

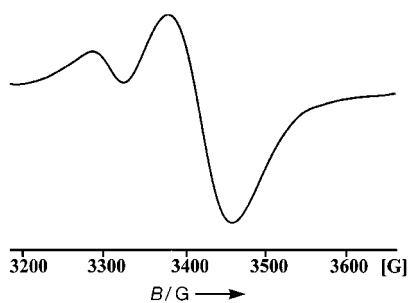


Figure 3. ESR spectrum of $\text{CuBrCu}_{12}\text{TeS}_2$ at 3.5 K and 9.64281 GHz.

Table 1. ESR data of radicals with 19 valence electrons.

	g_1	g_2/g_3	$(g_{\perp})$	$\Delta g = g_1 - g_3$	T [K]	Ref.
O_3^-	2.0174	2.0025/2.0013	(2.0019)	0.0161	77	[20]
SeO_2^-	2.0317	2.0066/1.9975	(2.0021)	0.0342	77	[17]
TeS_2^-	2.0804	2.0085/2.0085 ^[a]	(2.0085)	0.0719	3.5	this work

[a] g_2 and g_3 can differ by at most 0.01.

stituted by heavier homologues with much higher spin–orbit coupling constants (Table 1).^[14, 17] Since a major part of the spin density of, for example, SeO_2^- is located at the central atom, g_1 and Δg are significantly higher when tellurium is present instead of selenium. The results of the ESR investigations (Figure 3), including the considerable linewidth and the fast relaxation, are in accord with the structural identification of TeS_2^- . Thus, a new example has been added to this group of well-known inorganic radicals.

Experimental Section

$\text{CuBrCu}_{12}\text{TeS}_2$ (**1**) was prepared by the reaction of stoichiometric amounts of CuBr, Cu, Te, and S in the ratio 1:1.2:1:2 in evacuated silica ampoules. The mixture of starting materials was melted at 600 °C, homogenized by grinding, and then tempered at 390 °C. Black, shiny square or rectangular platelets were obtained together with a microcrystalline powder after 14 d. The purity and the sample quality was checked by X-ray powder diffraction. Microcrystalline samples with the composition $\text{CuBrCu}_{12}\text{TeS}_2$ were investigated at 3.5 K with an Bruker ESP300 X-band ESR spectrometer. The composition of selected single crystals was determined by semi-quantitative energy dispersive X-ray analysis (EDX): found: Cu:Br:Te:S = 0.350:0.169:0.158:0.324 (calcd: 0.355:0.161:0.161:0.322).

Received: February 5, 1998 [Z11438IE]

German version: *Angew. Chem.* **1998**, *110*, 2057–2059

Keywords: chalcogens • copper • EPR spectroscopy • radical ions • solid-state chemistry

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- [10] X-ray structure determination of $\text{CuBrCu}_{12}\text{TeS}_2$: tetragonal, space group $I4_1/a$ (no. 88), $a = 7.297(3)$, $c = 41.882(8)$ Å, $V = 2230.1(8)$ Å³, $Z = 16$, $\rho_{\text{calcd}} = 4.904$ g cm⁻³. Data collection: 2139 reflections, 998 symmetry-independent reflections ($R_{\text{int}} = 0.098$), room temperature, ω scans, $\text{MoK}\alpha$ radiation, $\lambda = 0.71073$ Å, $2\theta_{\text{max}} = 50^\circ$, crystal dimensions $0.3 \times 0.3 \times 0.01$ mm, numerical absorption correction. Structure solution: direct methods, refinement against F^2 (full matrix, JANA98^[11]), 64 refined parameters, R ($I > 3\sigma_I$) = 0.0853, wR ($I > 3\sigma_I$) = 0.1134, R (all reflections) = 0.1319, wR (all reflections) = 0.1166, GOF = 2.12, $\Delta\rho_{\text{min}}/\Delta\rho_{\text{max}} = -4.97/3.42$ e Å⁻³. Twinning ($4/mmm$) was refined and gave a volume of 8% for the second individual. From the X-ray data neither a superstructure ordering of the TeS_2^- and the TeS_2^- units (both tellurium atoms on 8e) nor ordering of the copper atoms Cu4 could be derived. Further details of the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-408253.
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Rapid Phosphodiester Hydrolysis by Zirconium(IV)

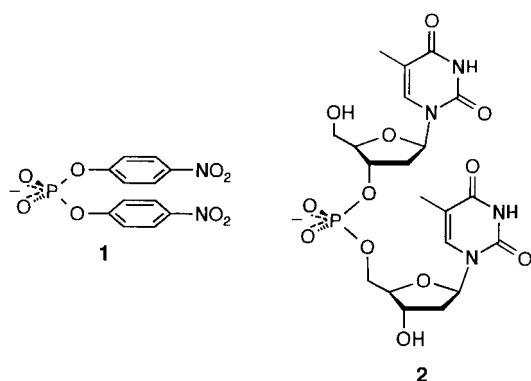
Reina Ott and Roland Krämer*

Nonenzymatic hydrolysis of the phosphodiester backbone of nucleic acids is an attractive research aim in molecular biology. Bioconjugates of hydrolytically active metal complexes and antisense-oligonucleotides may have important applications as artificial restriction enzymes since they have much greater sequence-specificity than their natural counterparts.^[1] In addition, the treatment of incurable diseases by the in-vivo silencing of the genetic code of pathogenic proteins on the RNA or DNA level has been attempted.^[2] RNA is more susceptible to hydrolysis than DNA and various low molec-

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ular weight cleaving agents are available for this. The efficient hydrolysis of linear DNA^[3] under mild conditions is possible with Ce^{IV}, a hard Lewis acid with a high charge/size ratio that will strongly activate the phosphate group. Heterogeneous systems (Ce^{IV}–hydroxide gels) are particularly efficient and accelerate the rate of DNA cleavage up to 10¹¹ fold at pH 7 and 30 °C.^[4, 5a] Homogeneous Ce^{IV} solutions also display high reactivity. Other metal ions, for example trivalent lanthanides, hydrolyze linear DNA either very slowly or only at high temperature.^[6] A disadvantage of Ce^{IV} compounds in potential applications in molecular biology is their sensitivity to reduction (formation of Ce^{III}). While many studies on phosphodiester hydrolysis by middle and late transition metal ions have been reported, little is known about the d⁰ ions of the early transition metals. No evidence of Zr^{IV} compounds having outstanding reactivity has so far been discussed.^[7]

We have investigated the hydrolysis of the “activated” phosphodiester bis(*p*-nitrophenyl)phosphate **1**. Cleavage of **1**



is monitored spectrophotometrically by the release of *p*-nitrophenol in weakly acidic solutions ($\lambda_{\text{max}} = 317 \text{ nm}$, $\epsilon = 10000 \text{ M}^{-1} \text{ cm}^{-1}$). The pH-dependence of the hydrolysis of **1** in the presence of excess ZrCl₄ at 20 °C is shown in Figure 1.

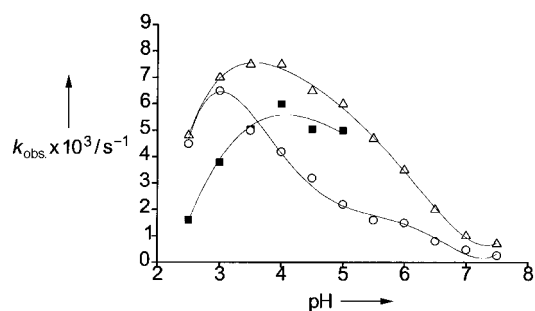


Figure 1. The pH-dependence of the hydrolysis of **1** in the presence of 5 mM ZrCl₄ (■), 5 mM ZrCl₄ + 5 mM **1** (○), 5 mM ZrCl₄ + 10 mM **1** (△). Conditions: H₂O, (20 ± 0.5) °C, 2 × 10^{−5} M **1**. The data are average values of two measurements with a reproducibility within 20 %.

Kinetic studies were carried out in unbuffered, aqueous solutions since the metal salt solutions themselves have sufficient buffer capacity. Maximum reactivity is observed at pH 4; at a pH greater than 5 zirconium hydroxide is formed. The Zr^{IV}-mediated hydrolysis of **1** is 5 × 10⁸ times faster than the spontaneous hydrolysis at pH 7 and 25 °C ($k = 10^{-11} \text{ s}^{-1}$).^[8] Conclusions on the reaction mechanism are not possible from

the pH–rate constant profile. The chemistry of aqueous ZrCl₄ solutions is complicated, and governed by the formation of cationic polynuclear polyhydroxo species.^[9] Nucleophilic attack of the Zr-coordinated hydroxide to the P atom of the coordinated phosphodiester is likely since [Zr(OH)]³⁺ species form at a pH less than 1. The first-order rate constant (k_{obs}) for the reaction of **1** to the monoester *p*-nitrophenylphosphate and nitrophenol was determined from the initial rate of reaction (<10% conversion). *p*-Nitrophenylphosphate is cleaved to phosphate and *p*-nitrophenol at a similar rate ($k_{\text{obs}} = 3.4 \times 10^{-3} \text{ s}^{-1}$). In the determination of k_{obs} for the hydrolysis of **1** the release of *p*-nitrophenol from the monoester was ignored.

Additionally, the cleavage rate of **1** was investigated at various ZrCl₄ concentrations. Michaelis–Menten behavior is observed as shown by a linear relationship between 1/ ν and 1/[ZrCl₄] (Figure 2). From Figure 2 the cleavage rate for the

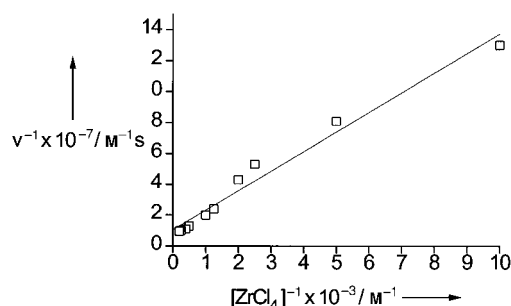


Figure 2. Relationship between the reciprocal rate (1/ ν) of the hydrolysis of **1** and the reciprocal concentration of ZrCl₄. Conditions: H₂O, pH 3.5, (20 ± 0.5) °C, 2 × 10^{−5} M **1**. The data are average values of two measurements with a reproducibility within 20 %.

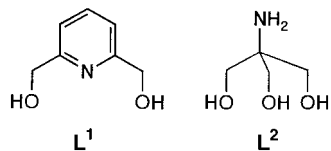
Zr-coordinated phosphodiester **1** ($k_{\text{cat}} = 4.9 \times 10^{-3} \text{ s}^{-1}$ (20 °C, pH 3.5)), and the Michaelis constant K_{M} , whose reciprocal value $1/K_{\text{M}} = 770 \text{ M}^{-1}$ corresponds to the formation constant of the **1**–Zr complex, were determined. Application of the Michaelis–Menten law implies a fast equilibration occurs in the formation of the complex between Zr and **1**. The coordination chemistry of the zirconium(IV) ion is determined by fast ligand-exchange kinetics.^[9] To confirm this an NMR study was performed using the less reactive dimethylphosphate derivative; after several hours virtually no hydrolysis was observed. In a D₂O solution containing ZrCl₄ (10 mM) and dimethylphosphate (2 mM) at pH 3.5 a broad CH₃ signal of coordinated dimethylphosphate ($\delta = 3.7$) and a sharp signal of small intensity for free dimethylphosphate ($\delta = 3.52$) are observed after approximately 30 s. The equilibrium ratio of complexed to uncomplexed dimethylphosphate is in the range expected from the stability constant of the **1**–Zr complex. The relative intensities of the signals remain unchanged even after several hours. Thus, thermodynamic equilibrium is also reached after 30 s.^[10]

When substrate **1** is added in excess the initial hydrolysis rate is still high, but a deviation from Michaelis–Menten behavior is apparent. For [ZrCl₄] = 10^{−4} M and [**1**] = 4 × 10^{−4} M at pH 3.5 and 20 °C the rate of *p*-nitrophenol release is $\nu = 6 \times 10^{-8} \text{ M s}^{-1}$ (expected: $\nu = 11 \times 10^{-8} \text{ M s}^{-1}$). Catalytic turnover is

not observed. After the release of one equivalent of *p*-nitrophenol per zirconium ion the reaction rate is very slow, possibly because of the formation of unreactive zirconium(IV) phosphate complexes. A noticeable decrease in the reaction rate in the presence of excess substrate was also described for the hydrolysis of **1** with lanthanide(III) ions.^[11]

Kinetic investigations with Ce^{IV} salts under the same conditions are complicated by the intense UV absorption of the metal center. Recent studies on aqueous micellar solutions of Ce^{IV} and Th^{IV} salts have confirmed that **1** is hydrolyzed much faster ($k \approx 2 \times 10^{-2} \text{ s}^{-1}$ at 37 °C) than by transition metal or lanthanide(III) salts.^[12] The reactivity of ZrCl₄ at 37 °C ($k_{\text{obs}} = 1.3 \times 10^{-2} \text{ s}^{-1}$) is comparable to those of the micellar Ce^{IV} and Th^{IV} systems.

Carboxylate-containing ligands such as ethylenediamine-tetraacetate (EDTA) form stable 1:1 complexes with Zr^{IV} ions at neutral pH, but they quench reactivity.^[11] In contrast, with the amino alcohols 2,6-bis(hydroxymethyl)pyridine (**L**¹) and especially with tris(hydroxymethyl)aminomethane (**L**²) high reactivity is retained in weakly acidic solutions. ¹H NMR



spectra were recorded of D₂O solutions containing **L**¹ and ZrCl₄ under the conditions of the kinetic experiments (pH 4.0, 5 mM ZrCl₄). For **L**¹:Zr ratios of 0.5:1 and 1:1 broad signals

of the coordinated ligand are observed at $\delta = 8.1$ (py-H4), 7.3 (d, py-H3,5), and 5.6 (s, CH₂) (py = pyridine). At a **L**¹:Zr ratio of 2:1 the excess **L**¹ does not coordinate and is present in its protonated form ($\delta = 8.5$ (py-H4), 7.9 (d, py-H3,5), and 5.0 (s, CH₂)). ¹H NMR data indicate formation of a complex containing one equivalent of **L**¹ per zirconium ion although oligomerization by formation of hydroxo- or alkoxo-bridged complexes cannot be excluded. The significant decrease of the reactivity of the complexes at high pH may be a result of aggregation (Figure 1).

The complex derived from **L**² forms homogeneous solutions up to pH 6 and pH 8 with one and two equivalents of **L**², respectively, while in the absence of the ligand precipitates are formed in a ZrCl₄ solution (5 mM) at pH > 5.0. Addition of one equivalent of **L**² to the ZrCl₄ solution causes a significant increase in the reactivity (Figure 1), but no further change in the reactivity is apparent on addition of a second equivalent of **L**². This indicates formation of a 1:1 complex. Even with an excess of **L**² only one CH₂ signal is seen in the ¹H NMR spectrum, a consequence of the exchange between the free and coordinated **L**² being fast on the NMR timescale. The observation that the dialcohol 2-amino-1,3-propanediol neither prevents the formation of zirconium hydroxide precipitates nor affects the reactivity of the complex suggests that **L**² is bound as a tridentate *O,O,O*-chelating ligand. Solutions of Ce^{IV} salts are not stabilized by **L**¹ and **L**² at pH > 4.

Hydrolysis of the phosphodiester linkage in the DNA-dinucleotide thymidylyl(3' → 5')thymidine (**2**) by ZrCl₄ (5 mM) was analyzed by quantification of the reaction products by reversed-phase HPLC (Figure 3). While **2** is cleaved into two equivalents of thymidine and phosphate, only trace amounts of the intermediates thymidine 3'phosphate and thymidine 5'-

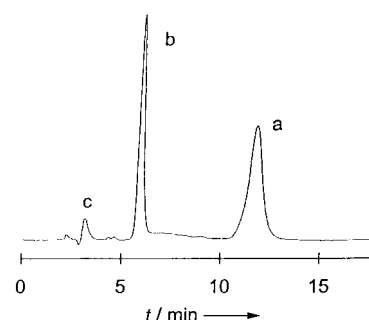


Figure 3. HPLC elution profile of an aqueous solution of **2** (10^{-4} M) in the presence of ZrCl₄ (5 mM) and **L**² (10 mM) after 440 h at pH (5.5 ± 0.1) and (20 ± 0.5) °C. a) **2**; b) thymidine; c) thymidine-3' phosphate and thymidine-5' phosphate.

phosphate are detectable owing to rapid monoester hydrolysis. At pH 3.0 and 20 °C, where the initial rate of the reaction was constant at less than 15 % conversion, $k_{\text{obs}} = (1.4 \pm 0.3) \times 10^{-7} \text{ s}^{-1}$. The DNA-dinucleotide **2** is converted into thymidine and phosphate a little faster by (NH₄)₂Ce^{IV}(NO₃)₆ ($k_{\text{obs}} = 2.0 \pm 0.4 \times 10^{-7} \text{ s}^{-1}$). Considering the strong temperature dependence of the Ce^{IV}-mediated cleavage,^[4c] this value is comparable to literature data for the hydrolysis of **2** by homogeneous Ce^{IV} solutions.^[5a]

The Zr^{IV} complex of **L**² (5 mM ZrCl₄, 10 mM **L**²) hydrolyzes **2** with $k_{\text{obs}} = (2.9 \pm 0.4) \times 10^{-7} \text{ s}^{-1}$ at pH 5.5 and 20 °C, a rate that corresponds to a half-life of 28 days. The zirconium-mediated hydrolysis proceeds 3×10^9 times faster than the spontaneous hydrolysis of the DNA – phosphodiester linkage at pH 7 and 25 °C with an estimated k_{obs} of 10^{-16} s^{-1} .^[8] Under physiological conditions (pH 7.0, 37 °C) we have determined $k_{\text{obs}} = (1.3 \pm 0.2) \times 10^{-7} \text{ s}^{-1}$.

In conclusion, Zr^{IV} salts and Zr^{IV} complexes display high reactivity toward activated and nonactivated phosphodiester in weakly acidic, homogeneous solution and an efficiency similar to that of Ce^{IV} compounds. In potential applications in molecular biology nonredox-active Zr^{IV} compounds should be an alternative to the reduction-sensitive Ce^{IV} ion.

Received: October 31, 1997

Revised version: March 27, 1998 [Z11108IE]

German version: *Angew. Chem.* **1998**, *110*, 2064–2067

Keywords: DNA cleavage • hydrolyses • kinetics • phosphodiester • zirconium

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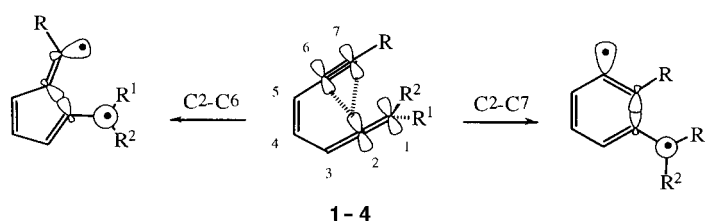
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Regioselectivity of Biradical Cyclizations of Enyne-Allenes: Influence of Substituents on the Switch from the Myers–Saito to the Novel C^2 – C^6 Cyclization**

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The Myers–Saito C^2 – C^7 cyclization of enyne-allenes^[1] has recently received a lot of attention owing to the involvement of the $\alpha,3$ -didehydrotoluene biradicals (Scheme 1) in DNA-cleavage reactions^[2] and subsequent reactions of synthetic interest.^[3]

The synthetic potential of thermal enyne-allene reactions was extended when Schmittel and co-workers found a complete switch from the Myers–Saito C^2 – C^7 cyclization to



Scheme 1. Thermal reaction of enyne-allenes: C^2 – C^6 cyclization (left) and Myers–Saito C^2 – C^7 cyclization (right). **1**: R = H, **2**: R = Ph, **3**: R = *t*Bu, **4**: R = NH_2 ; $\text{R}^1 = \text{R}^2 = \text{H}$.

a C^2 – C^6 cyclization (Scheme 1).^[4] For different groups R^1 and R^2 , the new C^2 – C^6 cyclization takes place if the terminal hydrogen atom of the alkyne group (R = H) is replaced by an aryl group (R = Ph) or by sterically bulky groups (e.g., R = *t*Bu, SiMe_3). Later Gillmann et al.^[5] and Rodriguez et al.^[6] found a similar reaction switch, which indicates that the new C^2 – C^6 cyclization constitutes a general reaction motif.

As indicated on the right-hand side of Scheme 1, the rate-determining step of the Myers–Saito reaction is the formation of a (σ, π) biradical. Experimental studies^[7, 8] on the new C^2 – C^6 cyclization (shown on the left-hand side of Scheme 1) also suggest that biradical formation is the rate-determining step, but the final proof for a biradical intermediate was missing so far. Although the switch from the C^2 – C^7 to the C^2 – C^6 cyclization is experimentally well established, the reasons are still unclear.

In the present investigation quantum-chemical calculations^[9] address for the first time the regioselectivity of biradical cyclizations in enyne-allenes with different substituents—namely, R = H (**1**), Ph (**2**), *t*Bu (**3**), and NH_2 (**4**)—at the alkyne terminus (with $\text{R}^1 = \text{R}^2 = \text{H}$). In addition, the hitherto postulated biradical intermediate of the C^2 – C^6 cyclization could be trapped by hydrogen transfer, thus providing the most direct proof of its biradical nature.

The theoretical results are summarized in Table 1, and the optimized geometrical structures of the reactants and of the transition states are shown in Figure 1. We will first compare

Table 1. Summary of the theoretical data. Energy differences are given with respect to the reactants (in kcal mol^{-1}). Thermochemical corrections were made at a temperature of 298 K.

		R =			
		H	Ph	<i>t</i> Bu	NH_2
C^2–C^7 cyclization					
TS ^[a]	$R_{\text{C}^2-\text{C}^7}$ ^[c]	2.07	2.06	2.07	2.08
	ΔE^*	22.4	28.0	29.0	20.9
	ΔH^*	21.4	26.7	27.9	19.8
	ΔG^*	24.0	29.8	31.1	22.7
product ^[b]	$R_{\text{C}^2-\text{C}^7}$ ^[c]	1.43	1.41	–	1.50
	ΔE_{r}	– 21.3	– 23.3	–	– 34.7
C^2–C^6 cyclization					
TS ^[a]	$R_{\text{C}^2-\text{C}^6}$ ^[c]	1.90	1.96	1.90	2.13
	ΔE^*	30.8	27.2	33.0	16.9
	ΔH^*	29.0	25.1	31.4	15.4
	ΔG^*	31.4	28.7	33.3	17.8
product ^[b]	$R_{\text{C}^2-\text{C}^6}$ ^[c]	1.51	1.50	–	1.47
	ΔE_{r}	12.0	1.3	–	– 37.0

[a] DF(B3LYP) in combination with a 6-31G* basis set. TS = transition state. [b] MR-CI in combination with a DZP basis set. [c] Distance in Å.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 344, project Schm 647/7-1) and the Fonds der Chemischen Industrie. The services and computer time of the Computing Center of the Universität Köln and HRLZ Jülich have been essential to the present study.