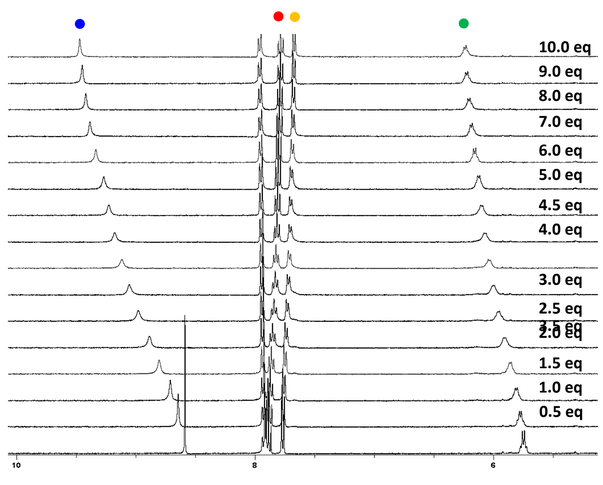
Binding Affinity

^{1}H-NMR Titration

The binding affinity of **3** to dihydrogen phosphate in 2.5 % *v/v* D_2O/DMSO-d_6 was investigated by using ^{1}H-NMR titrations. The stability constants of the dihydrogenphosphate complex of **3** was calculated using HypNMR2008 on the basis of the observed changes in the chemical shifts of the proton signals of the receptor **3.**

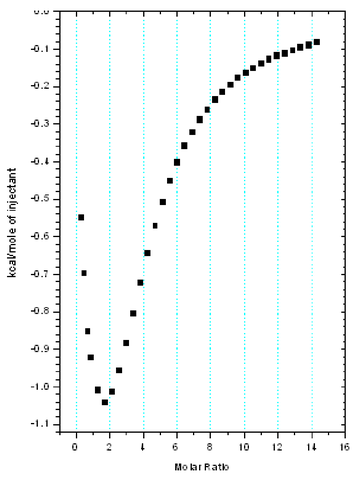


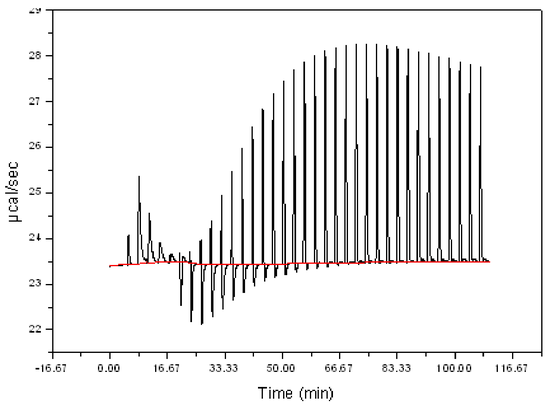




Isothermal Titration Calorimetry

The binding affinity of **3** to dihydrogen phosphate in 2.5 % *v/v* H_2O/DMSO was investigated by using ITC at 298 K. The stability constants of the dihydrogenphosphate complex of **3** was calculated using SEDPHAT.





Results and Discussion

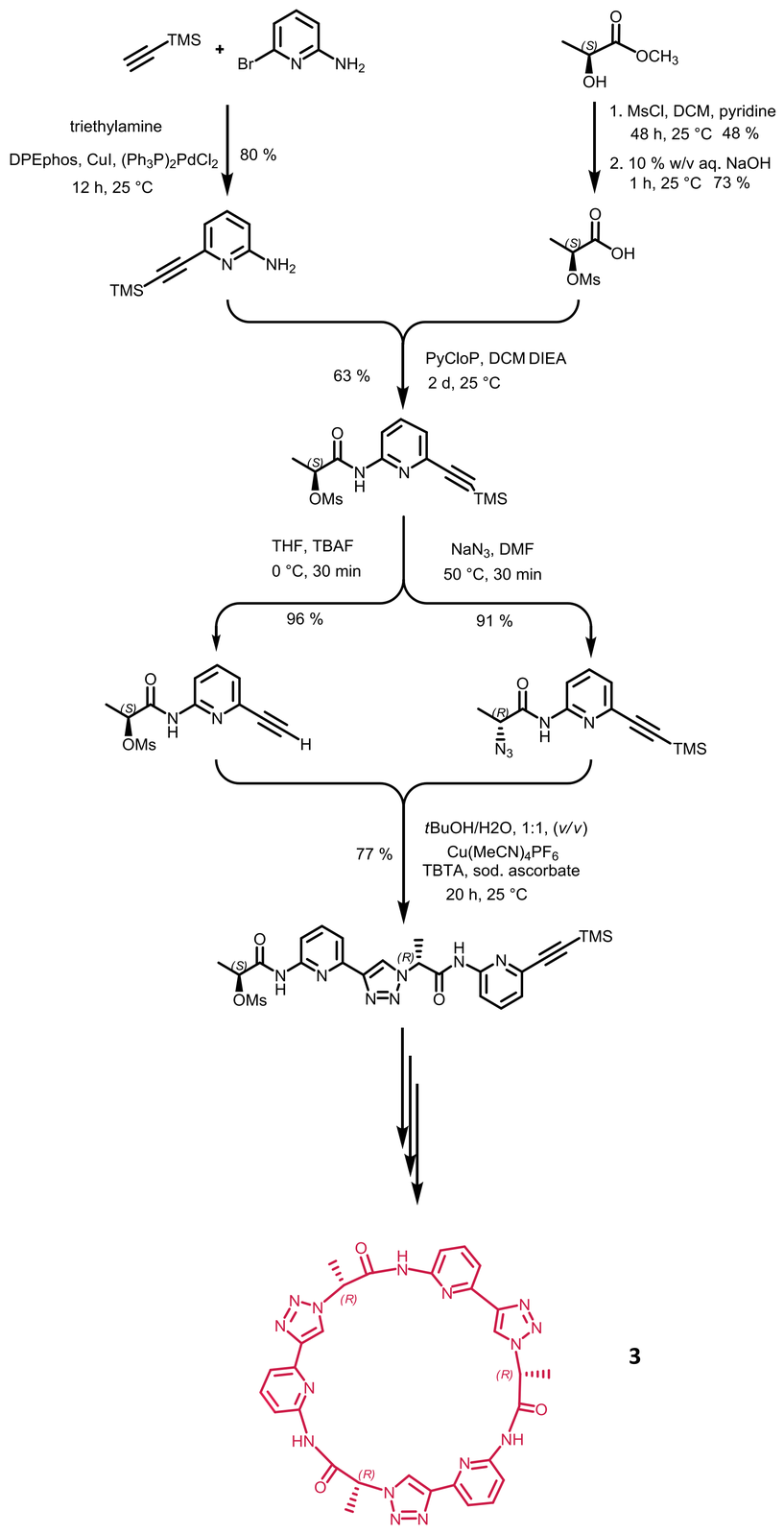
ITC Measurement

	$3\cdot H_2PO_4$	$3\cdot(H_2PO_4)_2$
Log K_a	3.45(5)	6.3(1)
ΔH(kJ/mol)	-4.1	-21.2
TΔS(kJ/mol)	15.6	-14.7
ΔG (kJ/mol)	-19.7	-35.8

^{1}H-NMR Spectroscopy

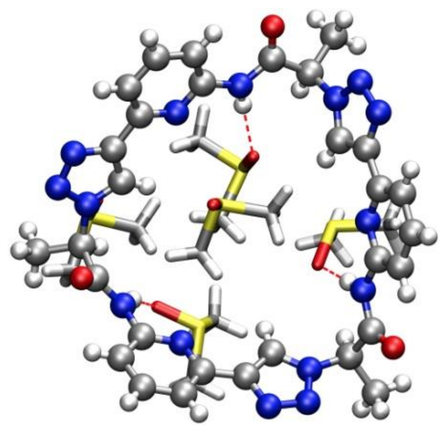
	$3\cdot H_2PO_4$	$3\cdot(H_2PO_4)_2$
Value	3.21(1)	6.31(5)

Synthesis

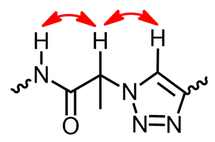


3

Conformation



Crystal Structure of 3•5 DMSO



NOESY-NMR Correlations

Conclusions and Outlook

The novel cyclic pseudopeptide **3** was prepared and conformational investigations were performed successfully. ^{1}H-NMR titration and ITC indicate that the pseudopeptide binds to two dihydrogenphosphate anion. The stability constant log K_a of the dihydrogenphosphate complex amounts to ca. 6. Future experiments will involve the quantitative evaluation of the stabilities of other oxoanion complexes of **3**.

References

[1] S. Kubik, R. Goddard, R. Kirchner, D. Nolting, J. Seidel, *Angew. Chem. Int. Ed.* **2001**, *40*, 2648-2651

[2] M. R. Krause, R. Goddard, S. Kubik, *J. Org. Chem.* **2011**, *76*, 7084-7095, M. R. Krause, R. Goddard, S. Kubik *Chem. Commun.* **2010**, *46*, 5307-5309

[3] B. Schulze, U. S. Schubert, *Chem. Soc. Rev.* **2014**, 43, 2522-2571

Acknowledgement

Financial support through **ISMSC 2015** allowing me to participate in the conference is kindly acknowledged.

TECHNISCHE UNIVERSITÄT KAISERSLAUTERN