observed for the monosubstituted compound (*R*)-**1**; however, in the CD spectrum the intensity of the signal is less than that of (*R*)-**2**. Thus, the presented compounds combine optoelectronical properties and chirality. These results are of relevance in several applications: a) chiral fluorophores within sensor systems,[15] b) circular-polarized photoluminescence[16] and also electrochemiluminescence, c) organic light-emitting diodes (OLED) with circular polarized luminescence,[17] and d) light-emitting diodes (LED) powered by spin-polarized carriers.[18]

Experimental Section

Cyclic voltammetry: solvent acetonitrile; potentials [mV] versus ferrocenium/ferrocene (Fc^+/Fc) as internal standard; reversible half wave potential $E_{1/2}$. Measurement conditions: room temperature, scan speed 250 $mV s^{-1}$, working electrode: platinum-disc electrode, quasi reference electrode: Ag/AgCl, counter electrode: platinum electrode, supporting electrolyte: 0.1 M tetrabutylammonium hexafluorophosphate.

UV/Vis and CD spectroelectrochemistry: solvent acetonitrile, transmission cell with minigrid gold working electrode.

Optical spectra: concentration 10^{-5} to 10^{-6} M in acetonitrile.

Received: March 2, 2000 [Z14793]

[1] a) M. Kollmannsberger, T. Gareis, S. Heinl, J. Breu, J. Daub, *Angew. Chem.* **1997**, *109*, 1391 – 1393; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1333 – 1335; b) T. Gareis, C. Huber, O. S. Wolfbeis, J. Daub, *Chem. Commun.* **1997**, 1717 – 1718; c) T. Werner, C. Huber, S. Heinl, M. Kollmannsberger, J. Daub, O. S. Wolfbeis, *Fresenius J. Anal. Chem.* **1997**, *359*, 150 – 154; d) M. Kollmannsberger, K. Rurack, U. Resch-Genger, J. Daub, *J. Phys. Chem. A* **1998**, *102*, 10211 – 10220; e) K. Rurack, M. Kollmannsberger, U. Resch-Genger, J. Daub, *J. Am. Chem. Soc.* **2000**, *122*, 968 – 969.

[2] F. Li, S. I. Yang, Y. Ciringh, J. Seth, C. H. Martin, D. L. Singh, D. Kim, R. R. Birge, D. F. Bocian, D. Holten, J. S. Lindsey, *J. Am. Chem. Soc.* **1998**, *120*, 10001 – 10017.

[3] a) T. G. Pavlopoulos, J. H. Boyer, G. Sathyamoorthi, *Appl. Opt.* **1998**, *37*, 7797 – 7800; b) T. G. Pavlopoulos, *Appl. Opt.* **1997**, *36*, 4969 – 4980.

[4] a) T. Gareis, Thesis, Universität Regensburg, **1997**; b) M. Kollmannsberger, Thesis, Universität Regensburg, **1999**; c) A. Burghart, H. Kim, M. B. Welch, L. H. Thoresen, J. Reibenspies, K. Burgess, F. Bergström, L. Johansson, *J. Org. Chem.* **1999**, *64*, 7813 – 7819.

[5] a) R. W. Wagner, J. S. Lindsey, *Pure Appl. Chem.* **1996**, *68*, 1373 – 1380.

[6] Fluorescence quantum yields were determined relative to 1,3,5,7-tetramethyl-8-phenyl-4-difluorobora-3a-4a-diaza-*s*-indacene.

[7] J. Daub, K. Kelnhofer, T. Gareis, A. Knorr, M. Kollmannsberger, Y-H. Tak, H. Bässler, *Polym. Prepr.* **1997**, *38*, 339 – 340.

[8] Theoretical methods: The molecular geometries of (*R*)-**1** and (*R*)-**2** were optimized at the semiempirical MNDO level [8a, 8c] of theory by employing the MOPAC program system.[8b] The CD spectra (transition energies and rotatory strengths) were calculated with a method combining the Kohn – Sham density functional theory (DFT) and the random-phase-approximation (RPA).[8d, 8e] The DFT calculations were performed with the TURBOMOLE suite of programs,[8f, 8g] whereby the BH-LYP exchange-correlation functional[8h] and a SV basis set[8i] were employed. In the RPA treatment all valence orbitals and the energetically lowest half of the virtual orbitals were included. a) J. J. P. Stewart, *QCPE Bull.* **1985**, *5*, 133; b) M. J. S. Dewar, W. Thiel, *J. Am. Chem. Soc.* **1977**, *99*, 4899 – 4907; c) M. J. S. Dewar, W. Thiel, *J. Am. Chem. Soc.* **1977**, *99*, 4907 – 4917; d) S. Grimme, *Chem. Phys. Lett.* **1996**, *259*, 128 – 137; e) S. Grimme, S. D. Peyerimhoff in *The role of Rydberg states in spectroscopy and reactivity* (Ed.: C. Sandorfy), Kluwer Academic Publishers, Dordrecht, **1999**, pp. 93 – 119; f) R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165 – 169; g) O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346 – 354; h) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372 – 1377; i) A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571 – 2577.

[9] K. Nakanishi, N. Berova in *Circulardichroism: Principles and Applications* (Eds.: K. Nakanishi, N. Berova, R. W. Woody), VCH, New York, **1994**, pp. 361 – 398.

[10] J. Karolin, L. B.-A. Johansson, L. Strandberg, T. Ny, *J. Am. Chem. Soc.* **1994**, 116, 7801 – 7806.

[11] To show that the experimentally observed, highly asymmetrical couplet is consistent with two closely adjacent transitions with large rotatory strengths of opposite sign, the splitting ΔE and the rotatory strengths R_1 and R_2 of the first two transitions as well as the half width δ of the Gaussian curves were determined from the experimental CD spectrum by a least-squares fit. Different fits were tried for which almost equal values for the root-mean-square deviation with the following parameters were obtained: $\Delta E = 1.5$ to 4 meV, $R_1 = 300$ to 600×10^{-40} cgs, $R_2 = -270$ to -570×10^{-40} cgs, and $\delta = 0.083$ eV. With much larger or smaller absolute values of R_1 and R_2 significantly worse fits were obtained, which demonstrates the presence of an exciton couplet. The absolute value of the rotatory strength R_2 is always 30×10^{-40} cgs smaller than the rotatory strength R_1. These results are in qualitative agreement with the quantum-chemical calculations.

[12] O. E. Weigang, Jr., *J. Am. Chem. Soc.* **1979**, *101*, 1965 – 1975.

[13] a) J. Daub, I. Aurbach, J. Salbeck, *Angew. Chem.* **1988**, *100*, 278 – 280; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 291 – 293; b) J. Salbeck, I. Aurbach, J. Daub, *DECHEMA Monogr.* **1989**, *112*, 117 – 191.

[14] a) C. Westermeier, H.-C. Gallmeier, M. Komma, J. Daub, *Chem. Commun.* **1999**, 2427 – 2428.

[15] A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515 – 1566.

[16] H. P. J. M. Dekkers in *Circulardichroism: Principles and Applications* (Eds.: K. Nakanishi, N. Berova, R. W. Woody), VCH, New York, **1994**, pp. 121 – 152.

[17] E. Peeters, M. P. T. Christiaans, R. A. J. Janssen, H. F. M. Schoo, H. P. J. M. Dekkers, E. W. Meijer, *J. Am. Chem. Soc.* **1997**, *119*, 9909 – 9910.

[18] a) R. Fiederling, M. Keim, G. Reuscher, W. Ossau, G. Schmidt, A. Waag, L. W. Molenkamp, *Nature* **1999**, *402*, 787 – 790

Allosteric Regulation of Artificial Phosphoesterase Activity by Metal Ions**

Igor O. Fritsky, Reina Ott, and Roland Krämer*

In enzyme catalysis allosteric regulation is the control of enzyme activity by noncovalent modifiers (molecules or ions) which bind to the enzyme at a site other than the active site but alter the conformation of the active site. Often, metal ions are involved in allosteric regulation in enzymes. In the active site of *E. coli* alkaline phosphatase a phosphate monoester substrate is hydrolyzed at a dizinc(II) site, while a "structure-stabilizing" Mg^{2+} ion located about 6 Å away from the zinc ions is a strong allosteric activator.[1] Replacement of Mg^{2+} by

[*] Prof. Dr. R. Krämer, Dr. I. O. Fritsky,[+] Dipl.-Chem. R. Ott
Anorganisch-chemisches Institut
Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-548-599
E-mail: roland.kraemer@urz.uni-heidelberg.de

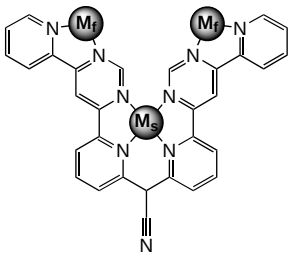
[+] Dr. I. O. Fritsky is on leave from the Department of Chemistry, Shevchenko University, 01033 Kiev (Ukraine)

[**] This work was funded by the DFG (Gerhard Hess Programm).

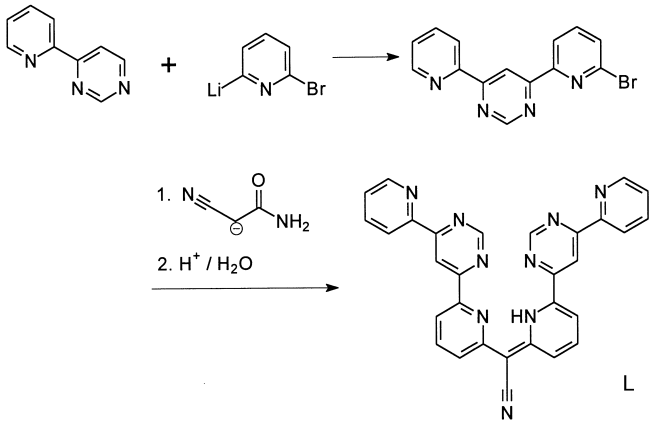
other divalent metal centers alters or even inhibits the catalytic activity of natural alkaline phosphatases[2] or their mutants.[3]

For artificial systems allosteric tuning of the receptor properties by metal ions or organic molecules has been widely explored in supramolecular host–guest chemistry.[4] However, reports on allosteric regulation of synthetic molecular catalysts are very rare. On the basis of kinetic data allostery was proposed for cyclodextrin-catalyzed ester and alkyl nitrite hydrolysis which is enhanced by the addition of certain organic molecules.[5]

Herein we describe allosteric regulation of a synthetic metal-based catalyst for phosphodiester cleavage. In our system two functional metal ions (denoted M_f) are exposed for direct interaction with the substrate while reactivity is modulated by a third "structural" metal (M_s).



The novel polypyridyl ligand L which has one tetradentate and two bidentate metal binding sites was prepared in two steps from 4-(2-pyridyl)pyrimidine (Scheme 1).[6] The carbon–carbon coupling with 2-bromo-6-lithiopyridine gave 4-(6-bromo-2-pyridyl)-6-(2-pyridyl)pyrimidine. By using

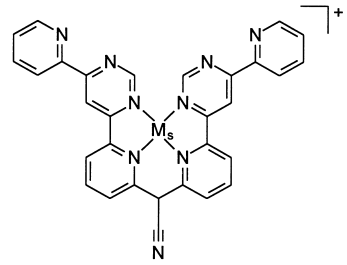


Scheme 1. Synthesis of L.

a method for the preparation of macrocycles from bromobipyridines and cyanacetamide[7] L was obtained as a dark red crystalline solid. The single-crystal X-ray data[8] shows that L exists in a fully conjugated form in which a proton is localized at the nitrogen atom of an internal pyridine unit.

Reaction of M^{2+} salts with L gave 1:1 complexes $[(L-H)Cu]NO_3$, $[(L-H)Ni]NO_3$, and $[(L-H)Pd]ClO_4$ as purple microcrystalline solids which were identified by $[(L-H)M]^+$ patterns in matrix-assisted laser desorpsion ionization (MALDI) mass spectra and C,H,N analyses (L–H (L "minus" H) corresponds to the deprotonated form of the ligand). The EPR spectrum of $[(L-H)Cu]^+$ in a $CHCl_3$/methanol glass at 77 K indicates a planar N_4 coordination of the Cu center ($g_{\|} = 2.207$, $A_{\|} = 196$ G). The ^{1}H NMR spectrum of the square-planar Pd complex suggests C_2 symmetry. In the ^{1}H NMR spectrum of $[(L-H)Ni]^+$ in [D$_6$]DMSO paramagnetic shifts ($\Delta\delta = 6-90$) relative to the signals of the free ligand and extensive line broadening for five ^{1}H signals (coordinated pyridine (py) and pyrimidine (pym)) are observed, while four signals (uncoordinated py) are shifted $\Delta\delta < 2$ ppm. Clearly, octahedral Ni^{II}, with axial solvent coordination, is favored in solution over a diamagnetic square-planar structure.

The high stability of the mononuclear complexes in solution is demonstrated by photometry: strong chelating ligands like ethylenediamine and ethylenediaminetetraacetate (EDTA) in 20-fold excess (at pH 8) do not extract the metal ions from the complexes. The formation of trinuclear complexes $[(L-H)M_sCu_2]^{5+}$ was studied by the photometric titration of $[(L-H)M_s]^+$ with copper(II) nitrate solution. We carried out the titrations under the same conditions as the kinetic experiments (see below), but 2-(hydroxypropyl)-*p*-nitrophenylphosphate (HPNP) was replaced by more stable dimethylphosphate. The coordination of Cu^{II} to the bidentate sites of L is monitored by a decrease of the absorbance at 500 nm and an increase of the absorbance at 635 nm (Figure 1) for which sharp isosbestic



$[(L-H)M_s]^+$ M_s = Cu^{II}, Ni^{II}, Pd^{II}

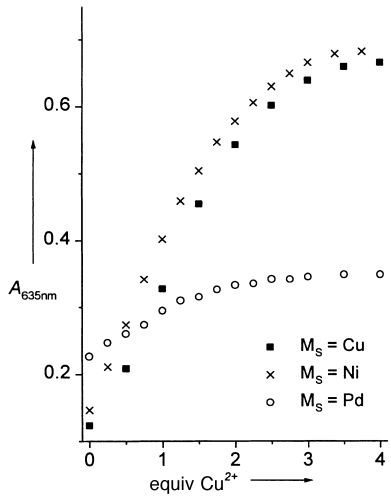


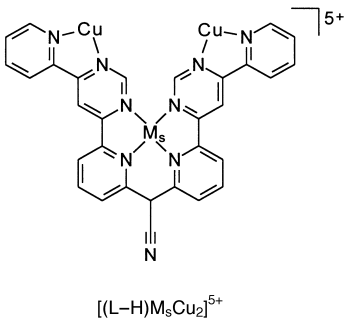
Figure 1. Increase of the absorbance at 635 nm on photometric titration of $[(L-H)M_s]^+$ (10^{-4} M) with copper(II) nitrate solution. Water:DMSO 3:1, pH 7.0, 5×10^{-4} M sodium dimethylphosphate, buffer 5 mM 3-(*N*-morpholino)propanesulfonic acid (MOPS), $T = 20\,^{\circ}C$.

points are seen. The color of the solutions changes from purple to dark blue, for $M_s = Cu$, Ni, or to bluish-purple for $M_s = Pd$. The bathochromic shift of λ_{max} for this Pd complex and therefore the increase of the absorbance at 635 nm (Figure 1) are less significant than for the other complexes.

From their intensities ($\varepsilon = 6000-9000\,M^{-1}cm^{-1}$) we conclude that optical bands of the complexes are ligand-centered

  1433-7851/00/3918-3256 $ 17.50+.50/0

$\pi-\pi^*$ transitions, while metal d–d transitions make only a minor contribution to the band intensity. Less efficient complexation of Cu by the bidentate sites of L is readily evident since excess Cu is required for the quantitative formation of $[(L-H)M_sCu_2]^{5+}$ (ca. 4 equiv). Under electrospray MS ionization conditions labile Cu ions dissociate from the complex and intense $[(L-H)M_s]^+$ peaks are observed. However, minor patterns for polynuclear species $[(L-H)Cu_2(CH_3CO_2)]^{2+}$ and $[(L-H)Cu_3(CH_3CO_2)_3]^{2+}$ are seen in the spectrum of an aqueous solution containing $[(L-H)Cu]NO_3$ and 10 equivalents copper(II) acetate.

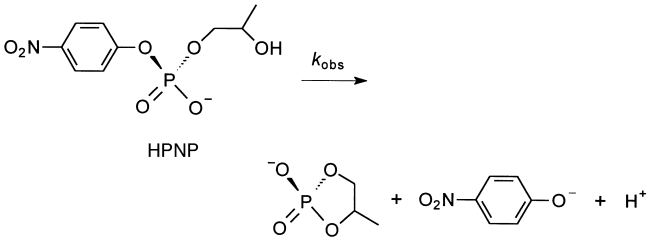


$[(L-H)M_sCu_2]^{5+}$

Reaction of $[(L-H)Cu]NO_3$ with two equivalents of copper(II) perchlorate and KH_2PO_4 gave a dark blue microcrystalline complex with the correct elemental analysis for $[(L-H)Cu_3(PO_4)](ClO_4)_2$.

We have explored the possibility that in complexes $[(L-H)NiCu_2]^{5+}$ and $[(L-H)PdCu_2]^{5+}$ Cu may substitute Ni and Pd in the tetradentate site. Solutions containing $[(L-H)M_s]^+$ (M_s = Ni, Pd) and four equivalents of Cu^{II} (for conditions see caption to Figure 1) were kept at 20 °C for 15 min and then subjected to MALDI mass spectrometry. Since we found strong patterns corresponding to $[(L-H)Ni]^+$ and $[(L-H)Pd]^+$ but only trace (<1%) $[(L-H)Cu]^+$ patterns, metal exchange at the tetradentate site is negligible for short reaction times. Control experiments with mixtures of freshly prepared solutions of $[(L-H)M_s]^+$ (M = Ni, Pd) + 4 Cu and $[(L-H)Cu]^+ + 4$ Cu gave patterns corresponding to $[(L-H)M_s]^+$ and $[(L-H)Cu]^+$ in the expected ratio.

Reactivity studies were performed with the RNA analogue HPNP which is widely used to investigate the phosphoesterase activity of metal complexes. The intramolecular cyclization of this phosphodiester (Scheme 2) can be easily monitored photometrically by the increase in the absorbance at 400 nm, which corresponds to released nitrophenolate. Kinetic studies were performed in a buffered water:DMSO (3:1) mixture (pH 7.0, complex 10^{-4} M, HPNP 5×10^{-4} M). Cleavage activity of the mononuclear complexes is very low ($k_{obs} < 2\times10^{-6}\ s^{-1}$) because the Pd complex is coordinatively saturated and interaction of the substrate with the axial coordination sites (for Ni and possibly even Cu complexes) provides, at best, modest activation.



Scheme 2. Intramolecular cleavage of the phosphodiester 2-(hydroxypropyl)-*p*-nitrophenylphosphate (HPNP).

The cleavage rate increases dramatically when Cu^{2+} ions are added to the $[(L-H)M_s]^+$ solution (Figure 2). In agreement[9] with photometric results (Figure 1) more than two equivalents of Cu are required for quantitative formation of

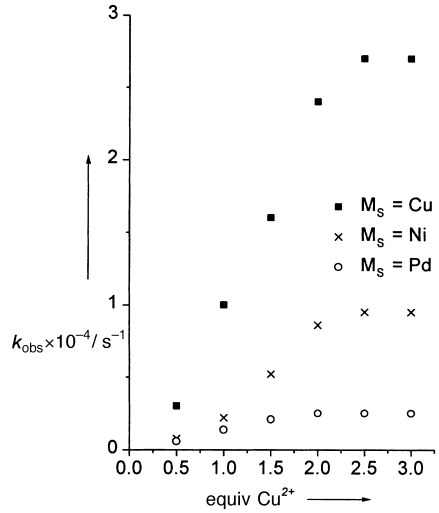


Figure 2. Values of k_{obs} for the cleavage of HPNP (5×10^{-4} M) by $[(L-H)M_s]^+$ (10^{-4} M) at varying copper(II) nitrate concentrations derived from initial reaction rates for reaction times of < 15 min. Water:DMSO 3:1, pH 7.0, buffer 5 MOPS, $T = 20$ °C. Average values of three kinetic runs, that were reproducible to within 15%.

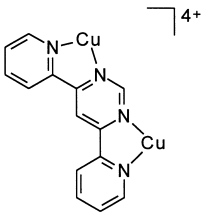
$[(L-H)M_sCu_2]^{5+}$ and for the maximum level of activity to be achieved. Many examples for the efficient cleavage of phosphate esters by the cooperation of two metal ions in phosphoesterase model complexes have been reported.[10] In its reactivity toward HPNP our system with two functional Cu ions is comparable to other artificial dicopper(II) phosphoesterases.[11]

The kinetics of in situ prepared $[(L-H)Cu_3]^{5+}$ solutions were explored in more detail. The pH rate profile has a maximum at pH 7, the reaction is first order in complex concentration (range $0.5-3\times10^{-4}$ M) and first order in HPNP (substrate) concentration (range $10^{-4}-10^{-3}$ M). At least two catalytic turnovers without loss of activity were detected for a HPNP concentration of 2.5 mM and a complex concentration of 10^{-4} M. Addition of one equivalent of PO_4^{3-} per complex completely inhibits HPNP cleavage, whereas the addition of five equivalents of $NaClO_4$ or $NaNO_3$ has no effect on k_{obs}.

Remarkably, the reactivity of $[(L-H)M_sCu_2]^{5+}$ complexes toward HPNP depends strongly on the structural metal M_s. The complex $[(L-H)NiCu_2]^{5+}$ is three times more reactive and $[(L-H)Cu_3]^{5+}$ is ten times more reactive than $[(L-H)PdCu_2]^{5+}$. In our view this must be a consequence of differences in catalyst conformation and thus in the preorganization of functional copper ions, depending on the identity of the structural metal ions M_s. Even subtle differences in the ionic radius of M_s and in its tendency to distort the N_4M_s coordination plane are expected to have substantial effects on both the M_f-M_f distance and the ligand conformation. A

  1433-7851/00/3918-3257 $ 17.50+.50/0

direct contribution of the structural metal M_s to Cu-mediated catalysis, and even hydrogen bonding of the phosphate oxygen atoms of a Cu-coordinated phosphate with axial M_s-H_2O, appear sterically impossible from a ball-and-stick model. Also, efficient cooperation of two metals across the bridging pyrimidine is ruled out by experiment: with the dicopper(II) complex of 4,6-di(2-pyridyl)pyrimidine, $[(dppm)Cu_2]^{4+}$, k_{obs} for HPNP cleavage is only $8\times10^{-6}\ s^{-1}$ (for conditions see caption from Figure 2).



$[(dppm)Cu_2]^{4+}$

Our system may be considered as a prototype of a synthetic allosteric catalyst having well defined catalytic and allosteric subunits, although it does not mimic the typical case of enzyme regulation in which a metal ion reversibly binds to the allosteric site as an external modifier. We see, however, certain parallels between our system and alkaline phosphatase enzymes in which the replacement of a structural Mg^{2+} ion by other divalent metal ions strongly influences the catalytic activity mediated by two functional Zn^{2+} ions.[2, 3] Another remarkable aspect is the possibility of fine-tuning the preorganization of the two functional metal ions M_f by variation of the structural metal M_s. This allows the systematic investigation of metal–metal cooperation in various reactions for a range of M_f-M_f separations and relative orientations of the M_f coordination polyhedra. Other approaches to this problem have been described but require laborious syntheses of a series of binucleating ligands with different spacers.[12]

Received: March 15, 2000 [Z14854]

[1] E. E. Kim, H. W. Wyckoff, *J. Mol. Biol.* **1991**, *218*, 449–464.

[2] a) G. Cathala, C. Brunel, D. Chappelet-Tordo, M. Lazdunski, *J. Biol. Chem.* **1975**, *250*, 6046–6053; b) G. Linden, D. Chappelet-Tordo, M. Lazdunski, *Biochem. Biophys. Acta* **1977**, *483*, 100–106.

[3] J. E. Murphy, T. T. Tibbits, E. R. Kantrowitz, *J. Mol. Biol.* **1995**, *253*, 604–617.

[4] Review: T. Nabeshima, *Coord. Chem. Rev.* **1996**, *148*, 151–169; selected examples: b) F. Wang, A. W. Schwabacher, *J. Org. Chem.* **1999**, *64*, 8922–8928; c) Y. Kubo, Y. Murai, J.-I. Yamanaka, S. Tokita, Y. Ishimaru, *Tetrahedron Lett.* **1999**, *40*, 6019–6023; d) R. Baldes, H.-J. Schneider, *Angew. Chem.* **1995**, *107*, 380–383; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 321–323, and references therein.

[5] a) O. S. Tee, M. Bozzi, N. Clement, T. A. Gadosy, *J. Org. Chem.* **1995**, *60*, 3509–3517; b) E. Iglesias, *J. Am. Chem. Soc.* **1998**, *120*, 13057–13069; allosteric induction of intramolecular reactions by metals have been reported: c) J. Rebek, Jr., T. Costello, R. Wattley, *J. Am. Chem. Soc.* **1985**, *107*, 7487–7493.

[6] E. Bejan, H. A. Aït-Haddou, J.-C. Daran, G. G. A. Balavoine, *Synthesis* **1996**, 1012–1018.

[7] S. Ogawa, R. Narushima, Y. Arai, *J. Am. Chem. Soc.* **1984**, *106*, 5760–5762.

[8] Triclinic crystals, space group $P\bar{1}$, $a=8.635(1)$, $b=11.581(3)$, $c=13.850(2)$ Å, $\alpha=104.14(1)$, $\beta=96.83(1)$, $\gamma=111.29(1)^\circ$, $V=1217.9(5)$ Å^3, $R1=0.0396$ for 5213 data with $[I>2\sigma(I)]$.

[9] The increase in k_{obs} for $2\rightarrow3$ equivalents of Cu is slightly less than expected from the titration data in Figure 1. Inhibition of HPNP cleavage by excess Cu which binds to the bridging hydroxide groups of the catalyst is a possible explanation of this effect, see E. Kövari, J. Heitker, R. Krämer, *Chem. Commun.* **1995**, 1205–1206.

[10] R. Krämer, T. Gajda in *Perspectives on Bioinorganic Chemistry*, *Vol. 4* (Eds.: R. W. Hay, J. R. Dilworth, K. B. Nolan), JAI, **1999**, pp. 209–240.

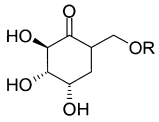
[11] a) M. Wall, R. C. Hynes, J. Chin, *Angew. Chem.* **1993**, *105*, 1696–1697; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1633–1635; b) S. Liu, A. D. Hamilton, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1785; c) P. Molenveld, J. F. J. Engbersen, H. Kooijmann, A. L. Spek, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1998**, *120*, 6726–6737.

[12] W. H. Chapman, Jr., R. Breslow, *J. Am. Chem. Soc.* **1995**, *117*, 5462–5469.

Hexacyclinic acid, a Polyketide from *Streptomyces* with a Novel Carbon Skeleton**

Regina Höfs, Martina Walker, and Axel Zeeck*

As shown in former investigations, *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013) only produces the carbasugars gabosine D (**1**) and E (**2**) when cultivated in Erlenmeyer flasks with a rolled oats medium.[1] Applying the OSMAC approach (OSMAC = one strain/many compounds)[2] in combination with the well established chemical screening method,[3] we intended to examine whether the production of new metabolites can be induced in this strain.



1: R = H
2: R = $COCH_3$

The OSMAC approach is based on the observation that individual strains are able to produce more metabolites than normally detected in a routine screening program. So it is easy to discover new natural products even when cultivating well-examined strains within the group of actinomycetes or fungi, with the aim being to induce or promote the biosynthesis of metabolites by variation of the cultivation parameters. According to this, one can discuss whether the detection of a new metabolite depends only on an increased production rate of a former, not previously provable, substance or if the natural product is formed for the first time. Within the OSMAC approach, the cultivation medium and culture vessel can be varied effectively, besides the temperature, aeration, pH value, and/or light intensity. C and N sources, as well as the addition of inorganic salts, enzyme inhibitors, or adsorbent materials, play an important role as part of the media. The intention of the OSMAC approach is the generation of

[*] Prof. Dr. A. Zeeck, Dr. R. Höfs, Dr. M. Walker
Institut für Organische Chemie
Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399-660
E-mail: azeeck@gwdg.de

[**] We express our thanks to Hoechst AG (Frankfurt) for providing us with *Streptomyces cellulosae* (strain S1013) and Mr. M. Decke for excellent technical assistance. We wish to thank Prof. Dr. W. Beil for determining the cytotoxic activity. This work was supported by the Fonds der Chemischen Industrie.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/00/3918-3258 $ 17.50+.50/0