Changing the Reactivity of Enediynes by Metal-Ion Coordination

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Dedicated to Prof. Dr. Armin de Meijere on the ocasion of his 60th birthday

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The complex molecular structure and interesting activation mechanisms of naturally occurring enediynes have inspired the synthesis of a variety of simpler model systems to mimic their properties. While in most model compounds nucleophilic attack, isomerization or bioreduction are used to activate the unsaturated system for diradical cyclization, some attempts have been made to employ metal-ion coordination for this purpose. Significant enhancement of the thermal reactivity has been achieved by metal-ion induced conformational and electronic changes of suitably substituted enediynes, such as **1**, **5**, **6**, **17** and **18**. Enediyne activation by stoichiometric or catalytic formation of vinylidene complexes, such as **22**, from terminal alkynes has also been investigated. This paper summarizes recent results pursuing the activation of enediyne diradical cyclization by metal ions.

Introduction

The investigation of the chemistry of enediynes, cumulene-eneynes and related compounds began in the 1960′s with the work of Sondheimer, Masamune and Bergman, but it was the discovery of the molecular structure of natural products, such as Calicheamicin γ_1^I, Dynemicin A or the Neocarzinostatin chromophore, which stimulated the tremendous interest in this topic over the last 15 years.[1] Today more than five different classes of enediynes antibiotics and many derivatives are known. The total synthesis of almost all naturally occurring enediynes and cumulene-eneynes has been achieved.[2] The compounds also attracted the attention of biologists, because of their cytotoxic properties, and that of chemists, due to their fascinating structures. Highly reactive diradicals, that arise from thermal cyclization of the strained enediyne or cumulene-eneyne chromophores have been identified as the source of their cytotoxicity: the radicals abstract hydrogen atoms from the desoxyribose backbone of DNA, which leads to DNA-strand cleavage and ultimately to cell death.[3] The synthesis of model systems and natural products, and the biological properties of various enediynes, have been recently reviewed.[1]

One of the most intriguing features of enediyne antibiotics is that their reactivity is masked until they are activated. The molecular mechanisms of activation of the natural products have been investigated in detail and mimicked with model systems. In most cases, a strained and therefore, even at room temperature, highly reactive cyclic enediyne or cumulene-eneyne is held in a conformation which kinetically disfavors the cyclization reaction. A strain-modulat-

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Burkhard König, born 1963 in Wiesbaden, received his doctorate in 1991 from the University of Hamburg under the direction of Prof. de Meijere. He continued his scientific education as a postdoctoral fellow with Prof. M. A. Bennett, Canberra, Australia, and Prof. B. M. Trost, Stanford, U.S.A. In 1996 he obtained his "Habilitation" at the University of Braunschweig and since 1999 he is Professor at the University of Regensburg. His current research interests focus on the chemistry of macrocycles, including cyclic enediynes, and their application in supramolecular chemistry.

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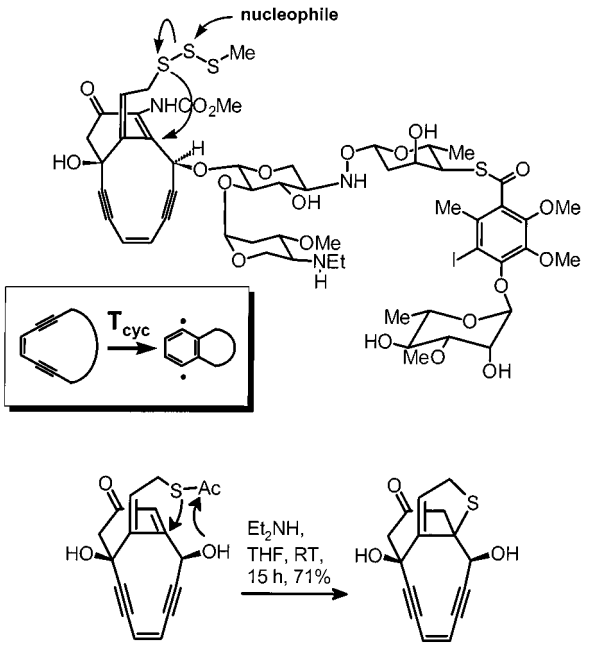
ing reaction, caused, for example, by a nucleophile which adds to a double bond or an epoxide, releases the constraint and the cyclization to the arene diradical proceeds instantaneously.[4] In addition, a carrier protein to which the active enediyne chromophore is tightly non-covalently bound plays an important role in the direction, protection and regulation of the chromophore, e.g. in the case of the Neocarzinostatin chromophore.[5]

Other mechanisms of activation have been explored in model systems,[6] such as the formation of a highly strained enediyne by retro Diels–Alder reaction,[7] base-induced isomerization of enediynes to more reactive allene-eneynes[8] or, more recently, photo-induced cyclization reactions.[9]

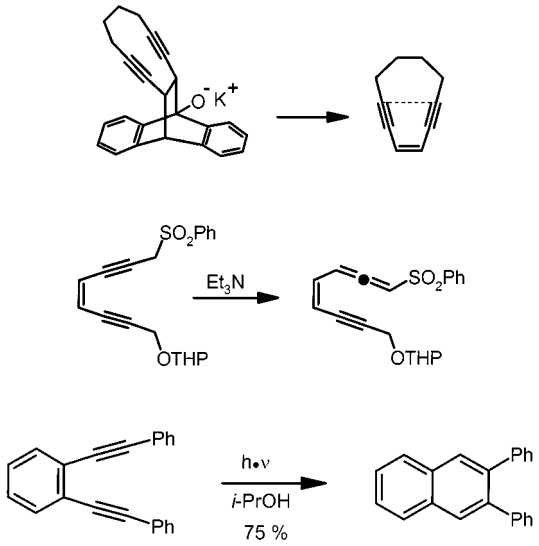


Scheme 1. Molecular mechanism of activation of Calicheamicin γ_1^I by nucleophilic attack (top) and imitation of the process in a model system (bottom)

Without precedence in nature is a different approach to enediyne activation that uses metal ions. The thermal reactivity of enediynes can be changed either by inducing conformational changes upon binding of the metal ion to enediynes bearing coordination sites or by direct participation of a metal fragment in a radical-generating cycloaromatization. This contribution will summarize the results of investigations following this strategy and shall provide some conclusions that can be derived.

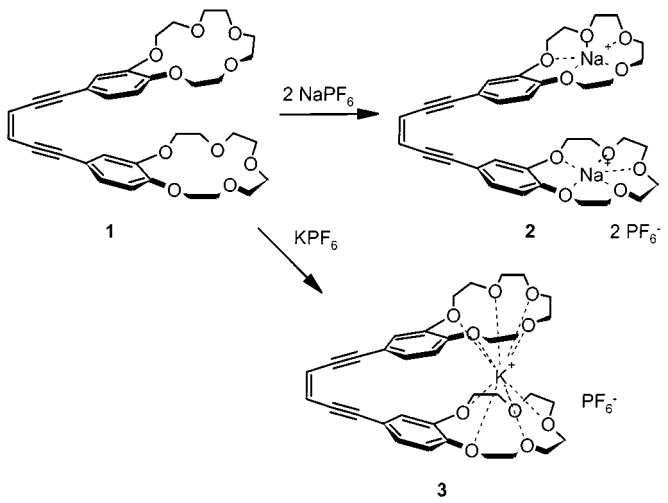
Results and Discussion

The most obvious way of changing the conformation of a simple acyclic enediyne by metal-ion coordination is to use it as a bidentate ligand that is suitably functionalized at both terminal alkyne carbons. We have investigated whether the thermal reactivity of a simple acyclic enediyne is changed by the complexation of adjacent crown ether moieties with different metal ions.[10] 1,6-Bis(4′-benzo-15-crown-5)-hex-3-en-1,5-diyne (**1**) was synthesized by a palladium-catalyzed coupling of 1,4-hexadiyn-3-ene with two equiv. of 3′-iodo-benzo-15-crown-5 in 65% yield under standard conditions.[11] Upon treatment with excess $NaPF_6$ or $NaClO_4$ in acetonitrile at room temperature the corresponding bis-sodium complex **2** was obtained quantitatively, while reaction with KPF_6 gave a potassium sandwich complex (**3**), as confirmed by FAB mass spectra and combustion analysis.[12] To ascertain the reactivity of the enediyne units upon heating, the thermal properties of the bis-benzocrown ether ligand and its complexes were investigated by differential scanning calorimetry (DSC). A clear-cut exothermic dip is observed which reflects the cyclization process beginning at 415 K for **1**, at 430 K for **2** and at 442 K for **3**.[13] Thermolysis experiments in solution in the presence of hydrogen donors confirm the formation of Bergman cyclization products, although in very poor yield. Therefore the effect of metal-ion coordination on the reactivity of the bis-crown ether enediyne must be regarded as very small.



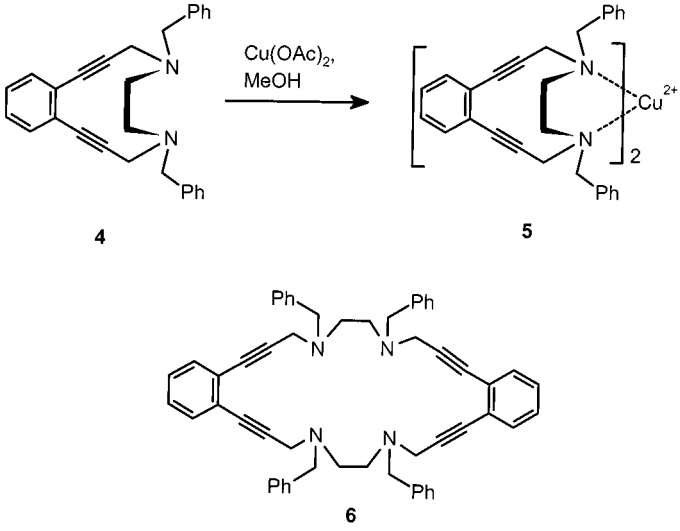
Scheme 2. Examples of enediyne activation mechanisms realized in model systems (from top to bottom): anion accelerated *retro*-Diels–Alder reaction, base-induced propargyl-allene isomerization and photochemical cyclization reaction

The use of macrocyclic enediynes with suitable coordination sites should give rise to much larger effects upon metal-ion coordination because of a more rigid structure, ring strain and leverage effects. Basak et al.[14] have recently reported the synthesis of a macrocyclic diazaenediyne by twofold *N*-alkylation, and its conversion into a copper(II) complex. When treated with $Cu(OAc)_2$ in methanol ligand **4** gave a brown copper(II) complex **5**, which shows a significantly lower thermal stability: while **4** is stable up to 210 °C a thermal reaction of the complex **5** takes place at 110 °C. However, no trapping products of the thermal reactions were isolated to confirm the proposed Bergman cyclization mode. The same group reported the synthesis of an enediyne tetraaza-macrocycle (**6**).[15] Again, the thermal reac-



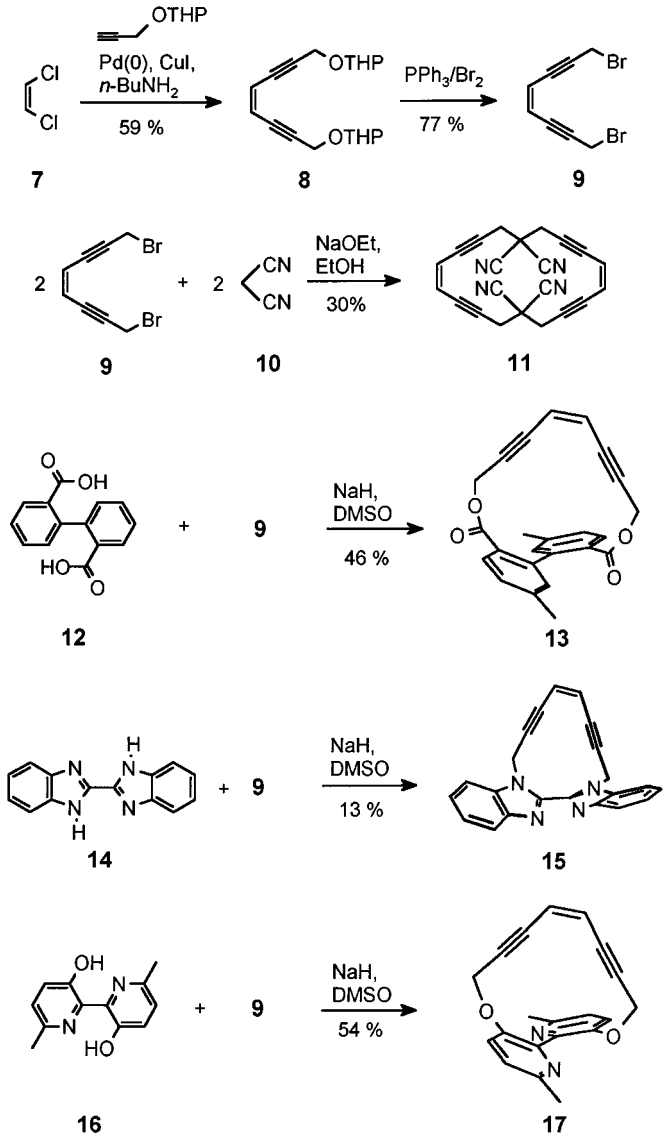
Scheme 3. Enediyne bis-crown ethers and their sodium and potassium complexes

tivity of **6** increased by copper(II) complexation from 160°C to 90°C as indicated by the observed onset temperatures of thermal reaction in DSC, but the products of the thermal process have not been isolated.



Scheme 4. 1,2-Benzodiynes with amino coordination sites

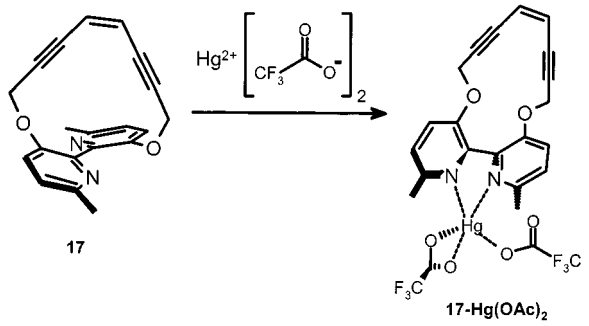
A versatile building block for the synthesis of macrocyclic enediynes is compound **9**. The enediyne is readily available from commercial starting materials in two steps.[16] The bromine atoms can be substituted by weakly basic nucleophiles, such as malonates,[16] carboxylates[17] or phenolates.[18] With stronger bases the compound decomposes, presumably by a propargyl-allene isomerization[19] followed by a Myers–Saito cyclization.[20] The reaction of **9** with malonate derivatives yields 18-membered bis-enediynes such as **11** in a 2:2 substitution process.[16] The enediyne-bridged biaryls **13** and **15** were obtained from biphenyl-2,2′-dicarboxylic acid (**12**) or bisbenzimidazol **14**.[18] The preorganization of the bisnucleophile and the biselectrophile favors the formation of macrocycles in this reaction. The application of high dilution conditions is not necessary and macrocycles were obtained at substrate concentrations of 10^{-3} mol L^{-1}.



Scheme 5. Synthesis of macrocyclic enediynes by substitution reaction

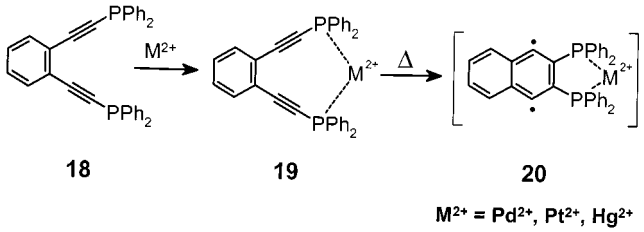
With 3,3′-dihydroxy-2,2-bipyridine (**16**) as the bisnucleophile the enediyne-bridged biaryl **17** with coordination sites for metal-ion binding was obtained from the reaction with **9**.[21] Without metal-ion coordination the compound shows a *transoid* conformation of the 2,2′-bipyridine unit. Upon metal-ion binding the 2,2′-bipyridine moiety must change its conformation to *cisoid* for bidentate coordination. The thermal stability of compounds **17** and **17**-$Hg(TFA)_2$ was investigated by DSC, which indicated a significant increase of the reactivity of the complex. While temperatures above 230°C are necessary to induce the irreversible thermal reaction of **17**, compound **17**-$Hg(TFA)_2$ reacts at ca. 135°C. Solution studies and hydrogen-trapping experiments revealed that the observed exothermic reaction corresponds to a radical polymerization initiated by en-

ediyne cyclization to 1,4-aryl diradicals. It can therefore be concluded that the induced conformational change of **17** by metal-ion coordination results in a drop of its cyclization temperature of almost 100 degrees.



Scheme 6. Activation of enediyne **17** by formation of a mercury complex

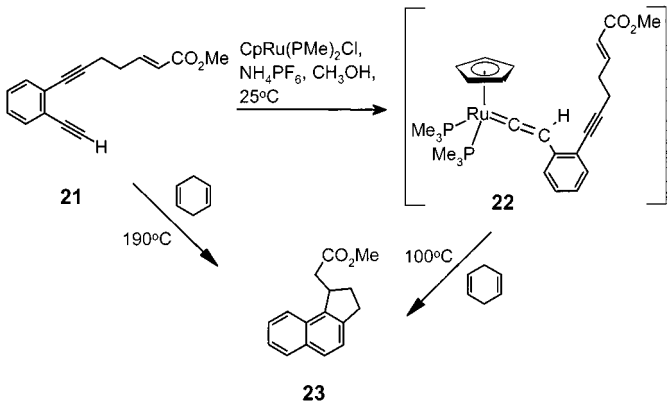
A related example has been reported by Buchwald et al.[22] He used the coordination of metal-ions to a bisphosphane 1,2-aryldiyne **18** to change the 1,2-aryldiyne cyclization temperature.[23] With Pd^{2+} and Pt^{2+} ions a significant increase in reactivity was observed, whereas Hg^{2+} ions stabilize the 1,2-aryldiyne moiety. In this example both conformational and electronic effects may contribute to the change of the 1,2-aryldiyne reactivity.



Scheme 7. Activation of aryldiyne **18** by metal ion coordination

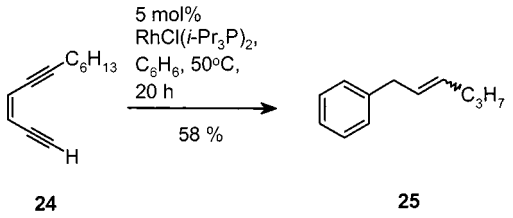
So far, in all examples the metal ion was coordinated to the enediyne through a heteroatom, but organometallic fragments have also been used for enediyne activation. The synthesis of vinylidene complexes from terminal alkynes offers a way of transforming enediynes into more reactive 1-yne-3-ene-5-cumulenes. 1,2-Benzodiyne **(21)** was converted into the air-stable vinylidene complex **22** by treatment with $CpRu(PMe_3)_2Cl$ and NH_4PF_6.[24] The thermolysis of **21** or **22** in the presence of 15 equiv. of 1,4-cyclohexadiene was investigated. In both cases after 4−6 h the hydrogen-trapped product of a tandem radical cyclization **23** was isolated in 50−70% yield. However, compound **21** had to be heated to 190°C, whereas thermolysis of **22** required only a temperature of 100°C; this clearly illustrates the increased thermal reactivity of the vinylidene complex **22** in a Myers-Saito cyclization.

A similar, but catalytic, process was reported with a rhodium complex.[25] Treatment of enediyne **24** with 5 mol-% of $RhCl(PiPr_3)_2$ and triethyl amine in benzene at 50°C resulted in the formation of arene **25** in 58% yield. The proposed mechanism of the catalytic cycle starts with the reaction of the terminal acetylenic carbon and the rhodium



Scheme 8. Activation of 1,2-benzodiyne by formation of a vinylidene complex

compound to yield a vinylidene complex, that subsequently cyclizes in the Myers-Saito mode to give an aryl rhodium diradical. Stepwise 1,5-hydrogen transfers from the alkyl side chain to the arene ring and the rhodium atom, and reductive elimination of the product conclude the cycle and regenerate the catalyst.



Scheme 9. Metal catalyzed induction of diradical cyclization via an intermediate vinylidene complex

Conclusion

The last examples illustrate that the formation of vinylidene complexes from enediynes leads to thermally more-reactive compounds. The process is in close analogy to the base-induced isomerization of enediynes to cumulene-eneynes, which show increased thermal reactivity. The coordination of metal ions to suitable substituted enediynes can modify the reactivity of enediynes, too. If metal-ion binding induces only conformational changes the observed effects are significant, but they remain small compared to changes in thermal reactivity if both conformation and electronic structure are altered by complexation. So far metal-ion activated enediynes still require temperatures above the physiological range to induce the Bergman cyclization. However, based on the acquired knowledge the design of enediynes that are stable and unreactive until activated by a metal ion, and then reactive enough to undergo spontaneous cyclization at physiological temperatures might be envisaged. In such compounds the metal-ion coordination must simultaneously change the conformation and electronic structure to induce a large increase in reactivity.

Acknowledgments

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