M. W. Day, *J. Am. Chem. Soc.* **1996**, *118*, 915; e) J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *J. Am. Chem. Soc.* **1997**, *119*, 3179; f) C. S. Tomooka, D. D. LeCloux, H. Sasaki, E. M. Carreira, *Org. Lett.* **1999**, *1*, 149.

[7] For an excellent review, see: a) E. D. Cox, J. Cook, *Chem. Rev.* **1995**, *95*, 1797; b) J. E. Saxton, *Nat. Prod. Rep.* **1997**, 559.

[8] J. P. Kutney in *The Total Synthesis of Natural Products*, *Vol. 3* (Ed.: J. ApSimon), Wiley, New York, **1977**, p. 273.

[9] For a discussion of charge affinity patterns and retrosynthetic analysis, see: D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, *7*, 147.

[10] a) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, 89, 165; b) for an excellent review see: S. Danishefsky, *Acc. Chem. Res.* **1977**, *12*, 66.

[11] The reactivity cyclopropanes towards nucleophiles is typically limited to those activated by two electron-withdrawing groups or those that are highly strained. Exceptions to this generalization occur with strong nucleophiles such as metal selenides and Ni-catalyzed additions of organolaluminum compounds, see: a) A. B. Smith, R. M. Scarborough, Jr., *Tetrahedron Lett.* **1978**, 1649; b) L. Bagnell, A. Meisters, T. Mole, *Aust. J. Chem.* **1975**, *28*, 821.

[12] MgI_2 has been observed to function as a uniquely effective catalyst in asymmetric Diels–Alder and aldol addition reactions. Its superiority has been attributed to the facile dissociation of iodide from L_2MgI_2, see: E. J. Corey, W. Li, G. A. Reichard, *J. Am. Chem. Soc.* **1998**, *120*, 2330.

[13] a) C. Crestini, R. Saladino, *Syn. Commun.* **1994**, *24*, 2835; b) the sulfonylimines were prepared using known methods, see: R. Albrecht, G. Kresze, B. Mlagar, *Chem. Ber.* **1963**, *97*, 483.

[14] G. P. Claxton, L. Allen, J. M. Grisar, *Org. Synth. Coll. Vol. VI* **1988**, 968.

[15] It is important to note that in the absence of added metal salts, no reaction was observed.

[16] In this context, we have shown that the *p*-tolylsulfonyl protecting group could be removed in good yields (Na/naphthalene, THF, $-100\,^{\circ}C$, 68% yield).

Specific RNA Dinucleotide Cleavage by a Synthetic Calix[4]arene-Based Trinuclear Metallo(II)-phosphodiesterase**

Peter Molenveld, Johan F. J. Engbersen,* and David N. Reinhoudt*

Dedicated to Professor H. C. Beyerman on the occasion of his 80th birthday

Phosphodiesterase enzymes such as nuclease P1 use three divalent metal ions (e.g. Zn^{II}) in the active site to catalyze the hydrolytic cleavage of phosphate diester bonds in nucleotides like RNA and DNA.[1] Synthetic catalysts that cleave RNA at specific sites are of interest, for example, for future application in gene technology.[2, 3] There are several mononuclear complexes of trivalent metal ions[3, 4] (e.g. lanthanide(III) and Co^{III}) that efficiently cleave RNA because they are strong Lewis acids. According to previous studies, mononuclear and even dinuclear Zn^{II} complexes[2, 5, 6] generally exhibit only a moderate catalytic activity in RNA cleavage. Recently, we have shown that synthetic dinuclear and trinuclear[7] metallophosphodiesterases based on calix[4]arenes[8] exhibit a very high catalytic activity in the transesterification of the RNA model substrate 2-hydroxypropyl-*p*-nitrophenyl phosphate (HPNP).[6, 9, 10]

Here we report that **1**-Zn_3 efficiently catalyzes the cleavage of RNA dinucleotides (3′,5′-NpN) by the cooperative action of the Zn^{II} centers, with high rate enhancement and significant nucleobase specificity. The heterotrinuclear complex **1**-Zn_2Cu is even more active; it mimics phosphodiesterases with a heterotrinuclear metal cluster including a Zn^{II} center in the active site.[1]

Catalytic cleavage of the RNA dinucleotides 3′,5′-NpN (0.09 mM) by the complexes **1**-M_3 (0.9 mM) was carried out in 35% EtOH/20 mM aqueous HEPES buffer[11] at $50\,^{\circ}C$ and monitored by HPLC. The formation of cyclic ribonucleoside monophosphates (2′,3′-cNMP) and the corresponding nucleosides show that the RNA dinucleotides are cleaved by intramolecular transesterification of the hydroxyl group at the 2′-position.[12] The catalytic activity of **1**-Zn_3 was measured for a series of RNA dinucleotides, namely, GpG, UpU, CpC, GpA, ApG, and ApA (Table 1). The trinuclear complex **1**-Zn_3 exhibits a very high catalytic activity; rate accelerations over the uncatalyzed reactions are on the order of 10^4–10^5.[5b, 13] Moreover, **1**-Zn_3 is a genuine catalyst that exhibits turnover. A threefold excess of UpU is completely converted, while a reference solution of UpU without catalyst is unaffected. Surprisingly, for different nucleobases in the dinucleotides large differences in rate were observed: GpG ≫ UpU ≫ ApA (see below).

Table 1. Observed pseudo-first-order rate constants ($k_{obs}/10^5\ s^{-1}$) for the cleavage of RNA dinucleotides.[a]

Substrate	**1**-Zn_3	**1**-Zn_2Cu	**1**-Cu_3	**2**-Zn_2	**3**-Zn
GpG	72	88	28	0.45	–[b]
UpU[c]	8.5	13	1.2	0.45	0.56
CpC	6.1	7.1	1.9	0.58	–[b]
GpA	4.6	5.9	–[b]	–[b]	–[b]
ApG	2.7	2.4	–[b]	–[b]	–[b]
ApA[d]	0.44	0.46	0.47	0.28	0.31

[a] In 35% EtOH/20 mM HEPES (pH 8.0) at $50\,^{\circ}C$; [substrate] = 0.09 mM; [**1**-Zn_3] = [**1**-Cu_3] = [**2**-Zn_2] = 0.9 mM; **1**-Zn_2Cu is a statistical mixture of [**1**] = 0.9 mM, [Zn] = 1.8 mM, and [Cu] = 0.9 mM;[15] [**3**-Zn] = 2.7 mM. [b] Not determined. [c] $k_{uncat} \approx 9.8 \times 10^{-9}\ s^{-1}$.[5b] [d] $k_{uncat} \approx 1.7 \times 10^{-9}\ s^{-1}$.[13]

The dependence of rate on the pH value for the **1**-Zn_3-catalyzed cleavage of UpU shows a bell-shaped curve with an optimum at pH 8. The apparent pK_a of a Zn^{II}-bound water molecule in **3**-Zn is 7.9;[9] the value is lower for **1**-Zn_3 due to hydrophobic and cooperative effects.[9, 10] Therefore, it is likely that at pH 8 one or two Zn^{II} centers in **1**-Zn_3 are coordinated by a hydroxide ion. Furthermore, the activity reaches a

[*] Prof. Dr. J. F. J. Engbersen, Prof. Dr. D. N. Reinhoudt, Dr. P. Molenveld
Laboratory of Supramolecular Chemistry and Technology
MESA+ Research Institute, University of Twente
P.O. Box 217, NL-7500 AE Enschede (The Netherlands)
Fax: (+31) 53-489-4645
E-mail: smct@ct.utwente.nl

[**] This work was supported by the Council for Chemical Sciences of the Netherlands Organization for Scientific Research (CW-NWO). We thank Dr. F. C. J. M. van Veggel for molecular modeling, and Dr. F. Venema and Dr. H. van Schijndel of Organon Teknika BV for their help with preliminary experiments with RNA oligonucleotides.

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

  1433-7851/99/3821-3189 $ 17.50+.50/0

maximum with three equivalents of Zn^{II} per molecule of **1**, which indicates that all three Zn^{II} ions in **1**-Zn_3 are involved in the catalysis. The trinuclear complex **1**-Zn_3 is a factor of 10, 19, and even 160 times more active than the dinuclear complex **2**-Zn_2 for the cleavage of CpC, UpU, and GpG, respectively. These differences in activity are much higher than that observed in the transesterification of the *p*-nitrophenyl-activated phosphate diester HPNP catalyzed by **1**-Zn_3 and **2**-Zn_2 (factor of 1.4).[9] This can only be due to additional catalytic effects originating from the third Zn^{II} center in the transesterification of the RNA dinucleotides. Since the basicity of the alkanolate leaving group in an RNA dinucleotide is much higher, one of the catalytic centers in **1**-Zn_3 might stabilize this leaving group.

So far, Cu^{II} ions have not been found in the active sites of phosphodiesterases, but they exhibit generally a high hydrolytic activity in abiotic catalysts.[10, 14] Whereas **1**-Zn_3 is superior to its analogue **1**-Cu_3 (except for the case of ApA), a statistical mixture of **1**, two equivalents of Zn^{II}, and one equivalent of Cu^{II}—to form the heterotrinuclear analogue **1**-Zn_2Cu as the main species[15]—shows a higher activity (Table 1, Figure 1). This may be due to synergy of the

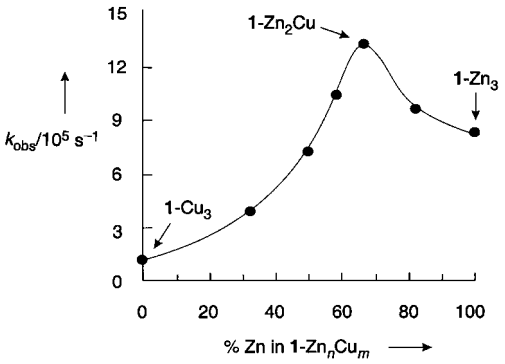
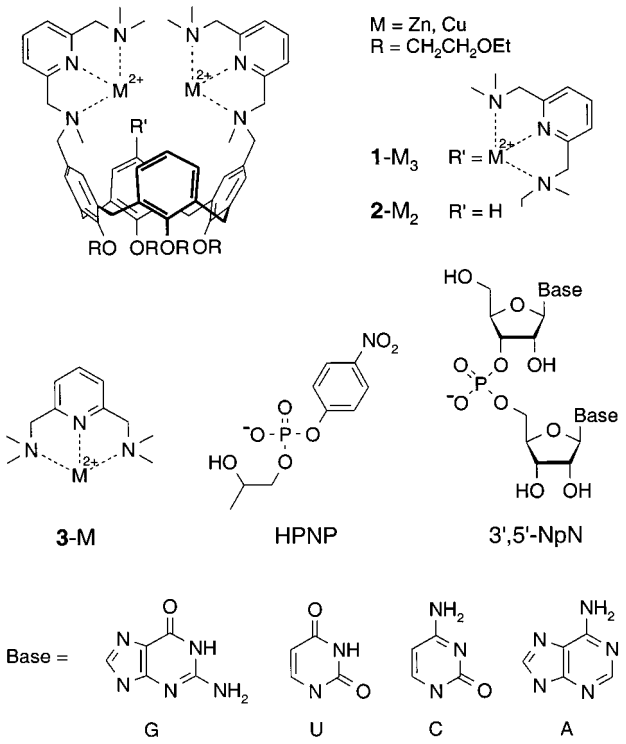


Figure 1. Dependence of the rate k_{obs} for the cleavage of UpU catalyzed by **1**-Zn_nCu_m ($n+m=3$) on the percentage of $Zn(ClO_4)_2$ with respect to the total concentration of $M(ClO_4)_2$ (M = Zn, Cu; 2.7 mM) at a fixed concentration of ligand **1** (0.9 mM) in 35% EtOH/20 mM HEPES buffer (pH 8.0) at 50 °C. At the rate optimum, **1**-Zn_2Cu is the main species in solution.[15]

favorable properties[9, 10] of Zn^{II} in the binding (K_{ass})[16] and Cu^{II} in the conversion (k_{cat}) of the phosphate diester substrate.

The catalytic activities of the trinuclear complexes are dependent on the structure of the nucleobases in the RNA dinucleotides. The activity of **1**-Zn_3 in the cleavage of GpG is a factor of 8.5 higher than of UpU, and even a factor of 160 higher than of ApA. For **1**-Zn_2Cu the selectivities are even more pronounced, that is, factors of 190 and 28 for GpG and UpU over ApA. The mixed dinucleotides GpA and ApG are also more reactive than ApA, but they are far less reactive than GpG. It seems that an adenyl nucleobase in an RNA dinucleotide reduces the activity of the catalyst **1**-M_3. Comparison of the activity of **1**-Zn_3 with that of the reference complexes **2**-Zn_2 and **3**-Zn indicates that in the cleavage of ApA the three metal centers in **1**-M_3 do not cooperate in the catalysis (Table 1). This was confirmed when we measured the rates as a function of the concentration of catalyst **1**-Zn_3



(Figure 2). For ApA the rate linearly increases with the catalyst concentration. The small slope ($k_2 = 4.3 \times 10^{-3}\,M^{-1}\,s^{-1}$) suggests that only small amounts of a reactive catalyst–substrate complex are formed. The highly reactive substrates UpU (Figure 2) and GpG show saturation kinetics, indicating

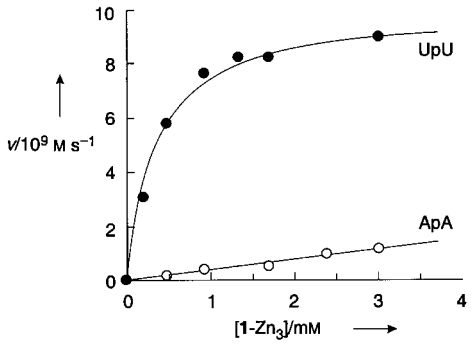


Figure 2. Plot showing the dependence of the rate of cleavage of UpU and ApA (0.09 mM) on the concentration of **1**-Zn_3 in 35% EtOH/20 mM HEPES (pH 8.0) at 50 °C. The experimental data points for cleavage of UpU are fitted to the Michaelis–Menten equation with $K_m = 0.34$ mM and $k_{cat} = 1.1 \times 10^{-4}\,s^{-1}$. The experimental data for cleavage of ApA are fitted according to second-order reaction kinetics with $k_2 = 4.3 \times 10^{-3}\,M^{-1}\,s^{-1}$.

a strong binding to the catalyst **1**-Zn_3. The saturation curves obey Michaelis–Menten kinetics and were analyzed by means of Eady–Hofstee plots. Although the binding constant (K_{ass}) is a factor of 3.8 lower for GpG ($7.7 \times 10^2\,M^{-1}$) than for UpU ($29 \times 10^2\,M^{-1}$), the catalytic rate constant (k_{cat}) is a factor of 16.4 higher (GpG: $18 \times 10^{-4}\,s^{-1}$; UpU: $1.1 \times 10^{-4}\,s^{-1}$). These studies indicate that the higher activity in the reactions of GpG and UpU than of ApA is due to enhanced binding to **1**-Zn_3. The higher reactivity of GpG compared with UpU is due to a higher rate of conversion.

  1433-7851/99/3821-3190 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1999**, *38*, No. 21

The most reactive nucleotides GpG and UpU have an acidic amide NH moiety that can be deprotonated by a Zn^{II}-bound hydroxide group, the resulting anionic nitrogen atom can coordinate to form a stable nucleobase – Zn^{II} complex.[17] In this way one of the Zn^{II} centers in **1**-Zn_3 might orient the RNA dinucleotide within the catalytic site (Figures 3 and 4).

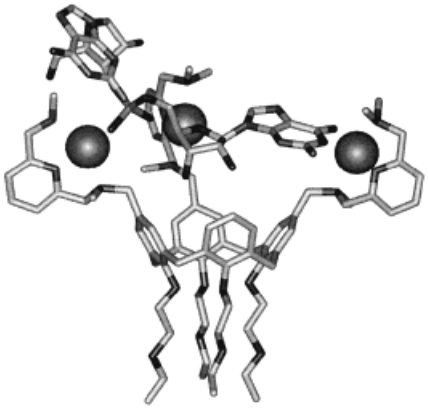


Figure 3. Computer-generated model of the complex between catalyst **1**-Zn_3 and the substrate GpG, formed by coordination of the phosphoryl group and a deprotonated guanosine group to Zn^{II}. Hydrogen atoms are omitted for clarity.

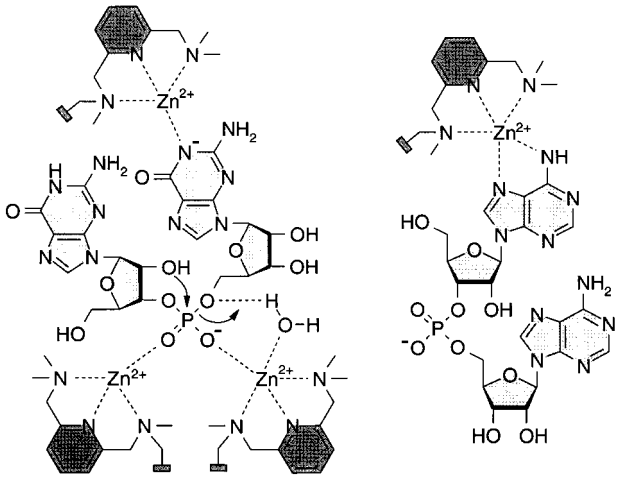


Figure 4. Schematic representations of possible modes of binding of RNA dinucleotides to **1**-Zn_3. Left: mechanism for GpG cleavage. Right: nonproductive binding mode for ApA.

Subsequently, the two remaining Zn^{II} centers may activate the phosphoryl group by double Lewis acid coordination. Elimination of the leaving group may be assisted by protonation by a Zn^{II}-bound water molecule. The specificity for GpG over UpU might originate from a better fit owing to the different sizes of the nucleobases. The adenyl group has multiple metal ion binding sites, including a bidentate binding site formed by the nitrogen atoms on the 6- and 7-positions. Bidentate coordination of a substrate adenyl group results in a different, less favorable substrate orientation within the catalyst **1**-Zn_3 compared to monodentate binding of a deprotonated uracyl or guanine group (Figure 4).

Preliminary experiments with a 24-mer RNA[18] show that **1**-Zn_3 and **1**-Zn_2Cu exhibit catalytic activity in the cleavage of RNA oligonucleotides. This opens possibilities for sequence-selective cleavage of RNA.[2, 3]

Experimental Section

The synthesis and characterization of the complexes **1**-M_3, **2**-M_2, and **3**-M (M = Zn, Cu) was described previously.[9] Solutions for kinetic measurements were made by adding up to 35% (v/v) EtOH to a 20 mM aqueous buffer solution adjusted with NaOH to the desired pH value.[11] Aliquots of the reaction mixtures were analyzed by reverse-phase HPLC (Waters) with elution (1.0 mL min^{-1}) with mixtures of 10 mM KH_2PO_4 (pH 4.7 or pH 5.5) and MeOH/H_2O (3/2) and detection of guanosine, uridine, cytidine, and adenosine at $\lambda = 254$, 260, 272 and 260 nm, respectively. In a typical experiment, the ligand **1** (10 μL, 50 mM in EtOH) and $M(ClO_4)_2$ (30 μL, 50 mM in water) were added to 0.5 mL of the buffer solution and thermostated at 50 °C. After a couple of minutes equilibration time, 3′,5′-NpN (10 μL, 5 mM in water) was injected. Aliquots (20 μL) of the reaction mixture were quenched with an excess of tris(2-aminomethyl)amine (20 μL, 50 mM in EtOH) and analyzed with HPLC (2.0 μL injection, 25 min elution). Initial rates were determined by analysis of at least four aliquots (< 10% conversion). The concentration of the formed nucleoside was determined by means of a calibration curve made with commercially obtained nucleoside (correlation coefficient > 0.95). The observed pseudo-first-order rate constants k_{obs} (s^{-1}) were calculated from the initial rates (correlation coefficient > 0.95).

Received: March 24, 1999
Revised version: July 5, 1999 [Z13208IE]
German version: *Angew. Chem.* **1999**, *111*, 3387 – 3390

Keywords: calixarenes · enzyme mimetics · RNA · transesterifications · zinc

[1] N. Sträter, W. N. Lipscomb, T. Klabunde, B. Krebs, *Angew. Chem.* **1996**, *108*, 2158; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2024; b) D. E. Wilcox, *Chem. Rev.* **1996**, *96*, 2435.
[2] S. Matsuda, A. Ishikubo, A. Kuzuya, M. Yashiro, M. Komiyama, *Angew. Chem.* **1998**, *110*, 3477; *Angew. Chem. Int. Ed.* **1998**, *37*, 3285.
[3] a) B. N. Trawick, A. T. Daniher, J. K. Bashkin, *Chem. Rev.* **1998**, *98*, 939; b) A. De Mesmaeker, R. Häner, P. Martin, H. E. Moser, *Acc. Chem. Res.* **1995**, *28*, 366; c) M. Komiyama, *J. Biochem.* **1995**, *118*, 665.
[4] M. Komiyama, Y. Matsumoto, H. Takahashi, T. Shiiba, H. Tsuzuki, H. Yajima, M. Yashiro, J. Sumaoka, *J. Chem. Soc. Perkin Trans. 2* **1998**, 691, and references therein.
[5] a) M. Yashiro, A. Ishikubo, M. Komiyama, *J. Chem. Soc. Chem. Commun.* **1995**, 1793; b) W. H. Chapman, Jr., R. Breslow, *J. Am. Chem. Soc.* **1995**, *117*, 5462; c) F. Chu, J. Smith, V. M. Lynch, E. V. Anslyn, *Inorg. Chem.* **1995**, *34*, 5689.
[6] P. Molenveld, S. Kapsabelis, J. F. J. Engbersen, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1997**, *119*, 2948.
[7] M. Yashiro, A. Ishikubo, M. Komiyama, *Chem. Commun.* **1997**, 83.
[8] a) "Calixarenes": C. D. Gutsche in *Monographs in Supramolecular Chemistry, Vol. 1* (Ed.: J. F. Stoddart), Royal Society of Chemistry, Cambridge, **1989**; b) V. Böhmer, *Angew. Chem.* **1995**, *107*, 785; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713; c) A. F. Danil de Namor, R. M. Cleverley, M. L. Zapata-Ormachea, *Chem. Rev.* **1998**, *98*, 2495.
[9] P. Molenveld, W. M. G. Stikvoort, J. F. J. Engbersen, H. Kooijman, A. L. Spek, D. N. Reinhoudt, *J. Org. Chem.* **1999**, *64*, 3896.
[10] P. Molenveld, J. F. J. Engbersen, H. Kooijman, A. L. Spek, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1998**, *120*, 6726, and references therein.
[11] Because the calix[4]arenes are insoluble in pure water, EtOH was added as a cosolvent. The pH value discussed in the text refers to the pH value of the aqueous portion of the reaction mixture before dilution with EtOH.
[12] The ribonucleoside monophosphates 2′-NMP and 3′-NMP were identified in the reaction mixture. This shows that **1**-M_3 is also catalytically active in the hydrolysis of the cyclic monophosphates 2′,3′-cNMP.
[13] M. Komiyama, K. Yoshinari, *J. Org. Chem.* **1997**, *62*, 2155.

  1433-7851/99/3821-3191 $ 17.50+.50/0

[14] a) M. Wall, R. C. Hynes, J. Chin, *Angew. Chem.* **1993**, *105*, 1696; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1633; b) M. J. Young, J. Chin, *J. Am. Chem. Soc.* **1995**, *117*, 10577; c) S. Liu, Z. Luo, A. D. Hamilton, *Angew. Chem.* **1997**, *109*, 2794; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2678.

[15] Assuming that the metal ions and **1** are present only as complexed species within a trinuclear complex **1**-M_3 and that the binding of the second and third metal ion is independent of the contents of the ligands in **1**-M and **1**-M_2, then **1**-Zn_2Cu is theoretically present in 44% in a statistical mixture together with **1**-Zn_3 (30%), **1**-$ZnCu_2$ (22%), and **1**-Cu_3 (4%). Moreover, two complexes with the composition **1**-Zn_2Cu (44%) can exist, that is, **1**-ZnZnCu and **1**-ZnCuZn in theoretical amounts of 29 and 15%. When considering the catalytic activity by pure **1**-ZnZnCu or **1**-ZnCuZn over **1**-Zn_3, the enhanced activity is much higher than the factor of 1.3 for **1**-Zn_2Cu shown in Table 1 and Figure 1.

[16] A. E. Martell, R. M. Smith, *Critical Stability Constants*, *Vol. 2*, Plenum, New York, **1974**.

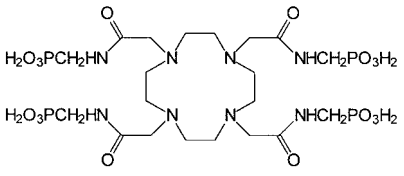
[17] a) E. Kimura, T. Koike, *Chem. Commun.* **1998**, 1495; b) K. Weis, M. Rombach, H. Vahrenkamp, *Inorg. Chem.* **1998**, *37*, 2470; c) H. Sigel, *Chem. Soc. Rev.* **1993**, 255; d) H. Sigel, *Inorg. Chem.* **1998**, *37*, 2066.

[18] A synthetic RNA: 5′-NH_2-GAAUGGGAUAGAGUGCAUCCA-GUG-3′.

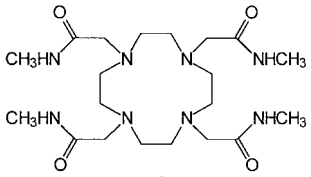
A Novel pH-Sensitive MRI Contrast Agent**

Shanrong Zhang, Kuangcong Wu, and A. Dean Sherry*

Most gadolinium complexes enhance relaxation of water protons by rapid exchange of inner-sphere water molecules with bulk solvent.[1] However, recent kinetic results have shown that the lifetime of an inner-sphere water molecule in Gd^{III} complexes can range from 0.84 ns for aqueous Gd^{III}, 208 ns for [Gd(dota)]$^-$, (dota = 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetate) to over 19000 ns in the tetraamide analogue, [Gd(**2**)].[1d, 2, 3] Recently reported examples of gadolinium-based contrast agents that are sensitive to enzyme activity[4a] and Ca^{2+}[4b] has stimulated synthesis of new cyclen-based ligands bearing different types of pendant arms. Given that tetraamide derivatives of cyclen have been reported to form both thermodynamically stable and kinetically inert complexes with Gd^{III} in aqueous solution,[3, 5, 6] we have been exploring tetraamide-based ligands with extended phosphonate or carboxylate noncoordinating side chains with the intent of generating new systems with specific ion-pairing capabilities. In characterizing one new derivative in this series, we observed that the water proton R_1 relaxivity of [Gd(**1**)] has



1



2

an unusual pH dependence, increasing between pH 4 and 6, reaching a maximum near pH 6, gradually decreasing to a minimum near pH 8.5, then remaining relatively insensitive to pH 10.5 before increasing once again at higher pH values (Figure 1). This feature is quite different from that of [Gd(**2**)] whose R_1 is essentially independent of pH between 2 and 8 before increasing at higher pH values.[3] Similarly, the R_1 of $[Gd(dotp)]^{5-}$ (dotp is the tetraphosphonate analogue of dota) is independent of pH over an extended pH range (3–13).[7]

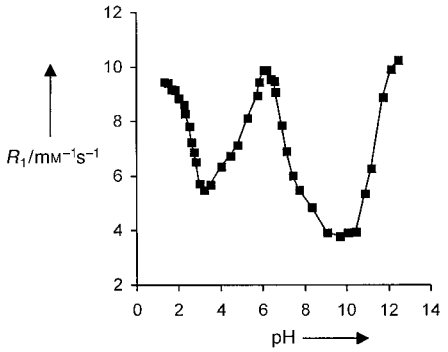


Figure 1. The pH dependence of the water proton relaxivity of [Gd(**1**)] at 20 MHz, 25°C. The solid line is included to guide the eye and does not represent a fit of these data to theory.

To provide further insight into the unusual relaxation behavior of [Gd(**1**)], we examined the solution structures of various [Ln(**1**)] complexes by NMR spectroscopy. ^{31}P NMR spectra of all [Ln(**1**)] complexes (except Gd^{III}) had single resonances with chemical shifts not dramatically different from that of the free ligand. In comparison with the highly shifted ^{31}P resonances in the analogous $[Ln(dotp)]^{5-}$ complexes,[8] this indicated that the four phosphonate groups of [Ln(**1**)] are situated relatively far from the paramagnetic center, likely not coordinated to the central ion. ^1H and ^{13}C NMR spectra of [Ln(**1**)] were all consistent with one main molecular species having high stereochemical rigidity. The hyperfine shifts of the macrocyclic protons of [Yb(**1**)] mirrored those of $[Yb(dotp)]^{5-}$,[8] $[Yb(dota)]^-$,[9] and

[*] Prof. Dr. A. D. Sherry, S. Zhang, K. Wu
Department of Chemistry
University of Texas at Dallas
P.O. Box 830688, Richardson
TX 75083-0688 (USA)
and
The Rogers Magnetic Resonance Center
Department of Radiology
University of Texas Southwestern Medical Center
5801 Forest Park Road
Dallas, TX 75235-9085 (USA)
Fax: (+1) 972-883-2925
E-mail: sherry@utdallas.edu

[**] This work was supported in part by grants from the Robert A. Welch Foundation (AT-584) and the Division of Research Resources, National Institutes of Health (RR-02584). We also thank Dr. Evelyn Babcock, Rogers Magnetic Resonance Center, UT-Southwestern Medical Center, Dallas, for help with the imaging experiments.

  1433-7851/99/3821-3192 $ 17.50+.50/0