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The Hydrolysis of Trimetaphosphate Catalyzed by Lanthanide(III) Aminopolycarboxylate Complexes: Coordination, Stability, and Reactivity of Intermediate Complexes

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Abstract: The hydrolysis of trimetaphosphate (P_{3m}) is catalyzed dramatically by La(NTA) (NTA: nitrilotriacetate), but less pronounced by La(EDTA) (EDTA: ethylenediaminetetraacetate). Reaction products are tripolyphosphate (PPP), diphosphate (PP), and monophosphate (P). A multinuclear magnetic resonance study shows that there are only marginal differences between La(NTA)(P_{3m}) and La(EDTA)(P_{3m}) regarding complex geometry and P−O bond activation of P_{3m}. The affinity of P_{3m} is lower for Ln(EDTA) than for Ln(NTA). The catalyzed hydrolysis probably leads to tridentate coordinated PPP, after which ligand rearrangement takes place. Complexation of PPP to Ln(NTA) or Ln(EDTA), as also reflected in the formation constants, caused decoordination of one carboxylate group of NTA and two of EDTA. The gain in free energy, which is larger for Ln(NTA) than for Ln(EDTA), going from complexed P_{3m} to PPP may be a driving force of the reaction. Another important factor in this respect is the much higher stability of La(NTA)(OH) compared to that of La(EDTA)(OH). This leads to substantially higher concentrations of reactive complex La(L_l)(P_{3m})(OH) for L_l = NTA, from which it is concluded that the hydrolysis of P_{3m} catalyzed by La(NTA) proceeds *via* attack of coordinated hydroxide onto coordinated P_{3m}. The reactions catalyzed by La(EDTA) are probably initiated by both free and coordinated hydroxide. A kinetic model is developed, in which stabilities and rate constants are incorporated, to predict the speciation during the hydrolysis. Because of the fast subsequent hydrolysis of PPP and PP, competition between P_{3m} and P for complexation to La(III) is the most important factor governing the inhibition observed during the hydrolysis of P_{3m} at prolonged reaction times.

Introduction

Phosphates are crucial in many biochemical processes, and phosphate hydrolysis takes place in energy and signal transmission in living systems. The lanthanide(III) catalyzed hydrolysis of phosphate esters and oligophosphates[1−3] is especially important because of the unprecedentedly high acceleration factors found for the hydrolysis of energy carriers, such as ATP,[4−7] signal transmitters, such as cAMP,[8,9] and nucleic acids,[10] especially RNA.[11−14]

Much attention is paid to trimetaphosphate, because it is one of very few inorganic phosphorylating agents. Possible substrates are alcohols,[15−17] nucleosides and nucleotides,[18−20] and amino compounds.[21] The hydrolysis of trimetaphosphate has been investigated, using acid,[22] base,[23] or metal ions[24] as the catalysts. Lanthanides have also been tested,[24] but determination of the kinetics is difficult owing to precipitation of various species, especially lanthanide(III) monophosphate.

In this paper, we report the results of a kinetic study on the Ln(III) catalyzed hydrolysis of trimetaphosphate. We used the complexation of Ln(III) with simple aminopolycarboxylate ligands, nitrilotriacetate (NTA) and ethylenediaminetetraacetate (EDTA), to prevent precipitation of lanthanide(III) phosphate species. The coordination and the stability of the intermediate complexes are investigated, and the relationship between the structure of these intermediates and the reactivity is discussed.

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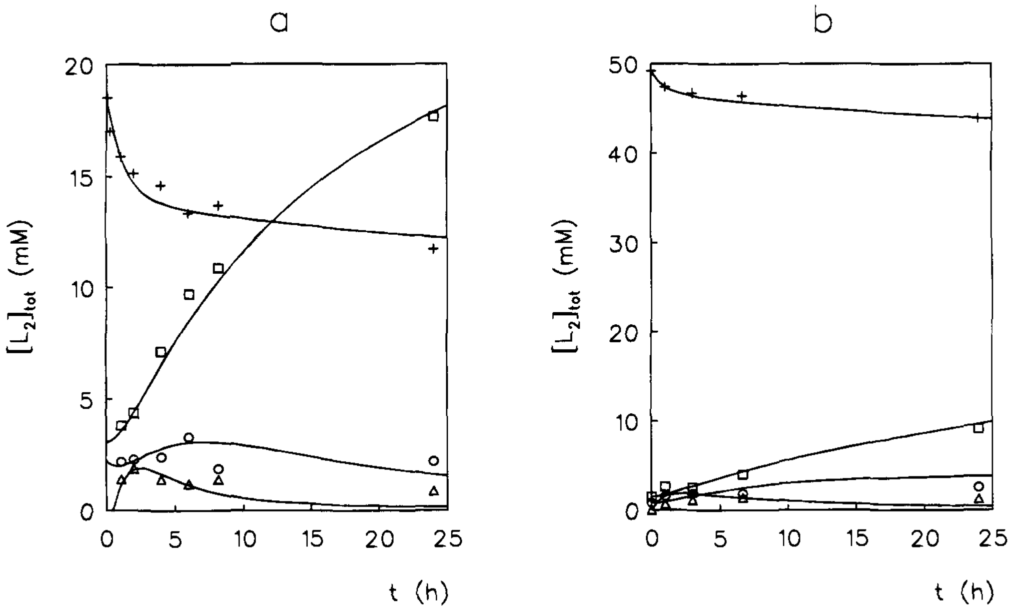
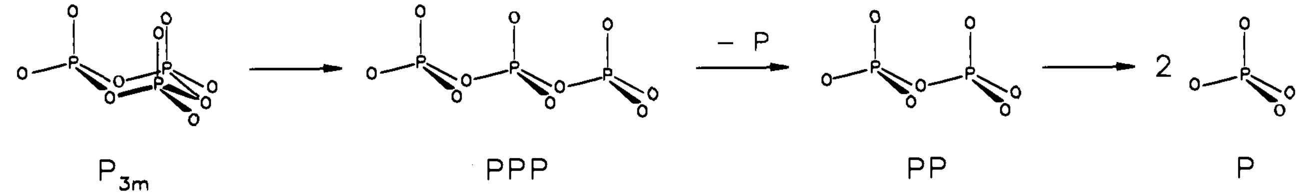


Figure 1. Concentrations of the phosphate species L_2 versus time in the hydrolysis of P_{3m} catalyzed by La(NTA): (a) P_{3m}:La:NTA = 2:1:1, $[P_{3m}]_{tot}$ = 0.02 M; (b) P_{3m}:La:NTA = 10:1:1, $[P_{3m}]_{tot}$ = 0.05 M) at 343 K, and pH 7 (experimental values: (+) P_{3m}, (△) PPP, (○) PP, (□) P; solid lines: calculated with the use of the kinetic model, described in the text, and the reaction rates and stability constants given in Table 7).

Scheme 1



Results

Hydrolysis of Trimetaphosphate. Trimetaphosphate (P_{3m}) hydrolyzes to tripolyphosphate (PPP), diphosphate (PP), and (mono)phosphate (P),[24] (see Scheme 1). Characteristic species distributions of the hydrolysis of P_{3m} catalyzed by LaNTA are shown in Figure 1. It can be seen that when La(NTA) was used as the catalyst, the hydrolysis started at a very high rate, which dropped at prolonged reaction times, showing product inhibition. The consecutive reactions to PP and to P are fast.

In general, the reaction rate of the hydrolysis at a given pH can be expressed as in eq 1, in which $[P_{3m}]_{tot}$ is the total concentration of P_{3m}, and $[P_{3m}]$ is the free ligand concentration.

$$-d[P_{3m}]_{tot}/dt = k_{1,f}[P_{3m}] + k_{1,c}[La(L_1)(P_{3m})] \qquad (1)$$

Here, $k_{1,f}$ and $k_{1,c}$ are the first-order reaction rate constants of the uncatalyzed and catalyzed hydrolysis of P_{3m}, respectively, which are pH dependent. The concentration of the reactive complex, $[La(L_1)(P_{3m})]$, in which L_1 is NTA or EDTA, is given by eq 2, where K is the (stepwise) formation constant of $La(L_1)(P_{3m})$ from $La(L_1)$ and P_{3m}.

$$[La(L_1)(P_{3m})] = K[La(L_1)][P_{3m}] \qquad (2)$$

With this definition and the mass balance for P_{3m} ($[P_{3m}]_{tot} = [P_{3m}] + [La(L_1)(P_{3m})]$), eq 1 can be rearranged to eq 3, in which the pseudo-first-order reaction rate constant k' is given by eq 4.

$$-d[P_{3m}]_{tot}/dt = k'[P_{3m}]_{tot} \qquad (3)$$

$$k' = (k_{1,f} + k_{1,c}K[La(L_1)])/(1 + K[La(L_1)]) \qquad (4)$$

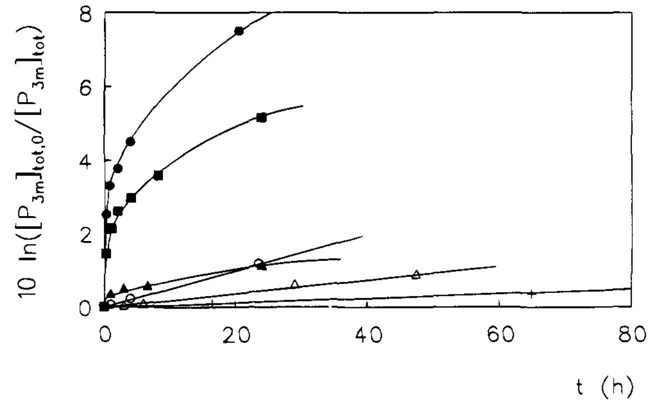


Figure 2. Conversion plots (ln ($[P_{3m}]_{tot,0}/[P_{3m}]_{tot}$) versus time; $[P_{3m}]_{tot,0}$ is the initial total concentration of P_{3m}) of the hydrolysis of P_{3m} at 343 K and pH 7 (P_{3m}:La:L_1 (L_1; $[P_{3m}]_{tot}$ (M)): (+) 1:0:0 (–; 0.02); (△) 10:1:1 (EDTA, 0.05); (○) 1:1:1 (EDTA, 0.02); (▲) 10:1:1 (NTA, 0.05); (■) 2:1:1 (NTA, 0.05); (●) 1:1:1 (NTA, 0.05)); the uncatalyzed reaction (+) was followed until 300 h, and all data fit the given line.

Thus a plot of ln ($[P_{3m}]_{tot,0}/[P_{3m}]_{tot}$) versus time (see Figure 2) is a straight line when k' is constant in time. From Figure 2, it can be concluded that this is the case for the uncatalyzed reaction ($k' = k_{1,f}$) and for the experiments with La(EDTA) as the catalyst ($[LaL_1]$ is constant). With La(NTA), however, product inhibition was observed. This can be attributed to the linear phosphates, which form relatively stable complexes with $La(L_1)$, and, therefore, lead to a decrease of $[La(L_1)]$ in eq 4. This is not observed for the La(EDTA) catalyzed reactions owing to the low conversions obtained in the time period of observation.

In Table 1, initial pseudo-first-order reaction rate constants

Table 1. Initial Rate Constants of the Hydrolysis of Trimetaphosphate at 343 K and pH 7

catalyst	$[P_{3m}]_{tot}$ (M)	P_{3m}:La:L_1	k' (h^{-1})[a]
none	0.020	1:0:0	0.00062
La(EDTA)	0.050	10:1:1	0.0020
	0.020	1:1:1	0.0050
La(NTA)	0.050	10:1:1	0.060
	0.020	2:1:1	0.25
	0.020	1:1:1	0.45
	0.020	2:1:2	0.00062
	0.020	2:2:3	0.24

[a] Slope of the curve of ln ($[P_{3m}]_{tot,0}/[P_{3m}]_{tot}$) versus time at $t = 0$; $[P_{3m}]_{tot,0}$ is the initial total concentration of P_{3m}.

Table 2. Stabilities[a] of Intermediate Complexes $Ln(L_1)(L_2)$ at 298 K and an Ionic Strength of 0.1 M

	L_2				
$Ln(L_1)$	P_{3m}[b]	PPP	PP	P	OH
La(NTA)	1.84 ± 0.03	7.1 ± 0.3	5.9 ± 0.4	9.9 ± 0.2	4.6 ± 0.1
Nd(NTA)	1.97 ± 0.03	7.3 ± 0.4[c]		11.5 ± 0.2	
La(EDTA)	1.15 ± 0.03	3.4 ± 0.1	4.2 ± 0.2	4.1 ± 0.4	1.7 ± 0.1
Nd(EDTA)	1.00 ± 0.06	3.9 ± 0.1	4.5 ± 0.3	5.1 ± 0.1	
H	2[d]	8.0[e]	8.4[e]	11.7[e]	13.8[e]

[a] Log *K* values given; $K = [Ln(L_1)(L_2)]/[Ln(L_1)][L_2]$ (M^{-1}). [b] Determined by Ln(III)-induced ^{31}P NMR shifts (ref 26). [c] Determined by Nd(III)-induced relaxation rate enhancements: 7.5 ± 0.2 (ref 26). [d] Reference 27. [e] Reference 25.

k' are given, which are the slopes of the curves of ln ($[P_{3m}]_{tot,0}/[P_{3m}]_{tot}$) versus time at $t = 0$. Compared to the uncatalyzed case, 1 mol equiv of La(NTA) caused an initial acceleration with a factor of 726, while the corresponding La(EDTA) catalyzed reaction was only 8 times faster. It can also be seen that $La(NTA)_2$ (P_{3m}:La:NTA = 2:1:2) is not catalytically active, while the activity with P_{3m}:La:NTA = 2:2:3 is exactly the same as for that with P_{3m}:La:NTA = 2:1:1, which demonstrates that in the former case the reactivity can be fully attributed to La(NTA), and not to traces of free La(III).

Stabilities of Intermediate Complexes. The formation constants of the mixed ligand complexes $Ln(L_1)(L_2)$, in which L_1 is NTA or EDTA, and L_2 is a phosphate ligand, have been determined and are collected in Table 2. All stabilities were determined at 298 K in order to prevent decomposition of L_2 by hydrolysis, as was verified. For the complexes of the linear phosphates (PPP, PP, and P), the stabilities were investigated by potentiometry, because these ligands have pK_as which are in the neutral pH region.[25] Also included in Table 2 are literature values for the highest pK_a of L_2.[25] For Nd(NTA)(PPP), Nd(III)-induced ^{31}P NMR shifts and relaxation rate enhancements were measured in a competition experiment of $Nd(NTA)_2$ with PPP.[26] From these data, a stability constant was calculated which was in good agreement with that obtained by potentiometry. Details of these measurements have been described elsewhere.[26] The stabilities of $Ln(L_1)(OH)$ were determined by potentiometry.

The highest pK_a of P_{3m}, which is about 2,[27] is far too low to allow potentiometric determination of the stability of $Ln(L_1)(P_{3m})$; at neutral pH, complexation of P_{3m} with $La(L_1)$ will cause no pH effect. Therefore, the amounts of $Ln(L_1)(P_{3m})$ (Ln = La, Nd) were determined directly by Ln(III)-induced ^{31}P NMR shifts at different concentrations of P_{3m} and different ratios of P_{3m} to $Ln(L_1)$.[26] As can be seen from Table 2, PPP and PP behave as relatively strong ligands under the conditions employed in the hydrolysis reactions (pH = 7) and the NMR measurements, while P_{3m} is a rather weak ligand. The coordination of monophosphate (P) is much stronger with L_1 = NTA than with L_1 = EDTA.

Structure of Intermediate Complexes. The number of water molecules present in the first coordination sphere of the mixed ligand complexes $Ln(L_1)(L_2)$ was investigated by Dy(III)-induced ^{17}O shift measurements. The contact contribution to the paramagnetic Ln(III)-induced shift (LIS) of a Ln(III)-bound ^{17}O nucleus is almost independent of the nature of the ligand in question as well as of other ligands coordinated to the same metal ion.[28] Therefore, these shifts are useful for the determination of the hydration numbers and, hence, the complex stoichiometry,[29] provided that the ligand denticity is known. The use of Dy(III) is advantageous, since for this Ln(III) ion the contact term dominates (usually >85%) and then a laborious dissection of the observed shift into the contact, pseudocontact, and diamagnetic contributions can be avoided. The exchange between bound and bulk water is fast on the NMR time scale. Accordingly, the observed LIS represents a concentration weighted average of the shifts of the individual species in solution.[29]

The number of coordinated water molecules (N_w) in the complexes $Dy(L_1)(L_2)$ was examined by measuring the ^{17}O water shift at 333 K of an aqueous solution of L_2 at varying amounts of $Dy(L_1)$ and plotting the chemical shift (δ) versus ϱ_w ($=[Dy]_{tot}/[H_2O]$). By comparison of the initial slope, *a*, of these curves with the slope, a_{Dy}, of a calibration line,[30] obtained by addition of $DyCl_3$ to water, N_w was calculated, according to eq 5.

$$N_w = CN_{Dy}(a/a_{Dy}) \tag{5}$$

In the absence of other ligands, the number of coordinated water molecules of the Dy(III) aquo ion (CN_{Dy}) is 8.[31-33] However, upon complexation of a ligand and especially in the case of the formation of ternary complexes, the coordination number may increase to 9, owing to steric effects and the repulsion between negatively charged ligands. Experimental slopes and calculated numbers of coordinated water molecules in $Dy(L_1)(L_2)$ are given in Table 3.

For $L_2 = P_{3m}$, the stability of $Ln(L_1)(L_2)$ and the solubility of $Ln(L_1)$ and L_2 are too low to obtain complete formation of this ternary complex. So, a correction was needed for the amount of uncomplexed $Dy(L_1)$. This was achieved by calculation of the mole fraction, *f*, of $Dy(L_1)$ present in the complex $Dy(L_1)(L_2)$ from estimated stabilities with eq 6.

$$f = [Dy(L_1)(L_2)]/[Dy(L_1)]_{tot} = K[L_2]/(K[L_2] + 1) \tag{6}$$

At low $[Dy(L_1)]_{tot}$, $[L_2] \approx [L_2]_{tot}$. Then, the corrected slope, a_c, was obtained from the experimental slope (*a*) and the slope of the line for the addition of $Dy(L_1)$ to water (a_{DyL1}), according to eq 7.

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Table 3. Initial Slopes of ^{17}O Water Shift versus $\varrho_w = [Dy(L_1)]/[H_2O]$ at 333 K and Number of Coordinated Water Molecules in the Complexes $Dy(L_1)(L_2)$

L_1	L_2	$-a$ (10^3 ppm)	N_w[a]
none	none	18.0	8.0
NTA	none	8.7	3.9
	P_{3m}	4.7	2.0[b]
	PPP	3.5	1.6
EDTA	none	4.6	2.0
	P_{3m}	3.6	1.5[b]
	PPP	2.0	0.9
	PP	1.6	0.7
	P	2.7	1.2

[a] ±0.2 (estimated from the experimental error of a). [b] ±0.3, after correction for the amount of complexed P_{3m}; $K = [Dy(L_1)(P_{3m})]/[Dy(L_1)][P_{3m}]$. L_1 = NTA, log $K = 2.1 \pm 0.3$; L_1 = EDTA, log $K = 1.3 \pm 0.3$.

$$a = fa_c + (1 - f)a_{DyL1} \tag{7}$$

The stability constants of $Ln(L_1)(L_2)$ tend to increase slightly across the Ln(III) series. Therefore, from the stability constants given in Table 2, the log K values of $Dy(L_1)(P_{3m})$ are estimated to be 1.3 and 2.1 for L_1 = EDTA or NTA, respectively. No corrections for the temperature difference between the stability constant determinations and the ^{17}O NMR measurements have been made. From these values and the concentration of P_{3m} (0.21 M and 0.093 M, respectively), f was calculated to be 0.81 and 0.92, respectively. The large inaccuracy of the stability constant of $Dy(L_1)(P_{3m})$ had only a small effect on the error in a_c, and, therefore, the standard deviation of the corresponding N_w is only slightly higher than that of the other data.

The geometry of the phosphate ligand L_2 and the aminopolycarboxylate ligand L_1 in the ternary complexes $Ln(L_1)(L_2)$ was studied by measurement of Nd(III)-induced ^{31}P and ^{13}C longitudinal relaxation rate enhancements. The relaxation rate enhancement, RE, of a nucleus i of a ligand coordinated to Ln(III) can be calculated from the longitudinal relaxation times, T_1, according to eq 8, provided that the T_1 values are significantly greater than the mean residence time of the ligand in the first coordination sphere of the metal ion.[34-36]

$$n\varrho RE_i = (1/T_1)_i - (1/T_1)_{0,i} \tag{8}$$

In eq 8, $(1/T_1)_i$ and $(1/T_1)_{0,i}$ are the longitudinal relaxation rates in the presence and absence of Ln(III), respectively, n is the number of ligands present in the complex, and ϱ is the metal-to-ligand ratio. Geometrical information can be obtained from the difference in relaxation rate caused by complexation to Nd(III) and La(III), with the use of eq 9.

$$RE_i^{Nd} - RE_i^{La} = C/r_i^6 \tag{9}$$

Here, r_i is the distance between the Ln(III) center and the nucleus i under investigation, and C is a nucleus dependent constant, which is given by eq 10.

$$C = (4/3)(\mu_0/4\pi)^2\mu^2\gamma^2\beta^2T_{1e} \tag{10}$$

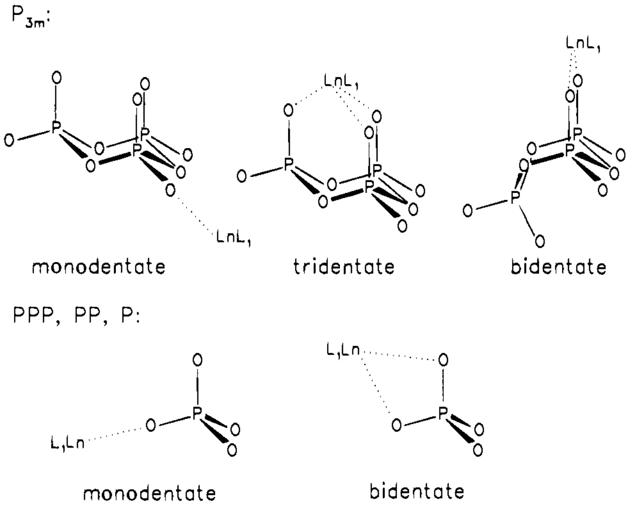
Here, $\mu_0/4\pi$ is the magnetic permeability of a vacuum, μ is the effective magnetic moment of Nd(III), γ is the magnetogyric ratio, β is the Bohr magneton, and T_{1e} is the longitudinal electron spin relaxation time. Equation 10, can be deduced from the Solomon–Bloembergen equation.[37,38] For Nd(III), T_{1e} is dominating the correlation time (τ_c) and then $\omega_I^2\tau_c^2 \ll 1$ and $\omega_s^2\tau_c^2 \ll 1$. T_{1e} (1.15×10^{-13} s for the Nd(III) aquo ion) is shown to be rather independent of the ligation of the Ln(III) cation.[39] Therefore, for ^{13}C and ^{31}P, the value of C is estimated to be 8.08×10^3 and 2.09×10^4 Å^6 s^{-1}, respectively.

Table 4. ^{31}P Relaxation Rate Enhancements[a] for L_2 in the Ternary Complexes $Nd(L_1)(L_2)$ Measured at 298 K and Predicted Values from Crystal Structure Data

			PPP[b]			
		P_{3m}	P_1	P_2	PP	P
L_1	NTA	6.4[c]	13.7	12.3		
	EDTA	5.5[c,d]	14.8	12.6	9.0	15.4
n	1	1.7	6	4.6	5.8	4.6
	2	4.4	32	29.9	31	29.9
	3	6.5				

[a] In s^{-1}; ± 0.5 s^{-1}; measured at 81.0 MHz. [b] P_1, terminal phosphate group; P_2, middle phosphate group. [c] After correction for the amount of complexed P_{3m}. [d] ± 1.0 s^{-1}, due to a low bound fraction (0.2).

Scheme 2



In Table 4, the bound ^{31}P REs of the phosphate ligands, L_2, in the ternary complexes $Nd(L_1)(L_2)$ are presented. The REs were determined by measurement of T_1 of L_2 in aqueous samples of L_2 at varying amounts of LnL_1 (Ln = La, Nd). The La(III)-induced REs were negligible (for ^{31}P). The denticity, N_P, which is the mean number of coordination sites on the Ln(III) ion that is occupied by L_2, was calculated from these data by comparison of the experimental REs with calculated values for structural models of the various possible coordination modes and related crystal structure data[40-43] (see Scheme 2: Table 4), as outlined below.

The coordination of P_{3m} in $Ln(NTA)(P_{3m})$ is tridentate, as can be seen by the excellent match between observed and calculated RE for this coordination mode. In $Ln(EDTA)(P_{3m})$, a somewhat lower RE is observed. It is possible that in this case P_{3m} is bound in a bidentate fashion and adopts a boat conformation (N_P = 2), as is found in some crystal structures.[44,45]

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Table 5. Denticities of L_1 and L_2 and Number of Coordinated Water Molecules in $Ln(L_1)(L_2)$

L_1	L_2	N_w[a]	N_P[b]	N_C[c]
NTA	none	3.9		4.1[d]
	P_{3m}	2.0	3.0	4.0
	PPP	1.6	3.9	3.5
EDTA	none	2.0		6.0[d]
	P_{3m}	1.5	2.0, 2.6[e]	5.5, 4.9[e]
	PPP	0.9	4.0	4.1
	PP	0.7	2.3	6.0
	P	1.2	1.4	6.4

[a] ±0.2. [b] ±0.1. [c] ±0.3. [d] $CN_{Ln} = 8$. [e] See text: bidentate coordination or mixture of tri- and monodentate, respectively.

Alternatively, the experimental RE can be explained by a mixture of 21% mono- and 79% tridentate coordination ($N_P = 2.6$). From the RE data alone, no distinction between these possibilities can be made.

The linear phosphates PPP, PP, and P are rather flexible, which means that no rigid ligand structure within the complex was observed but an averaged one. This is reflected in the REs, which are between the expected values for mono- and bidentate coordination for all acyclic phosphates. The mole fraction m_n of the phosphate group with denticity n (1 or 2) can be calculated from eq 11.

$$RE_{exp} = \sum m_n RE_{calc,n} \tag{11}$$

Then, the overall denticity of the ligand, N_P, was found, according to eq 12.

$$N_P = \sum n m_n p \tag{12}$$

Here, p is the number of magnetically different P atoms in ligand L_2, so: $p = 1$ for P and P_2 of PPP; $p = 2$ for PP and P_1 of PPP. The denticity obtained for PPP (4.0) was in excellent agreement with the coordination behavior observed for $Ln(PPP)_2$.[46]

The denticity, N_C, of the aminopolycarboxylate ligand, L_1, can be estimated from the phosphate denticities, N_P, and the number of coordinated water molecules, N_w, according to eq 13.

$$CN_{Ln} = N_P + N_C + N_w \tag{13}$$

As already mentioned for Dy(III), the coordination number, CN_{Ln}, of a Ln(III) ion is between 8 and 9. We used 9 in the calculations of the denticities, N_C, of the ternary complexes, because of electronic repulsion and steric hindrance between the two ligands within the complex (see Table 5). For the binary complexes LnL_1, a coordination number of 8 was assumed, as for the Ln(III) aquo ion.[31-33]

As can be seen in Table 5, the normal denticity N_C of 4 (complete coordination by N and each carboxylate group) was found for NTA, except in the ternary complex with Nd(III) and PPP. For EDTA, a substantial deviation of the expected denticity of 6 (coordination of both N atoms and all four carboxylate groups) was observed only for the ternary complexes with Nd(III) and P_{3m} or PPP. The value of 6.4 for the denticity of EDTA in Ln(EDTA)(P) is probably due to a mixture of 8- and 9-coordinated Ln(III) species. For the ternary complexes $Ln(L_1)(PPP)$ and $Ln(EDTA)(P_{3m})$, the coordination of L_1 was further investigated by ^{13}C RE measurements. The relaxation rates ($1/T_1$) of the complexes involved are listed in Table 6.

Table 6. ^{13}C Relaxation Rates[a] of L_1 in $Ln(L_1)(L_2)$ measured at 298 K and Predicted Values from Crystal Structure Data

L_1	complex	COO	CH$_2$COO	NCH$_2$CH$_2$N
NTA	NTA	0.0	1.2	
	La(NTA)	0.1	2.3	
	Nd(NTA)	8.1	8.6	
	Nd(NTA)(PPP)	5.9	8.7	
	calcd: Nd(NTA)	9.2/0.8[c]	7.5	
EDTA	EDTA	0.1	2.2	2.7
	La(EDTA)	0.2	6.8	7.3
	Nd(EDTA)	11.5	12.5	14.5
	Nd(EDTA)(P_{3m})[b]	11.2	12.8	14.0
	La(EDTA)(PPP)	0.2	6.8	7.5
	Nd(EDTA)(PPP)	5.8	13.1	13.1
	calcd: Nd(EDTA)	11.3/0.9[c]	12.0	13.6

[a] In s^{-1}; for Ln = Nd, ±0.5 s^{-1}, others, ±0.2 s^{-1}. [b] Without correction for the fraction of Nd(EDTA) not bound to P_{3m}, which was about 0.7 in the sample. [c] For coordinated and uncoordinated carboxylate group, respectively.

The obtained relaxation rates were compared with REs calculated from crystal structure geometries for Ln(NTA) and Ln(EDTA),[47,48] using eq 9. The values for the binary complexes $Ln(L_1)$ agreed very well with a tetradentate coordination mode for NTA ($N_C = 4$) *via* nitrogen and the three carboxylate groups and analogous hexadentate coordination for EDTA ($N_C = 6$). However, for the ternary complexes with PPP, the average REs for the carboxylate carbons were lower for both NTA and EDTA, compared to the binary complexes. For NTA, the observed REs are in excellent agreement with tridentate coordination ($N_C = 3$) *via* nitrogen and only two carboxylate groups, while EDTA is coordinated in a tetradentate fashion ($N_C = 4$) *via* the two nitrogen atoms and two of the four carboxylates. These results are in accordance with the number of coordinated water molecules and the denticity of PPP, as shown in Table 5.

For the ternary complex $Ln(EDTA)(P_{3m})$, ^{13}C REs showed complete coordination of EDTA ($N_C = 6$), as expected from the low stability of complexation of P_{3m} to Ln(EDTA). From the values for N_w and N_C, it is estimated that there are only 1.5 sites (N_P) available for coordination of P_{3m}. This agrees better with the bidentate coordination mode ($N_P = 2$) than with a mixture of mono- and tridentate coordination ($N_P = 2.6$). So very probably, the ring of P_{3m} adopts the boat conformation in the ternary complex with Ln(EDTA).

Discussion

Kinetic Model of the Hydrolysis of Trimetaphosphate. The kinetic data of the hydrolysis of P_{3m} were fitted with a model in which all phosphate ligands, L_2, form complexes with $La(L_1)$, and in which both free and Ln(III) coordinated P_{3m}, PPP, and PP hydrolyze (see Scheme 3). We focused our attention on the hydrolysis of P_{3m} catalyzed by La(NTA), because the inhibition by the linear phosphate products was more pronounced than in the reaction catalyzed by La(EDTA).

The log K_i and the $k_{i,c}$ values (Table 7) were varied until an optimal fit was obtained between the experimental and the calculated phosphate ligand concentrations for the hydrolysis reactions catalyzed by La(NTA). Examples of the fit of the speciation of the reaction, catalyzed by 0.5 and 0.1 equiv of La(NTA), are shown in Figure 1a and 1b, respectively. Here, total concentrations of the phosphate ligands are given, which include both free ligand and complexed form.

The stabilities of the ternary complexes of P_{3m} and P with La(NTA) are somewhat lower than those obtained by NMR and

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Scheme 3

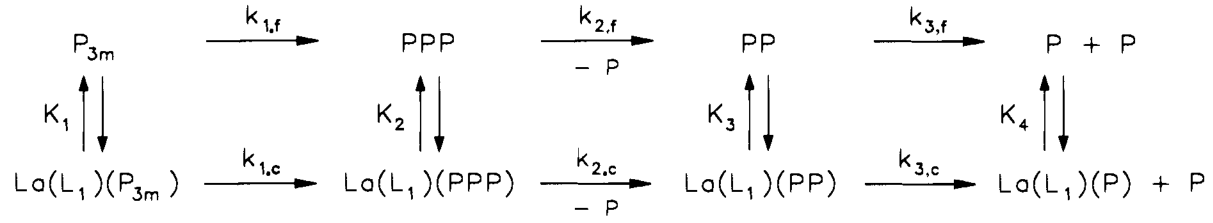

Table 7. Parameters for the Speciation Model of the Hydrolysis of P_{3m} Catalyzed by La(NTA) at 343 K, and pH 7, As Obtained by Minimization of the Differences between the Experimental and Calculated Phosphate Ligand Concentrations

i	log K_i[a]	$k_{i,f}$ (h^{-1})	$k_{i,c}$ (h^{-1})
1	1.5	0.00062[b]	1.5 ± 0.1
2	7.1	c	0.25 ± 0.05[d]
3	5.9	c	0.08 ± 0.03[e]
4	9.1		

[a] ±0.2; K = [La(NTA)(L_2)]/[La(NTA)][L_2] (in M^{-1}). [b] Experimental values; see Table 1. [c] Not incorporated into the model because the free ligand concentrations of PPP and PP were too low to contribute to the hydrolysis of these species. [d] Experimental value, 0.2, obtained from a similar hydrolysis reaction with PPP as the starting material. [e] Experimental value, 0.08; see footnote *d*.

potentiometry (Table 2), probably owing to the higher temperature in the hydrolysis reactions. This probably also holds for PP and PPP, but the relevant stability constants are relatively high, and, consequently, the hydrolysis of free PPP and PP is negligible in these cases. The high initial hydrolysis rate is mainly determined by $k_{1,c}$ and K_1, while after that the reaction course is largely influenced by the competition between P_{3m} and P for complexation to Ln(L_1). Competition between P_{3m} and PPP or PP was of little importance, because both PPP and PP hydrolyze fast enough to maintain low concentrations. The rate constants $k_{2,c}$ and $k_{3,c}$ for the catalyzed hydrolysis were modelled for optimal fit between experimental and calculated concentrations of PPP and PP. These rate constants agree reasonably well with experimental values obtained by a hydrolysis reaction with PPP as the starting material (see Table 7).

Structure and Stability of Intermediate Complexes. The pK_as of P_{3m} are much lower than those of the linear phosphates owing to the lack of phosphate termini in the former. This results in much higher complex stabilities of the complexes of Ln(NTA) with all linear phosphates than that of the complex with P_{3m}. This explains the product inhibition observed in the hydrolysis of P_{3m} catalyzed by Ln(NTA). The kinetic model, however, shows that competition for complexation with Ln(NTA) between P_{3m} and P is more important than between P_{3m} and PPP or PP.

The much lower stepwise stability constant of PPP with Ln(EDTA) than with Ln(NTA) is not caused by a low affinity for PPP, for the denticity of PPP is 4 in both Nd(NTA)(PPP) and Nd(EDTA)(PPP). Apparently, the coordination of PPP to Ln(L_1) leads to a relatively large steric strain and electronic repulsion, which is also reflected in the decomplexation of two carboxylate groups of EDTA upon coordination of PPP to Ln(EDTA) (see Table 6).

The denticity of P_{3m} in Ln(NTA)(P_{3m}) was determined to be 3, while in Ln(EDTA)(P_{3m}) it is about 2. It can be concluded that in the latter P_{3m} probably adopts a bidentate coordination mode, in which the ring of P_{3m} has the boat conformation.

Reaction Mechanism of the Hydrolysis of Trimetaphosphate. Obviously, the rate constant $k_{1,c}$ (1.5 h^{-1}) of the hydrolysis of P_{3m} in the complex Ln(NTA)(P_{3m}) (Table 7) is higher than the reaction rates shown in Table 1. This can be explained by the weak complexation of P_{3m} with Ln(NTA) under the experimental conditions. When it is assumed that the stability of La(EDTA)(P_{3m}) at 363 K is somewhat lower (log K = 1.0) than at 298 K as found for La(NTA)(P_{3m}), $k_{1,c}$ for La(EDTA) can be calculated to be 0.030 h^{-1}. So, the hydrolysis of P_{3m} in the complex with La(NTA) is 2400 times higher than the uncatalyzed reaction at pH 7, while the complex with La(EDTA) reacts only 48 times faster. Because the initial hydrolysis rates of P_{3m} with different La(NTA) concentrations can all be fitted with the same complexation constant for La(NTA)(P_{3m}) and the same hydrolysis rate constant, it is concluded that the assumption made in the modelling that the reaction is first order in La(III) is correct. Therefore, the catalytically active species contains only one metal center. This agrees with the Ln(III) catalyzed hydrolysis of 2′,3′-cUMP.[8]

The coordination of P_{3m} is tridentate in the ternary complex with Ln(NTA), and probably bidentate in the complex with Ln(EDTA). However, we do not believe that the difference between chair and boat conformation of P_{3m} in La(NTA)(P_{3m}) and La(EDTA)(P_{3m}), respectively, creates a large difference in accessibility for uncoordinated hydroxide. P−O bond activation of P_{3m} upon complexation can be studied by diamagnetic La(III)-induced ^{31}P shifts, which may give information on the charge density of the P atom(s). Analogously, the introduction of a positive charge on the terminal carbon atom of unsaturated carboxylic acids upon complexation to Ln(III) has been shown in Ln(III) catalyzed Michael-type additions.[30] The bound La(III)-induced ^{31}P shift for P_{3m} is about 1 ppm for both La(NTA) and La(EDTA).[26] This means that, per P atom, the induced chemical shift is even larger with La(EDTA) than with La(NTA), because the denticity of P_{3m} is 2 with the former and 3 with the latter. However, this rather small chemical shift difference may also be ascribed to the difference in coordinating geometry. So, it is unlikely that the large difference in hydrolysis rate between La(NTA)(P_{3m}) and La(EDTA)(P_{3m}) can be explained by a difference in complex geometry or activation of P_{3m} within the complex.

Most likely, hydrolysis of P_{3m} in La(L_1)(P_{3m}) leads to La(L_1)(PPP) with a tridentately coordinated PPP, after which ligand rearrangement takes place. As already discussed, the stepwise stability constant of La(EDTA)(PPP) is much lower than that of La(NTA)(PPP). Because of the larger steric hindrance and electronic repulsion for complexation with La(EDTA), the complexation strength of the initially formed tridentate PPP will also be lower with La(EDTA). Consequently, the driving force for the catalyzed hydrolysis, which has a contribution from the gain in free energy of complexation going from complexed P_{3m} to complexed PPP, will be higher with La(NTA) as the catalyst. This may suggest a smaller free energy of activation for L_1 = NTA than for L_1 = EDTA.

In Table 2 are also included the stabilities of La(L_1)(OH), as determined by potentiometry and given as stepwise stability constants K (=[La(L_1)(OH)]/[La(L_1)][OH]). As can be calculated from the large log K difference of 2.9, the fraction of La(L_1) present as La(L_1)(OH) at pH 7 is 800 times higher for

NTA (5×10^{-3}) than for EDTA (6×10^{-6}). In fact, at pH 7 and $[La(L_1)]_{tot} = 0.02$ M, the concentration of La(EDTA)(OH) is about the same as the free hydroxide concentration, while the concentration of La(NTA)(OH) is about 800 times higher. Of course, the deprotonation of a coordinated water molecule will be harder in the ternary complex with P_{3m}, but we believe that the difference between NTA and EDTA will be maintained. It is, however, not possible to determine the (quaternary) stability constant of $La(L_1)(P_{3m})(OH)$, because P_{3m} hydrolyzes in this complex too fast to allow potentiometric titration even at room temperature. Furthermore, there may be some difference in reactivity between a hydroxide anion coordinated to La(NTA) or La(EDTA). From this evaluation, we conclude that, at pH 7, the hydrolysis in the La(NTA) catalyzed reactions is initiated by attack of a coordinated hydroxide anion on a complexed P_{3m}, while in the La(EDTA) catalyzed reactions both coordinated and free hydroxide anions react with complexed P_{3m}.

This mechanism of attack by coordinated hydroxide is found to be crucial in the hydrolysis of PPP[49] and ATP[7] catalyzed by Co(III) complexes, and the metal ion promoted hydrolysis of 2′,3′-cUMP,[8] as concluded by evaluation of hydrolysis reactions performed at different pHs. In the Ln(III) catalyzed hydrolysis of a phosphate diester,[2] no evidence was found for coordinated hydroxide initiation, in contrast to the Ln(III) catalyzed hydrolysis of ATP,[7] where some support was found for the presence of coordinated hydroxide, despite the fact that precipitation of $LnPO_4$ occurred. The mechanism of attack by coordinated hydroxide is in accordance with the extremely high acceleration factors (10^6 to 10^9) found in the hydrolysis of nucleic acids catalyzed by Ln(III) hydroxide slurries.[8,9,12] In our case, an acceleration factor of at least 5×10^5 for La(NTA)-(P_{3m})(OH) can be estimated, assuming that no increase in the pK_a of coordinated water takes place going from La(NTA) to La(NTA)(P_{3m}).

Conclusions

The hydrolysis of P_{3m} is catalyzed remarkably by La(NTA), but only moderately by La(EDTA). There may be some structural differences between the ternary complexes with P_{3m}, but no difference in P−O bond activation of P_{3m} itself was found, as shown by the equal values for the La(L_1)-induced ^{31}P NMR shift of P_{3m} for L_1 = EDTA and NTA. Therefore, the hydrolysis proceeds *via* attack of coordinated hydroxide on P_{3m} in the La(NTA) catalyzed reactions, while, in the La(EDTA) catalyzed reactions, the reaction probably proceeds *via* both coordinated and noncoordinated hydroxide. Probably, also the larger stability difference for complexation with La(NTA) upon hydrolysis of $La(L_1)(P_{3m})$ to $La(L_1)$(PPP) contributes to the larger catalytic activity of La(NTA).

The combination of several multinuclear magnetic resonance techniques and potentiometry provides a complete view of the coordination behavior of both the aminopolycarboxylate ligands, NTA and EDTA, and the phosphate ligands in their ternary complexes with Ln(III). The complexation of PPP to Ln(L_1) causes the decomplexation of one or two carboxylate groups of NTA or EDTA, respectively.

Stabilities and kinetic data led to the model for the hydrolysis of P_{3m}, in which the initial reaction rate is determined by the complex stability of $Ln(L_1)(P_{3m})$ and its reaction rate constant, while the competition between P_{3m} and P for coordination to Ln(L_1) plays an important role upon progress of the reaction.

Experimental Section

Materials. All compounds were purchased from Janssen Chimica. The sodium salts of P_{3m} and PPP were technical grade and were purified by recrystallization from water−ethanol mixtures.[50] NTA was obtained as the free acid, EDTA as the trisodium salt. Water used in the hydrolysis reactions, the potentiometric titrations, and the NMR measurements was demineralized. Lanthanum chloride was obtained as a mixed hydrate; the La(III) content was determined by complexometric titration with xylenol orange as the indicator.[51] Nd(III) and Dy(III) chloride were obtained as the hexahydrate and used as such. Sodium perchlorate was obtained as the dihydrate. In the NMR measurements, Ln(NTA) and NaLn(EDTA) were used, which were prepared by addition of a stoichiometric amount of $LnCl_3$ to a solution of the sodium salt of NTA or EDTA and subsequent lyophilization.

Calculations. The calculations for the potentiometric titrations were performed using a spreadsheet program.[52,53] For each point of the titration, the speciation and the stability constant were determined. The obtained stability was used as verification in a speciation simulation, generating pH values. In all cases, good agreement between the calculated pH curve and the experimental one was observed.

The same spreadsheet program was used for the calculation of the kinetic model. Each line in the spreadsheet contained the speciation for one point of time. The mass balances for P_{3m}, PPP, PP, and P were adjusted using the hydrolysis rate constants as given in Table 7. A simplex algorithm was used to calculate the mass balance in a time interval from that of a previous one. Convergence of the speciation and the reaction kinetics were obtained simultaneously. Time intervals of 0.1 h were used; decrease to 0.05 h gave the same speciation curves.

Hydrolysis Reactions. The catalyst solution was prepared by dissolving the appropriate amounts of $LaCl_3$ and NTA or EDTA in 100 mL of water, and adjustment of the pH to 7.0 with 1 M aqueous NaOH. The solution was stirred and heated to 343 K. The reaction was started by the addition of P_{3m} to the solution. The pH was maintained at 7.0 by continuous addition of aqueous NaOH. The concentration of the NaOH titrant was chosen (0.1−1 M) in such a way that pH fluctuations were below 0.1 pH unit. Analyses were performed by ^{31}P NMR. Samples of 2 mL were taken, cooled to room temperature, and DOWEX-H^+ was added to remove La(III). After filtering off the DOWEX, 3 mL of D_2O was added, and the pH was raised to 9 to obtain good resolution of all ^{31}P resonances. It was checked that none of the phosphate ligands was hydrolyzed during the sample preparation. An analogous hydrolysis reaction was performed using PPP as the starting material.

Potentiometry. The potentiometric titrations were conducted at 298 K in a jacketed vessel. Millivolt readings, obtained with a glass electrode, were converted to pH values using a calibration curve, which was determined from standard buffer solutions. The ionic strength was maintained constant at 0.1 M using $NaClO_4$. The stabilities of the ternary complexes of Ln(NTA) with PP and PPP were determined in competition experiments: 0.01 M $Ln(NTA)_2$ was titrated with 0.02 M Na_4HPPP or 0.02 M Na_3HPP. The formation constants of the complexes of Ln(L_1) with P were determined by titration of 0.01 M LnL_1 (Ln(NTA) or NaLn(EDTA)) in the presence of 0.001 M L_1 (Na_3-NTA or Na_4EDTA) with 0.01 M Na_2HP. For the ternary complexes of Ln(EDTA) with PPP and PP, 0.01 M NaLn(EDTA) in the presence of 0.005 M Na_4EDTA was titrated with 0.02 M Na_4HPPP or 0.02 M Na_3HPP. The complexation constant of La(NTA)(OH) was determined by titration of 0.01 M La(NTA) in the presence of 0.001 M Na_3NTA with 0.1 M or 0.01 M NaOH, and that of La(EDTA)(OH) by titration of 0.05 M NaLa(EDTA) in the presence of 0.005 M Na_4EDTA with 0.1 M NaOH. Some of these titrations were repeated and always found to reproduce well. All calculations were performed with a spreadsheet program as described above.

NMR Measurements. All measurements were performed on a Nicolet NT-200 WB NMR spectrometer at a temperature of 295 K,

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unless stated otherwise. The aqueous samples were measured in the presence of 30% D_2O for locking.

The ^{31}P NMR shift and longitudinal relaxation rate measurements were performed at 81.0 MHz. Phosphoric acid (1%) was used as an external standard. Sample preparation for the hydrolysis analyses as described above. For PPP, PP, and P, La(L_1) or Nd(L_1) was added stepwise (0 to 2 equiv) to a solution of the phosphate ligand (0.02 M). The pH was about 7 for PPP and PP, and about 9 for P. The ^{31}P NMR shifts and REs were determined simultaneously, using the inversion recovery pulse sequence. Recycle times were 20−30 s for the free ligand solutions and for the La(III)-induced REs. For the Nd(III)-induced REs, recycle times were diminished from 30 to 2 s upon increase of the amount of Nd(III). The relaxation times were calculated with the aid of a nonlinear least-squares three parameters curve fitting routine.[54] For P_{3m}, the shift measurements have been described previously, together with the stability determinations.[26] The relaxation rate was determined by plotting $1/T_1$ versus the chemical shift for various metal-to-ligand ratios, and extrapolation to the bound shift.

The Dy(III)-induced ^{17}O water shift measurements were conducted at 27.1 MHz and at 333 K. Samples were prepared by stepwise addition (0 to 0.7 equiv) of Dy(L_1) to a solution of the phosphate ligand (L_1 = EDTA, $[L_2]_{tot}$ = 0.050 M, except for P_{3m}, 0.21 M; L_1 = NTA, P_{3m}, 0.093 M, PPP, 0.10 M). For the linear phosphates, straight lines were observed of the shift versus ϱ_w ($=[Dy]_{tot}/[H_2O]_{tot}$). For all ligands, the initial slopes were used (see Table 3). Calibration lines were obtained by stepwise addition of $DyCl_3$ or Dy(L_1) to 30% D_2O in water.

The ^{13}C relaxation times were measured at 50.3 MHz. *tert*-Butyl alcohol in D_2O was used as an external standard. The relaxation times the C atoms of L_1 in Ln(L_1) and Ln(L_1)(L_2) (see Table 6) were determined by measurement of a solution of the complex, using the same technique and calculation procedure as for the ^{31}P REs. Recycle times were between 30 and 150 s for the free ligand solutions and for the La(III)-induced REs. For the Nd(III)-induced REs, recycle times were diminished from 60 to 1 s upon increase of the amount of Nd(III).

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Supplementary Material Available: Experimental speciations of the hydrolysis reactions and ^{17}O shift and ^{31}P RE data (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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