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DNA hydrolysis by cerium(IV)–saccharide complexes

Ayako Kajimura, Jun Sumaoka, Makoto Komiyama *

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Tokyo 113-8656, Japan

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Abstract

Homogeneous solutions are prepared by mixing $Ce(NH_4)_2(NO_3)_6$ with either lyxose, ribose, xylose, gentiobiose, isomaltose, or palatinose at pH 7, under the conditions that [monomeric residue of saccharide]$_0$/[Ce(IV)]$_0 > 1$. Melibiose and dextran give homogeneous solutions of Ce(IV) when the ratio is greater than 2. Formation of Ce(IV) hydroxide gel is efficiently suppressed by these saccharides. Sugar alcohols (arabinitol, galactitol, mannitol, ribitol, glucitol, and xylitol), glucamine (1-amino-1-deoxy-D-glucitol), lyxosylamine, and *N*-methylglucamine (1-deoxy-1-methylamino-D-glucitol) are also effective for the solubilization of Ce(IV). In contrast, other monosaccharides (fructose, galactose, and glucose), disaccharides (cellobiose, lactose, maltose, sucrose, and trehalose), cyclodextrins [α-cyclodextrin (cyclomaltohexaose), β-cyclodextrin (cyclomaotoheptaose), and γ-cyclodextrin (cyclomaltooctaose)], and amyloses (as well as galacturonic acid and glucosamine) are poor for the solubilization. The activities of the homogeneous solutions for DNA hydrolysis are in the following order: glucamine > > gentiobiose, isomaltose, ribose, lyxosylamine > lyxose, xylose, arabinitol, galactitol, mannitol, ribitol, glucitol, xylitol, *N*-methylglucamine. The pseudo-first-order rate constant ($5.0\times10^{-3}\,h^{-1}$) for the hydrolysis of thymidylyl (3′–5′) thymidine by the Ce(IV)–glucamine system at pH 7.0 and 50 °C ([Ce(IV)]$_0$ = [glucamine]$_0$ = 10 mmol L^{-1}) is far greater than those of the Ce(IV) complexes of iminodiacetate and ethylenediaminetetraacetate.

Keywords: Cerium(IV); DNA Hydrolysis; Glucamine

1. Introduction

Design of catalysts for DNA hydrolysis has been attracting interest, mainly because they should be useful tools for the future biotechnology and molecular biology [1]. However, DNA is strongly resistant to hydrolysis (the intrinsic half-life of the phosphodiester linkage therein at pH 7 and 25 °C is estimated to be 200 million years [2]). Thus, enormously active catalysts are required to hydrolyse DNA under physiological conditions. A few years ago, the authors found that lanthanide ions are quite effective for DNA hydrolysis [3]. The Ce(IV) ion has an especially great activity [1,4–7]. Furthermore, artificial restriction enzymes, which hydrolyse DNA at the aimed site with a desired specificity, were prepared by tethering Ce(IV) to

* Corresponding author. Fax: +81-3-5802-3340; e-mail: mkomi@chembio.t.u-tokyo.ac.jp

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synthetic DNA oligomers (sequence-recognizing moieties) [1a,8,9].

However, the Ce(IV) ions readily form metal hydroxide gel at physiological pH, and this imposes a significant limitation to the scope of application of Ce(IV). Although the Ce(IV)–ethylenediaminetetraacetate complex is homogeneous in neutral solutions, this complex is inactive for DNA hydrolysis (vide ante). Some ligands which strongly bind the Ce(IV) ion without causing a significant damage on its catalytic activity are necessary for versatile application.[1]

The present paper reports that selected saccharides and their derivatives form homogeneous complexes with Ce(IV) in neutral aqueous solutions. The Ce(IV)-solubilizing activity is notably dependent on the structure of saccharide. Some of the resultant homogeneous solutions are sufficiently active for DNA hydrolysis.

2. Experimental

Materials.—Mono- and disaccharides (all in D-forms), as well as their derivatives, were purchased from Tokyo Kasei. Dextran [degree of polymerization (dp) 280–390], polyvinyl alcohol (dp 500), and $Ce(NH_4)_2(NO_3)_6$ were from Nacalai. Amyloses were cordial gifts from Ensuiko Seito Co. and Hayashibara Co. Thymidylyl(3′–5′)thymidine (TpT), starch, glycol chitosan, and poly (acrylic acid) (dp 6000) were commercially obtained. Water was purified by a Milli-XQ purification system (the specific resistance > 18.3 $M\Omega \cdot cm^{-1}$) and further sterilized in an autoclave immediately before use.

Preparation of homogeneous solutions composed of Ce(IV) and saccharides.—The required amounts of $Ce(NH_4)_2(NO_3)_6$ and saccharide were added to a 50 mM Hepes buffer. The pH of the mixture was adjusted to 7.0 by using a small amount of NaOH. The concentration of the Ce(IV) salt was kept constant at 0.1 mmol in 10 mL, unless noted otherwise.

Hydrolysis of TpT by cerium(IV)–saccharide complexes.—The hydrolysis of TpT at pH 7.0 (50 mM Hepes buffer) and 50 °C was followed by reversed-phase HPLC (a Merck LiChrosphere RP-18(e) ODS column; 92:8 water–acetonitrile). The initial concentration of the substrate was 0.1 mM. At appropriate intervals, a small specimen was taken and analyzed by HPLC. The peaks were assigned by co-injection with authentic samples. The reactions satisfactorily obeyed pseudo-first-order kinetics. The pH change during the reactions was less than 0.2 units.

NMR spectroscopy.—^1H and ^{13}C NMR spectra were measured in D_2O (at pD 7) on a JEOL JMN-EX 270 FT-NMR System. 2-Methyl-2-propanol was used as the internal standard for ^1H NMR spectroscopy, whereas 3-(trimethylsilyl)propionic acid was the external standard for ^{13}C NMR spectroscopy. Signal assignment was made by using two-dimensional COESY and NOESY spectra that were taken on a Bruker AMX 500 spectrometer.

Circular dichroism (CD) spectroscopy.—CD spectra of $Ce(NH_4)_2(NO_3)_6$–saccharide mixtures were recorded in the region of 250–600 nm on a Jasco J725 spectropolarimeter.

Redox titration of aqueous $Ce(NH_4)_2(NO_3)_6$–saccharide mixtures.—The amounts of Ce(IV) ions in the reaction mixtures were determined by the redox titration with aqueous solution of $FeSO_4$. 1,10-Phenanthroline was used as the indicator [the color of its complex with Fe(II) changes from red to blue when the Fe(II) is oxidized to Fe(III) by Ce(IV)].

Light-scattering photometry.—Homogeneous solutions of Ce(IV)–saccharide systems were analyzed by an Otsuka Electronics ELS-800 dynamic photoscattering photometer, in order to clarify whether any colloidal particles are formed or not in the mixtures. This analyzer can detect colloidal particles, if any, which are greater than 3 nm in diameter.

3. Results

Ce(IV)-solubilizing activities of various saccharides and their derivatives.—When $Ce(NH_4)_2(NO_3)_6$ is added to a pH 7 Hepes buffer in the absence of saccharides, polymeric aggregation of Ce(IV) hydroxide rapidly takes place and white precipitates are formed. However, it has been found that some saccharides and their derivatives greatly suppress the precipitate formation and provide homogeneous solutions (see Table 1). Here, the molar ratio of monomeric residue of saccharide to $Ce(NH_4)_2(NO_3)_6$ is kept constant at 1:1. The terms 'homo' and 'hetero' refer to the formation of

[1] It has been shown that the complexes of lanthanide(III) ions and sugar derivatives are effective for the hydrolysis of bis(4-nitrophenyl)phosphate and supercoiled plasmid DNA [10].

homogeneous solutions and of heterogeneous mixtures, respectively. The Ce(IV)-solubilizing activity is highly dependent on the kind of saccharide.

Monosaccharides and their derivatives. Of the monosaccharides examined, aldopentoses (lyxose, ribose, and xylose) and their derivative (lyxosylamine), satisfactorily solubilize Ce(IV) in neutral solutions [Table 1(A)]. The OH residue at the 2-position in ribose is essential, since 2-deoxyribose is unable to solubilize Ce(IV). On the other hand, aldohexoses (galactose and glucose), ketohexose (fructose), and their derivatives (galacturonic acid and glucosamine) are inactive for Ce(IV) solubilization. White precipitates of Ce(IV) hydroxide are formed even in their presence, and only heterogeneous mixtures are obtained [Table 1(B)]. The positions and numbers of the hydroxyl residues are crucially important for the solubilization of Ce(IV). Neither methyl β-galactopyranoside nor methyl α-glucopyranoside is active.

Quite interestingly, fucose (6-deoxygalactose) efficiently solubilizes Ce(IV), which is in contrast to the poor Ce(IV)-solubilizing activity of galactose. A subtle change in the structure of saccharide causes a marked effect on the activity. For example, *myo*-inositol is inactive, although it has six hydroxyl residues.

Disaccharides. Homogeneous Ce(IV) solutions are prepared by using gentiobiose, isomaltose, or palatinose [Table 1(C)]. These disaccharides are composed of either α- or β-(1→6)-glycosidic linkages. In contrast, all the disaccharides having glycosidic linkages other than (1→6)-forms are inactive for the solubilization. The disaccharides falling within this category are (a) cellobiose,

Table 1
Homogeneity of the 1:1 mixtures of the cerium(IV) ion and various saccharides as well as their activities for TpT hydrolysis[a–d]

(A) Mono- and disaccharides as well as their derivatives

Monosaccharide	State of mixture	Disaccharide	State of mixture
D-Fructose	hetero	Cellobiose	hetero
D-Galactose	hetero	Gentiobiose	homo (11)
D-Glucose	hetero	Isomaltose	homo (10)
D-Lyxosamine	homo (5)	Lactose	hetero
D-Lyxose	homo (2)	Maltose	hetero
D-Ribose	homo (8)	Melibiose	homo (8)[d]
D-Xylose	homo (< 1)	Palatinose	homo
L-Fucose	homo (9)	Sucrose	hetero
D-Glucosamine	hetero	Trehalose	hetero
Methyl β-D-galactopyranoside	hetero		
Methyl α-D-glucopyranoside	hetero		
myo-Inositol	hetero		

(B) Oligo- and polysaccharides as well as their derivatives

Saccharide		State of mixture	Saccharide	State of mixture
Dextran dp	280–390	homo (57)[d]	α-Cyclodextrin	hetero
Amylose dp	90	hetero	β-Cyclodextrin	hetero
	35	hetero	γ-Cyclodextrin	hetero
	18	hetero	Starch	hetero
	6	hetero	Glycol Chitosan	hetero
	3	hetero		

(C) Sugar alcohols and their derivatives

Sugar alcohols	State of mixture	Sugar alcohols	State of mixture
Arabinitol	homo (< 1)	Glucitol	homo (< 1)
Erythritol	hetero	Xylitol	homo (< 1)
Galactitol	homo (< 1)	Glucamine	homo (50)
Mannitol	homo (< 1)	*N*-Methylglucamine	homo (< 1)
Ribitol	homo (< 1)		

[a] The ratio of the Ce(IV) to the monomeric residue in saccharide is 1:1.
[b] The terms 'homo' and 'hetero' refer to homogeneous solutions and heterogeneous mixtures, respectively.
[c] The numbers in parentheses show the pseudo-first-order rate constants (in $10^{-4}\,h^{-1}$) for TpT hydrolysis at pH 7.0 and 50 °C by the homogeneous mixtures.
[d] Homogeneous solutions were obtained when $[\text{the monomeric residue of saccharide}]_0/[\text{Ce(IV)}]_0 > 2$ (see text for details).

lactose, and maltose [(1→4)-linkages], (b) sucrose [(1→2)-linkage], and (c) trehalose [(1→1)-linkage].

Consistently, melibiose, which has a (1→6)-glycosidic linkage, gives homogeneous Ce(IV) solutions when $[melibiose]_0/[Ce(IV)]_0 = 1$ ([monomeric residue in the sugar]$_0$/[Ce(IV)]$_0$ = 2).[2] With cellobiose, lactose, maltose, sucrose, or trehalose, however, homogeneous solutions of Ce(IV) are not formed even when $[saccharide]_0/[Ce(IV)]_0 = 1$.

Poly- and oligosaccharides and their derivatives. Dextran involving α-(1→6)-glycosidic linkages provide homogeneous Ce(IV) solutions, when [monomeric residue of dextran]$_0$/[Ce(IV)]$_0$ is 2 or greater (see footnote d in Table 1). However, amylose shows no measurable Ce(IV)-solubilizing activity, irrespective of the degree of polymerization. Starch is also inactive. These results fairly agree with the fact that only the disaccharides composed of (1→6)-glycoside linkages satisfactorily solubilize Ce(IV) in neutral aqueous solutions. Cyclodextrins (α-, β-, and γ-), glycol chitosan, poly(acrylic acid), and poly(vinyl alcohol) do not provide homogeneous solutions.[3]

Sugar alcohols and their derivatives. Sugar alcohols (arabinitol, galactitol, mannitol, ribitol, glucitol, and xylitol) solubilize Ce(IV) [see Table 1(C)]. Glucamine (an amino derivative of glucitol) and *N*-methylglucamine are also effective. However, erythritol, glycerol, and ethylene glycol are inactive for Ce(IV)-solubilization.

Physicochemical analysis on the Ce(IV)/saccharide mixtures. When $Ce(NH_4)_2(NO_3)_6$ and glucamine (or glucitol) are mixed at pH 7, notable Cotton effects are observed (see Fig. 1). Apparently, the Ce(IV) ion, which has an absorption maximum around 300 nm, is placed in the asymmetric environments provided by the saccharide derivatives. The complex formation has been clearly evidenced.[4] In ^1H and ^{13}C NMR spectroscopy, however, the changes in chemical shifts of the saccharides are only marginal (< 0.003 ppm) when [monomeric residue of saccharide]$_0$ = [Ce(IV)]$_0$ = 10 mM.

According to the redox titration, the Ce ions in all the Ce(IV) saccharide mixtures retain their tetravalent states. Reduction of Ce(IV) to Ce(III) by these saccharides takes place only in highly acidic solutions (pH < 2). It should be noted that light-scattering photometry on these homogeneous solutions gave no scattering signals. No colloidal particles (at least greater than 3 nm in diameter) are present in these mixtures (see the Experimental section).

DNA hydrolyzing activities of cerium(IV)–saccharide complex solutions. Fig. 2 depicts the reversed-phase HPLC patterns for the hydrolysis of TpT at pH 7.0 and 50 °C by a homogeneous solution composed of $Ce(NH_4)_2(NO_3)_6$ and glucamine ([Ce(IV)]$_0$ = [glucamine]$_0$ = 10 mM). TpT is hydrolysed to thymidine (T). The pseudo-first-order rate constant is $5.0\times10^{-3}\,h^{-1}$. The hydrolysis intermediates, thymidine 3′- and 5′-monophosphates, are rapidly converted to T and are not accumulated. No byproducts assignable to oxidative cleavage of the deoxyribose are formed. The scission of TpT proceeds via hydrolysis of the phosphodiester linkage (if the deoxyribose were to be oxidatively cleaved, thymine and other byproducts should be released). In contrast, the Ce(IV)–ethylenediaminetetraacetate complex shows no measurable activity for DNA hydrolysis under the comparable conditions. The Ce(IV)–iminodiacetate complex also has rather poor activity (the pseudo-first-order rate constant is smaller than $5\times10^{-4}\,h^{-1}$, when [the complex] = 10 mM). These carboxylate-based ligands greatly suppress the catalytic activity of Ce(IV).

The rate constants for TpT hydrolysis by other homogeneous solutions of the Ce(IV)–saccharide complexes are presented in the parentheses in Table 1. The activity is in the following order: glucamine≫gentiobiose, isomaltose, ribose, lyxosylamine > arabinitol, galactitol, mannitol, glucitol, xylitol, *N*-methylglucamine. The amino residue in glucamine is significant for the notable catalytic activity (compare glucamine versus glucitol). The Ce(IV)–dextran mixture (1:2 molar ratio with respect to the monomeric residue of dextran) also efficiently hydrolyses TpT.

4. Discussion

Interactions between Ce(IV) and saccharides for Ce(IV)-solubilization.—In the homogeneous solutions of Ce(IV)–saccharide systems, the hydroxyl

[2] The Ce(IV)-solubilizing activity of melibiose is smaller than those of gentiobiose, isomaltose, and palatinose, since homogeneous solutions are obtained only when $[melibiose]_0/[Ce(IV)]_0 > 1$. With the other three disaccharides, homogeneous solutions are formed even at $[saccharide]_0/[Ce(IV)]_0 = 0.5$ ([monomeric residue]$_0$/[Ce(IV)]$_0$ = 1).

[3] A homogeneous solution was obtained when [γ-Cyclodextrins]$_0$/[Ce(IV)]$_0$ = 5 [11].

[4] The complex formation constants could not be precisely evaluated by CD spectroscopy, because homogeneous solutions were obtained only in a rather narrow concentration range.

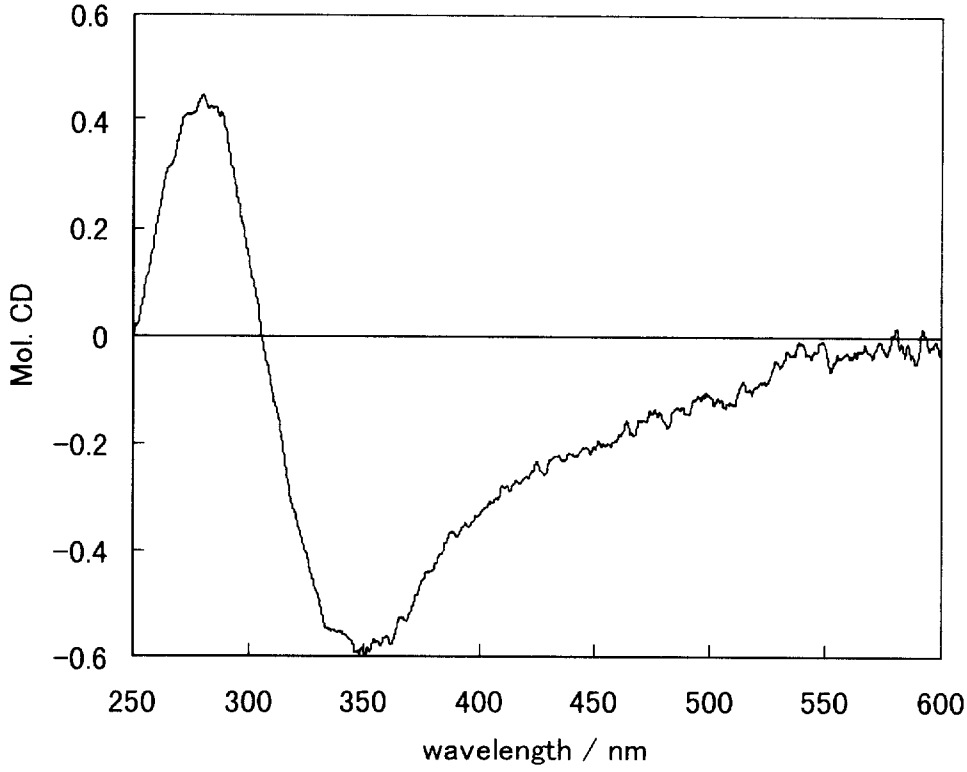

Fig. 1. The CD spectrum of a $Ce(NH_4)_2(NO_3)_6$–glucamine mixture at pH 7.0 (50 mM Hepes buffer) and 20 °C: $[Ce(IV)]_0 = [glucamine]_0 = 0.1$ mM.

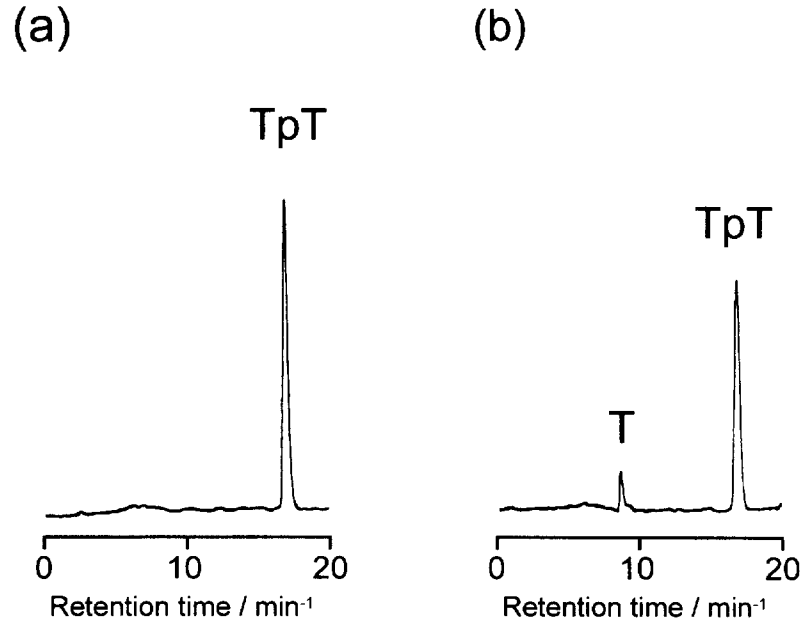

Fig. 2. Reversed-phase HPLC profiles for the homogeneous hydrolysis of TpT at pH 7.0 (50 mM Hepes buffer) and 50 °C by 1:1 mixture of Ce(IV) and glucamine: (a) $t = 0$ h and (b) $t = 24$ h. $[Ce(IV)]_0 = [glucamine]_0 = 10$ mM.

residues of the saccharides should be coordinated to the Ce(IV) ion in the same manner as was concretely shown previously in the lanthanide(III)–saccharide complexes [12,13]. The interactions would involve no deprotonation of the alcohol groups of saccharides, since the changes in ^1H and ^{13}C NMR chemical shifts of the saccharides are marginal.

Of all the monosaccharides investigated, aldopentoses (lyxose, ribose, and xylose) and lyxosylamine are effective for the solubilization of

Ce(IV). In aqueous solutions, these pentoses exist mostly (>99%) in their pyranose forms [14]. In contrast, aldohexoses (galactose and glucose) are inactive for the solubilization, although they also preferentially take the pyranoside forms in water [14]. Apparently, the 6-OH residues in monosaccharides suppress Ce(IV)-solubilizing activity. The argument is further confirmed by the fact that fucose, in which the 6-OH in galactose is replaced by a hydrogen atom, effectively solubilizes Ce(IV). The saccharide showing notable Ce(IV)-hydrolyzing activity has several OH residues in one side of the molecule, and, in addition, the other side of the molecule is rather apolar. These saccharides satisfactorily cover the surface of Ce(IV) ions and protect them from mutual aggregation. If the monosaccharides have additional OH residues, however, these residues probably serve as linkers to connect the Ce(IV)–saccharide complexes to each other and promote their aggregation. Only when the balance between the apolar character and the polar character in the saccharides is appropriate, can stable and homogenous Ce(IV) solutions be obtained. *myo*-Inositol is inactive, presumably because the six hydroxyl residues make the whole of the molecule polar.

The superb activities of di- and polysaccharides involving (1→6)-glycosidic linkages would be also ascribed to the appropriate balance between the apolar character (near the 6-carbon atoms) and the polar character (near the OH residues at the C-2–C-4 atoms). In the saccharides of (1→4)-linkages, however, all the parts in the molecules are rather polar. The smaller activity of amylose than dextran is not associated with its helical structure, since even the amylose of small dp (3 and 6), which can not take the helical form, was inactive [see Table 1(B)].[5]

DNA hydrolysis by the cerium(IV)–saccharide complexes.—In the TpT hydrolysis by the Ce(IV)–saccharide complexes, the phosphodiester linkage of TpT is coordinated to the Ce(IV) ion(s) and is activated for nucleophilic attack by the Ce(IV)–bound hydroxide ion [4c]. Subsequently, the Ce(IV) ion(s) and/or their coordination water (as acid catalysts) promote the removal of T from the phosphorus atom. Since most of the saccharides and their derivatives are electrically neutral under the reaction conditions, the net positive charge on the Ce(IV) ion is less affected by the complex formation. Thus, the remarkable catalytic activity of the metal ion remains rather intact. In the Ce(IV)–ethylenediaminetetraacetate and the Ce(IV)–iminodiacetate complexes, however, the positive charge on the metal ion is mostly compensated by the negative charges of the ligands. Thus the DNA-hydrolyzing activity is notably decreased (the sequence-selective DNA scission by the conjugates of Ce(IV)–iminodiacetate complex and DNA [1a,8] would be associated with the fact that the complex is placed correctly at the target phosphodiester linkage and thus its effective concentration is sufficiently great).

The superb activity of the Ce(IV)–glucamine complex is tentatively ascribed to 'electrostatic catalysis' by the positive charge of the ammonium ion of the glucamine, which electrostatically stabilizes the negatively charged transition state for DNA hydrolysis. Alternatively, the ammonium ion can function as a general acid catalyst. The possibility that the Ce(IV) ion in the glucamine complex binds the phosphate residue of DNA more strongly is also plausible. The amino residue interacts with the Ce(IV) more weakly than a hydroxyl residue since lanthanide ions generally prefer oxo ligands to nitrogen ligands ('oxophilicity') [15].

5. Conclusions

A few years ago [4] it was found that the phosphodiester linkages in DNA are efficiently hydrolysed by the Ce(IV) ion. In neutral aqueous solutions, however, Ce(IV) ions mostly exist as metal hydroxide gel. Thus, appropriate ligands for the metal ion are desirable for further application of the catalysis. The present work has shown that selected saccharides and their derivatives form complexes with the Ce(IV) ions and provide homogeneous solutions. Aldopentoses such as lyxose, ribose, and xylose (as well as lyxosylamine) are effective for the solubilization. Di- and polysaccharides involving (1→6)-glycosidic linkages, sugar alcohols, and their derivatives are also eminent for the purpose. Significantly, these homogeneous solutions hydrolyse the phosphodiester linkages in DNA under physiological conditions. The acceleration achieved by the Ce(IV)–glucamine complex is nearly 10^9 fold. It is indicated that saccharides are highly potent as the ligands that tether the Ce(IV) ion to substrate-

[5] The small activities of amylose and starch for Ce(IV) solubilization might be partially ascribed to their poor solubilities in water.

recognizing moieties in artificial enzymes. Furthermore, Ce(IV) ions (and other lanthanide ions also) can be delivered to target cells (such as cancer cells) by using the cell-recognizing abilities of saccharides. Thus a new way of therapy might be opened. These studies are currently underway in our laboratory.

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