Cobalt(III) Polyamine Complexes as Catalysts for the Hydrolysis of Phosphate Esters and of DNA. A Measurable 10 Million-Fold Rate Increase[1]

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Abstract: Complexes between cobalt(III) and eight different 1,4,7,10-tetraazacyclododecane (cyclen) as well as two tris(3-aminopropyl)amine (trpn) derivatives are reported with varying numbers and structures of peralkylammonium groups in side chains of the ligands. The presence of additional positive charges has small effects on hydrolysis rates of nitrophenyl- and bis(nitrophenyl)phosphate esters but leads to substantially enhanced cleavage of plasmid DNA. Increasing the number of the charged side groups and/or their distance to the metal ion center provides for better binding to the DNA groove, as shown also by affinity measurements with calf-thymus DNA. In line with this, saturation kinetics of plasmid DNA cleavage yield a corresponding increase of efficiency in Michaelis−Menten-type K_M values, with rather constant k_{cat} parameters. A **bi**nuclear cobalt complex with two cyclen centers separated by a $-(CH_2)_6\text{-}N^+(CH_3)_2\text{-}(CH_2)_6\text{-}N^+(CH_3)_2\text{-}(CH_2)_6-$ spacer shows, with only 5×10^{-5} M catalyst concentration, the largest known rate enhancement factor of $>10^7$ (corresponding to $>10^{11}$ at 1 M) against DNA; incubation with 0.05 mM at 37 °C for only 2 h leads to almost complete cleavage without appearance of products typical for redox cleavage. These results are in contrast to experiments with corresponding copper(II) complexes with added hydrogen peroxide, which has no effect with corresponding Co, Zn, Cd, or Ni complexes.

Cobalt(III) complexes have long been known to be among the most effective catalysts for the hydrolytic cleavage of amides, esters, and phosphates.[2] Chin et al.[3] have demonstrated the particular capabilities of cyclen or trpn complexes **1** and **2**, in which two kinetically unstable cis coordination sites of Co(III) are occupied by water molecules with p*K* values between 5 and 8. In the catalytic complexes, one of the water molecules is replaced by a substrate phosphate group.[4] This then is attacked by the neighboring cobalt-bound hydroxy anion, which is 10^7-10^8 less basic than free hydroxide anion but 10^5-10^6 times more nucleophilic than uncoordinated hydroxyde.[5] With diesters like bis(nitrophenyl)phosphates **BNPP** as substrates, the first formed hydrolytic product monophosphate is bound to the cobalt ion so tightly that turnover at neutral pH is limited severely.[3a,6] In practice, this goes unnoticed as long as one measures cleavage of one ester bond with an excess of the catalysts. In spite of this limitation, cobalt(III) complexes with enforced cis configuration at the labile coordination sites are one of the most promising elements for artificial nucleases, as they can accelerate hydrolysis even of unactivated phosphate esters[7] by factors of up to 10^{10}.

The efficiency of currently available chemical nucleases is impressive yet still far from that of natural enzymes. In the context of investigations with related lanthanoid catalysts[8,9] and studies of polyamine affinities toward DNA[10] we wanted to see how one can enhance the catalytic efficiency of cobalt(III) complexes by modification of the ligands. We chose peralkylated ammonium groups instead of free amines, as the latter can lead to formation of rather stable phosphoramides. Furthermore, we have shown previously[10] that peralkylkammonium ligands have approximately the same affinity for DNA as the corresponding protonated polyamines. The introduction of positive charges in side chains of the ligands (see Scheme 1) may open a way to activate the phosphates to ease the liberation of leaving phosphate anion and in particular to stabilize pretransition state complexes with nucleotides and with double-stranded (ds) DNA. With respect to the potential use of these

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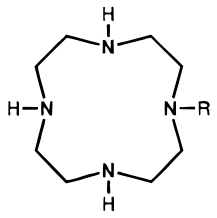
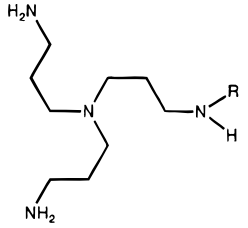
Scheme 1. Structure of Ligands, Cobalt Complexes, BNPP, and NPP





1 R = H *(Cyclen)*

3 R = (CH2)3-N+(CH3)3

4 R = (CH2)4-N+(CH3)3

5 R = (CH2)5-N+(CH3)3

6 R = (CH2)6-N+(CH3)3

7 R = (CH2)6-N+(CH3)2-(CH2)6-N+(CH3)3

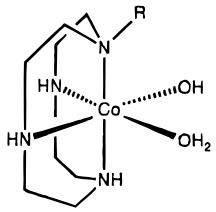
8 R = [(CH2)6-N+(CH3)2]3-CH3

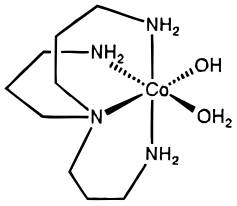
10 R = [(CH2)6-N+(CH3)2]2-(CH2)6-Cyclen

2 R = H *(Trpn)*

9 R = (CH2)6-N+(CH3)3

11 R = [(CH2)6-N+(CH3)2]2-(CH2)6-Trpn





12 R = H *([(Cyclen)Co]aq)*

14 R = (CH2)3-N+(CH3)3

15 R = (CH2)4-N+(CH3)3

16 R = (CH2)5-N+(CH3)3

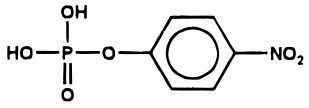
17 R = (CH2)6-N+(CH3)3

18 R = (CH2)6-N+(CH3)2-(CH2)6-N+(CH3)3

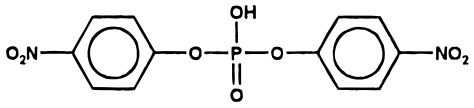
19 R = [(CH2)6-N+(CH3)2]3-CH3

20 R = [(CH2)6-N+(CH3)2]2-(CH2)6-[(Cyclen)Co]

13 *([Trpn)Co]aq)*



NPP



BNPP

catalysts in biotechnology it was furthermore important to establish that the cleavage is hydrolytic and is not a radical process by redox reactions.

Synthetic Pathways

Several options are available for the introduction of positive charges in the form of peralkylammonium centers in the side chains of cyclen. Handel et al.[11] have described monoalkylations of cyclen by blocking nitrogen atoms with $B(NMe_2)$ or CH_3SiCl_3. These techniques were not practical for our purpose, as the resulting very hydrophilic aminoalkyl derivatives cannot be dissolved for the workup in lipophilic solvents. They are furthermore not very stable as ammonium hydroxides under basic conditions. Similarly, the use of tritosylated cyclen as described by Kaden et al.[12] was considered to be less promising in view of the longer synthetic pathway and the difficulties

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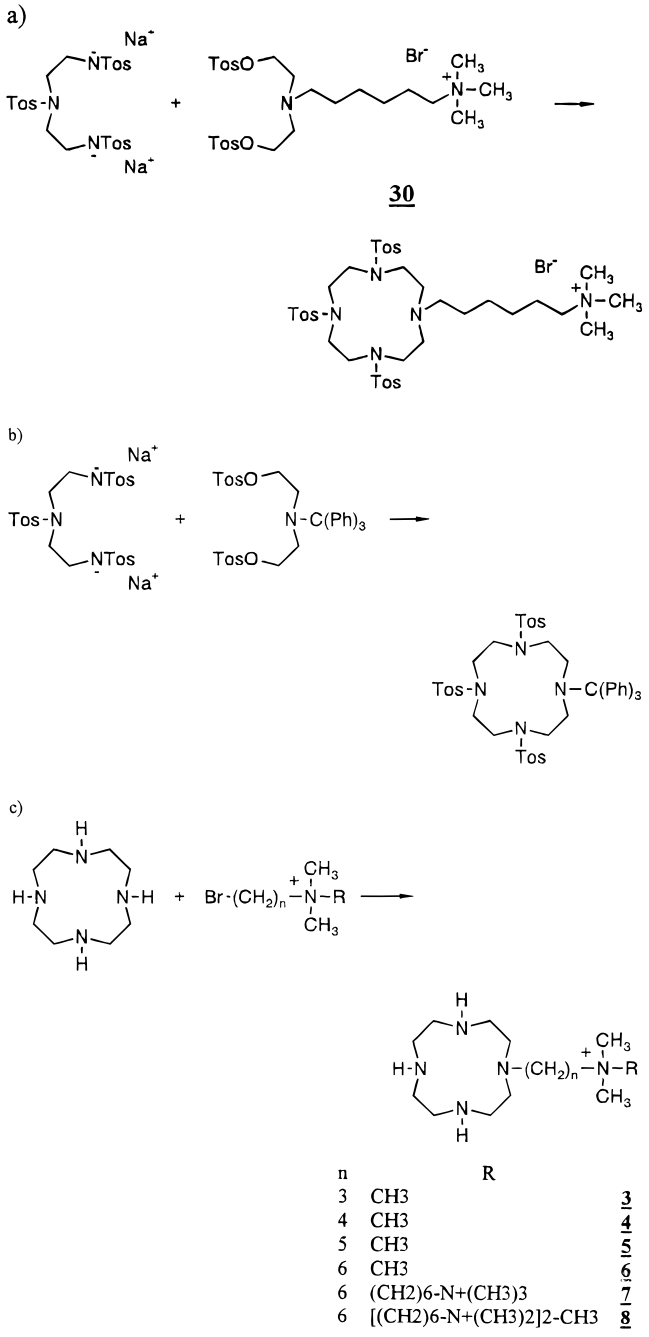
Scheme 2. Possible Synthetic Pathways



n	R	
3	CH3	**3**
4	CH3	**4**
5	CH3	**5**
6	CH3	**6**
6	(CH2)6-N+(CH3)3	**7**
6	[(CH2)6-N+(CH3)2]2-CH3	**8**

anticipated for the complete removal of the sulfate by concentrated sulfuric acid for deprotection.

Attempts to prepare monosubstituted cyclen ligands from prefunctionalized starting material (Scheme 2a) under known cyclization conditions[13] yielded, in spite of incomplete reaction, very inhomogenous products, likely as result of polymerizations. The same was found with cyclizations with a tritylated monomer (Scheme 2b). Alternative pathways based on selective introduction of ester or amide functions[14] have the problem that all of these functions are susceptible to hydrolytic degradation after complexation with cobalt ions. Consequently, reactions of the (peralkylammonium)alkyl bromides with an excess of unsubstituted cyclen (Scheme 2c) was found to be the best route to pure ligands without problematic separations. Although the starting material cyclen could be reused after recovery of up to 97%, its preparation was improved significantly from 35%[15] to 66% yield by modification of the hydrolytic cleavage of tosyl groups. Synthesis of trpn was with 94% yield also considerably improved by using borane−THF instead of Raney nickel[3a,16] for reduction of tris(cyanopropyl)amine. Selective introduction of one (peralkylammonium)hexyl chain into trpn was achieved similarly as with cyclen (see experimental part).

The peralkylammonium alkyl bromides were obtained in yields of up to 86% by reaction of the corresponding amines with ω-chloroalkanols and subsequent treatment with thionyl bromide, making use of the lower solubility of the resulting salts in ether in comparison to the alkylating bromides.

The complexes $[(Trpn)Co(OH)(OH_2)]^{2+}$ (**13**)[16] $[(Trpn)Co(CO_3)]ClO_4\times H_2O$,[17] and $[(Trpn)CoCl_2]ClO_4$[18] were synthesized according to literature procedures. Cobalt(III) complexes of cyclen and its substituted derivatives were prepared as described in the literature[19] for $[(cyclen)\ CoCl_2]Cl$ (**12**) and were characterized by their typical UV/vis spectra. Only the trpn-(peralkylammonium)alkyl derivative **9** could not be complexed with cobalt salts; similar failures have been reported in the literature.[6,20] In view of these problems and of the promising kinetic results with cyclen derivatives (see below), the study with trpn derivatives was not pursued furthermore.

Table 1. Rate Constants of **NPP** and **BNPP** Hydrolysis with Cobalt Complexes [0.01 M][a]

cobalt complex	k_{obs} [s^{-1}] × 10^3 (NPP)	$[k_{obs}/k_o]$ × 10^{-4} (NPP)	k_{obs} [s^{-1}] × 10^3 (BNPP)	$[k_{obs}/k_o]$ × 10^{-6} (BNPP)
	6.00×10^{-5}		3.00×10^{-7} [3a]	
13	30.8	51.3	46.0[3a]	15.3
12	19.3	32.2	25.0[3a]	83.3
14	3.4	5.6	1.24	4.1
15	2.4	3.9	4.14	1.4
16	2.0	3.4	1.30	4.3
17	2.0	3.3	1.57	5.2
18	2.0	3.3	1.44	4.8
19	1.9	3.1	1.16	3.9
20	2.3	3.8	1.33	4.4

[a] Except **20**: 5×10^{-3} M); 50 °C, pH 7.0.

Hydrolysis of Phenylphosphate Esters

The hydrolysis kinetics of **BNPP** and its monophenyl analog **NPP** (Scheme 1) in water at pH 7 and 50 °C were followed spectroscopically as described earlier,[9] observing pseudo-first-order behavior (linear correlation coefficients $r > 0.997$) usually over 6 half-life times. As with lanthanoid complexes, liberation of two phenolates was always observed, indicating faster hydrolysis of the first formed **NPP**. This was confirmed by separate measurements with **NPP** (Table 1), which in agreement with literature data[3a] shows enhancements of up to 5×10^7 in comparison to the only approximately known reaction rate

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Table 2. DNA Cleavage with Cobalt Complexes **14**−**17**[a]

	14		**25**		**16**		**17**	
concn [M]	RF I [%]	k_{obs} [s^{-1}] × 10^5	RF I [%]	k_{obs} [s^{-1}] × 10^5	RF I [%]	k_{obs} [s^{-1}] × 10^5	RF I [%]	k_{obs} [s^{-1}] × 10^5
1.0×10^{-5}	94.6	0.8	94.0	0.9	95.8	0.7	94.1	1.0
2.5×10^{-5}	89.7	1.6	91.6	1.3	89.2	1.7	86.3	2.1
5.0×10^{-5}	85.4	2.3	85.1	2.1	84.4	2.4	76.7	3.8
7.5×10^{-5}	80.6	3.1	76.0	3.9	80.0	3.2	65.9	5.9
1.0×10^{-4}	78.0	4.0	72.3	4.6	71.1	4.8	57.0	7.9
2.5×10^{-4}	68.0	5.4	65.4	6.0	61.4	6.8	51.2	9.4
5.0×10^{-4}	60.7	7.0	56.9	7.9	53.2	8.8	4.8	10.6
7.5×10^{-4}	47.2	10.5	48.9	10.0	48.5	10.1	43.1	11.8
1.0×10^{-3}	43.2	11.7	43.3	11.7	46.4	10.7	39.9	12.8
2.5×10^{-3}	34.4	14.6	35.0	14.6	38.9	13.1	31.3	16.1
5.0×10^{-3}	24.5	19.6	24.9	19.4	21.5	21.4	20.9	18.3

[a] 37 °C, pH 7.0 (Data corrected for reduced stainability of RF I and for RF II form already contained in the starting material).

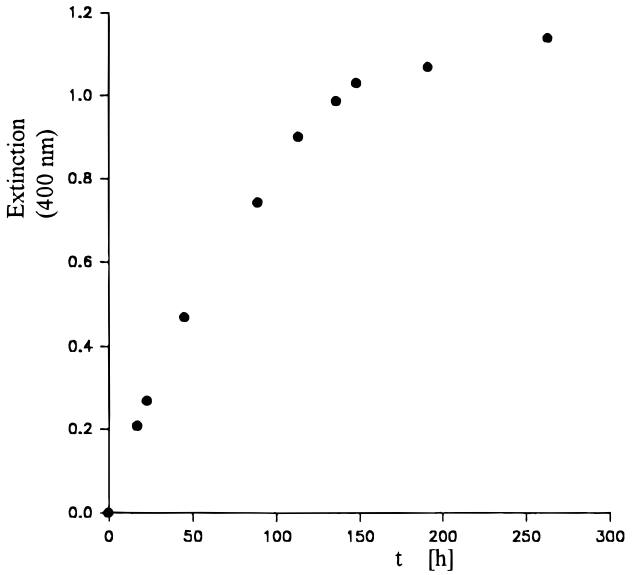

Figure 1. Kinetics of **BNPP** hydrolysis with catalyst **12** under turnover conditions (70 °C, pH 7.0, 0.01 M EPPS-buffer; [**12**] = 1×10^{-5} M, [BNPP] = 1.5×10^{-4} M).

constant of **NPP** alone. Similar rate enhancements were found with **BNPP** (Table 1). The presence of positive charges in the side chains of cyclen (**14**−**20**) leads to smaller catalytic efficiencies, which is attributed to competition of unproductive substrate binding to the peralkylammonium centers. These are, according to molecular modeling, separated from the cobalt ion for **18** by e.g., 9 Å. Nevertheless, the peralkylammonium-substituted cobalt complexes show activities close to, or better than, lanthanoid salts; they have the advantage of higher stability and solubility over a large pH range. The disadvantage of the cobalt complexes is formation of stable cyclic phosphate as primary hydrolysis product and therefore low turnover. This is obvious from an experiment with excess substrate **BNPP** over the catalyst **12**, showing incomplete release of the total phenolate even after 200 h at 70 °C (Figure 1). Nevertheless, this experiment demonstrates for the first time, to our knowledge, turnover of the cobalt complex.

Hydrolysis of DNA

Transition from supercoiled form RF I to the open circular form RF II of plasmid DNA was used as described earlier[9b,c] to measure cleavage of the double strand by densitometry after gel electrophoresis. Other than with lanthanoid complexes, EDTA was found to be insufficient to remove the metal before electrophoresis and had to be substituted by cyanide. Furthermore, the presence of multiple positive charges in the ligands made it necessary to develop an ion-exchange based microscale procedure (see Experimental Section) for removal of the ligands prior to electrophoresis, as neutralization of the negatively charged DNA by these strongly bound ligands prevents the DNA from moving in the electric field. As with catalysis by lanthanoids, careful optimization of electrophoretic and densitometric techniques with plasmid DNA leads to clean pseudo-first-order kinetics (linear correlation coefficients $r > 0.98$). This allows determination of rate constants (Tables 2−4) and also the extraction of Michaelis−Menten-type K_M and k_{cat} values, which is shown for one typical case with the corresponding saturation curve (Figure 2).

Table 3. DNA Cleavage with Cobalt Complexes **18**−**20**

	18		**19**		**20**	
concn[a] [M]	RF I [%]	k_{obs} [s^{-1}] × 10^5	RF I [%]	k_{obs} [s^{-1}] × 10^5	RF I [%]	k_{obs} [s^{-1}] × 10^5
1.0×10^{-5}	97.8	0.4	95.6	0.7	90.8	1.1
2.5×10^{-5}	91.0	1.4	87.0	2.0	78.7	3.4
5.0×10^{-5}	78.5	3.4	76.1	3.9	65.5	5.9
7.5×10^{-5}	64.2	6.2	68.1	5.4	40.1	12.8
1.0×10^{-4}	54.5	8.5	59.0	7.4	31.1	16.3
2.5×10^{-4}	47.4	10.4	47.2	10.5		
5.0×10^{-4}	40.2	12.7	34.9	14.7		
7.5×10^{-4}	31.0	16.3	27.0	18.3		
1.0×10^{-3}	24.9	19.4	19.0	23.1		
2.5×10^{-3}	14.3	27.1	9.8	32.3		
5.0×10^{-3}	5.3	40.9	2.1	53.7		

[a] Except **20** (half molarity). [b] See remarks to Table 2.

Table 4. K_M and k_{cat} Values for Cobalt(III) Complexes **12**−**17** from Saturation Kinetics

	compd				
	12	**14**	**15**	**16**	**17**
K_M [M] × 10^4	9.8	7.9	6.5	6.9	1.8
k_{cat} [s^{-1}] × 10^4	2.2	2.1	2.0	2.1	2.7

The rate constant of cobalt-catalyzed cleavage of pBR 322-DNA with the unsubstituted cyclen complex **12** is about three times higher than the one with europium(III) salts[9b] at the same concentration. Saturation kinetics (Figure 2) yield a K_M value somewhat lower than that with Eu^{3+} ($K_M = 2.8 \times 10^{-3}$ M),[9b] which is explainable by the smaller total charge of the cobalt complex in comparison to Eu^{3+} (at pH 7.0 +2 vs +3) and the steric shielding of the metal ion charges by the ligands. The lower binding affinity of **12** is more than compensated by the higher k_{cat} value in comparison to Eu^{3+} (2.2×10^{-4} s^{-1} vs 0.7×10^{-4} s^{-1}). The cobalt(III) cyclen complex **12** enhances the formation of the RF II form by a factor of up to 2×10^7 (with [**12**] = 5.0 mM, see Figure 2) in comparison to the estimated value without catalyst. The uncatalyzed hydrolysis of double stranded DNA has been estimated to proceed with $k < 10^{-11}$ s^{-1} at 37 °C on the basis of molecular weight measurements

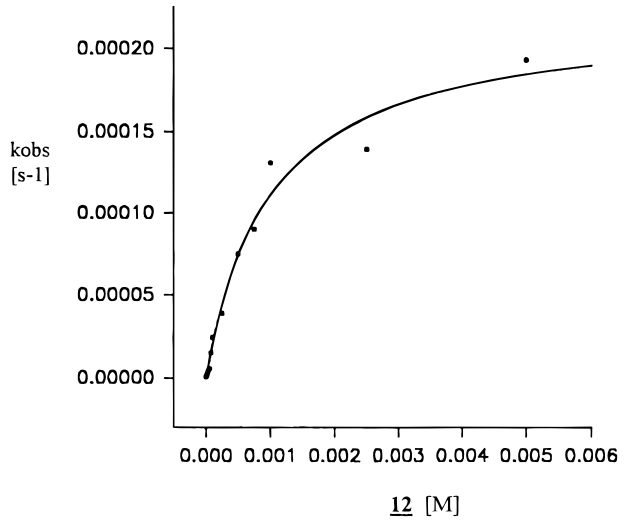

Figure 2. Saturation kinetics (experimental *k* values and fitted curve) of plasmid pBR 322-DNA cleavage as function of catalyst concentration [**12**].

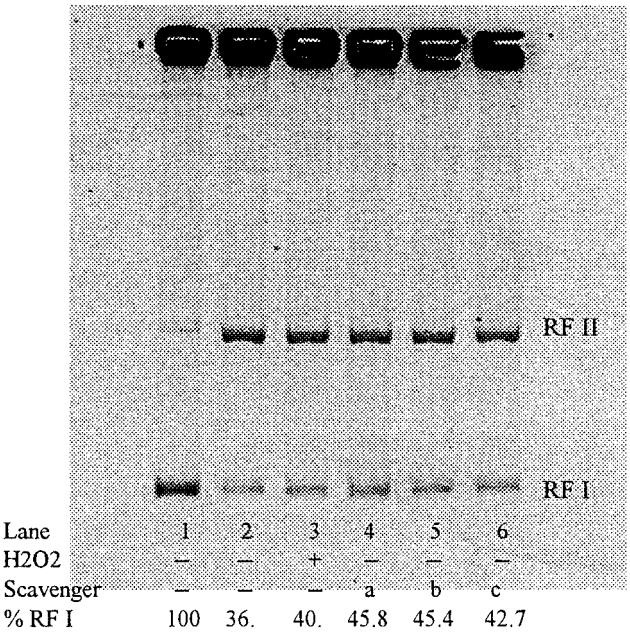

Figure 3. Electrophoretic separations of DNA cleavage with **12** under addition of H_2O_2 [1×10^{-4} M] or of scavengers (a = DMSO [1 M], b = sorbitol [0.1 M], c = EtOH [0.2 M].

with *E. coli* DNA.[21] A similar value for the limiting rate can be derived from $k = 1 \times 10^{-16}$ s^{-1} at 25 °C extrapolated by Chin et al.[3a] for the total hydrolysis of a dinucleotide. In view of the need to cleave only one out of 8800 nucleotide bonds in the plasmid DNA in order to see the appearance of the open circular RF II form, the limiting rate would be $k < 10^{-11}$ s^{-1} (after correction by a factor of about 10 for the temperature difference (25 °C vs 37 °C)).

Addition of hydrogen peroxide does not change the cleavage rates within the error, nor do radical scavengers like DMSO or alcohols (Figure 3, Table 8). This indicates the absence of radical cleavage, in line with the formation of only RF II and the absence of RF III or other, more cleaved DNA forms. Further evidence of the hydrolytic cleavage is discussed below. As with the phenylphosphates (Table 1), the Co(III) trpn **13** complex is even more active than the cyclen complex **12** but suffers from limited rate increases above 0.1 mM concentration (data not shown), which is—similar to literature[22] findings with nitriles—blamed on decomposition of the less stable trpn complex.

The positively charged side chains in the complexes indeed enhance the efficiency of the catalysts, as is obvious from the results with complexes **13**−**19** (Tables 2−4). Complexes **13**−**17** with single charges show small variation in k_{cat} but distinctly better K_M values with longer spacers (Table 4). This is expected from the higher flexibility which allows better contact to the DNA phosphate anions and is in line with the independently studied affinities of these ligands to ds DNA (see below). The presence of two or three side chain charges in complexes **18** and **19** leads to a further increase of catalytic factors. In these cases saturation could not be reached, but with 5 mM **19** one observes almost complete disappearance of RF I after 2 h at 37 °C without formation of products other than RF II.

The heretofore highest reported enhancement factor for an artificial hydrolytic nuclease—1.6×10^7 at only 0.05 mM catalyst concentration—is finally obtained with complex **20**, even though it bears no more charges than the complex with ligand **18** (Table 3, Scheme 1). Very recently, Komiyama et al.[23] reported a similar rate constant for simple dinucleotide hydrolysis (after correction for the concentrations); the reaction was, however, heterogeneous, and only the gel was reported to be active as catalyst. Obviously, both catalytic centers in the complex **20**, which are held together by a rather flexible spacer, act simultaneously on the DNA grooves. Again, no form is found other than the hydrolytic product RFII. Preliminary religation experiments with a Co(III) cyclen complex also show evidence for hydrolytic cleavage.[24]

DNA Cleavage with Some Other Transition Metal Cyclen and Trpn Complexes and with Added Hydrogen Peroxide—Further Evidence for a Hydrolytic Mechanism

Cleavage of DNA was also demonstrated earlier with zinc, nickel, cadmium, and copper complexes.[25] Since the introduction of positively charged centers in the side chains of simple complexes did partially lead to cleavage enhancements[25a] with plasmid DNA, we investigated whether the same strategy would also enhance efficiency, as it did with cobalt(III) as the center ion (see above). The activity of the Cd, Zn, Ni, and Cu complexes with ligands **1**−**11** toward the model ester **BNPP** was found to be below measuring limits. In contrast, these complexes were active against plasmid DNA, although to a much lower degree than cobalt or lanthanoid derivatives. As seen with the cobalt complexes, the presence of additional charges in the side chains does lead to accelerated cleavage (Table 5).

The largest effects are observed with the copper(II) complexes, which also provide a testing ground for the differentiation of radical and hydrolytic cleavage. Addition of hydrogen peroxide (Table 6) does not lead to enhanced formation of RFII with Zn, Ni, or Cd derivatives or without metal, in line with literature reports.[25c] Addition of ascorbate accelerates cleavage substantially (Table 7), whereas scavengers like alcohols or DMSO reduce the rates considerably only with Cu complexes

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Table 5. DNA Cleavage with Transition Metal Complexes[b]

ligand	metal Cd^{2+}	Ni^{2+}	Zn^{2+}	Cu^{2+}	lane
	100	100	100	100	1 and 13
1	96.6	96.5	98.4	95.8	2
3	97.1	93.9	96.9	86.0	3
4	97.8	94.5	95.4	86.6	4
5	98.0	94.2	95.8	81.8	5
6	97.9	93.1	95.3	80.7	6
7	96.0	93.8	93.3	80.3	7
8	95.1	93.0	93.3	80.0	8
10	96.4	96.4	96.8	87.1	9
2	98.0	96.2	96.6	94.4	10
9	97.8	95.4	95.9	86.3	11
11	*a*	*a*	*a*	*a*	12

[a] Cleavage rate not determined (DNA too less strained). [b] Concentration [5×10^{-3} M], except **10** and **11**: 2.5×10^{-3} M) (see remarks to Table 2).

Table 6. Results and Experimental Conditions of DNA Cleavage with Transition Metals Complexes in Presence and in Absence of Hydrogen Peroxide

	lane									
	1	2	3	4	5	6	7	8	9	10
ligand	−	−	**8**	**8**	**8**	**8**	**8**	**8**	−	−
metal ion	−	−	Zn^{2+}	Ni^{2+}	Cd^{2+}	Zn^{2+}	Ni^{2+}	Cd^{2+}	−	−
H_2O_2	−	+	−	−	−	+	+	+	+	−
RF I [%}	100	98.9	93.3	93.0	95.1	93.7	93.9	94.4	98.2	99.8

(Table 8). The formation of RF III (Figure 4) furthermore indicates redox cleavage with copper, particularly with added ascorbic acid. However, in the absence of hydrogen peroxide there is no indication of radical cleavage even with copper complexes. The contrasting results obtained in the presence of hydrogen peroxide with the copper and cobalt catalysts again support the hydrolytic nature of the latter. While our work was in progress, Sargeson et al.[26] reported new evidence that the cobalt(III) cyclen complex indeed leads to efficient hydrolytic DNA cleavage.

Affinities of the Polyamine Ligands Toward Calf-Thymus DNA

The strategy to enhance catalytic efficiency on the basis of higher pretransition state complex stability can be checked by measuring affinities of the new ligands toward DNA. As a convenient assay, we use the change in fluorescence intensity (I) of the dye ethidium bromide (**EB**) upon addition of the different ligands. It has been shown previously that the inverse of the concentration of the ligand necessary to lower I by 50%, $1/C_{50}$, is a linear function of the number of possible salt bridges between polyamines and DNA[27] and correlates with independently determined binding constants of natural polyamines.[10] Another, although less reliable, estimation of DNA affinity is based on measuring changes in the melting temperature (ΔT_M) of ds DNA.[10,28] Our own measurements (Table 9) indicate both $1/C_{50}$ and ΔT_M changes with ligands **1**−**11**; there is, however, no or only a very scattered correlation between the two parameters. Generally, low C_{50} values are observed with compounds bearing many charges, particularly if they are separated by longer flexible spacers (see Table 9). This is in line with the often simultaneously increased catalytic efficiency of such complexes (see above).

Conclusions

We have shown that introduction of DNA-affinity-enhancing ligands and of several metal centers in suitable metal complexes can lead to dramatic, enzyme-like rate enhancements of hydrolysis with the most resistant ester bonds of nature. Cobalt(III) complexes of cyclen or trpn show only moderately higher affinity for DNA than do the lanthanides. Modification of the cyclen ligand brings an efficiency increase of about 30. As is obvious from both the results with the phenylphosphate esters and from the saturation kinetics, the increased catalytic efficiency is based mainly on enhanced affinity or stabilization of pretransition state complexes and not on better k_{cat} values from electrostatic interactions with the positive charges in the ligands. Polyamine ligands are also a promising basis for the design of *selective* chemical nucleases, as they provide high affinity *without* substantial base selectivity. The latter can therefore be achieved by attaching at the complexes antisense- or triple helix oligonucleotides[29] or other ligands, which are known to provide base selectivity, but often rather low affinity.

Experimental Section

Physical Measurements. NMR spectra were measured on an AM 400 system (Bruker). Exchangeable signal assignments are denoted with the symbol "#". The cobalt content in the complexes was secured by atomic absorption spectroscopy (AAS) with a Perkin Elmer 2100 spectrometer. C_{50}-values were obtained with a F-2000 fluorescence system (Hitachi). Determination of rate constants and saturation kinetics were performed as described earlier.[9] Elemental analyses were carried out with a Leco CHNS-932 system. Several polyamines could be obtained only as oils and/or were very hygroscopic, in which cases no elemental analysis could be performed. All ligands, however, showed proton NMR spectra without contamination. Purities were partially also checked by NMR signal area comparison to an added internal standard of known concentration, such as dioxane.

Removal of Ligands Prior to Electrophoresis. Strongly acidic ion exchanger (Amberlyst 15, 50 g) was powdered and stirred with 400 mL of saturated NaCl solution for 24 h. After 15 min centrifugation at 4000 g, the liquid was decanted, replaced by fresh NaCl solution, and stirred again for 24 h. This procedure was repeated until the pH of the liquid was neutral. Afterwards, the ion exchanger was washed with boiled, doubly distilled water until the liquid was free of sodium. After final centrifugation, the humid ion exchanger was added in aliquots of about 500 mg to 1.5 mL Eppendorf vessels and stored at −18 °C (the exchanger keeps its activity this way for at least 1 year). Directly before use, 500 mg of the exchanger was mixed with 250 μL of water. After stopping the DNA-cleavage reaction by addition of EDTA or cyanide, 10 μL of the exchanger suspension was added, vortexed, and incubated at 37 °C for 5 min before centrifugation and electrophoresis.

Syntheses. 1,4,7,10-Tetraazacyclododecane (cyclen, 1) × 4HCl. A suspension of 29.9 g (37 mmol) of *N*,*N*′,*N*″,*N*‴-tetratosyl-1,4,7,10-tetraazacyclododecane[13] in 270 mL of concentrated sulfuric acid was heated 48 h to 120 °C.[15] The dark brown residue was cooled to room temperature and dropped slowly into an ice-cooled mixture of 500 mL of methanol/ether (1:1). The tetrahydrosulfate was filtered off, stirred with 3 × 250 mL of methanol/ether, filtered off, and dried in vacuo. The slightly brown crystals (22.1 g) were dissolved in water and chromatographed with a strongly basic Amberlyst A26-Ion exchange column (60 × 3 cm) with water as eluent. The basic part of the eluate was evaporated, and the slightly yellow oil was dissolved in 45 mL of methanol and precipitated by slow addition of 10 mL of concentrated

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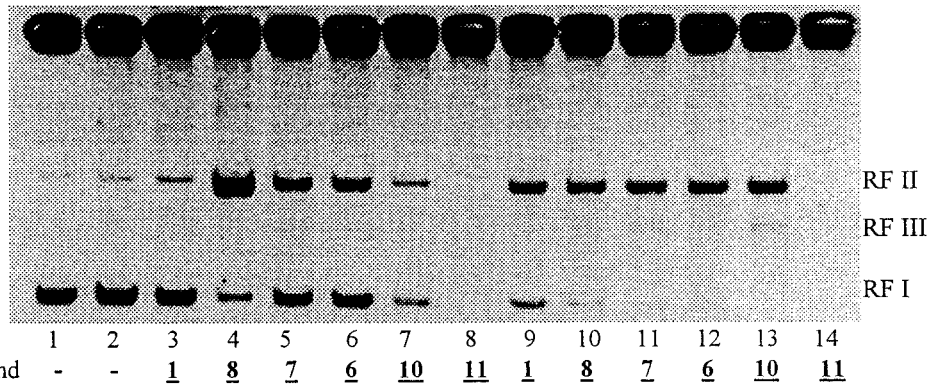

Figure 4. Electrophoretic separations of DNA cleavage with copper(II) complexes (lanes 3−8: [1×10^{-4} M]; lanes 9−14: [1×10^{-6} M] in presence of H_2O_2 [1×10^{-4} M] and ascorbic acid [1×10^{-4} M].

Table 7. DNA Cleavage with Copper Complexes in Presence of H_2O_2 and Ascorbic Acid[a]

lane	Cu^{2+} complex of compd	concn [M]	H_2O_2 [1×10^{-4} M]	ascorbate [1×10^{-4} M]	RF I [%]
1			−	−	100
2			+	−	99.5
3	1	1×10^{-4}	+	−	91.5
4	8	1×10^{-4}	+	−	33.0
5	7	1×10^{-4}	+	−	44.4
6	6	1×10^{-4}	+	−	59.8
7	10	5×10^{-4}	+	−	60.4
8	11	5×10^{-4}	+	−	
9	1	1×10^{-6}	+	+	37.2
10	8	1×10^{-6}	+	+	4.3
11	7	1×10^{-6}	+	+	4.9
12	6	1×10^{-6}	+	+	2.9
13	10	5×10^{-7}	+	+	5.3
14	11	5×10^{-7}	+	+	

Table 8. Influence of Radical Scavengers on the DNA Cleavage with Copper Complex of **8**

lane	concn of Cu^{2+}−**8** complex	H_2O_2 [1×10^{-4} M]	scavenger	RF I [%]
1		−		100
2	1×10^{-4} M	+	sorbit (0.1 M)	20.6
3	1×10^{-4} M	+	EtOH (0.2 M)	34.3
4	1×10^{-4} M	+		5.8
5	1×10^{-4} M	+	DMSO (1 M)	36.4
6	5×10^{-3} M	−		80.0
7	5×10^{-3} M	−	Sorbit (0.1 M)	78.3
8	5×10^{-3} M	−	EtOH (0.2 M)	79.5
9	5×10^{-3} M	−	DMSO (1 M)	79.3

Table 9. Affinity Data with Calf Thymus DNA: C_{50} Values and Melting points[a]

compd	C_{50} value [M] $\times 10^5$	ΔT_M [K]	compd	C_{50} value [M] $\times 10^5$	ΔT_M [K]
1	140.3	1.4	**11**	0.06	13.5
2	5.9	2.2	**13**	8.0	0.8
3	1.4	4.1	**12**	14.0	0.9
4	0.97	4.9	**14**	1.9	0.7
5	0.95	5.1	**15**	1.1	0.7
6	0.63	5.4	**16**	1.3	0.8
7	0.13	10.7	**17**	1.5	1.0
8	0.02	12.9	**18**	0.14	4.2
10	0.11	12.1	**19**	0.05	8.9
9	1.3	3.7	**20**	0.10	6.4

[a] [Substrate] = 5×10^{-6} M, [DNA] = 7.6×10^{-5} M (phosphate).

HCl. The colorless crystals were washed three times with methanol and ether and dried in vacuo. Yield: 7.97 g (24.4 mmol, 66%).

For generation of the free base, 1.5 g (4.72 mmol) of the tetrahydrochloride were dissolved in 15 mL of water and chromatographed with water as eluent over a strongly basic Amberlyst A26 ion exchange column (300 × 15 mm). The basic part of the eluate was collected and evaporated. Yield: 0.79 g (4.6 mmol, 97%).

Tris(3-aminopropyl)amine (trpn, 2) × 4HCl. A 300 mL aliquot of a 1 M borane−THF complex solution was added in a nitrogen stream to 9.0 g (51.1 mmol) tris(2-cyanoethyl)amine.[30] The mixture was refluxed 16.5 h and cooled to room tempature, and 200 mL of methanolic HCl was added slowly. The trimethyl ester of the boric acid and the solvent were removed by distillation, and the colorless crystals were washed with 4 × 50 mL absolute ether and dried in vacuo. Yield: 16.2 g (48 mmol, 94%).

For the generation of the free base, 1.4 g (4.17 mmol) of the tetrahydrochloride was chromatographed with an anion exchange column as described for cyclen. Yield: 762 mg (4.05 mmol, 97%) colorless oil.

Cyclen- and Trpn-Derivatives with Peralkylated Side Chains. General Procedure. A solution of the alkylating agent in absolute acetonitrile was added dropwise during 2 h to a refluxing solution of a double excess of the tetramine and an appropriate amount of potassium carbonate in absolute acetonitrile. The reaction mixture was refluxed 24 h, cooled to room temperature, and filtered, and the solvent was evaporated. The residue was stirred with 3 × 50 mL of absolute toluene and 3 × 50 mL of absolute ether for 24 h each. The liquids were decanted and collected, and the crystals of the monosubstituted products were dried in vacuo. For recovery of the unsubstituted tetramine, the collected liquids were combined, glass-filtered, and evaporated. The resulting oil was dissolved in methanol and precipitated as hydrochloride in 90% to 97% yield.

1-(3-(Trimethylammonio)propyl)-1,4,7,10-tetraazacyclododecanyl bromide (3) was prepared from 400 mg (2.32 mmol) of cyclen (**1**), 320 mg (2.32 mmol) of potassium carbonate in 25 mL of acetonitrile, and 303 mg (1.16 mmol) of 3-(*N*,*N*,*N*-trimethylammonio)-propyl bromide[31] in 25 mL of absolute acetonitrile. Colorless, hygroscopic crystals, mp 122 °C (decomposition). Yield: 353 mg (1.0 mmol, 86%). $C_{14}H_{34}BrN_5$, MW 352.36; purity by NMR ≥ 96%. ^{1}H NMR (D_2O, TMSP, δ): 2.72−2.51 (m, 18 H, cycle and C*H*$_2$-CH$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 1.93 (m, 2 H, C*H*$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 3.34 (m, 2 H, C*H*$_2$-N$^+$(CH$_3$)$_3$), 3.10 (s, 9 H, N$^+$(C*H*$_3$)$_3$). ^{13}C NMR (D_2O, TMSP, δ): 45.43, 44.68, 43.67 (cycle), 50.94 (cycle, *C*H$_2$-N-R), 50.72 (*C*H$_2$-CH$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 20.64 (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 65.44 (*C*H$_2$-N$^+$(CH$_3$)$_3$), 53.18 (N$^+$(*C*H$_3$)$_3$).

1-(4-(Trimethylammonio)butyl)-1,4,7,10-tetraazacyclododecanyl bromide (4) was prepared from 500 mg (2.9 mmol) of cyclen (**1**), 400.8 mg (2.9 mmol) of potassium carbonate in 25 mL of acetonitrile, and 399 mg (1.45 mmol) of 4-(*N*,*N*,*N*-trimethylammonio)butyl bromide[31] in 25 mL of absolute acetonitrile. Colorless, hygroscopic crystals, mp 118 °C (decomposition). Yield: 412 mg (1.13 mmol, 80%). $C_{15}H_{36}BrN_5$, MW 366.39; purity by NMR ≥ 97%. ^{1}H NMR (D_2O, TMSP, δ): 2.75−2.56 (m, 16 H, cycle), 2.51 (m, 2 H, C*H*$_2$-(CH$_2$)$_3$-N$^+$(CH$_3$)$_3$), 1.53 (m, 2 H, C*H*$_2$-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 1.83 (m, 2

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H, CH_2-CH$_2$-N$^+$(CH$_3$)$_3$), 3.35 (m, 2 H, CH_2-N$^+$(CH$_3$)$_3$), 3.12 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D$_2$O, TMSP, δ): 43.67, 44.79, 45.40 (cycle), 50.86 (cycle, *C*H$_2$-N-R), 53.02 (*C*H$_2$-(CH$_2$)$_3$-N$^+$(CH$_3$)$_3$ and (N$^+$(*C*H$_3$)$_3$)), 23.54 (*C*H$_2$-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 20.67 (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 66.77 (*C*H$_2$-N$^+$(CH$_3$)$_3$).

1-(5-(Trimethylammonio)pentyl)-1,4,7,10-tetraazacyclododecanyl bromide (5) was prepared from 600 mg (3.48 mmol) of cyclen (**1**), 481 mg (3.48 mmol) of potassium carbonate in 25 mL of acetonitrile, and 503 mg (1.74 mmol) of 5-(*N*,*N*,*N*-trimethylammonio)-pentyl bromide[31] in 50 mL of absolute acetonitrile. Colorless, hygroscopic crystals, mp 140 °C (decomposition). Yield: 557 mg (1.47 mmol, 84%). $C_{16}H_{38}BrN_5$, MW 380.42; purity by NMR ≥ 97%. ^{1}H NMR (D$_2$O, TMSP, δ): 2.74−2.54 (m, 16 H, cycle), 2.45 (t, 2 H, CH_2-(CH$_2$)$_4$-N$^+$(CH$_3$)$_3$), 1.51 (m, 2 H, CH_2-(CH$_2$)$_3$-N$^+$(CH$_3$)$_3$), 1.38 (m, 2 H, CH_2-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 1.79 (m, 2 H, CH_2-CH$_2$-N$^+$(CH$_3$)$_3$), 3.30 (m, 2 H, CH_2-N$^+$(CH$_3$)$_3$), 3.09 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D$_2$O, TMSP, δ): 43.73, 44.61, 45.40 (cycle), 50.89 (cycle, *C*H$_2$-N-R), 53.58 (*C*H$_2$-(CH$_2$)$_4$-N$^+$(CH$_3$)$_3$), 26.08 (*C*H$_2$-(CH$_2$)$_3$-N$^+$(CH$_3$)$_3$), 23.75[#] (*C*H$_2$-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 22.41[#] (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 66.88 (*C*H$_2$-N$^+$(CH$_3$)$_3$), 53.03 (N$^+$(*C*H$_3$)$_3$).

1-(6-(Trimethylammonio)hexyl)-1,4,7,10-tetraazacyclododecanyl bromide (6) was prepared from 669 mg (3.88 mmol) of cyclen (**1**), 536.4 mg (3.88 mmol) of potassium carbonate in 25 mL of acetonitrile and 506.8 mg (1.62 mmol) of 6-(*N*,*N*,*N*-trimethylammonio)-hexyl bromide[31] in 50 mL of absolute acetonitrile. Colorless, hygroscopic crystals, mp 118 °C (decomposition). Yield: 562 mg (1.43 mmol, 74%). $C_{17}H_{40}BrN_5$, MW 394.44; purity by NMR ≥ 95%. ^{1}H NMR (D$_2$O, TMSP, δ): 2.74−2.57 (m, 16 H, cycle), 2.46 (t, 2 H, CH_2-(CH$_2$)$_5$-N$^+$(CH$_3$)$_3$), 1.34[#] (m, 4 H, CH_2-CH$_2$-CH$_2$-CH_2-CH$_2$-N$^+$-(CH$_3$)$_3$), 1.47 (m, 2 H, CH_2-(CH$_2$)$_3$-N$^+$(CH$_3$)$_3$), 1.74 (m, 2 H, CH_2-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 3.26 (m, 2 H, CH_2-N$^+$(CH$_3$)$_3$), 3.06 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D$_2$O, TMSP, δ): 43.46, 44.26, 45.32 (cycle), 50.61 (cycle, *C*H$_2$-N-R), 53.56 (*C*H$_2$-(CH$_2$)$_5$-N$^+$(CH$_3$)$_3$), 26.30, 25.89 and 25.52 (*C*H$_2$-*C*H$_2$-*C*H$_2$-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 22.46 (*C*H$_2$-CH$_2$-N$^+$-(CH$_3$)$_3$), 66.68 (*C*H$_2$-N$^+$(CH$_3$)$_3$), 52.99 (N$^+$(*C*H$_3$)$_3$).

1-[7-(Dimethylammonio)-14-(trimethylammonium)tetradecyl]-1,4,7,10-tetraazacyclododecanyl Dibromide (7). As above, 570.3 mg (3.30 mmol) of cyclen (**1**) and 525.5 mg (3.30 mmol) of potassium carbonate in 40 mL of acetonitrile were reacted with 843.5 mg (1.65 mmol) of **21** in 100 mL of absolute acetonitrile. Colorless, hygroscopic crystals, mp 141 °C (decomposition). Yield: 830 mg (1.38 mmol, 83.5%). $C_{25}H_{58}Br_2N_6$, MW 602.58; purity by NMR ≥ 97%. ^{1}H NMR (D$_2$O, TMSP, δ): 2.59 (m, 16 H, cycle), 1.43 (m, 12 H, CH_2-CH_2-CH_2-CH_2-(CH$_2$)$_2$-N$^+$(CH$_3$)$_2$-(CH$_2$)$_2$-CH_2-CH_2-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 1.77 (m, 6 H, (CH$_2$)$_4$-CH_2-CH$_2$-N$^+$(CH$_3$)$_2$-CH$_2$-CH_2-(CH$_2$)$_2$-CH_2-CH$_2$-N$^+$-(CH$_3$)$_3$), 3.29 (m, 6 H, (CH$_2$)$_5$-CH_2-N$^+$(CH$_3$)$_2$-CH_2-(CH$_2$)$_4$- CH_2-N$^+$-(CH$_3$)$_3$, 3.04 (s, 6 H, N$^+$(CH_3)$_2$), 3.10 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D$_2$O, TMSP, δ): 43.71, 44.68, 45.36 (cycle), 50.97 (cycle, *C*H$_2$-N-R), 53.60 (N-CH$_2$), 26.27, 25.55, 25.38, 25.25 (N-CH$_2$-*C*H$_2$-*C*H$_2$-CH$_2$ and N$^+$-(CH$_2$)$_2$-*C*H$_2$-*C*H$_2$-(CH$_2$)$_2$-N$^+$), 22.32, 22.06, 21.94 (*C*H$_2$-CH$_2$-N$^+$), 64.35, 64.02 (*C*H$_2$-N$^+$(CH$_2$)$_2$), 66.61 (*C*H$_2$-N$^+$(CH$_3$)$_3$), 50.60 (N$^+$-(*C*H$_3$)$_2$), 53.00 (N$^+$(*C*H$_3$)$_3$.

1-[7,14-Bis(dimethylammonio)-21-(trimethylammonio)hemicosan]-1,4,7,10-tetraazacyclododecanyl Tribromide (8). As above, 690 mg (4.0 mmol) of cyclen (**1**) and 636 mg (4.0 mmol) of potassium carbonate in 40 mL of acetonitrile were reacted with 1.44 g (2.0 mmol) **24** in 150 mL of absolute acetonitrile. Colorless crystals, mp 161 °C (decomposition). Yield: 1.13 g (1.4 mmol, 70%). $C_{33}H_{76}Br_3N_7$, MW 810.73. Elemental Anal. Calcd: C, 48.89; H, 9.45; N, 12.08. Found: C, 48.34; H, 9.18; N, 11.18. Purity by NMR ≥ 94%. ^{1}H NMR (D$_2$O, TMSP, δ): 2.79 (m, 16 H, cycle), 1.52 (m, 16 H, CH_2-CH_2-CH_2-CH_2-(CH$_2$)$_2$-N$^+$(CH$_3$)$_2$-(CH$_2$)$_2$-CH_2-CH_2-(CH$_2$)$_2$-N$^+$(CH$_3$)$_2$-(CH$_2$)$_2$-CH_2-CH_2-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 1.66 (m, 10 H, (CH$_2$)$_4$-CH_2-CH$_2$-N$^+$(CH$_3$)$_2$-CH$_2$-CH_2-(CH$_2$)$_2$-CH_2-CH$_2$-N$^+$(CH$_3$)$_2$-CH$_2$-CH_2-(CH$_2$)$_2$-CH_2-CH$_2$-N$^+$(CH$_3$)$_3$), 3.43 (m, 10 H, CH_2-N$^+$, 3.13 (s, 12 H, N$^+$(CH_3)$_2$, 3.13 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D$_2$O, TMSP, δ): 43.74, 44.68, 45.40 (cycle), 50.96 (cycle, *C*H$_2$-N-R), 53.60 (N-*C*H$_2$), 25.58, 26.16, 26.33, and 25.20 (N-CH$_2$-*C*H$_2$ and N$^+$-(CH$_2$)$_2$-*C*H$_2$-*C*H$_2$-(CH$_2$)$_2$-N$^+$), 22.39 and 22.02 (N$^+$-CH$_2$-*C*H$_2$), 64.21 (N$^+$(CH$_3$)$_2$-*C*H$_2$), 66.63 (*C*H$_2$-N$^+$(CH$_3$)$_3$), 50.62 (N$^+$(*C*H$_3$)$_2$), 53.05 (N$^+$(*C*H$_3$)$_3$).

Trpn Derivative 9. As described above, 739 mg (3.92 mmol) of trpn (**2**) and 542 mg (3.92 mmol) of potassium carbonate in 40 mL of acetonitrile were reacted with 594 mg (1.96 mmol) of 6-(*N*,*N*,*N*-trimethylammonio)hexyl bromide[31] in 20 mL of absolute acetonitrile. Colorless oil. Yield: 795 mg (1.93 mmol, 98%). $C_{18}H_{44}N_5Br$, MW 410.48; purity by NMR ≥ 94%. ^{1}H NMR (D$_2$O, TMSP, δ): 2.58−2.44 (m, 16 H, (H$_2$N-CH_2-CH_2-CH_2)$_2$-N-CH_2-CH_2-CH$_2$-NH), 1.34 (m, 4 H, NH-CH_2), 1.58 (m, 4 H, NH-CH$_2$-CH_2-CH$_2$-CH_2-(CH$_2$)$_2$-N$^+$-(CH$_3$)$_3$), 1.75 (m, 2 H, CH_2-(CH$_2$)$_3$-N$^+$(CH$_3$)$_3$), 1.45 (m, 2 H, CH_2-CH$_2$-N$^+$(CH$_3$)$_3$), 3.27 (t, 2 H, CH_2-N$^+$(CH$_3$)$_3$), 3.06 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D$_2$O, TMSP, δ): 39.24 (H$_2$N-*C*H$_2$), 28.45 (H$_2$N-CH$_2$-*C*H$_2$ and *C*H$_2$-(CH$_2$)$_4$-N$^+$(CH$_3$)$_3$), 50.91 (H$_2$N-CH$_2$-CH$_2$-*C*H$_2$), 51.24 ((H$_2$N-CH$_2$-CH$_2$-CH$_2$)$_2$N-*C*H$_2$), 26.10, 25.48 and 25.24 ((H$_2$N-CH$_2$-CH$_2$-CH$_2$)$_2$N-CH$_2$-*C*H$_2$ and *C*H$_2$-*C*H$_2$-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 47.04 (*C*H$_2$-NH-(CH$_2$)$_6$-N$^+$(CH$_3$)$_3$), 48.43 (*C*H$_2$-(CH$_2$)$_5$-N$^+$(CH$_3$)$_3$), 22.32 (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 66.87 (*C*H$_2$-N$^+$(CH$_3$)$_3$), 53.00 (N$^+$(*C*H$_3$)$_3$).

Bifunctional Tetramine Derivatives. *N*,*N*′-Bis[6-(1-(1,4,7,10-tetraazacyclododecanyl))hexyl]-*N*,*N*′-bis(dimethylamino)hexanyldiammonium Bromide (10). The quantity 1.28 g (7.43 mmol) of cyclen (**1**) and 1.18 g (7.43 mmol) of potassium carbonate in 100 mL of absolute acetonitrile were reacted with 1.23 g (1.86 mmol) of **28** and worked up as described in the general procedure for monosubstituted tetramines. Colorless crystals, mp 135 °C. Yield: 1.33 g (1.58 mmol, 95%). $C_{38}H_{90}Br_2N_{10}$, MW 836.93. Elemental Anal. Calcd: C, 54.53; H, 9.63; N, 16.54. Found: C, 54.48; H, 9.32; N, 16.00. ^{1}H NMR (D$_2$O, TMSP, δ): 2.68 (m, 32 H, cycle), 1.49 (m, 20 H, N-CH_2-CH_2-CH_2-CH_2-CH$_2$-CH$_2$-N$^+$(CH$_3$)$_2$-CH$_2$-CH$_2$-CH_2), 1.79 (m, 8 H, CH_2-CH$_2$-N$^+$(CH$_3$)$_2$), 3.32 (m, 8 H, CH_2-N$^+$(CH$_3$)$_2$), 3.09 (s, 12 H, N$^+$(CH_3)$_2$). ^{13}C NMR (D$_2$O, TMSP, δ): 44.21, 43.95, 42.39 (cycle), 50.77 (cycle, *C*H$_2$-N-R), 53.67 (N-*C*H$_2$), 23.33 (N-CH$_2$-*C*H$_2$), 25.57 (N-CH$_2$-CH$_2$-*C*H$_2$), 25.23 (*C*H$_2$-CH$_2$-CH$_2$-N(CH$_3$)$_2$), 21.90 (*C*H$_2$-CH$_2$-N(CH$_3$)$_2$), 64.29 (*C*H$_2$-N(CH$_3$)$_2$), 50.62 (N(*C*H$_3$)$_2$).

Bis-trpn Derivative 11. The quantity 900 mg (4.78 mmol) of trpn (**2**) and 860 mg (4.78 mmol) of potassium carbonate in 50 mL of absolute acetonitrile were reacted with 0.79 g (1.20 mmol) of **28** and worked up as described in the general procedure for monosubstituted tetramines. Colorless oil, yield: 885 mg (1.03 mmol, 85%). $C_{40}H_{82}Br_2N_{10}$, MW 862.96; purity by NMR ≥ 90%. ^{1}H NMR (D$_2$O, TMSP, δ): 2.52 (m, 28 H, (H$_2$N-CH_2-CH$_2$-CH_2)$_2$N-CH_2-CH$_2$-CH_2-NH-CH_2), 1.47 (m, 8 H, H$_2$N-CH$_2$-CH_2), 1.35 (m, 16 H, N-CH$_2$-CH_2-CH$_2$-NH-(CH$_2$)$_2$-CH_2 and CH_2-CH$_2$-N$^+$(CH$_3$)$_2$), 3.27 (m, 8 H, CH_2-N$^+$(CH$_3$)$_2$), 3.03 (s, 12 H, N$^+$(CH_3)$_2$). ^{13}C NMR (D$_2$O, TMSP, δ): 39.27 (H$_2$N-*C*H$_2$), 28.50 (H$_2$N-CH$_2$-*C*H$_2$), 50.39 (H$_2$N-CH$_2$-CH$_2$-*C*H$_2$), 50.64 (N-*C*H$_2$), 26.18 (N-CH$_2$-*C*H$_2$ and NH-CH$_2$-*C*H$_2$-*C*H$_2$ and *C*H$_2$-CH$_2$-CH$_2$-N$^+$(CH$_3$)$_2$), 47.09 and 48.48 (NH-*C*H$_2$), 21.97 (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_2$), 64.11 (*C*H$_2$-N$^+$(CH$_3$)$_2$), 51.28 (N$^+$(*C*H$_3$)$_2$).

General Procedure for the Preparation of the Cobalt(III) Complexes. The dichloro complexes [(N$_4$)CoCl$_2$]Cl of cyclen and its substituted derivatives were prepared as described[32] for [(cyclen)CoCl$_2$]-Cl (**12**). The free amines in 10 mL of methanol/water (1:1) were heated 30 min to 70 °C with an equimolar amount of tris(sodium carbonato)-cobalt(III) trihydrate.[33] After filtration, 2 mL of HCl were added within 2 min. The solvent was evaporated, and the residue was treated with 5 × 2 mL concentrated HCl and evaporated again. The obtained crystals were stirred 5 min in 20 mL of absolute methanol. The liquid was discharged, and the solid was recrystallized from methanol. The conversion of the dichloro complexes to the diaquo complexes was achieved as described for [(Trpn)Co(OH)(OH$_2$)]$^{2+}$ (**13**).[34] [(Trpn)Co-(CO$_3$)]ClO$_4$ × H$_2$O[35]) and [(Trpn)CoCl$_2$]ClO$_4$[36]) were synthesized according to the literature.

[(1-(3-(Chlorotrimethylammonio)propyl)-1,4,7,10-tetraazacyclododecane)dichlorocobalt(III)] Chloride (14). As described above, 176 mg (0.5 mmol) of **3** were reacted with 181 mg (0.5 mmol) of tris(sodium carbonato)cobalt(III) trihydrate.[33] Violet-blue, hygroscopic crystals, mp 192 °C. Yield: 174 mg (0.37 mmol, 73%). $C_{14}H_{34}Cl_4CoN_5$, MW 473.20. Cobalt content of a 1×10^{-4} M solution of the complex (AAS): calcd. 5.1 ppm; found 6.3 ppm. UV-data (HCl 37%, λ (nm)): 560 (ϵ = 227), 454 (ϵ = 24), 388 (ϵ = 187), 362 (ϵ = 146).

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[(1-(4-(Chlorotrimethylammonio)butyl)-1,4,7,10-tetraazacyclododecane)dichlorocobalt(III)] Chloride (15). As above, 183 mg (0.5 mmol) of **4** was reacted with 181 mg (0.5 mmol) of tris(sodium carbonato)cobalt(III) trihydrate.[33] Violet-blue, hygroscopic crystals, mp 183 °C. Yield: 174 mg (0.36 mmol, 72%). $C_{15}H_{36}Cl_4CoN_5$, MW 487.23. Cobalt content of a 8×10^{-5} M solution of the complex (AAS): calcd. 4.6 ppm; found 4.0 ppm. UV-data (HCl 37%, λ (nm)): 553 ($\epsilon = 141$), 456 ($\epsilon = 37$), 385 ($\epsilon = 140$), 363 ($\epsilon = 119$).

[(1-(5-(Chlorotrimethylammonio)pentyl)-1,4,7,10-tetraazacyclododecane)dichlorocobalt(III)] Chloride (16). As above, 190 mg (0.5 mmol) of **5** was reacted with 181 mg (0.5 mmol) of tris(sodium carbonato)cobalt(III) trihydrate.[33] Violet-blue, hygroscopic crystals, mp 185 °C. Yield: 142 mg (0.28 mmol, 57%). $C_{16}H_{38}Cl_4CoN_5$, MW 501.26. Cobalt amount of an 8×10^{-5} M solution of the complex (AAS): calcd. 4.6 ppm; found 4.7 ppm. UV-data (HCl 37%, λ (nm)): 557 ($\epsilon = 209$), 456 ($\epsilon = 31$), 386 ($\epsilon = 185$), 361 ($\epsilon = 141$).

[(1-(6-(Chlorotrimethylammonio)hexyl)-1,4,7,10-tetraazacyclododecane)dichlorocobalt(III)] Chloride (17). As above, 151 mg (0.39 mmol) of **6** was reacted with 141 mg (0.39 mmol) of tris(sodium carbonato)cobalt(III) trihydrate.[33] Violet-blue, hygroscopic crystals, mp 183 °C. Yield: 152 mg (0.30 mmol, 76%). $C_{17}H_{40}Cl_4CoN_5$, MW 515.28. Cobalt amount of an 5×10^{-5} M solution of the complex (AAS): calcd. 2.9 ppm; found 2.3 ppm. UV-data (HCl 37%, λ (nm)): 557 ($\epsilon = 191$), 457 ($\epsilon = 41$), 386 ($\epsilon = 181$), 363 ($\epsilon = 147$).

[(1-[7-(Chlorodimethylammonio)-14-(chlorotrimethylammonio)-tetradecyl]-1,4,7,10-tetraazacyclododecane)dichlorocobalt(III)] Chloride (18). As above, 373 mg (0.62 mmol) of **7** was reacted with 224 mg (0.62 mmol) of tris(sodium carbonato)cobalt(III) trihydrate.[33] Violet-blue, hygroscopic crystals, mp 186 °C. Yield: 359 mg (0.53 mmol, 85%). $C_{25}H_{58}Cl_5CoN_6$, MW 678.97. Cobalt amount of an 8×10^{-5} M solution of the complex (AAS): calcd. 4.6 ppm; found 4.6 ppm. UV-data (HCl 37%, λ (nm)): 560 ($\epsilon = 158$), 454 ($\epsilon = 18$), 389 ($\epsilon = 127$), 360 ($\epsilon = 75$).

[(1-[7,14-Bis(chlorodimethylammonio)-21-(chlorotrimethylammoniochloride)hemicosane]-1,4,7,10-tetraazacyclododecane)dichlorocobalt(III)] Chloride (19). As above, 511.6 mg (0.63 mmol) of **8** was reacted with 226 mg (0.63 mmol) of trisodium triscarbonatocobalt-(III) trihydrate.[33] Violet-blue, very hygroscopic crystals. Yield: 414 mg (0.50 mmol, 79%). $C_{35}H_{76}Cl_6CoN_7$, MW 866.09. Cobalt amount of an 1×10^{-4} M solution of the complex (AAS): calcd. 5.8 ppm; found 5.8 ppm. UV-data (HCl 37%, λ (nm)): 557 ($\epsilon = 173$), 454 ($\epsilon = 19$), 389 ($\epsilon = 138$), 360 ($\epsilon = 89$).

[*N*,*N*′-Bis[6-(1-(1,4,7,10-tetraazacyclododecane))hexyl]-*N*,*N*′-bis-(dimethylamino)hexylchlorodiammonio)bis(dichloro)cobalt(III)] Dichloride (20). As above, 432.3 mg (0.51 mmol) of **10** was reacted with 371.4 mg (0.51 mmol) of tris(sodium carbonato)cobalt(III) trihydrate.[33] Violet-blue, hygroscopic crystals, mp 191 °C. Yield: 480 mg (0.44 mmol, 87%). $C_{38}H_{86}Cl_8Co_2N_{10}$, MW 1084.66. Cobalt amount of an 1×10^{-4} M solution of the complex (AAS): calcd. 11.6 ppm; found 10.3 ppm. UV-data (HCl 37%, λ (nm)): 560 ($\epsilon = 360$), 454 ($\epsilon = 52$), 389 ($\epsilon = 300$), 360 ($\epsilon = 198$).

Synthesis of the Alkylating Agents. *N*-(6-Hydroxyhexyl)-*N*,*N*,*N*′,*N*′-tetramethylhexylammonium Chloride (21). 1,6-Bis(dimethylamino)-hexane (14.06 g, 81.6 mmol) and 2.45 mL (18.3 mmol) of chlorohexanol in 100 mL of absolute acetonitrile were refluxed 28 h. After cooling to room tempature, absolute ether was added until turbidity occurred. The reaction mixture was cooled to −20 °C. The liquid was decanted and discarded. The slightly yellow solid was stirred with 3×40 mL ether and dried in vacuo. Colorless, hygroscopic crystals, mp 67 °C. Yield: 4.21 g (13.6 mmol, 75%). $C_{16}H_{37}ClN_2O$, MW 308.94. Elemental Anal. Calcd: C, 62.21; H, 12.07; N, 9.07. Found: C, 60.17; H, 11.62; N, 8.48. ^{1}H NMR (D_2O, TMSP, δ): 3.55 (t, 2 H, HO-CH_2), 1.70−1.31 (m, 16 H, HO-CH$_2$-CH_2-CH_2-CH_2-CH_2 and CH_2-CH_2-CH_2-CH_2-CH$_2$-N(CH$_3$)$_2$), 3.22 (m, 4 H, CH_2-N$^+$(CH$_3$)$_2$), 2.25 (t, 2 H, CH_2-N(CH$_3$)$_2$), 2.98 (s, 6 H, N$^+$(CH_3)$_2$), 2.11 (s, 6 H, N(CH_3)$_2$). ^{13}C NMR (D_2O, TMSP, δ): 61.72 (HO-*C*H$_2$), 31.12 (HO-CH$_2$-*C*H$_2$), 24.86, 25.41, 25.96 and 26.19 (HO-CH$_2$-CH$_2$-*C*H$_2$-*C*H$_2$ and (H$_3$C)$_2$N$^+$-(CH$_2$)$_2$-*C*H$_2$-*C*H$_2$-(CH$_2$)$_2$-N(CH$_3$)$_2$), 21.91 (*C*H$_2$-CH$_2$-N$^+$-(CH$_3$)$_2$), 64.12 ((*C*H$_2$-N$^+$(CH$_3$)$_2$), 50.69 (N$^+$(*C*H$_3$)$_2$), 40.05 ((*C*H$_2$-CH$_2$-N(CH$_3$)$_2$), 58.41 ((*C*H$_2$-N(CH$_3$)$_2$), 43.89 (N(*C*H$_3$)$_2$).

***N*,*N*-Dimethyl-*N*-(6-hydroxyhexyl)-*N*′,*N*′,*N*′-(trimethylamino)-1,6-hexanediyldiammonium Bromide Chloride (22).** A solution of 1.0 g (10.9 mmol) of methyl bromide in 10 mL of absolute acetonitrile was added dropwise within 10 min at 0 °C to 1.65 g (5.34 mmol) of **21** in 25 mL of absolute acetonitrile. The ice bath was removed, and the reaction was stirred at room temperature for 16 h. The liquid was discarded, and the crystals were stirred with 2×30 mL of absolute ether, filtered, washed with 4×10 mL of ether, and dried in vacuo. Slightly yellow, hygroscopic solid, mp 213 °C. Yield: 1.95 g (4.84 mmol, 91%). $C_{17}H_{40}BrClN_2O$, MW 403.87. Elemental Anal. Calcd: C, 50.58; H, 9.98; N, 6.94. Found: C, 48.55; H, 9.23; N, 6.55. ^{1}H NMR (D_2O, TMSP, δ): 3.59 (t, 2 H, HO-CH_2), 1.77−1.35 (m, 16 H, HO-CH$_2$-CH_2-CH_2-CH_2-CH_2 and CH_2-CH_2-CH_2-CH_2-CH$_2$-N(CH$_3$)$_2$), 3.30 (m, 6 H, CH_2-N$^+$), 3.04 (s, 6 H, N$^+$(CH_3)$_2$), 3.11 (s, 9 H, N$^+$-(CH_3)$_3$). ^{13}C NMR (D_2O, TMSP, δ): 61.67 (HO-*C*H$_2$), 31.07 (HO-CH$_2$-*C*H$_2$), 24.66, 25.38 and 25.23 (HO-CH$_2$-CH$_2$-*C*H$_2$-*C*H$_2$ and (H$_3$C)$_2$N$^+$-(CH$_2$)$_2$-*C*H$_2$-*C*H$_2$-(CH$_2$)$_2$-N(CH$_3$)$_2$), 21.94 (*C*H$_2$-CH$_2$-N$^+$-(CH$_3$)$_2$), 63.99 and 64.15 ((*C*H$_2$-N$^+$(CH$_3$)$_2$), 50.67 (N$^+$(*C*H$_3$)$_2$), 22.32 ((*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 66.58 ((*C*H$_2$-N$^+$(CH$_3$)$_3$), 53.01 (N$^+$(*C*H$_3$)$_3$).

***N*-(6-Bromohexyl)-*N*-(6-aminohexyl)-*N*,*N*,*N*′,*N*′,*N*′-pentamethyl-1,6-hexanediyldiammonium Dibromide (23).** A solution of 4 mL (45 mmol) of thionyl bromide in 4 mL of absolute toluene was added dropwise over 30 min to a suspension of 4.5 g (11.2 mmol) of **22** in 20 mL of absolute toluene. After having been stirred 1 h at room tempature the solution was heated to 80 °C for 1 h and then stirred again at room tempature for 26 h. The liquid was discarded, and the brown residue was recrystallized from isopropyl alcohol. The crystals were filtered, washed with 3×30 mL absolute ether and dried in vacuo over P_2O_5. Slightly yellow solid, mp 209 °C (decomposition). Yield: 3.43 g (7.95 mmol, 71%). $C_{17}H_{39}Br_3N_2$, MW 511.22. Elemental Anal. Calcd: C, 39.94; H, 7.69; N, 5.48. Found: C, 40.06; H, 7.17; N, 5.41. ^{1}H NMR ((D_2O, TMSP, δ): 3.57 (t, 2 H, Br-CH_2), 1.95−1.42 (m, 16 H, Br-CH$_2$-CH_2-CH_2-CH_2-CH_2 and CH_2-CH_2-CH_2-CH_2-CH$_2$-N(CH$_3$)$_2$), 3.36 (m, 6 H, CH_2-N$^+$), 3.10 (s, 6 H, N$^+$(CH_3)$_2$), 3.16 (s, 9 H, N$^+$-(CH_3)$_3$). ^{13}C NMR (D_2O, TMSP, δ): 35.17 (Br-*C*H$_2$), 31.80 (Br-CH$_2$-*C*H$_2$), 24.74, 26.87 and 25.23 (Br-CH$_2$-CH$_2$-*C*H$_2$-*C*H$_2$ and (H$_3$C)$_2$N$^+$-(CH$_2$)$_2$-*C*H$_2$-*C*H$_2$-(CH$_2$)$_2$-N$^+$(CH$_3$)$_3$), 21.93 and 21.84 (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_2$), 64.09 and 63.93 ((*C*H$_2$-N$^+$(CH$_3$)$_2$), 50.67 (N$^+$(*C*H$_3$)$_2$), 22.32 ((*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 66.61 ((*C*H$_2$-N$^+$(CH$_3$)$_3$), 53.04 (N$^+$(*C*H$_3$)$_3$).

***N*-6-Bis(dimethylamino)hexyl-*N*,*N*,*N*′,*N*′,*N*′-pentamethyl-1,6-hexanediyldiammonium Dibromide (24).** 6-(*N*,*N*,*N*-Trimethylammonio)-hexyl bromide[31] (4.82 g, 15.9 mmol) in 60 mL of absolute acetonitrile was added dropwise within 1 h to a solution of 10.95 g (63.3 mmol) of 1,6-bis(dimethylamino)hexane in 70 mL of absolute acetonitrile. The solution was refluxed for 24 h, cooled to room temperature, and filtered. The solvent was evaporated and dried in vacuo. The residue was stirred with 3×100 mL ether, and the crystals were filtered, washed with 3 $\times$ 50 mL ether and dried in vacuo. White crystals, mp 171 °C. Yield: 5.59 g (11.8 mmol, 73%). $C_{19}H_{45}Br_2N_3$, MW 475.39. Elemental Anal. Calcd: C, 48.00; H, 9.54; N, 8.84. Found: C, 48.14; H, 9.46; N, 8.78. ^{1}H NMR (D_2O, TMSP, δ): 2.20 (s, 6 H, N(CH_3)$_2$), 2.34 (t, 2 H, (CH$_3$)$_2$)N-CH_2), 1.86−1.74 and 1.55−1.34 (m, 16 H, (CH_2)$_4$-CH$_2$-N$^+$(CH$_3$)$_2$-CH$_2$-(CH_2)$_4$), 3.29 (m, 6 H, N$^+$-CH_2), 3.06 (s, 6 H, N$^+$(CH_3)$_2$), 3.13 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D_2O, TMSP, δ): 43.94 (N(*C*H$_3$)$_2$), 58.43 (CH$_3$)$_2$)N-*C*H$_2$), 26.25, 26.07, 25.54, 25.27 (*C*H$_2$-CH$_2$-*C*H$_2$-CH$_2$-CH$_2$-N$^+$(CH$_3$)$_2$-CH$_2$-CH$_2$-*C*H$_2$-CH$_2$), 21.95 (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_2$), 64.27 and 63.99 (*C*H$_2$-N$^+$(CH$_3$)$_2$), 50.71 (N$^+$(*C*H$_3$)$_2$), 22.34 (*C*H$_2$-CH$_2$-N$^+$(CH$_3$)$_3$), 66.64 (*C*H$_2$-N$^+$(CH$_3$)$_3$), 53.07 (N$^+$(*C*H$_3$)$_3$).

***N*,*N*,*N*′,*N*′-Tetramethyl-*N*-(6-hydroxyhexyl)-*N*′-(6-(bromotrimethylammonio)hexyl)-1,6-hexanediyldiammonium Bromide Chloride (25).** A suspension of 5.3 g (11.36 mmol) of **24** in 15.5 g (113 mmol) of chlorohexanol was heated 2 h to 90 °C, giving a clear solution after 10 min. After cooling to room tempature, 80 mL of ether was added slowly. The liquid was decanted and discarded. The residue was stirred with 2×100 mL of ether, filtered, washed with 3×50 mL ether, and dried in vacuo over P_2O_5. Colorless crystals, mp 202 °C. Yield: 6.44 g (10.5 mmol, 93%). $C_{25}H_{58}Br_2ClN_3O$, MW 612.01. Elemental Anal. Calcd: C, 49.06; H, 9.56; N, 6.87. Found: C, 49.24; H, 9.54; N, 6.65. ^{1}H NMR (D_2O, TMSP, δ): 3.59 (t, 2 H, HO-CH_2), 1.84−1.35 (m, 24 H, (CH$_3$)$_2$N$^+$-CH$_2$-(CH_2)$_4$), 3.29 (m, 10 H, N$^+$-CH_2), 3.05 (s, 12 H, N$^+$(CH_3)$_2$), 3.10 (s, 9 H, N$^+$(CH_3)$_3$). ^{13}C NMR (D_2O, TMSP, δ): 61.69 (HO-*C*H$_2$), 31.10 (HO-CH$_2$-*C*H$_2$), 24.67 and 25.32 ((CH$_3$)$_2$N$^+$-CH$_2$-CH$_2$-*C*H$_2$-*C*H$_2$), 21.97 ((CH$_3$)$_2$N$^+$-CH$_2$-*C*H$_2$), 63.95 and 64.16 ((CH$_3$)$_2$N$^+$-

CH_2), 50.61 ($N^+(CH_3)_2$), 22.36 (CH_2-CH_2-$N^+(CH_3)_3$), 66.61 (CH_2-$N^+(CH_3)_3$), 53.01 ($N^+(CH_3)_3$).

***N,N,N′,N′*-Tetramethyl-*N*-(6-bromohexyl)-*N′*-[6-(bromotrimethylammonio)hexyl]-1,6-hexanediyldiammonium Bromide (26).** A solution of 420 μL (4.5 mmol) of thionyl bromide in 5 mL of absolute toluene was added dropwise over 1 h to a suspension of 1.0 g (1.63 mmol) of **25** in 20 mL of absolute toluene and worked up as described for compound **23**. Colorless solid, mp 161 °C (decomposition). Yield: 851 mg (1.19 mmol, 73%). $C_{25}H_{57}Br_4N_3$, MW 719.36. Elemental Anal. Calcd: C, 41.74; H, 7.99; N, 5.84. Found: C, 41.38; H, 7.45; N, 5.84. ^{1}H NMR (D_2O, TMSP, δ): 3.52 (t, 2 H, Br-CH_2), 1.89−1.39 (m, 24 H, $(CH_3)_2N^+$-CH_2-(CH_2)$_4$), 3.29 (m, 10 H, N^+-CH_2), 3.05 (s, 12 H, $N^+(CH_3)_2$), 3.11 (s, 9 H, $N^+(CH_3)_3$). ^{13}C NMR (D_2O, TMSP, δ): 35.06 (Br-*C*H_2), 31.77 (Br-CH_2-*C*H_2), 26.85, 25.30 and 24.71 ($(CH_3)_2N^+$-CH_2-CH_2-*C*H_2-*C*H_2), 21.97 ($(CH_3)_2N^+$-CH_2-*C*H_2), 63.65 and 64.09 ($(CH_3)_2N^+$-*C*H_2), 50.60 ($N^+(CH_3)_2$), 22.35 (*C*H_2-CH_2-$N^+(CH_3)_3$), 66.58 (CH_2-$N^+(CH_3)_3$), 52.99 ($N^+(CH_3)_3$).

***N,N′*-Bis(6-hydroxyhexyl)-*N,N,N′,N′*-tetramethyl-1,6-hexanediyldiammonium Dichloride (27).** 1,6-Bis(dimethylamino)hexane (0.9 mL, 4.2 mmol) and 5.0 mL (42.1 mmol) chlorohexanol were heated to 90 °C for 24 h. After cooling to room tempature, 50 mL of absolute ether was added slowly and stirred for 2 h. The crystals were filtered, washed with 3 × 10 mL ether, and dried in vacuo. Colorless, hygroscopic solid, mp 139 °C. Yield: 1.60 g (3.59 mmol, 86%), $C_{22}H_{50}Cl_2N_2O_2$, MW 445.56. Elemental Anal. Calcd: C, 59.31; H, 11.31; N, 6.29. Found: C, 57.55; H, 10.27; N, 6.12. ^{1}H NMR (D_2O, TMSP, δ): 3.52 (t, 4 H, HO-CH_2), 1.49 (m, 4 H, HO-CH_2-CH_2), 1.32 (m, 12 H, HO-CH_2-CH_2-CH_2 and CH_2-CH_2-CH_2-N^+), 1.71 (m, 8 H, CH_2-CH_2-N^+), 3.21 (m, 8 H, CH_2-N^+), 2.97 (s, 12 H, $N^+(CH_3)_2$). ^{13}C NMR (D_2O, TMSP, δ): 61.70 (HO-*C*H_2), 31.18 (HO-CH_2-*C*H_2), 24.86, 25.30 and 25.41 (HO-CH_2-CH_2-*C*H_2 and *C*H_2-CH_2-CH_2-N^+), 21.94 (*C*H_2-CH_2-N^+), 63.97 and 64.22 (*C*H_2-N^+), 50.66 ($N^+(CH_3)_2$).

***N,N′*-Bis(6-bromohexyl)-*N,N,N′,N′*-tetramethyl-1,6-hexanediyldiammonium Dibromide (28).** A solution of 5.0 mL (60.2 mmol) of thionyl bromide in 25 mL of absolute toluene was added dropwise over 30 min to a suspension of 9.0 g (20.2 mmol) of **27** in 55 mL of absolute toluene and worked up as described for compound **23**. Colorless solid, mp 114 °C. Yield: 9.02 g (13.66 mmol, 68%). $C_{22}H_{48}Br_4N_2$, MW 660.25. Elemental Anal. Calcd: C, 40.02; H, 7.33; N, 4.24. Found: C, 40.36; H, 7.26; N, 4.31. ^{1}H NMR (D_2O, TMSP, δ): 3.50 (t, 4 H, Br-CH_2), 1.68 (m, 4 H, Br-CH_2-CH_2), 1.43 (m, 12 H, Br-CH_2-CH_2-CH_2 and CH_2-CH_2-CH_2-N^+), 1.76 (m, 8 H, CH_2-CH_2-N^+), 3.28 (m, 8 H, CH_2-N^+), 3.03 (s, 12 H, $N^+(CH_3)_2$). ^{13}C NMR (D_2O, TMSP, δ): 35.23 (Br-*C*H_2), 31.81 (Br-CH_2-*C*H_2), 24.75, 25.29 and 26.68 (Br-CH_2-CH_2-*C*H_2 and *C*H_2-CH_2-CH_2-N^+), 21.94 and 21.85 (*C*H_2-CH_2-N^+), 63.92 and 64.06 (*C*H_2-N^+), 50.77 ($N^+(CH_3)_2$).

Other Compounds. (Bromotrimethylammonio)hexyldiethanolamine (29). A solution of 1.44 g (4.75 mmol) of 6-(*N*,*N*,*N*-trimethylammonio)hexanyl bromide[31] in 30 mL of acetonitrile was added dropwise to a solution of 0.50 g (4.75 mmol) of diethanolamine and 650 mg (4.75 mmol) of potassium carbonate in 30 mL of boiling acetonitrile. The solution was refluxed 24 h, and the workup was performed as described in the general procedure for the preparation of amines with peralkylated side chains. Slightly yellow oil. Yield: 1.29 g (3.95 mmol, 83%). $C_{13}H_{31}BrNO_2$, MW 313.30; purity by NMR ≥ 95%. ^{1}H NMR (DMSO-d_6, TMS, δ): 3.23 (s, 9 H, $N^+(CH_3)_3$), 3.44 (t, 2 H, $(CH_3)_3N^+$-CH_2), 1.91 (m, 2 H, $(CH_3)_3N^+$-CH_2-CH_2), 1.50 (m, 4 H, $(CH_3)_3N^+$-$(CH_2)_2$-CH_2-CH_2), 1.63 (m, 2 H, $(CH_3)_3N^+$-$(CH_2)_4$-CH_2), 2.68 (m, 2 H, $(CH_3)_3N^+$-$(CH_2)_5$-CH_2), 2.82 (t, 4 H, CH_2-CH_2-OH), 3.81 (t, 4 H, CH_2-OH), 4.69 (s, 2 H, O*H*). ^{13}C NMR (DMSO-d_6, TMS, δ): 52.03 ($N^+(CH_3)_3$), 65.85 ($(CH_3)_3N^+$-*C*H_2), 21.33 ($(CH_3)_3N^+$-CH_2-*C*H_2), 24.32, 24.46 and 25.30 ($(CH_3)_3N^+$-$(CH_2)_2$-*C*H_2-*C*H_2-*C*H_2), 53.29 ($(CH_3)_3N^+$-$(CH_2)_5$-*C*H_2), 58.00 (*C*H_2-CH_2-OH), 54.35 (*C*H_2-OH).

***N*-(6-(Bromotrimethylammonio)hexyl)-*O,O′*-ditosyldiethanolamine (30).** Compound **29** (1.29 g, 3.95 mmol) in 4 mL of absolute pyridine was cooled to 0 °C, and 1.51 g (7.9 mmol) of tosyl chloride was added slowly such that the temperature did not exceed +10 °C. After stirring for 2 h at 0 °C, 12 mL of HCl (10.5 %) was added, and crystallization was allowed to proceed at −20 °C overnight. The solid was recrystallized from isopropyl alcohol, filtered, washed with isopropyl alcohol, and dried in vacuo. Colorless solid, yield 1.58 g (2.50 mmol, 63 %). $C_{27}H_{43}BrN_2O_6S_2$, MW 635.67. Elemental Anal. Calcd: C, 51.02; H, 6.82; N, 4.41. Found: C, 50.68; H, 6.43; N, 4.20. ^{1}H NMR (DMSO-d_6, TMS, δ): 3.26 (s, 9 H, $N^+(CH_3)_3$), 3.53 (m, 4 H, $(CH_3)_3N^+$-CH_2 and $(CH_3)_3N^+$-$(CH_2)_5$-CH_2), 1.89 (m, 4 H, $(CH_3)_3N^+$-CH_2-CH_2-CH_2-CH_2-CH_2), 1.50 (m, 4 H, $(CH_3)_3N^+$-$(CH_2)_2$-CH_2-CH_2), 3.31 (t, 4 H, CH_2-CH_2-OTos), 3.38 (t, 4 H, CH_2-OTos), 2.49 (s, 6 H, Tos-CH_3); 7.71 (d, 4 H) and 7.33 (d, 4 H, arom.). ^{13}C NMR (DMSO-d_6, TMS, δ): 52.09 ($N^+(CH_3)_3$), 65.30 ($(CH_3)_3N^+$-*C*H_2), 21.72 ($(CH_3)_3N^+$-CH_2-*C*H_2), 24.99, 22.49 and 25.28 ($(CH_3)_3N^+$-$(CH_2)_2$-*C*H_2-CH_2-*C*H_2), 55.37, 54.95 and 53.30 ($(CH_3)_3N^+$-$(CH_2)_5$-*C*H_2-N-*C*H_2-*C*H_2), 137.91, 125.41, 128.05 and 145.26 (arom), 20.66 (Tos-*C*H_3).

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Supporting Information Available: Tables 1 and 2: cleavage rates of DNA at different catalyst concentrations of complexes **12** and **13**; Table 3: effect of radical scavengers on the DNA-cleavage with the copper complex of compound **8**. Electrophoretic separations (gels) of plasmid DNA: Figure 1, effect of added ion exchanger, Figure 2−6: cleavage with different concentrations of complexes **12**−**20** at different concentrations; Figure 7: with transition metal complexes of ligands **1**−**11**; Figures 8 and 9: effect of scavengers on cleavage with transition metal complexes; Figure 10: structure of complex **18** with distance between metal ion and positive side chain charges from computer aided molecular modeling; Figure 11: saturation kinetics with trpn complex **13** (8 pages). See any current masthead page for ordering and Internet access instructions.

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