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Structural and in vivo studies of metal chelates of Ga(III) relevant to biomedical imaging

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Abstract

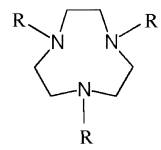
The solution chemistry and structure of the complex of the triazamacrocyclic ligand NOTP (1,4,7-triazacyclononane-1,4,7-tris(methylenephosphonate)) with Ga^{3+} in D_2O have been investigated by ^1H, ^{71}Ga and ^{31}P NMR spectroscopy. These NMR results show the presence of a 1:1 $Ga(NOTP)^{3-}$ complex, with a highly symmetrical, pseudo-octahedral geometry, possibly with a C_3 axis. The ^1H spectrum shows that the triazamacrocyclic chelate ring is very rigid, with all the ring protons non-equivalent. The complex is stable in aqueous solution in a wide pH range. Its high thermodynamic stability agrees well with previous results from biodistribution and γ imaging studies in Wistar rats with $^{67}Ga^{3+}$ chelates of triaza macrocyclic ligands, which showed that the neutral chelates $^{67}Ga(NOTA)$ (where NOTA is 1,4,7-triazacyclononane-1,4,7-triacetate) and $^{67}Ga(NOTPME)$ (where NOTPME is 1,4,7-triazacyclononane-1,4,7-tris(methylenephosphonate monoethylester)) have similar in vivo behaviour, with high stability and rapid renal excretion, but the high negatively charged $^{67}Ga(NOTP)^{3-}$ has a considerably slower kidney uptake and elimination.

Keywords: Gallium; Triazamacrocycle; Phosphonate; Structure; Biodistribution

1. Introduction

Polyazamacrocyclic ligands, with their specific coordination behaviour, highly selective and pH dependent, form stable complexes with a large number of metal ions [1], which have found a variety of analytical and biomedical applications [2–4]. The importance of complexes of gallium(III) in biomedicine has led to an increasing interest in its coordination chemistry. The positron-emitting radioisotope ^{68}Ga (β^+, $t_{1/2}=68$ min) is an important isotope for positron emission tomography (PET), while ^{67}Ga (γ, $t_{1/2}=3.35$ days) is a useful tracer in immunoscintigraphy [5]. Since both metal ions and free ligands have high toxicity, high thermodynamic and kinetic stability is required for chelates to be used in vivo, in order to ensure that the radiopharmaceutical remains intact during its lifetime in the body. The triazamacrocyclic ligands display a high conformational and size selectivity towards cations, and the high stability of their Ga^{3+} complexes, such as Ga(NOTA) [6], may arise from the good fit of the small metal ion (ionic radius 0.76 Å) in the triazacyclononane cavity [7]. This class of ligands seems to encapsulate the metal ion efficiently [6,8], insulating it from competing ligands, namely, from transferrin, the main competitor for Ga^{3+} in the bloodstream ($\log K_{ML}=20.3$ [9]).

We have previously reported [10] the in vivo behaviour of the $^{67}Ga^{3+}$ chelates of NOTA (1,4,7-triazacyclononane-1,4,7-triacetate), NOTP (1,4,7-triazacyclononane-1,4,7-tris(methylenephosphonate)) and NOTPME (the monoethyl ester of NOTP, 1,4,7-triazacyclononane-1,4,7-tris(methylenephosphonate monoethylester)) (Fig. 1). The γ imaging studies and biodistribution studies, performed in Wistar rats, have demonstrated that the neutral chelates $^{67}Ga(NOTA)$ and $^{67}Ga(NOTPME)$ show a much higher depuration efficiency and faster transit time through the kidneys than the negatively charged $^{67}Ga(NOTP)^{3-}$, a tracer which has slow uptake and long retention by these organs.



R= CH_2COOH NOTA

R = $CH_2PO_4H_2$ NOTP

R = $CH_2PO_2H(OC_2H_5)$ NOTPME

Fig. 1. Chemical structures of the triazamacrocyclic ligands investigated in this work.

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The main reason for this different in vivo behaviour may be the neutral versus negative charge of the complexes. All the three $^{67}Ga^{3+}$ complexes cleared the bloodstream rapidly, as shown by the observation that less than 0.03% of the injected dose stayed in the blood 30 min after administration, suggesting that the chelates remain intact during their transit time in the blood. For all $^{67}Ga^{3+}$ chelates after 24 h, almost all the radioactivity was cleared from tissues and organs, and no deposition of the complexes or any $^{67}Ga^{3+}$ particle in the liver–spleen region was observed. No evidence of bone marrow accumulation was found, which is seen when the Ga^{3+}–transferrin complex is formed [11].

Besides proving the high in vivo stability of these chelates, this study also illustrated how the biodistribution and excretion properties of complexes injected into the blood stream are influenced by their molecular size, molecular weight, charge and hydrophilicity [12,13]. Other examples are found in the literature of very stable complexes of ^{67}Ga with triazamacrocycles containing different pendant arms, conferring to some of them different biodistribution and clearance pathways [14–16]. High liver uptake was found for 2-nitroimidazole conjugates of ^{67}Ga(NOTA) [16], as opposed to ^{67}Ga(NOTA), and its tris(methylenemethylphosphinic acid) analogue, ^{67}Ga(NOTMP) [14,15]. Some hypoxic tumour localization was also found for both ^{67}Ga(NOTA) and its 2-nitroimidazole conjugate [15].

In the present work, the aqueous solution chemistry and structure of the complex of the triazamacrocyclic ligand NOTP (Fig. 1) with Ga^{3+} have been investigated by ^{1}H, ^{71}Ga and ^{31}P NMR spectroscopy, and the results obtained are compared with previous studies of chelates of this cation with the triazamacrocyclic ligands NOTA and DETA (1,4,7-triazacyclodecane-1,4,7-triacetate) [6,8,16,17]. This type of study is relevant in the correlation of the molecular properties of chelates with their in vivo pharmacokinetics, helping the design of new, more specific, radiopharmaceuticals.

2. Experimental

2.1. Reagents

The triazamacrocyclic ligands NOTA, NOTP and NOTPME were synthesized and characterized by NMR spectroscopy, as described elsewhere [18–20]. Other reagents and solvents were obtained from either Aldrich or Sigma and used as received. The purity of the ligands was checked by proton NMR spectroscopy.

2.2. NMR spectroscopic studies

For the NMR studies, complexes were prepared in D_2O (99.8% D) solutions at 10 mM concentrations, by adding stoichiometric amounts of the macrocyclic ligand to stock solutions of the gallium(III) nitrate. The pH of the solutions was adjusted with DCl and CO_2-free NaOD using a Crison MicropH 2002 pH-meter with an Ingold 405-M5 combined electrode. ^{1}H, ^{71}Ga and ^{31}P NMR spectra were recorded on a VARIAN UNITY-500 spectrometer (at an external field of 11.8 T) operating at 499.84, 152.40 and 202.34 MHz, respectively. The ^{1}H resonance shifts were measured relative to tetramethylsilane (TMS), and the ^{67}Ga and ^{31}P chemical shifts were measured relative to the $[Ga(H_2O)_6]^{3+}$ species present in a 0.1M $Ga(NO_3)_3$ solution in D_2O and H_3PO_4 (85% v/v), respectively, used as external references. ^{31}P NMR spectra were measured with broad-band proton decoupling. Assignments of the proton NMR spectra were based on literature data for similar systems, in the results of two-dimensional homonuclear correlation spectra (COSY) and on ^{31}P-decoupling effects. NMR spectra were obtained at temperatures from 293 to 353 K, in the pH range of 0.5 to 13.0. The experiments at variable temperature were run with a precision of ± 0.5 °C.

3. Results and discussion

The complexation behaviour of Ga^{3+} with NOTP (Fig. 1) in aqueous solution and the structure of the complex formed were studied by multinuclear NMR. The pH interval of stability for the complex was analysed by ^{71}Ga NMR, its protonation by ^{31}P NMR, and its structure and dynamics by ^{1}H and ^{71}Ga NMR.

The ^{71}Ga NMR spectrum of an aqueous solution containing Ga^{3+} and the ligand NOTP in a 10 mM concentration 1:1 stoichiometric ratio at pH 7 consists of a relatively narrow singlet at $\delta = 110$ ppm ($\Delta\nu_{1/2} = 434$ Hz) (Fig. 2(a)), which does not change appreciably in the pH range 2–10. This indicates the presence of a very stable $Ga(NOTP)^{3-}$ complex in aqueous solution, with a highly symmetric, possibly pseudo-octahedral geometry. In the pH range studied, the signal corresponding to the free cation $[Ga(H_2O)_6]^{3+}$ ($\delta = 0$ ppm) was not observable, but above pH 8 the signal from the $[Ga(OH)_4]^{-}$ species ($\delta = 222$ ppm) was present, implying that this complex is stable towards acid- and base-catalysed hydrolysis in the pH 2–8 interval. Ga^{3+} (ionic radius 0.76 Å) forms a more stable chelate with NOTA ($\log K_{ML} = 30.98$ for Ga(NOTA)) than Fe^{3+} (ionic radius 0.64 Å) ($\log K_{ML} = 28.3$ for Fe(NOTA)) [21]. Thus, if this trend applies to all triazamacrocyclic ligands, the $Ga(NOTP)^{3-}$ complex should have a very high thermodynamical stability, possibly even more stable than $Fe(NOTP)^{3-}$, which has a $\log K_{ML} = 29.6$ [18]. However, the triphosphonate $Ga(NOTP)^{3-}$ is less stable to hydrolysis at basic pH than the carboxylate analogue Ga(NOTA), which shows a very wide pH range (pH 0.7 to 12) of thermodynamic and kinetic stability towards acid- and base-catalysed hydrolysis [6,8]. $[Ga(OH)_4]^{-}$ starts to form at pH 8–9 for the phosphonate and only above pH 10 for the carboxylate [21]. Also, the hydroxo complex $[ML(OH)]^{-}$ forms at much higher pH for the Ga^{3+}–carboxylate complex (pH 9–10, $\log K_{Ga(NOTA)(OH)} = -9.7$ [21]) than for the Fe^{3+}–phos-

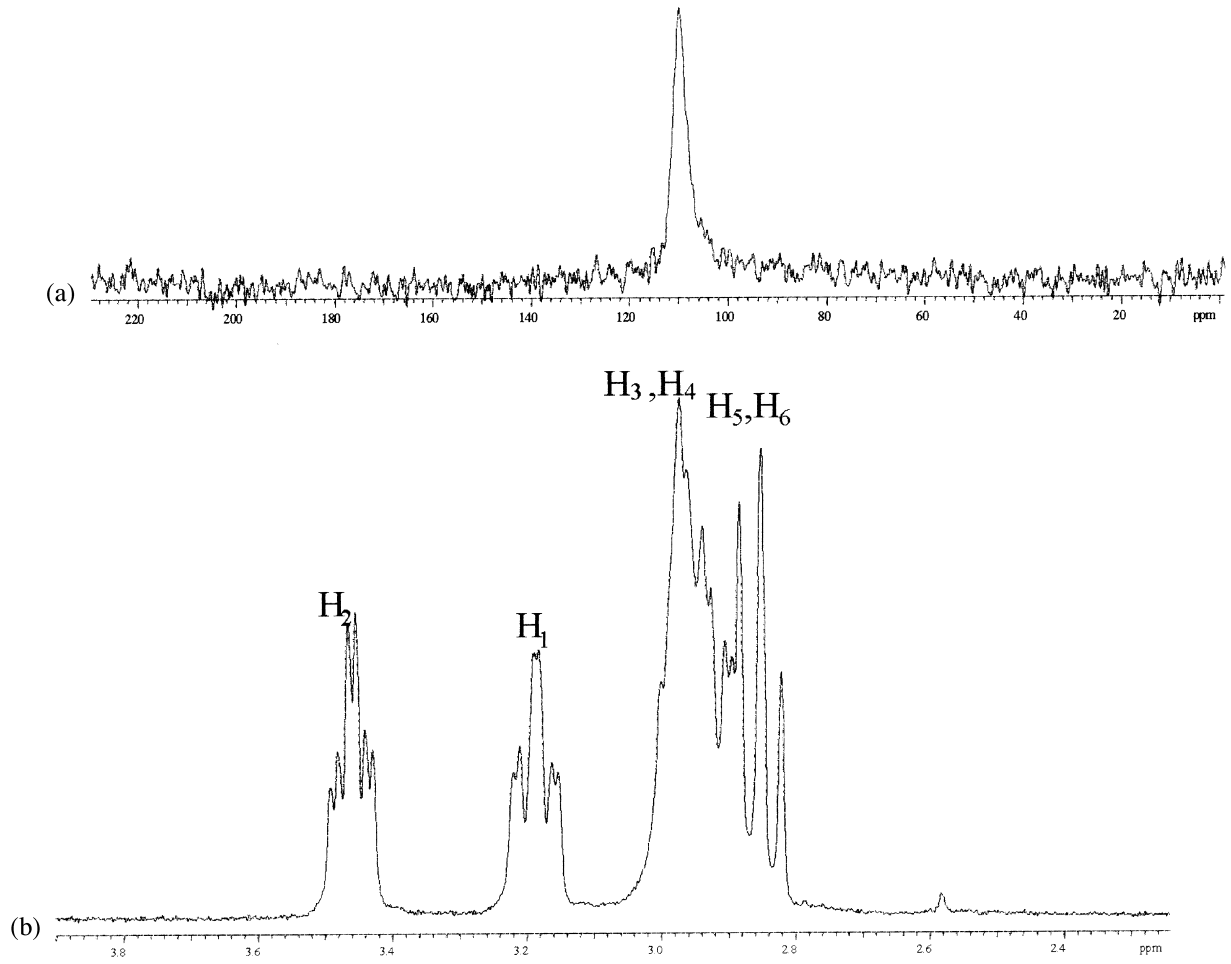

Fig. 2. NMR spectra of the 1:1 complex of Ga^{3+} and the ligand NOTP studied in aqueous solution (pH 7, 298 K, ligand and metal ion concentration of 10 mM): (a) ^{71}Ga NMR at 152 MHz; (b) ^{1}H NMR at 500 MHz.

phonate complex (pH 4–5, $\log K_{Fe(NOTP)(OH)} = -5.0$ [18]). The increased sensitivity to hydroxide attack of the phosphonate relative to the carboxylate chelate might result from the more open chelate bite angle N–M–O in the former, due to longer P–C and P–O bonds in the former than the C–O and C–C bonds in the latter [16].

Previous observations of narrow ^{71}Ga NMR signals for triazamacrocyclic chelates of Ga^{3+} are summarized in Table 1, and compared with the present results. A singlet at $\delta = 165$ ppm ($\Delta\nu_{1/2} = 1000$ Hz) was also obtained from ^{69}Ga NMR for Ga(NODASA) [23]. The ^{71}Ga shift observed for $Ga(NOTP)^{3-}$ is somewhat below the range observed for the other chelates, but is closer to Ga(NOTMP), indicating that the shift effect of the coordinated oxygens of the pendant arms decreases in the order carboxylate > phosphinate ester > phosphonate. The Ga(NOTA) complex has a highly symmetric crystal structure, with the Ga^{3+} cation in a slightly distorted octahedral coordination polyhedron, with two opposite almost parallel faces N_3 (from the three ring nitrogens) and O_3 (from the pendant carboxylate oxygens) [6,8,24]. The degree of distortion of the crystal structures of the triazamacrocycles of Ga^{3+} from a regular octahedral coordination is defined by the relative twist of the N_3 and O_3 planes from the symmetrical staggered conformation, which is 12.4° for Ga(NOTA) [6,8,24], 14.6° for Ga(NODASA) [23] and

Table 1
^{71}Ga NMR chemical shifts (δ_i (ppm)) and linewidths of some triazamacrocyclic complexes of Ga^{3+}

Complex	δ ^{71}Ga (ppm)	$\Delta\nu_{1/2}$ (Hz)
Ga(NOTP)	110	434
Ga(NOTA) [a]	171	210
Ga(NODASA) [b,c]	165	1000
Ga(DETA) [a]	132.5	2000
Ga(NOTMA) [d]	149	
Ga(NOTPP) [e]	132	560
Ga(NOTBzP) [f]	130	1220
Ga(NOTMP) [g]	139	200

[a] [6,8].
[b] NODASA is 1,4,7-triazacyclononane-1-succinic acid–4,7-diacetic acid.
[c] ^{69}Ga NMR signal.
[d] NOTMA is (*R*)-1,4,7-tris(2′-methylcarboxymethyl)-triazacyclononane) [17].
[e] NOTPP is 1,4,7-triyltrimethylenetris(phenylphosphinic acid) [16].
[f] NOTBzP is 1,4,7-triyltrimethylenetris(benzylphosphinic acid) [16].
[g] NOTMP is 1,4,7-triazacyclononane-1,4,7-tris[methylene(methylphosphinic acid)] [16,22].

10.4° for Ga(TS-TACN) (TS-TACN is 1,4,7-tris(2-mercaptoethyl)-1,4,7-triazacyclononane) [25]. The ^{71}Ga NMR ($I=3/2$, 39.6% natural abundance, quadrupolar moment 0.112 [26]) signal linewidths are determined by the quadrupolar relaxation induced by the electric-field gradients present in the distorted Ga^{3+} coordination polyhedron. Thus, they can be used as a sensitive measure of that degree of distortion in solution, corrected for changes of the rotational correlation time [16,26]. Based on the solution NMR and X-ray crystal data, such a relative degree of distortion can be proposed as: Ga(NOTA) ~ Ga(NODASA) ~ Ga(NOTMP) < $Ga(NOTP)^{3-}$ < Ga(NOTPP) ≪ Ga(NOTBzP) ≪ Ga(DETA) ≪ Ga(DOTRA) ≪ Ga(UNTA) (^{71}Ga signal linewidth is 3500 Hz for Ga(DOTRA) and no signal is observed for Ga(UNTA) [8]; UNTA is 1,4,7-triazacycloundecane-1,4,7-triacetate, DOTRA is 1,4,7-triazacyclododecane-1,4,7-triacetate [14]). The large ^{69}Ga signal linewidth of Ga(NODASA) relative to the X-ray defined octahedral distortion [23] results in part from a slower rotation of the chelate caused by the uncoordinated, heavily hydrated, β-carboxylate bound to one of the acetate arms of the NOTA-type structure, and also from the somewhat larger quadrupolar moment of the ^{69}Ga isotope relative to ^{71}Ga [26].

The Ga^{3+}/NOTP system displays only one ^{31}P NMR signal in the range of pH 2–12 studied, which indicates that the three phosphonate groups are equivalent, possibly coordinating the metal ion through one negatively charged oxygen in the $Ga(NOTP)^{3-}$ chelate. Since the ^{1}H NMR spectra (see before) are consistent with slow Ga–O bond formation and rupture, the single ^{31}P resonance indicates that all phosphonate groups are coordinated, which is consistent with the constant shift value of about +18 ppm observed above pH 4 (Fig. 3). These groups stay unprotonated down to pH 4, but below this value down to pH 1, the ^{31}P shift gradually increases to +22 ppm, as protonated chelates $[Ga(NOTPH_n)]^{(3-n)-}$ form, due to proton binding at the non-coordinated negatively charged oxygen, of the metal-coordinated phosphonate groups, as has been shown for many NOTP metal chelates [18].

The proton NMR spectrum of an aqueous stoichiometric mixture of NOTP and Ga^{3+} at pH 7 displays only the signals from the 1:1 chelate, $Ga(NOTP)^{3-}$ (Fig. 2(b)). Spectral assignments used published data on other triazamacrocyclic chelates [6,8,19,22,25,27], the results of two-dimensional

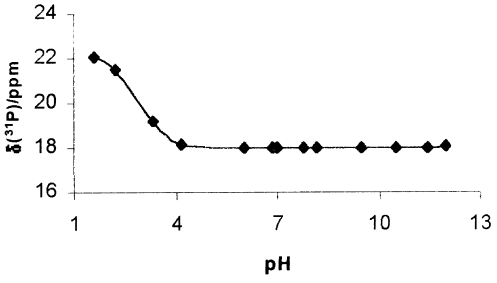

Fig. 3. ^{31}P NMR shift/pH titration curve of Ga(NOTP) (298 K, ligand and metal concentration of 10 mM).

Table 2
Proton NMR chemical shifts (δ_i (ppm)) of some complexes of Ga^{3+} (298 K, D_2O solution, pH 7)

System	δ(1,4)	δ(2,3)	δ(5,6)
$Ga(NOTP)^{3-}$	3.18(m); 2.98(m); 2.92(m)	3.46(m); 2.92(m)	2.88(m); 2.84(m)
Ga(NOTA) [a]	3.23(m)	3.51(m)	3.88(s)
Ga(NOTPP) [b]	3.60(m); 3.35(m)	3.76(m); 3.24(m)	3.50(m); 3.30(m)

[a] [6,8].
[b] [16].

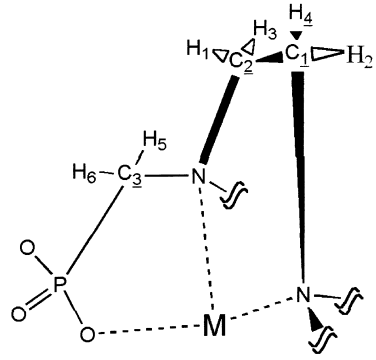

Fig. 4. Schematic representation of the conformations of the ethylenediamine chelate ring (M–N–C_1–C_2–N) in a δ conformation, formed in the $Ga(NOTP)^{3-}$ complex; 1,2 and 3,4 refer to the axial and equatorial ring protons, respectively. The ring interconversion to a λ conformation exchanges the 1,2 and 3,4 protons into equatorial and axial positions, respectively.

homonuclear correlation spectra (COSY) and the effect of ^{31}P decoupling on the resonances of the methylenephosphonate protons. Table 2 summarizes the observed ^{1}H shift data for this system, together with the data for the Ga(NOTA) chelate previously described [6,8,25]. The proton assignments refer to the numbering scheme of Fig. 4, where the ethylenediamine ring (M–N–C_1–C_2–N), formed in the $Ga(NOTP)^{3-}$ complex, is shown in a δ conformation, and where 1,2 and 3,4 refer to the axial and the equatorial ring protons, respectively. From Fig. 2(b) and Table 1 one can notice that the high rigidity of the Ga^{3+}-bound NOTP macrocycle results in the magnetic non-equivalence of the axial and equatorial ethylenediamine (en) ring protons, corresponding to a slow (δδδ) ⇔ (λλλ) ring conformational interconversion on the NMR time scale, leading to a ADMX pattern. The equatorial 3,4 protons, with two observable couplings, are distinct from the axial 1,2 protons, with three couplings [16]. The complex overlapping pattern of the 5,6 methylenephosphonate protons was simplified by ^{31}P decoupling, and was consistent with their non-equivalence due to long lifetimes for the Ga–O bonds. This contrasts with the Ga(NOTA) system [6,9], where the diastereotopic CH_2N ring protons gave symmetrical multiplets centred at 3.23 and 3.51 ppm, corresponding to a well-resolved AA′MM′ multiplet pattern, consistent with a local C_3 symmetry. As the δ ⇔ λ conformational interconversion of each en ring averages the protons

2 and 3 (which become more deshielded by the cation charge) and the protons 1 and 4, this means that the Ga(NOTA) chelate ring is flexible, as was shown for many other NOTA metal chelates [27]. The methylene CH_2CO protons gave a singlet at 3.88 ppm, consistent with short Ga–O bond lifetimes. The proton spectrum of Ga(DETA), reported before [8], is also consistent with a similar flexibility of the macrocyclic ring and lability of the Ga–O bonds of the acetate pendant arms. The increased rigidity of metal-bound macrocyclic rings with phosphonate pendant arms when compared with the same rings with carboxylate arms has also been observed for the tetraaza systems, the $Ln(DOTP)^{3-}$ macrocycle being more rigid than $Ln(DOTA)^{-}$ [28]. The single ^{31}P signal, together with the proton data, suggests inert Ga–O bonds and quite strong Ga–N bonds for this NOTP complex.

4. Conclusions

From the present NMR studies, we would expect a high solution stability for the Ga^{3+}–NOTP complex, although more susceptible to hydroxide attack than the Ga(NOTA) complex. This ligand forms with Ga^{3+} a high symmetrical, pseudo-octahedral 1:1 complex, possibly with a C_3 axis. The ^1H spectra of the aqueous $Ga(NOTP)^{3-}$ show that the tri-azamacrocyclic ring in this chelate is very rigid, yielding a non-equivalence of all the ring protons.

The high stability and rapid renal excretion of NOTA and NOTPME chelates support their possible application as kidney imaging agents, for both structural and functional studies.

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