

Nuclear and Electronic Relaxation of $\text{Eu}^{2+}_{(\text{aq})}$: An Extremely Labile Aqua Ion¹

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Abstract: Variable-temperature (at 4.7 and 9.4 T) and variable-pressure (9.4 T) ^{17}O nuclear relaxation rates were measured for the $\text{Eu}(\text{II})$ aqua ion. Variable-temperature ^1H nuclear magnetic relaxation dispersion (NMRD) profiles were recorded. In addition, EPR spectra of the $\text{Eu}(\text{II})$ aqua ion are reported as a function of temperature at 0.34, 2.7, 5.4, and 8.1 T. The simultaneous fit of the nuclear and electronic relaxation rate data results in $k_{\text{ex}}^{298} = 4.4 \times 10^9 \text{ s}^{-1}$ for the water exchange rate with activation parameters $\Delta H^\ddagger = 15.7 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = -7.0 \text{ J K}^{-1} \text{ mol}^{-1}$, $\Delta V^\ddagger = -11.3 \text{ cm}^3 \text{ mol}^{-1}$ for the volume of activation for exchange, and $\tau_{\text{R}}^{298} = 16.3 \text{ ps}$ for the rotational correlation time. Water exchange at $\text{Eu}^{2+}_{(\text{aq})}$ occurs via an associative mechanism and has the highest rate ever measured at an aqua ion by magnetic resonance. The high-field EPR spectra, reported here for the first time for divalent Eu , show hyperfine coupling to ^{151}Eu and ^{153}Eu and the coupling constants are determined (37.3 and 16.4 G for ^{151}Eu and ^{153}Eu , respectively). The electronic relaxation times, T_{1e} and T_{2e} , are longer than for the isoelectronic $\text{Gd}(\text{III})$ aqua ion. The implications of these results for ligand exchange at $\text{Ca}(\text{II})$ and for magnetic resonance imaging contrast agents are discussed.

Introduction

The europium(II) ion has received little interest from coordination chemists. It is intermediate in size² between strontium(II) and calcium(II), and often behaves structurally similar to strontium. In terms of its solution chemistry (discounting its redox abilities), $\text{Eu}(\text{II})$ forms complexes with the same types of ligands as the alkaline earth ions and with stability constants similar to $\text{Ca}(\text{II})$ and $\text{Sr}(\text{II})$.^{3,4} Williams recognized these similarities 30 years ago⁵ and proposed using the $\text{Eu}(\text{II})$ ion as a spectroscopic probe for $\text{Ca}(\text{II})$ in biological systems. Dwek et al. used proton relaxation enhancement (PRE) and EPR to compare the $\text{Eu}(\text{II})$ and $\text{Gd}(\text{III})$ complexes of EGTA.⁶ Homer and Mortimer reported a study involving the substitution of $\text{Eu}(\text{II})$ for $\text{Ca}(\text{II})$ in Concanavalin A exploiting the near-UV circular dichroism spectrum of $\text{Eu}(\text{II})$ to monitor $\text{Eu}(\text{II})$ binding.⁷ They found that $\text{Eu}(\text{II})$ acted as both a structural and functional mimic of $\text{Ca}(\text{II})$ in this system.

Despite the similarity to calcium, the use of $\text{Eu}(\text{II})$ as a probe of calcium function did not materialize. This is likely a result of the ease of oxidation of $\text{Eu}(\text{II})$. Aqueous $\text{Eu}(\text{II})$ and its

complexes require working in an anaerobic environment. In addition, $\text{Eu}(\text{II})$ is isoelectronic with $\text{Gd}(\text{III})$; it has seven unpaired electrons in an ^8S ground state. This makes $\text{Eu}(\text{II})$ an excellent relaxation agent, but renders characterization of $\text{Eu}(\text{II})$ complexes by high-resolution NMR impossible because of extreme line broadening.

However, the magnetic properties of $\text{Eu}(\text{II})$ enable very fast dynamic events to be explored by NMR. In a preliminary communication, it was shown that inner-sphere water exchange at the $\text{Eu}(\text{II})$ aqua ion is one of the fastest water exchange rates.⁸ The symmetric electronic ground state also means that $\text{Eu}(\text{II})$ has an observable EPR spectrum in solution.⁶

The objective of the present work was 3-fold: (i) to extend the previous ^{17}O NMR study by assessing the water exchange mechanism for $\text{Eu}^{2+}_{(\text{aq})}$, (ii) to use $\text{Eu}(\text{II})$ as a surrogate alkaline earth to estimate ligand substitution at $\text{Sr}(\text{II})$ or $\text{Ca}(\text{II})$, and (iii) to exploit the isoelectronic relationship between $\text{Eu}(\text{II})$ and $\text{Gd}(\text{III})$ in an effort to understand the electronic relaxation mechanisms in ^8S ions in general. To accomplish these goals, proton and oxygen-17 relaxation rates have been measured on $\text{Eu}(\text{II})$ solutions at several magnetic fields and temperatures. This study was coupled with variable-temperature and variable-field EPR line width measurements, and, to our knowledge, we report here the first high-field solution EPR spectrum on the divalent europium ion.

Experimental Section

Preparation of the Samples. The source of $\text{Eu}(\text{II})$ was the triflate salt, $\text{Eu}(\text{O}_3\text{SCF}_3)_2 \cdot \text{H}_2\text{O}$, which was prepared by distilling degassed triflic acid onto EuCO_3 and then removing water and excess triflic acid under reduced pressure. This process was repeated twice more, followed by drying at 90 °C in vacuo overnight to give $\text{Eu}(\text{O}_3\text{SCF}_3)_2 \cdot \text{H}_2\text{O}$. Anal.

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Calcd for $C_2H_2EuF_7O_7S_2$: C, 5.13; H, 0.43; S, 13.70; F, 24.35. Found: C, 5.37; H, 0.46; S, 13.54; F, 23.91. Solutions were prepared under nitrogen in a glovebox by dissolving $Eu(\text{trif})_2$ in water degassed by a triple freeze–pump–thaw cycle. For the ^{17}O NMR measurements, solutions were enriched with $H_2^{17}\text{O}$ -labeled water (3–6%). $Eu(\text{II})$ concentration ranged from 0.02 to 0.15 mol kg^{-1} for ^{17}O NMR, 0.04–0.17 mol L^{-1} for EPR, and 0.004–0.012 mol L^{-1} for NMRD measurements. The concentration was checked after oxidation to Eu^{3+} by titrating the total Eu content with EDTA; the concentration agreed with that calculated from the analytical composition of the solid $Eu(O_3SCF_3)_2 \cdot H_2O$.

^{17}O NMR Measurements. A variable-temperature ^{17}O NMR study on Eu^{2+} was performed at two different magnetic fields using Bruker spectrometers: AM-400, 9.4 T and 54.2 MHz; and AC-200, 4.7 T and 27.1 MHz. The samples were sealed in glass spheres and placed in 10 mm NMR tubes, to eliminate susceptibility effects. Bulk water longitudinal relaxation rates, $1/T_1$, were obtained by the inversion recovery method,⁹ and transverse relaxation rates, $1/T_2$, by the Carr–Purcell–Meiboom–Gill spin–echo technique.¹⁰

Variable-pressure NMR spectra were recorded up to a pressure of 200 MPa on a Bruker AM-400 spectrometer equipped with a home-built high-pressure probe.¹¹ The temperature was controlled by a circulating fluid from an external temperature bath and measured with a built-in Pt resistor.

EPR Measurements. The X-band (0.34 T) EPR spectra were recorded on a Bruker ESP 300E spectrometer. The EPR spectra at $B = 2.7$ (resonance frequency 75 GHz), 5.4 (150 GHz), and 8.1 T (225 GHz) were obtained on a home-built spectrometer (Department of Experimental Physics, Technical University of Budapest, Hungary).¹² In these measurements the microwave source is a quartz-stabilized Gunn diode oscillator (Radiometer Physics) operating at 75 GHz, followed by a frequency doubler for the 150 GHz and a frequency tripler for the 225 GHz measurements. The transverse electronic relaxation rates, $1/T_{2e}$, were obtained from the EPR line widths according to Reuben.¹³

NMRD. The $1/T_1$ nuclear magnetic relaxation dispersion (NMRD) profiles of the solvent protons at 8, 28, 40, and 60 °C were obtained on a Spinmaster FFC fast field cycling NMR relaxometer (Stelar), covering a continuum of magnetic fields from 7×10^{-4} to 0.47 T (corresponding to a proton Larmor frequency range 0.03–20 MHz).

In all ^{17}O NMR, X-band EPR, and NMRD measurements the temperature was measured by a substitution technique,¹⁴ whereas in the high-field EPR measurements a Pt resistor, built into the probehead, was used.

Data Analysis. The simultaneous least-squares fit of EPR, ^{17}O NMR, and NMRD data was performed with the program Scientist for Windows by Micromath, version 2.0. The reported errors correspond to one standard deviation obtained by statistical analysis.

Results and Discussion

The reduced longitudinal and transverse water ^{17}O relaxation rates and chemical shifts, $1/T_{1r}$, $1/T_{2r}$, and $\Delta\omega_r$, the proton relaxivities, r_1 (longitudinal water ^1H relaxation rates normalized to 1 mM concentration), as well as the transverse electronic relaxation rates, $1/T_{2e}$, were fit simultaneously to eqs 1–18 in the Appendix. The simultaneous analysis of EPR, ^{17}O NMR, and NMRD data is based on the fact that several influencing parameters are common to these techniques. The same integrated approach has been successfully applied for several Gd(III) complexes.¹⁵ The experimental data and the fits are shown in

Figure 1, and the fitted parameters are given in Table 1. Figure 1 comprises EPR data at four fields over a 90 deg temperature range, ^{17}O data at two fields over a 90 deg temperature range, and ^1H data at 20 fields over a 52 deg temperature range. The fit to the data is remarkable given the large magnetic field range covered in this study (5×10^{-4} to 9.4 T).

The analysis of the ^{17}O NMR and ^1H relaxation data requires the knowledge of the inner-sphere coordination number. Furthermore, the longitudinal relaxation rates are associated with the Eu –water O and Eu –water H distances. Due to the lack of any data on $Eu(\text{II})$, assumptions were made based upon comparison with the available data for $Sr(\text{II})$. Shannon² lists ionic radii for eight-coordinate $Eu(\text{II})$ and $Sr(\text{II})$ as 1.25 and 1.26 Å, respectively. Hence, it is likely that $Eu(\text{II})$ has the same coordination number in water as $Sr(\text{II})$. In the solid state, $[Sr(\text{H}_2\text{O})_8](\text{OH})_2$ crystallized with the $Sr(\text{II})$ ion surrounded by eight water molecules in a distorted Archimedean antiprism with mean strontium–oxygen distances of 2.63 Å.¹⁶ In solution, a neutron diffraction study¹⁷ and a large-angle X-ray scattering study¹⁶ both suggest a CN = 8 for the strontium(II) aqua ion, which was more recently supported by EXAFS measurements.¹⁸ Therefore, in the calculations we assumed CN = 8 for the $Eu(\text{II})$ aqua ion. Accordingly, the Eu –O and Eu –H distances were also estimated on the basis of $Sr(\text{II})$ data^{16,18} as $r_{EuO} = 2.63$ Å and $r_{EuH} = 3.23$ Å. (It should be noted that the Eu –O bond distance used in the preliminary communication⁸ and taken from the neutron diffraction study¹⁷ was probably an overestimation. The value obtained from neutron diffraction was the result of a very low quality fit and was not supported by either the X-ray scattering or the EXAFS study, which both gave 2.63 Å). The distance of closest approach of the outer-sphere water to the aqua complex, a_{EuH} , determining the outer-sphere relaxivity contribution (eq 16) was fixed to 3.64 Å.

It is worth mentioning that the variation of the inner-sphere coordination number would have only a slight effect on the parameters listed in Table 1. A coordination number of 7, which could be imagined, would result in a 15% increase for the water exchange rate, k_{ex} , for the rotational correlation time, τ_R , or for the hyperfine coupling constant, A/\hbar , the activation entropy would become more positive (-0.8 J mol^{-1} K^{-1}), whereas the electronic relaxation parameters (τ_v and Δ^2) would change by less than 5%. Changes in the Eu –O and Eu –H distances affect exclusively the rotational correlation time. Since distance enters as the sixth power into the equation of the dipolar interactions (eqs 8 and 14), this influence can be significant.

Water Exchange. The water exchange rate is determined almost exclusively from the transverse ^{17}O relaxation rates. For $Eu^{2+}_{(aq)}$, transverse relaxation for ^{17}O in an inner-sphere water molecule occurs via a scalar mechanism. In the fast water exchange regime studied here, the observed reduced relaxation rate, $1/T_{2r}$, is given by the relaxation rate of the bound inner-sphere water molecule, $1/T_{2m}$. Therefore, the observed effect in T_{2r} is determined by the water residency time ($\tau_m = 1/k_{ex}$), the longitudinal electronic relaxation time T_{1e} , and the $Eu(\text{II})$ ion electron spin– ^{17}O nuclear hyperfine coupling constant A/\hbar (see eq 9 in the Appendix).

The hyperfine coupling constant was obtained from the slope of the $Eu(\text{II})$ induced water ^{17}O chemical shift as a function of temperature (eqs 6 and 7, but in the present case eq 6 simplifies to eq 7 as $\Delta\omega_r \approx \Delta\omega_m$). As it happens, the water exchange rate

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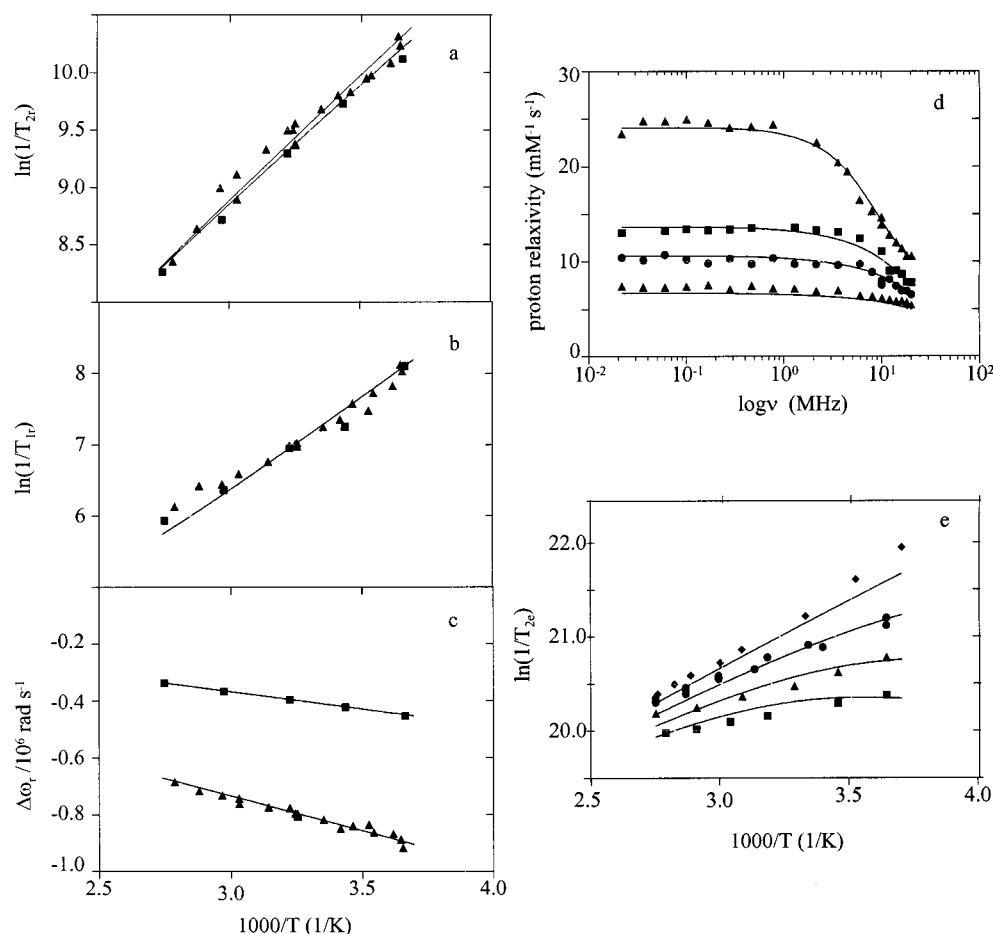


Figure 1. Temperature dependence of (a) reduced transverse and (b) longitudinal ^{17}O relaxation rates and (c) chemical shifts for $[\text{Eu}(\text{H}_2\text{O})_8]^{2+}$ at $B = 9.4$ (▲) and 4.7 T (■); (d) NMRD profiles at 8 (▲), 28 (■), 40 (●), and 60 °C (▲); and (e) temperature dependence of transverse electronic relaxation rates at 0.34 (◆), 2.7 (●), 5.4 (▲), and 8.1 T (■). The lines represent the simultaneous least-squares fit to all data points as described in the text.

Table 1. Parameters Obtained from the Simultaneous Fit of EPR, ^{17}O NMR, and NMRD Data

	$[\text{Eu}(\text{H}_2\text{O})_8]^{2+}$	$[\text{Gd}(\text{H}_2\text{O})_8]^{3+ a}$
$k_{\text{ex}}/10^9 \text{ s}^{-1}$	4.4 ± 0.3	0.8 ± 0.06
$\Delta H^\ddagger/\text{kJ mol}^{-1}$	15.7 ± 0.2	15.3 ± 1.3
$\Delta S^\ddagger/\text{J mol}^{-1}\text{K}^{-1}$	-7.0 ± 0.7	-23.1 ± 4.0
$\Delta V^\ddagger/\text{cm}^3 \text{ mol}^{-1}$	-11.3 ± 0.7	-3.3 ± 0.2
$A/\hbar/10^6 \text{ rad s}^{-1}$	-3.7 ± 0.1	-5.3 ± 0.1
$\tau_R/298/\text{ps}$	16.3 ± 0.3	41 ± 2
$E_R/\text{kJ mol}^{-1}$	21.3 ± 0.4	15.0 ± 1.3
$\tau_v/298/\text{ps}$	1.0 ± 0.2	7.3 ± 0.5
$E_v/\text{kJ mol}^{-1}$	12.5 ± 1	18.4 ± 1.4
$\Delta^2/10^{20} \text{ s}^{-2}$	1.13 ± 0.02	1.19 ± 0.09
$D_{\text{LH}}/10^{-10} \text{ m}^2 \text{ s}^{-1}$	22.9 ± 1	23
$E_{\text{DLH}}/\text{kJ mol}^{-1}$	20.1 ± 0.3	22

^a From ref 15.

is much faster than the electronic relaxation rate, *vide infra*, $(1/T_1)_e$ contributes at most 10% to τ_{s1} at the magnetic fields used), such that the plot of $\ln(1/T_{2r})$ versus $1/T$ is essentially a modified Eyring plot with the slope approximating $\Delta H^\ddagger/R$.

The hyperfine coupling constant is a measure of electron delocalization from the ion onto the ligand nucleus. For a longer bond length, one would expect a smaller value of A/\hbar . Indeed, a smaller hyperfine coupling constant is found for $\text{Eu}^{2+}_{(aq)}$ than for $\text{Gd}^{3+}_{(aq)}$, which is consistent with a weaker bond between the Eu(II) ion and the water oxygen.

The pressure dependence of the reduced transverse relaxation rates, $1/T_{2r}$, for $\text{Eu}^{2+}_{(aq)}$ at 298 K and 9.4 T is shown in Figure

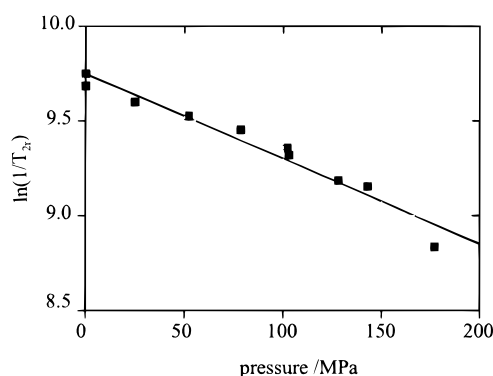


Figure 2. Pressure dependence of the reduced transverse ^{17}O relaxation rates for $[\text{Eu}(\text{H}_2\text{O})_8]^{2+}$ at 9.4 T and 298 K. The line represents the least-squares fit as explained in the text.

2. At this temperature and magnetic field, $1/T_{2r}$ is in the fast exchange limit and is dominated by the scalar interaction. The decrease of $1/T_{2r}$ with pressure is, therefore, due to an acceleration of the water exchange process and suggests an associative (A) or associatively activated interchange (I_a) mechanism.¹⁹ The scalar coupling constant (A/\hbar) was previously found to be independent of pressure,²⁰ so we assume that it is constant and equal to the value in Table 1. τ_v was also assumed to be pressure independent. In fact, ascribing a pressure dependence equivalent

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to activation volumes between -4 and $+4$ $\text{cm}^3 \text{mol}^{-1}$ to τ_v had a negligible effect on both fitted parameters ($<1\%$). The result of the least-squares fit is shown in Figure 2; the fitted parameters are $(k_{\text{ex}})_0^{298} = (4.1 \pm 0.1) \times 10^9 \text{ s}^{-1}$ and $\Delta V^\ddagger = (-11.3 \pm 0.7) \text{ cm}^3 \text{mol}^{-1}$.

The volume of activation is very large and corresponds to a limiting associative mechanism. This suggests that water exchange for an eight-coordinate $\text{Eu}^{2+}_{(\text{aq})}$ (typically square antiprismatic) would proceed through a nine-coordinate transition state (tricapped trigonal prism), similar to that of $[\text{Gd}(\text{H}_2\text{O})_8]^{3+}$.²¹ However, the water exchange rate for $\text{Eu}^{2+}_{(\text{aq})}$ is 5–6 times faster than that for $\text{Gd}^{3+}_{(\text{aq})}$.

Contrary to the expectation for a limiting associative process, the activation entropy, ΔS^\ddagger , calculated for $\text{Eu}^{2+}_{(\text{aq})}$ is less negative than that for $\text{Gd}^{3+}_{(\text{aq})}$. However, usually quite large errors are associated with the entropy for paramagnetic systems (even if the calculated statistical error is small).²² Since the activation entropy and enthalpy are correlated, it also can be the reason the ΔH^\ddagger values obtained for the two aqua ions are so similar, despite the fact that the water exchange rates are considerably different. It must be noted, however, that both the water exchange rate and the activation volume are very well determined.

Rotation. The rotational correlation time is obtained primarily from water ^1H and ^{17}O T_1 measurements. The proton relaxivity of the europium(II) aqua ion is quite low, $7.8 \text{ mM}^{-1} \text{ s}^{-1}$ at 20 MHz and 28 °C. If one compares this value with those of $\text{Gd}^{3+}_{(\text{aq})}$ ($14.5 \text{ mM}^{-1} \text{ s}^{-1}$, 28 °C, with eight bound water molecules), $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^-$ ($4.3 \text{ mM}^{-1} \text{ s}^{-1}$, 25 °C, with one bound water molecule),²³ and $[\text{Gd}(\text{TTAHA})(\text{H}_2\text{O})_2]$ ($9.5 \text{ mM}^{-1} \text{ s}^{-1}$, 25 °C, with two bound water molecules),²⁴ it is clear that $\text{Eu}^{2+}_{(\text{aq})}$ is not as an efficient relaxation agent as $\text{Gd}(\text{III})$ on a per coordinated water basis.

Proton longitudinal relaxation is primarily determined by the electron spin–nuclear spin distance, r , and the rotational correlation time, τ_R , and at low frequencies (less than 10 MHz for ^1H) the electronic relaxation times T_{1e} and T_{2e} . The Eu(II)–H (or O) distance, r , is longer than that for the Gd(III) analogue. Since dipolar relaxation has an r^{-6} dependence, proton relaxivity of $\text{Eu}^{2+}_{(\text{aq})}$ is expected to be about 70% that of $\text{Gd}^{3+}_{(\text{aq})}$. The fact that it is smaller suggests a shorter rotational correlation time.

Indeed, the rotational correlation time is rather short for this ion. It is about 2 times smaller than τ_R for $\text{Gd}^{3+}_{(\text{aq})}$. The reason for this is unclear. It may again be related to the large ionic size. What is measured here is rotation of the Eu–O or Eu–H vector and this should reflect rotation of the entire aqua complex. For small, highly charged ions such as $\text{Al}^{3+}_{(\text{aq})}$ and $\text{Cr}^{3+}_{(\text{aq})}$ it is known that a well-defined second solvation shell exists. A previous report on second-sphere water exchange at $\text{Cr}^{3+}_{(\text{aq})}$ showed that the residence time of a water molecule in the second coordination sphere of $\text{Cr}^{3+}_{(\text{aq})}$ was long compared to the rotational correlation time of the complex.²⁵ For $\text{Cr}^{3+}_{(\text{aq})}$, rotational correlation times measured by NMR likely refer to the hydrated $\{[\text{Cr}(\text{H}_2\text{O})_6(\text{H}_2\text{O})_{12}]^{3+}$ ion, i.e., the rotation of the ion with two layers of solvation. In contrast, it is unlikely that

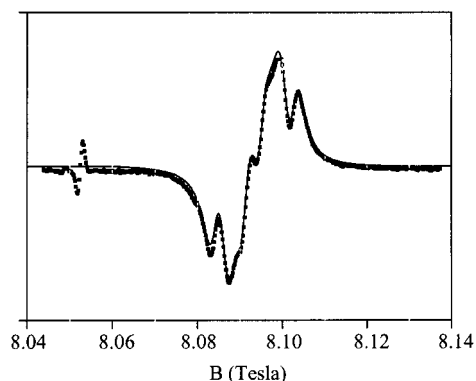


Figure 3. A representative EPR spectrum of $\text{Eu}^{2+}_{(\text{aq})}$ at $B = 8.1$ T and $T = 365$ K. The squares correspond to the experimental spectrum and the solid line is the fitted spectrum. The small low-field peak is the signal of the BDPA used as a g -factor reference (BDPA = *a,g*-bis(diphenyl)-*b*-phenylallyl).

$\text{Eu}^{2+}_{(\text{aq})}$ possesses a well-defined second-coordination sphere because of its large size, more diffuse charge, and longer Eu–O bond lengths. The rotational correlation time measured here is likely an indication of rotation of the discrete $[\text{Eu}(\text{H}_2\text{O})_8]^{2+}$ entity.

EPR Spectra and Electronic Relaxation. The EPR spectra of $\text{Eu}^{2+}_{(\text{aq})}$ display a similar behavior as those of $\text{Gd}^{3+}_{(\text{aq})}$ in that the line widths decrease dramatically with increasing frequency. This is consistent with a modulated transient zero field splitting (ZFS) relaxation mechanism.²⁶ Unlike $\text{Gd}^{3+}_{(\text{aq})}$, the X-band EPR spectrum of $\text{Eu}^{2+}_{(\text{aq})}$ begins to show fine structure above 70 °C and this fine structure becomes more apparent as the frequency is increased.

The EPR spectra were interpreted as superimposed isotropic hyperfine structures of naturally abundant ^{151}Eu and ^{153}Eu isotopes. Both nuclei have a nuclear spin of $5/2$ and a similar natural abundance (47.82% and 52.18%, respectively). At the wings of the spectra the outermost lines of ^{151}Eu hyperfine sextet can be recognized, since its nuclear g -factor is larger by a factor of 2.264 than that of ^{153}Eu , while in the center of the spectra the four inner lines of ^{151}Eu and the six line-pattern of ^{153}Eu are superimposed ($\gamma(^{151}\text{Eu}) = 6.55 \times 10^7 \text{ T}^{-1} \text{ s}^{-1}$ and $\gamma(^{153}\text{Eu}) = 2.94 \times 10^7 \text{ T}^{-1} \text{ s}^{-1}$).

An automatic fitting program was used that adjusts EPR parameters (g -factor, coupling constant, line width).²⁷ A mixed absorption–dispersion line shape was used. The measured g -factor is 1.99345 with statistical confidence 5×10^{-5} . The hyperfine couplings (37.3 and 16.4 G for ^{151}Eu and ^{153}Eu , respectively) show a small negative temperature coefficient, but the variation is comparable with the confidence interval (1 G). The line width was found identical for the two isotopes (confidence interval is 2–5 G) and no significant line width alteration is found within the hyperfine multiplet, which indicates a negligible anisotropic hyperfine relaxation. The line width decreases both with temperature and resonance frequency and its change is significantly larger than the respective confidence intervals. The transverse electronic relaxation rates, $1/T_{2e}$, were calculated from the EPR line widths.²⁸

Figure 3 shows the EPR spectrum of $\text{Eu}^{2+}_{(\text{aq})}$ at $T = 365$ K and $B = 8.1$ T (225 GHz). The line is a fit based upon two superimposed six-line patterns for ^{151}Eu and ^{153}Eu as described

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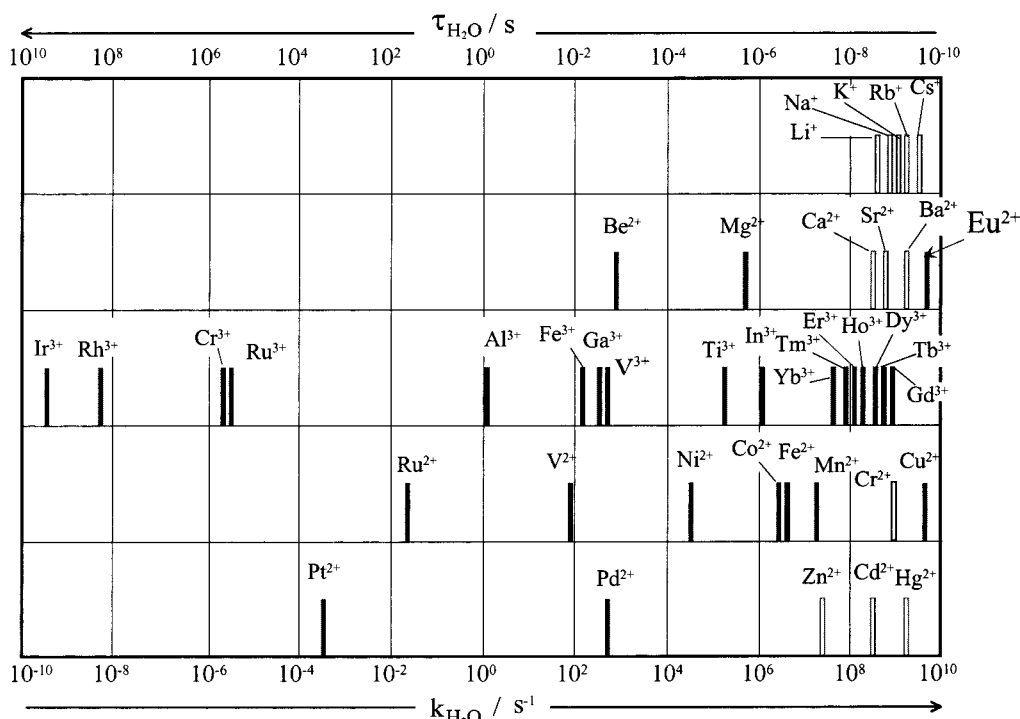


Figure 4. Mean lifetimes of a particular water molecule in the first coordination sphere of a given metal ion, $\tau_{\text{H}_2\text{O}}$, and the corresponding water exchange rate constants, $k_{\text{H}_2\text{O}}$, at 298 K. The full bars indicate directly determined values whereas the empty bars represent values deduced from complex formation studies.

above. To our knowledge this is the first high field solution EPR spectrum reported for divalent europium.

The parameters which define electronic relaxation for the europium(II) aqua ion, Δ^2 , τ_v , and E_v (eqs 1–3 in the Appendix), are similar to those for the gadolinium(III) aqua ion with the notable exception of τ_v . The square of the trace of the ZFS tensor, Δ^2 , has a value that is close to that for $\text{Gd}^{3+}_{(\text{aq})}$, which suggests that the magnitude of the transient ZFS distortion is similar for both aqua ions. However, τ_v , the correlation time that describes the modulation of this distortion is shorter for $\text{Eu}^{2+}_{(\text{aq})}$. A shorter τ_v means that the transient ZFS for $\text{Eu}^{2+}_{(\text{aq})}$ is being modulated at a faster rate; the physical consequence of this faster modulation is that the transient ZFS distortions are better averaged for $\text{Eu}^{2+}_{(\text{aq})}$ than for $\text{Gd}^{3+}_{(\text{aq})}$, which leads to a longer value of T_{1e} and T_{2e} for $\text{Eu}^{2+}_{(\text{aq})}$.

Implications for Group 2 Water Exchange Estimates. The estimates for water exchange at $\text{Ca}^{2+}_{(\text{aq})}$, $\text{Sr}^{2+}_{(\text{aq})}$, and $\text{Ba}^{2+}_{(\text{aq})}$ are now almost 40 years old²⁹ and based upon ultrasound studies of sulfate exchange. These estimated water exchange rates are shown in Figure 4 along with the measured value for $\text{Eu}^{2+}_{(\text{aq})}$. It is likely that the group 2 water exchange rate estimates are too low and should be revisited. One could expect that $\text{Sr}^{2+}_{(\text{aq})}$ lies close to $\text{Eu}^{2+}_{(\text{aq})}$ with $\text{Ca}^{2+}_{(\text{aq})}$ to the left of $\text{Eu}^{2+}_{(\text{aq})}$ and $\text{Ba}^{2+}_{(\text{aq})}$ to the right.

Implications for Gd(III) Contrast Agent Research. The design of magnetic resonance imaging contrast agents has evolved to produce complexes with much higher ^1H relaxivities than those currently commercially available. New approaches have involved increasing the rotational correlation time by linking the gadolinium(III) chelate either covalently³⁰ or non-covalently³¹ to a macromolecule. For compounds with long

(nanosecond) rotational correlation times, it has been proposed that electronic relaxation limits proton relaxivity at medium fields (20 MHz). The analogous europium(II) complexes may illuminate this area of research. The Eu(II) compounds would be expected to have similar rotational correlation times and would differ primarily in terms of electronic relaxation and water exchange properties. Development of isoelectronic Eu(II) complexes may prove to be a valuable mechanistic tool in understanding the various parameters which influence relaxivity for Gd(III) contrast agents. Work in this laboratory is ongoing to exploit this isoelectronic relationship.

$\text{Eu}^{2+}_{(\text{aq})}$ Has the Fastest Inner-Sphere Water Exchange Ever Measured by Magnetic Resonance. Because of its paramagnetism and its relatively slow electronic relaxation rate, the water exchange rate for $\text{Eu}^{2+}_{(\text{aq})}$ can be accurately determined, even though this process is occurring billions of times each second. Yet, the observed water residency time, 227 ps, is still considerably longer than typical times calculated from translational diffusion, ≈ 3 ps.²⁵

The exchange rate is similar to that of $\text{Cu}^{2+}_{(\text{aq})}$ (both $4.4 \times 10^9 \text{ s}^{-1}$).³² In the case of $\text{Cu}^{2+}_{(\text{aq})}$, it is only the two axial water molecules in the Jahn–Teller distorted octahedron which are exchanging with the bulk; however, the rate of Jahn–Teller distortion is much faster than the rate of axial water exchange. Thus all six water molecules are effectively undergoing water exchange at the same rate. For $\text{Eu}^{2+}_{(\text{aq})}$ all eight equivalent water molecules are exchanging with the same rate constant. The exchange rate constant, k_{ex} , refers to the exchange of a particular coordinated water molecule.¹⁹ However, from the viewpoint of the metal ion, there are 8 times as many exchange events taking

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place at $\text{Eu}^{2+}_{(\text{aq})}$, i.e., $3.5 \times 10^{10} \text{ s}^{-1}$. Comparing the two metal ions, there are 8/6 more exchange events taking place at $\text{Eu}^{2+}_{(\text{aq})}$ than at $\text{Cu}^{2+}_{(\text{aq})}$. This is the fastest water exchange rate determined for an aqua ion by magnetic resonance. Herdman and Salmon^{33,34} have shown that incoherent quasielastic neutron scattering (IQENS) can distinguish water protons which have exchange rates faster than 10^{10} s^{-1} , such as those of the alkali metals. However, the IQENS method is not as precise as NMR techniques and generally gives order of magnitude estimates.

Conclusion

This work establishes the exceedingly fast nature of water exchange at the Eu(II) aqua ion. The large negative volume of activation determined from variable-pressure ^{17}O NMR studies clearly indicates an associative mechanism of water exchange. For the first time, high field solution EPR spectra of $\text{Eu}^{2+}_{(\text{aq})}$ have been reported, and the field dependent electronic relaxation behavior can be interpreted by the same model that is used for Gd(III) complexes. The high field EPR spectra also allow for the first time the observation and determination of hyperfine coupling of the electron spin to both isotopes of the europium nucleus. This publication also marks the first ^1H NMRD profiles reported for a Eu(II) complex.

In addition to the delineation of dynamic and electronic parameters for the Eu(II) aqua ion, this work has implications for kinetic events taking place at the alkaline earth ions, notably strontium and calcium. It is likely that the water exchange rates for these ions have been underestimated. It may be possible to substitute Eu(II) for Ca(II) in other systems and exploit its paramagnetism to study ligand exchange rates. Furthermore, the isoelectronic relationship between Eu(II) and Gd(III) may provide a means of exploring the effect of tuning water exchange and electronic relaxation rates and observing how this influences proton relaxivity.

Although the water exchange rates of Ca(II), Sr(II), and Ba(II) aqua ions are unlikely to ever be measured directly, high level molecular dynamics (MD) simulations may provide good estimates of exchange parameters. The Eu(II) system allows the validation of MD simulations by comparison with experimental results. Presumably an MD model that can explain the $\text{Eu}^{2+}_{(\text{aq})}$ dynamics would also explain solvation dynamics for the alkaline earth aqua ions. In addition, solution EXAFS studies on $\text{Eu}^{2+}_{(\text{aq})}$ could be performed and the observed radial distribution functions used in the MD simulations. These questions are currently being addressed in this laboratory and will be reported in due course.

Appendix

EPR. The electron spin relaxation rates for metal ions in solution with $S > 1/2$ are mainly governed by a transient zero-field-splitting mechanism (ZFS). The ZFS terms can be expressed by eqs 1 and 2,^{35,36} where Δ^2 is the trace of the square of the transient zero-field-splitting tensor, τ_v is the correlation time for the modulation of the ZFS with the activation energy E_v , and ω_s is the Larmor frequency of the electron spin:

$$\left(\frac{1}{T_{1e}}\right)^{\text{ZFS}} = \frac{1}{25} \Delta^2 \tau_v \{4S(S+1) - 3\} \left[\frac{1}{1 + \omega_s^2 \tau_v^2} + \frac{4}{1 + 4\omega_s^2 \tau_v^2} \right] \quad (1)$$

$$\left(\frac{1}{T_{2e}}\right)^{\text{ZFS}} = \Delta^2 \tau_v \left[\frac{5.26}{1 + 0.372\omega_s^2 \tau_v^2} + \frac{7.18}{1 + 1.24\omega_s \tau_v} \right] \quad (2)$$

$$\tau_v = \tau_v^{298} \exp\left\{ \frac{E_v}{R} \left(\frac{1}{T} - \frac{1}{298.15} \right) \right\} \quad (3)$$

Oxygen-17 NMR. From the measured ^{17}O NMR relaxation rates and angular frequencies of the paramagnetic solutions, $1/T_1$, $1/T_2$, and ω , and of the acidified water reference, $1/T_{1A}$, $1/T_{2A}$, and ω_A , one can calculate the reduced relaxation rates and chemical shift, $1/T_{1r}$, $1/T_{2r}$, and ω_r , which may be written as in eqs 4–6,³⁷ where $1/T_{1m}$, $1/T_{2m}$ are the relaxation rates of the bound water and $\Delta\omega_m$ is the chemical shift difference between bound and bulk water.

$$\frac{1}{T_{1r}} = \frac{1}{P_m} \left[\frac{1}{T_1} - \frac{1}{T_{1A}} \right] = \frac{1}{T_{1m} + \tau_m} \quad (4)$$

$$\frac{1}{T_{2r}} = \frac{1}{P_m} \left[\frac{1}{T_2} - \frac{1}{T_{2A}} \right] = \frac{1}{\tau_m} \frac{T_{2m}^{-2} + \tau_m^{-1} T_{2m}^{-1} + \Delta\omega_m^2}{(\tau_m^{-1} + T_{2m}^{-1})^2 + \Delta\omega_m^2} \quad (5)$$

$$\Delta\omega_r = \frac{1}{P_m} (\omega - \omega_A) = \frac{\Delta\omega_m}{(1 + \tau_m T_{2m}^{-1})^2 + \tau_m^2 \Delta\omega_m^2} \quad (6)$$

$\Delta\omega_m$ is determined by the hyperfine or scalar coupling constant, A/\hbar , according to eq 7, where B represents the magnetic field, S is the electron spin, and g_L is the isotropic Landé g factor.

$$\Delta\omega_m = \frac{g_L \mu_B S(S+1) B A}{3k_B T \hbar} \quad (7)$$

We assume that outer-sphere contributions are negligible.

The ^{17}O longitudinal relaxation rates are given by eq 8,^{38,39} where γ_S is the electron and γ_I is the nuclear gyromagnetic ratio ($\gamma_S = 1.76 \times 10^{11} \text{ rad s}^{-1} \text{ T}^{-1}$, $\gamma_I = -3.626 \times 10^7 \text{ rad s}^{-1} \text{ T}^{-1}$), r is the effective distance between the electron charge and the ^{17}O nucleus, I is the nuclear spin (5/2 for ^{17}O), χ is the quadrupolar coupling constant, and η is an asymmetry parameter:

$$\frac{1}{T_{1m}} = \left[\frac{1}{15} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{r_{\text{EuO}}^6} S(S+1) \right] \left[6\tau_{d1} + 14 \frac{\tau_{d2}}{1 + \omega_s^2 \tau_{d2}^2} \right] + \frac{3\pi^2}{10} \frac{2I+3}{I^2(2I-1)} \chi^2 (1 + \eta^2/3) \tau_R \quad (8)$$

In the transverse relaxation the scalar contribution, $1/T_{2sc}$, is the most important one (eq 9).⁴⁰ In eq 9, $1/\tau_{s1}$ is the sum of the exchange rate constant and the electron spin relaxation rate.

$$\frac{1}{\tau_{s1}} = \frac{1}{\tau_m} + \frac{1}{T_{1e}}$$

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$$\frac{1}{T_{2m}} \cong \frac{1}{T_{2sc}} = \frac{S(S+1)(A)^2}{3} \left(\frac{A}{\hbar}\right)^2 \tau_{s1} \quad (9)$$

The binding time (or exchange rate, k_{ex}) of water molecules in the inner sphere is assumed to obey the Eyring equation (eq 10), where ΔS^\ddagger and ΔH^\ddagger are the entropy and enthalpy of activation for the exchange process, and k_{ex}^{298} is the exchange rate at 298.15 K.

$$\frac{1}{\tau_m} = k_{\text{ex}} = \frac{k_B T}{h} \exp\left\{\frac{\Delta S^\ddagger}{R} - \frac{\Delta H^\ddagger}{RT}\right\} = \frac{k_{\text{ex}}^{298} T}{298.15} \exp\left\{\frac{\Delta H^\ddagger}{R} \left(\frac{1}{298.15} - \frac{1}{T}\right)\right\} \quad (10)$$

The pressure dependence of $\ln(k_{\text{ex}})$ is linear (eq 11), where ΔV^\ddagger is the activation volume and $(k_{\text{ex}})_0^T$ is the water exchange rate at zero pressure and temperature T .

$$\frac{1}{\tau_m} = k_{\text{ex}} = (k_{\text{ex}})_0^T \exp\left\{-\frac{\Delta V^\ddagger P}{RT}\right\} \quad (11)$$

NMRD. The measured proton relaxivities (normalized to 1 mM Eu^{2+} concentration) contain both inner-sphere and outer-sphere contributions:

$$r_1 = r_{\text{lis}} + r_{\text{los}} \quad (12)$$

The inner-sphere term is given by eq 13, where q is the number of inner-sphere water molecules.

$$r_{\text{lis}} = \frac{1}{1000} \frac{q}{55.55} \frac{1}{T_{1m}^H + \tau_m} \quad (13)$$

The longitudinal relaxation rate of inner-sphere protons, $1/T_{1m}^H$ can be expressed as in eq 14:^{41,42}

$$\frac{1}{T_{1m}^H} = \frac{2}{15} \left(\frac{\mu_o}{4\pi}\right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{r_{\text{EuH}}^6} S(S+1) \left[\frac{3\tau_{d1}}{1 + \omega_1^2 \tau_{d1}^2} + \frac{7\tau_{d2}}{1 + \omega_S^2 \tau_{d2}^2} \right] \quad (14)$$

In eq 14 r_{EuH} is the effective distance between the Eu(II) electron spin and the water protons, ω_1 is the proton resonance frequency, and τ_{di} is given by eq 15:

$$\frac{1}{\tau_{di}} = \frac{1}{\tau_m} + \frac{1}{\tau_R} + \frac{1}{T_{ie}} \quad i = 1, 2 \quad (15)$$

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The outer-sphere contribution can be described by eq 16,^{43,44} where N_A is the Avogadro constant, and J_{os} is a spectral density function.

$$r_{\text{los}} = \frac{32N_A \pi (\mu_o)^2}{405} \left(\frac{\mu_o}{4\pi}\right)^2 \frac{\hbar^2 \gamma_S^2 \gamma_I^2}{a_{\text{EuH}} D_{\text{EuH}}} S(S+1) [3J_{\text{os}}(\omega_1, T_{1e}) + 7J_{\text{os}}(\omega_S, T_{2e})] \quad (16)$$

$$J_{\text{os}}(\omega, T_{je}) = \text{Re} \left[\frac{1 + \frac{1}{4} \left(i\omega\tau_{\text{EuH}} + \frac{\tau_{\text{EuH}}}{T_{je}} \right)^{1/2}}{1 + \left(i\omega\tau_{\text{EuH}} + \frac{\tau_{\text{EuH}}}{T_{je}} \right)^{1/2} + \frac{4}{9} \left(i\omega\tau_{\text{EuH}} + \frac{\tau_{\text{EuH}}}{T_{je}} \right) + \frac{1}{9} \left(i\omega\tau_{\text{EuH}} + \frac{\tau_{\text{EuH}}}{T_{je}} \right)^{3/2}} \right]_{j=1,2} \quad (17)$$

For the temperature dependence of the diffusion coefficient for the diffusion of a water proton away from a Eu(II) complex, D_{EuH} , we assume an exponential temperature dependence, with an activation energy $E_{D_{\text{EuH}}}$:

$$D_{\text{EuH}} = D_{\text{EuH}}^{298} \exp\left\{\frac{E_{D_{\text{EuH}}}}{R} \left(\frac{1}{T} - \frac{1}{298.15}\right)\right\} \quad (18)$$

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Supporting Information Available: Variable-temperature reduced transverse and longitudinal ^{17}O relaxation rates and chemical shifts (Table S1); proton relaxivities as a function of the magnetic field (Table S2); reduced transverse ^{17}O relaxation rates as a function of pressure (Table S3), and variable-temperature, multiple field transverse electronic relaxation rates (Table S4) (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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