Hydrolysis of Diribonucleoside Monophosphate Diesters Assisted by a Manganese(II) Complex

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An Mn^{2+} complex with 2,2′:6′,2″-terpyridine (terpy) was found to promote the hydrolysis of NpN (NpN = diribonucleoside monophosphate diester) efficiently at pH 7.0 and 50 °C under ambient conditions. The structure of the Mn^{2+} complex involving a phosphodiester molecule, $[(terpy)(dpp)Mn^{II}(\mu\text{-}dpp)_2Mn^{II}(dpp)(terpy)]$, dpp = diphenyl phosphate anion, was established by X-ray crystallography, and the coordination mode of Mn^{2+} to a phosphodiester molecule was considered.

The metal-ion assisted hydrolysis of nucleic acids has been attracting much attention, and many mimics of enzymatic catalytic centers have been reported.[1]

Manganese(II) is believed to be an essential co-factor for some enzymes for phosphoester hydrolysis.[2] However, little is known about the chemistry of Mn^{2+} in phosphoester hydrolysis;[3] limited studies under slightly acidic conditions were reported.[3e] This is partially because, under neutral pH or above, Mn^{2+} is readily converted into insoluble MnO_2, unless oxygen is strictly removed from the solution.[4] The present study reports that an appropriate design of an Mn^{2+} complex is useful for the creation of an RNA cleaving agent.

Results and Discussion

The hydrolyses of diribonucleoside monophosphate (3′-5′)diesters (NpN), where N = A, G, C, or U, in the presence of $MnCl_2$ or $[MnCl_2(terpy)]$[5] were conducted at pH 7.0 (HEPES 50 $mmol\,dm^{-3}$) and 50 °C. An inert atmosphere, e.g. N_2, was needed for the reaction with $MnCl_2$ in order to prevent the formation of MnO_2. In contrast, the reaction with $[MnCl_2(terpy)]$ did not need an inert atmosphere in order to keep the Mn^{2+} in solution, and the reaction with or without a N_2-treatment of the solution before the reaction gave essentially identical results.

In either case, the reaction yielded a mixture of products expected for NpN hydrolysis: a nucleoside 2′,3′-cyclicmonophosphate (2′,3′-cNMP), a nucleoside 3′-monophosphate (3′-NMP), a nucleoside 2′-monophosphate (2′-NMP), and a nucleoside (Scheme 1).[6,7] The reactions were followed both by a decrease of NpN and an increase of the products, and showed pseudo-first-order kinetics.

The results are summarized in Table 1. The hydrolysis of NpN was promoted by the Mn^{2+} complex considerably at pH 7.0. Furthermore, ApA hydrolysis with $[MnCl_2(terpy)]$ was about 30-times more accelerated than that with $MnCl_2$. The effect of the Mn^{2+}–terpy complex on ApA hydrolysis was much greater than that of Mg^{2+} (15% conversion after 90-h reaction in the presence of 100 $mmol\,dm^{-3}$ $MgCl_2$ at pH 7.3 (HEPES 50 $mmol\,dm^{-3}$) and 50 °C),[6c] but comparable to those of Zn^{2+} complexes[6a,6d,8] (for example, $k_{obs} = (68–185) \times 10^{-3}\ h^{-1}$ in the presence of 2.5 $mmol\,dm^{-3}$ dinuclear Zn^{2+} complexes with a dinucleating tetrapyridyl ligand at pH 7.0 (HEPES 50 $mmol\,dm^{-3}$) and 50 °C)[6a,b,d] or a Cu^{2+}–terpy complex ($k_{obs} = 45 \times 10^{-7}\ s^{-1}$ in the presence of 2.0 $mmol\,dm^{-3}$ Cu^{2+}–terpy complex at pH 8.0 (HEPES 50 $mmol\,dm^{-3}$) and 25 °C).[9]

The effect of the nucleic acid base on the present Mn^{2+}-complex-assisted hydrolysis was small. In the NpN hydrolysis assisted by Zn^{2+} complexes[6b,d] or Cu^{2+} complexes,[9] much higher base selectivities have been reported. Such high selectivities were interpreted by the interaction between the metal complex and the nucleic acid base during the reaction.[6d,9] The relatively low selectivity on the kind of the nucleic acid base in the present reaction indicates that the Mn^{2+}–terpy complex does not interact with the base moiety significantly.

The coordination modes of the phosphoester and terpyridine to Mn^{2+} were confirmed by X-ray crystallography. Various phosphoesters were tried to co-crystallize with the Mn^{2+}–terpy complex. The 1:1 mixture of $[MnCl_2(terpy)]$ and diphenyl hydrogenphosphate (Hdpp) in an aqueous solution gave good crystals suitable for crystallography. Figure 1 shows the molecular structure of the resulting complex $[(terpy)(dpp)Mn^{II}(\mu\text{-}dpp)_2Mn^{II}(dpp)(terpy)]$. The complex is constituted with two Mn^{2+}, two terpy, and four dpp units. Two of four dpp bridge the two Mn^{2+}. As a result, an eight-membered ring involving two Mn (–Mn–O–P–O–Mn–O–P–O–) is formed. The coordi-

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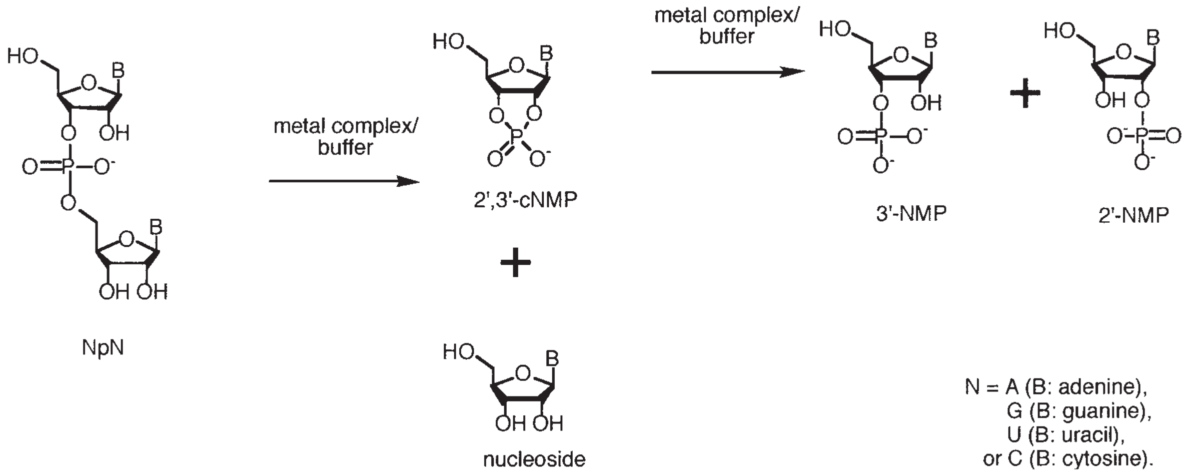

Scheme 1.

Table 1. Pseudo-First-Order Rate Constants and Product Ratios for NpN (0.1 mmol dm^{-3}) Hydrolysis Assisted by [MnCl$_2$(terpy)] (20 mmol dm^{-3}) at pH 7.0 (HEPES 50 mmol dm^{-3}) and 50 °C

	k_{obs}	Product ratio/%[a]			
NpN	10^{-3} h^{-1}	2′,3′-cNMP	3′-NMP	2′-NMP	Nucleoside
ApA	48	6	20	17	57
ApA[b]	1.7	19	15	14	52
GpG	80	1	28	12	59
UpU	32	—[c]	31	19	50
CpC	35	—[c]	18	13	69

a) After 21 h reaction. b) The reaction was conducted by using MnCl$_2$ instead of [MnCl$_2$(terpy)] under N$_2$. c) Under detection.

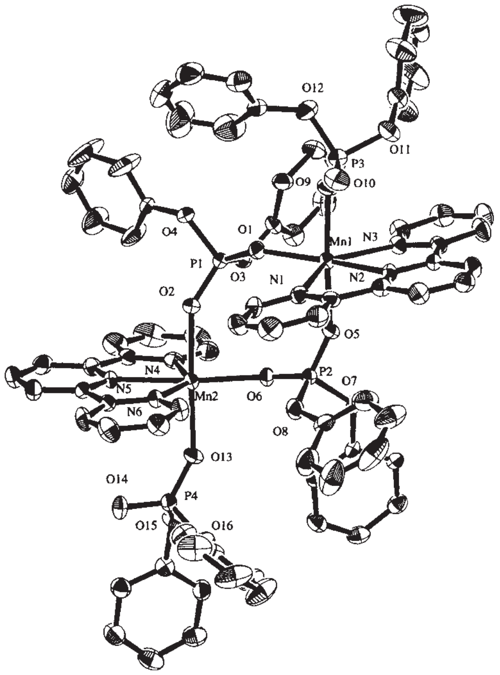

Fig. 1. ORTEP drawing of [(terpy)(dpp)Mn^{II}(μ-dpp)$_2$Mn^{II}-(dpp)(terpy)] showing the 30% probability thermal ellipsoids for all non-hydrogen atoms.

nation geometries around the two Mn^{2+} ions are similar to each other; Mn^{2+} is coordinated with a tridentate terpy molecule, a monodentate dpp molecule, and two bridging dpp molecules.

Table 2 lists selected bond distances and angles. The angles around Mn^{2+} are remarkably deviated from 90°, 126.2(3)° for O1–Mn1–N3 and 119.3(2)° for O6–Mn2–N6, or from 180°, 141.1(2)° for N1–Mn1–N3 and 142.4(2)° for N4–Mn2–N6. The results indicate that the geometry around Mn^{2+} is a highly distorted octahedron.

In order to examine the nature of the coordination bond between Mn^{2+} and phosphate moieties, the M–O bond distances between various divalent metal cations and phosphoester molecules (d(M–O)) in reported crystal structures[10–14] were compared (Table 3). In the fourth column of Table 3, the Δ values obtained by subtracting known values of ionic radii of the divalent metal cation from the d(M–O) values are listed. The Δ values span the range 1.09–1.34 Å, and the values found in the present crystal structure are normal. However, the two Δ values for a μ-phosphate bridge in the present crystal structure are considerably different from each other, i.e. 1.14 vs 1.20 Å (Entry 1), and 1.20 vs 1.15 Å (Entry 2). Such unsymmetrical μ-phosphate bridge was not found in crystal structures involving Zn^{2+} and Co^{2+} (Entry 6),[10] 2Mg^{2+} (Entries 10 and 11),[11] or 2Ca^{2+} (Entry 13),[11] except that involving 2Zn^{2+} (Entry 5).[12] The Cu^{2+} complex in Ref. 13 (Entry 9) is exceptional, because unsymmetrical bond distances in such a Cu^{2+} compound is interpreted by a Jahn–Teller effect, which is generally observed in Cu^{2+} complexes.

Since the structure established by the crystallography is a stable one in the solid state, it does not necessarily exhibit a truly active state of the molecule in solution. However, the result suggests the structure of the Mn^{2+} species during the reaction; three coordination sites of Mn^{2+} are occupied with a tridentate terpy ligand, and the remaining sites can be available for other ligands, i.e. H$_2$O, OH$^-$, or a phosphoester molecule. In the present crystal structure, all of the three remaining sites of Mn^{2+}–terpy were found to be occupied with dpp molecules, probably due to crystallization.

In the Zn^{2+}-assisted hydrolysis of RNA, the metal ion has been suggested to promote the reaction as both general base

Table 2. Selected Bond Distances (Å) and Angles (deg) with Standard Deviations in Parentheses

Distances			
Mn1–O1	2.108(4)	Mn1–O5	2.172(4)
Mn1–O9	2.131(5)	Mn1–N1	2.295(6)
Mn1–N2	2.259(5)	Mn1–N3	2.331(6)
Mn2–O2	2.165(4)	Mn2–O6	2.117(4)
Mn2–O13	2.115(5)	Mn2–N4	2.272(6)
Mn2–N5	2.259(6)	Mn2–N6	2.305(6)
P1–O1	1.473(4)	P1–O2	1.483(4)
P1–O3	1.587(5)	P1–O4	1.610(5)
P2–O5	1.478(4)	P2–O6	1.474(5)
P2–O7	1.597(5)	P2–O8	1.594(5)
P3–O9	1.467(5)	P3–O10	1.462(6)
P3–O11	1.610(5)	P3–O12	1.590(6)
P4–O13	1.478(5)	P4–O14	1.456(5)
P4–O15	1.611(5)	P4–O16	1.605(5)
O3–C31	1.398(8)	O4–C37	1.401(8)
O7–C43	1.401(8)	O8–C49	1.384(9)
O11–C55	1.384(9)	O12–C61	1.392(9)
O15–C67	1.383(8)	O16–C73	1.380(8)
Angles			
O1–Mn1–O5	90.5(2)	O1–Mn1–O9	87.7(2)
O1–Mn1–N1	92.6(2)	O1–Mn1–N2	162.1(2)
O1–Mn1–N3	126.2(2)	O5–Mn1–O9	166.2(2)
O5–Mn1–N1	93.0(2)	O5–Mn1–N2	96.9(2)
O5–Mn1–N3	84.1(2)	O9–Mn1–N1	100.7(2)
O9–Mn1–N2	88.8(2)	O9–Mn1–N3	86.0(2)
N1–Mn1–N2	70.9(2)	N1–Mn1–N3	141.1(2)
N2–Mn1–N3	71.0(2)	O2–Mn2–O6	87.5(2)
O2–Mn2–O13	176.9(2)	O2–Mn2–N4	88.8(2)
O2–Mn2–N5	90.5(2)	O2–Mn2–N6	89.6(2)
O6–Mn2–O13	90.7(2)	O6–Mn2–N4	98.1(2)
O6–Mn2–N5	169.4(2)	O6–Mn2–N6	119.3(2)
O13–Mn2–N4	93.9(2)	O13–Mn2–N5	91.8(2)
O13–Mn2–N6	89.2(2)	N4–Mn2–N5	71.4(2)
N4–Mn2–N6	142.4(2)	N5–Mn2–N6	71.0(2)
O1–P1–O2	119.5(3)	O1–P1–O3	111.2(3)
O1–P1–O4	104.3(3)	O2–P1–O3	107.1(3)
O2–P1–O4	109.5(3)	O3–P1–O4	104.1(3)
O5–P2–O6	120.0(3)	O5–P2–O7	103.3(3)
O5–P2–O8	111.7(3)	O6–P2–O7	111.7(3)
O6–P2–O8	104.6(3)	O7–P2–O8	104.7(3)
O9–P3–O10	119.3(3)	O9–P3–O11	109.4(3)
O9–P3–O12	110.8(3)	O10–P3–O11	107.3(3)
O10–P3–O12	111.5(3)	O11–P3–O12	95.9(3)
O13–P4–O14	120.4(3)	O13–P4–O15	105.0(3)
O13–P4–O16	108.6(3)	O14–P4–O15	111.3(3)
O14–P4–O16	112.2(3)	O15–P4–O16	96.5(3)
Mn1–O1–P1	149.0(3)	Mn2–O2–P1	142.8(3)
P1–O3–C31	126.5(4)	P1–O4–C37	126.6(4)
Mn1–O5–P2	151.9(3)	Mn2–O6–P2	140.6(3)
P2–O7–C43	127.0(4)	P2–O8–C49	127.3(5)
Mn1–O9–P3	138.4(3)	P3–O11–C55	121.8(5)
P3–O12–C61	126.1(5)	Mn2–O13–P4	149.3(3)
P4–O15–C67	123.4(4)	P4–O16–C73	126.6(5)

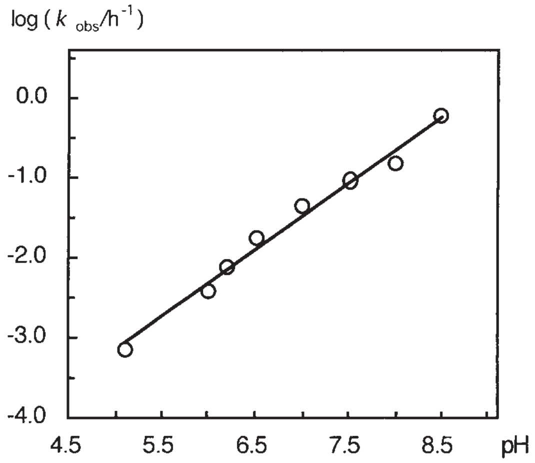

Fig. 2. pH–Rate constant profiles for ApA hydrolysis in the presence of [MnCl$_2$(terpy)] at 50 °C. [ApA]$_0$ = 0.1 mmol dm^{-3}, [[MnCl$_2$(terpy)]] = 20 mmol dm^{-3}, [HEPES] = 50 mmol dm^{-3}.

and acid catalysts,[8b] although the reaction shows characteristics of a base-catalyzed reaction; the rate increases on increasing the pH.[8b] In the present reaction by the Mn^{2+} complex, a similar pH dependence of the reaction was observed, as shown in Fig. 2; the log k_{obs} vs pH plot showed a linear dependence of the reaction on pH in the pH range 5.0–8.5 (the slope was 0.84).[15] Accordingly, possible roles of the Mn^{2+}–terpy in NpN hydrolysis are to bind to the phosphodiester moiety, and to provide an intracomplex base and acid catalysts, similar to the case of Zn^{2+} or its complex.[6,8] A possible interpretation for the higher activity of [MnCl$_2$(terpy)] than MnCl$_2$ toward ApA hydrolysis is due to higher acidity of Mn^{2+} in the terpyridine complex than the free Mn^{2+}.[15] However, the difference in acidity of the Mn^{2+} ion, which can be evaluated by the pK_a value of the coordinated water molecule, seems to be not enoughly large to explain the 30-fold acceleration. Another possibility is that the [MnCl$_2$(terpy)] forms a dinuclear structure in solution in the presence of NpN, as suggested by the present X-ray crystallography. Higher activity of a dinuclear metal complex than its mononuclear analog toward phosphoester hydrolysis has been demonstrated in recent studies.[6,8a,8c,9,12,16]

In conclusion, an Mn^{2+} compound was found to promote the hydrolysis of NpN considerably. The present results will open a way to study the Mn^{2+} complex as an RNA cleaving agent, and as a model of the catalytic center of an enzyme.[1,2]

Experimental

Hydrolysis of NpN. In a typical experiment, a solution (1.0 mL) of ApA (0.1 mmol dm^{-3}), [MnCl$_2$(terpy)] (20 mmol dm^{-3}), and HEPES (50 mmol dm^{-3}) was adjusted to pH 7.0, and heated to 50 °C in an Eppendorf tube. After an appropriate reaction period, a 40-µL aliquot of the reaction mixture was removed, quenched by adding 10% phosphoric acid (10 µL), and analyzed by HPLC (column, Merck LiChrospher 100 RP-18(e) ODS-column; eluent, pH 5.0 water/acetonitrile (92:8, v/v) mixture containing phosphate (3 mmol dm^{-3}) and acetate (40 mmol dm^{-3}); flow rate, 0.5 mL min^{-1}; detection, 260 nm). Identification and quantification of the products were carried out by comparing the reten-

Table 3. Comparison of the M–O Bond Length (d(M–O)) between a Divalent Metal Cation and a Phosphoester Molecule

Entry	Phosphoester[a)] (coordination mode)	Metal Ion (coordination number)	d(M–O)/Å	Δ/Å[b)]	Reference
1	DPP (μ-bridge)	Mn^{2+} (6)	2.108(4) 2.165(4)	1.14 1.20	This work
2	DPP (μ-bridge)	Mn^{2+} (6)	2.172(4) 2.117(4)	1.20 1.15	This work
3	DPP (monodentate)	Mn^{2+} (6)	2.131(5)	1.16	This work
4	DPP (monodentate)	Mn^{2+} (6)	2.115(5)	1.15	This work
5	DPP (μ-bridge)	Zn^{2+} (6)	2.007(3) 2.163(3)	1.13 1.28	Ref. 12
6	DPP (μ-bridge)	Zn^{2+} (4) Co^{2+} (6)	1.930(4) 2.095(5)	1.19 1.21	Ref. 10
7	DPP (monodentate)	Zn^{2+} (4)	1.936(4)	1.20	Ref. 10
8	NPP (μ_3-bridge)	Zn^{2+} (5)	1.917(4) 1.936(4) 1.917(4)	— — —	Ref. 14
9	DEP (μ-bridge)	Cu^{2+} (5)	2.018(4) 2.186(4) 2.042(4) 2.209(4)	1.15 1.32 1.17 1.34	Ref. 13
10	DPP (μ-bridge)	Mg^{2+} (6)	2.003(7) 2.003(7)	1.14 1.14	Ref. 11
11	DPP (μ-bridge)	Mg^{2+} (6)	2.015(4) 2.018(5)	1.16 1.16	Ref. 11
12	DPP (monodentate)	Mg^{2+} (6)	1.949(4)	1.09	Ref. 11
13	DPP (μ-bridge)	Ca^{2+} (6)	2.295(3) 2.282(2)	1.16 1.14	Ref. 11
14	DPP (monodentate)	Ca^{2+} (6)	2.306(2)	1.17	Ref. 11

a) DPP = diphenyl phosphate anion, NPP = 4-nitrophenyl phosphate dianion, DEP = diethyl phosphate anion. b) $\Delta = d(\text{M–O}) - (\text{Radius of the metal ion})$. Values of the radius of the metal ion were taken from "Kagaku Binran Kisohen," 3rd ed, Maruzen, Tokyo (1984), pp. II-717–718: Mn^{2+} (6, high spin) = 0.97 Å, Zn^{2+} (6) = 0.88 Å, Zn^{2+} (4) = 0.74 Å, Co^{2+} (6, high spin) = 0.89 Å, Cu^{2+} (6) = 0.87 Å, Mg^{2+} (6) = 0.86 Å, and Ca^{2+} (6) = 1.14 Å.

tion times and the peak areas, respectively, with those of standard samples. During the entire procedures, great care was taken in order to avoid contamination that may cause enzymatic hydrolysis.

X-ray Crystallography. An aqueous solution containing [$MnCl_2$(terpy)] and diphenyl hydrogenphosphate (Hdpp) (1:1) was allowed to stand at r.t. After several days, yellow prismatic crystals suitable for the crystallographic study were obtained.

Diffraction data were collected on a Rigaku AFC7R four-circle automated diffractometer at 294 K with graphite-monochromatized Mo Kα radiation ($\lambda = 0.71069$ Å) using the ω–2θ scan technique ($5 < 2\theta < 50^\circ$). Crystallographic data for [(terpy)(dpp)Mn^{II}(μ-dpp)$_2$$Mn^{II}$(dpp)(terpy)] are as follows: $C_{78}H_{62}Mn_2N_6O_{16}P_4$, $M = 1573.15$, monoclinic, space group $P2_1/n$ (no. 14), $a = 11.159(4)$, $b = 57.325(3)$, $c = 11.326(4)$ Å, $\beta = 96.84(3)^\circ$, $U = 7193(3)$ Å^3, $Z = 4$, $D_c = 1.452$ g cm^{-3}, unique data 12671, $R1 = 0.070$ [$I > 2.0\sigma(I)$], $wR2 = 0.174$ (all data).

The structure solution and refinements were carried out by using the teXsan crystallographic software package.[17] The positions of the non-hydrogen atoms were determined by Patterson methods (DIRDIF PATTY[18]) and subsequent Fourier syntheses. All non-hydrogen atoms were refined by full-matrix least-squares techniques with anisotropic thermal parameters. Hydrogen atoms were placed at the calculated positions ($d_{\text{C–H}} = 0.95$ Å) and were included with fixed isotropic parameters.

Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 211624.

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