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Potentiometric Titration of Metal Ions in Ethanol

Graham T. T. Gibson, Mark F. Mohamed, Alexei A. Neverov, and R. S. Brown*

Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

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The potentiometric titrations of Zn^{2+}, Cu^{2+} and 12 Ln^{3+} metal ions were obtained in ethanol to determine the titration constants (defined as the $^{s}_{s}$pH at which the $[^{-}OEt]/[M^{x+}]_t$ ratios are 0.5, 1.5, and 2.5) and in two cases (La^{3+} and Zn^{2+}) a complete speciation diagram. Several simple monobasic acids and aminium ions were also titrated to test the validity of experimental titration measurements and to establish new $^{s}_{s}pK_a$ constants in this medium that will be useful for the preparation of buffers and standard solutions. The dependence of the titration constants on the concentration and type of metal ion and specific counterion effects is discussed. In selected cases, the titration profiles were analyzed using a commercially available fitting program to obtain information about the species present in solution, including La^{3+} for which a dimer model is proposed. The fitting provides the microscopic $^{s}_{s}pK_a$ values for deprotonation of one to four metal-bound ethanol molecules. Kinetics for the La^{3+}-catalyzed ethanolysis of paraoxon as a function of $^{s}_{s}$pH are presented and analyzed in terms of La^{3+} speciation as determined by the analysis of potentiometric titration curves. The stability constants for the formation of Zn^{2+} and Cu^{2+} complexes with 1,5,9-triazacyclododecane as determined by potentiometric titration are presented.

Introduction

In the past few years, we have studied extensively the kinetic behavior of lanthanide and transition metal ions in catalyzing acyl[1] and phosphoryl[2] transfer reactions in methanol. Of the organic solvents, methanol is closest to water in terms of structure and function in solvolytic processes and has good solubility characteristics for both hydrophobic substrates and the active $M^{x+}(^{-}OCH_3)_y$ forms of the catalysts. Due to its low dielectric constant relative to water (31.5 vs 78.5 at 25 °C)[3] MeOH also improves association of oppositely charged ions which apparently enhances metal ion catalysis of processes that involve pre-equilibrium binding prior to the acyl or phosphoryl transfer reaction. The net result from a reactivity perspective is that these metal-ion-catalyzed transfer reactions to the solvent are remarkably accelerated relative to the situation in water. Furthermore, recent findings in these laboratories have indicated that the seemingly subtle change from methanol to ethanol has an additional profound rate-accelerating influence on the Zn^{2+}-catalyzed alcoholysis of a model compound for RNA, namely hydroxypropyl *p*-nitrophenyl phosphate.[4a]

As it is generally accepted that the active sites of enzymes have dielectric constants resembling organic solvents rather than water,[5] studies of nonenzymatically catalyzed processes in reduced-dielectric-constant media are of fundamental interest, particularly those promoted by metal ions which

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* To whom correspondence should be addressed. E-mail: rsbrown@chem.queensu.ca. Fax: 613-533-6669. Phone: 613-533-2400.

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might offer some clues to the high reactivity of metalloenzymes promoting hydrolytic and group transfer reactions. To conduct meaningful mechanistic and kinetic studies, reliable and simple measurement and control of the solution ${}^{s}_{s}$pH[6] is essential.[7] Our previous work on titration of metal ions in methanol solution[8] gave some indication of the speciation of certain lanthanide and transition metal ions in solution, as well as the effects of counterions and ligands on metal ion ${}^{s}_{s}pK_a$ values[2a,9] which, when viewed in conjunction with kinetic studies in the presence of the metal ions, was particularly helpful in identifying catalytically active species. The same principles can be extended to titration in alcohols such as ethanol and *n*-propanol, which are seen as more environmentally friendly than methanol with lower dielectric constants of 24.3 and 20.1, respectively, at 25 °C.[3]

Potentiometric titration methods are relatively simple and reliable for obtaining acid dissociation constants or metal ion complex stability constants, and in favorable cases, the speciation of mixtures of metal-ion-containing complexes in solution can be proposed.[10] Such titrations in nonaqueous solvents are not widely reported, particularly in cases with metal ions.[11] Determination of ‘pH’ in a nonaqueous solvent referenced to that solvent has traditionally been difficult due to the lack of a way to relate the electrode EMF readings to absolute ${}^{s}_{s}$pH,[6] so nonaqueous solvents were generally inconvenient to use[12] for detailed studies of reaction mechanisms where pH control was required. Many years ago, Bates et al.[13] and Grunwald et al.[14] independently determined a correction constant (denoted as δ) which is related to the electrode junction potential between the two solvents ($\bar{E}_j$) and the primary medium effect for the solvent (${}_{m}\gamma_H$) by the equation $\delta = \bar{E}_j - \log {}_{m}\gamma_H$.[15a] The practical measurement of ${}^{s}_{s}$pH in ethanol is accomplished by subtracting this constant ($\delta = -2.91$ or -2.36[15b] on the molality scale for Bates[13] and Grunwald,[14b] respectively) from the measured electrode reading. These constants are related to the molarity scale by the solvent density (ρ) where $pH_{molarity} = pH_{molality} - \log \rho/\rho°$ (with $\rho° = 1$ g/mL). Once a reliable correction constant is available, the routine for a practical measurement of ${}^{s}_{s}$pH in ethanol becomes as simple[6] as subtracting the correction constant from the measured electrode reading made in ethanol $\left({}^{s}_{w}pH - \delta\right)$ provided that this is determined under ‘ideal conditions’[13] of low ionic strength and a ${}^{s}_{s}$pH neither too high nor too low. Although the Bates and Grunwald δ correction factors differ substantially, there appear to be no criteria to assess which is better so we have chosen for our work to use the mean of these numbers ($\delta = -2.54$). Should an agreed-upon factor become available at a later date, our numbers can be easily corrected.

In what follows, we report various acid dissociation constants $\left({}^{s}_{s}pK_a\right)$ for some standard acids and buffering agents in ethanol. The titration of metal ions in alcohol is particularly complicated for several reasons, mainly attributable to changes in speciation due to dimerization and oligomerization, and forms the majority of the present report. We have analyzed the potentiometric data for two common transition metal ions (Zn^{2+}, Cu^{2+}) and 12 Ln^{3+} metal ions in two ways depending upon the level of information required concerning the ${}^{s}_{s}$pH-dependent species formed in solution. In addition, we have determined qualitatively the effect of some added counterions often used as supporting electrolytes and as anionic components of buffers used for pH control in kinetic experiments. We show the utility of the titration/speciation analysis in a real kinetic analysis of the La^{3+}-catalyzed ethanolysis of paraoxon, a pesticide sometimes used as a chemical weapons simulant. Last, the binding constants for some ligands used in our catalytic systems with Cu^{2+}, Zn^{2+}, and La^{3+} are determined along with an analysis of the metal ion speciation in ethanol.

Experimental

Materials. Benzoic acid, 2,4-dinitrobenzoic acid, 2,6-lutidine, 1-methylimidazole, 4-ethylmorpholine, triethylamine, and 2,9-dimethyl-1,10-phenanthroline were purchased from Aldrich. Glacial acetic acid was purchased from Fisher, 3,5-dinitrobenzoic acid from Eastman Kodak, and 1,10-phenanthroline from Acros; all commercially available materials were used without further purification. Trifluoromethanesulfonate (triflate, $^{-}$OTf) salts of all the trivalent

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lanthanide ions (except cerium, promethium, and lutetium) were purchased from Aldrich and used as received. Divalent zinc and copper triflates were purchased from Acros and used as received. Perchloric acid was purchased from Aldrich and was subsequently titrated to be 11.46 M (aq). Stock solutions (2×10^{-2} M) of each compound were prepared using absolute ethanol (99.9% anhydrous) from Commercial Alcohols, Inc. sparged with anhydrous nitrogen gas for >45 min. If the stated water content of the commercial ethanol held true, it would be <0.1% (v/v). Karl Fischer titrations of aliquots of the EtOH used showed levels of 0.118−0.157% (v/v), which is comparable to that stated and should not affect the ${}^{s}_{s}$pH enough to alter the interpretation of data so that the correction factor of −2.54 is sufficiently precise for our purposes, especially given the inherent error in its determination. NaOEt titrant was prepared and stored under argon and used within 5 days to avoid possible effects of "aging" which have been observed with KO*t*-Bu in *t*-BuOH.[16] All other solutions were prepared and stored in septum-sealed volumetric flasks and used within 2 days. Tetra-*n*-butylammonium perchlorate, triflate, bromide, and iodide salts were purchased from Aldrich, while the chloride was purchased from Fluka; all were used as received to prepare 0.4 M stock solutions in sparged absolute ethanol.

The azacrown ligand 1,5,9-triazacyclododecane (12N3) was prepared as a clear, slightly yellow oil (10.5% overall yield) according to the published procedure.[17] By ^{1}H NMR, its purity was >98%. ^{1}H NMR (400 MHz, $CDCl_3$): 2.80−2.70 (t, 12H), 2.49 (s, 3H), 1.69−1.60 ppm (q, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 48.72, 27.25 ppm.

Titrations. Potentiometric titrations were performed in triplicate (except where stated) using a Metrohm 798 MPT Titrino autotitrator equipped with a Radiometer pHC2501-8 double junction electrode. The outer sleeve of the electrode which was in direct contact with the ethanolic medium was filled with a 1 M $LiClO_4$ solution in ethanol, while the inner sleeve was filled with a saturated aqueous solution of KCl. Solutions were titrated in a jacketed glass cell thermostated at 25 °C while being sparged with Ar gas. The electrode was calibrated using aqueous Fisher-certified buffers at pH 4.0 and 10.0. Subsequent ${}^{s}_{w}$pH meter readings in EtOH were converted to the ${}^{s}_{s}$pH values by subtracting the δ correction factor of −2.54. The sodium ethoxide titrant was standardized by titrating an aqueous solution of Fisher-certified HCl (N/50) at least once per day. All aliquots of stock solutions were transferred into the titration cell via syringe, and the total volume was brought to 20.0 mL by adding sparged anhydrous ethyl alcohol. The final *in situ* concentration of sample acid was 1×10^{-3} M with 5×10^{-4} M added perchloric acid. In the case of the amines, sufficient perchloric acid was added to give 1×10^{-3} M of the aminium perchlorate with 5×10^{-4} M excess of free perchloric acid. Added tetrabutylammonium salts were used at a concentration of 0.02 M. For the metal ion/ligand binding experiments, the concentration of metal ion and ligand was 1×10^{-3} M.

Titration profiles were fitted using the Hyperquad 2000 NT computer program[18] to determine ${}^{s}_{s}\mathrm{p}K_a$ values for each carboxylic acid and aminium ion studied taking the autoprotolysis constant of pure ethanol to be $10^{-19.1}$ at 25.0 °C, a value commonly used[19] and very similar to others reported.[20] Though it may be true that completely anhydrous ethanol has an autoprotolysis constant $({}^{s}_{s}\mathrm{p}K_{\mathrm{EtOH}})$ closer to 19.5 as suggested by Grunwald and Berkowitz,[14a] the one chosen here is probably more accurate for the more practical solvent grade used in this work. Actually, the use of a different constant does not affect values for ${}^{s}_{s}\mathrm{p}K_a$'s in the normal ${}^{s}_{s}$pH range, but formation constants involving ethoxide depend on this constant and would be different according to the expression $\log \beta_2 - \log \beta_1 = n({}^{s}_{s}\mathrm{p}K_{\mathrm{EtOH^2}} - {}^{s}_{s}\mathrm{p}K_{\mathrm{EtOH^1}})$ where β_1 and β_2 are the corrected and original formation constants, ${}^{s}_{s}K_{\mathrm{EtOH^2}}$ and ${}^{s}_{s}K_{\mathrm{EtOH^1}}$ are the corrected and original autoprotolysis constants and n is the number of ethoxides associated with the complex. Where possible, Hyperquad fittings were also used to determine binding constants between metal ions and ligands. The experimental ${}^{s}_{s}\mathrm{p}K_a$ of the last ligand−H^+ dissociation was determined and set as a constant in the program for the analysis of the same dissociation during titration of the ligand in the presence of the metal ion.

Kinetics. The rate of ethanolysis of paraoxon was followed by monitoring the increase in absorbance at 315 nm with a Varian Cary 100 Bio UV−Vis spectrophotometer at 25.0 ± 0.1 °C. All runs were repeated in duplicate. Reactions were done under pseudo-first-order conditions of excess La^{3+} ions at $[La^{3+}] = 2 \times 10^{-3}$ M and $[\text{paraoxon}] = 5 \times 10^{-5}$ M. Reactions were initiated by addition of an aliquot of a 5×10^{-3} M stock solution of paraoxon in ethanol to make up 2.5 mL of reaction mixture and were followed for at least four half-lives over which they displayed good first-order behavior. Pseudo-first-order rate constants (k_{obs}) were determined by NLLSQ fitting of the absorbance vs time traces to a standard exponential model. Second-order rate constants were determined as $k_{\mathrm{obs}}/[La^{3+}]$ under the assumption that k_{obs} vs $[La^{3+}]$ plots are linear in the concentration range used with negligible background rates.[21] In most cases, solution ${}^{s}_{s}$pH was controlled by the La^{3+} and the addition of some amount of NaOEt. The ${}^{s}_{s}$pH corresponding to the number of equivalents of $^{-}$OEt added was obtained from the potentiometric titration of 2×10^{-3} M La^{3+} performed as described in this paper. Below the buffering capacity of La^{3+} (< ${}^{s}_{s}$pH 6.3) pyridine was used as a buffer $({}^{s}_{s}\mathrm{p}K_a = 5.13$, determined in this work by half-neutralization method) half-protonated with 70% $HClO_4$, and the [buffer] was extrapolated to zero. To avoid chloride ion contamination from the glass electrode that might affect the metal ion reactions, the ${}^{s}_{s}$pH values of the reaction solutions were measured following their completion. Duplicate solutions had ${}^{s}_{s}$pH values within 0.01 units, where different [buffer] solutions had ${}^{s}_{s}$pH values within 0.16 units. The ${}^{s}_{s}$pH of the stock buffer solution was taken prior to reaction and was within 0.02 units of the ${}^{s}_{s}$pH measured for the highest [buffer] reaction solution.

Mass Spectrometry. Mass spectra were determined on ethanol solutions of the metal ions under various conditions using a Waters/Micromass ZQ (Manchester, UK) single-quadrupole mass spectrometer equipped with an electrospray source operating at cone voltages between 22 and 67 V. The solutions contained either

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Table 1. ${}^{s}_{s}pK_a$ Values of Various Monobasic Acids and Aminium Ions as Determined by Hyperquad Analysis of Titration Data at 1×10^{-3} M in 99.9 % Anhydrous Ethanol, $T = 25.0$ °C

acid	pK_a (water)	${}^{s}_{s}pK_a$(methanol){n}^{a}	${}^{s}_{s}pK_a$(ethanol){n}^{a}	literature value (ethanol)
acetic acid	4.76^{b}	9.77 ± 0.10 {3}	10.58 ± 0.08 {5}	10.43 ± 0.19^{c}
benzoic acid	4.21^{b}	9.12 ± 0.02 {4}	10.40 ± 0.08 {5}	10.24 ± 0.12^{d}
2,4-dinitrobenzoic acid	1.42^{e}	6.48 ± 0.03 {3}	7.29 ± 0.05 {4}	
3,5-dinitrobenzoic acid	2.82^{e}	7.14 ± 0.02 {6}	8.01 ± 0.05 {2}	8.07 ± 0.04^{f}
4-nitrophenol	7.15^{g}	11.30^{h}	11.79 ± 0.17 {4}	11.55 ± 0.50^{i}
2,6-lutidine	6.72^{j}	6.86^{h}	6.37 ± 0.06 {4}	
1-methylimidazole	6.95^{g}	7.60^{k}	7.50 ± 0.14 {3}	
4-ethylmorpholine	7.76^{j}	8.28^{m}	7.98 ± 0.04 {3}	
triethylamine	11.01^{g}	10.78^{h}	10.22 ± 0.05 {4}	
1,10-phenanthroline	$4.86^{l,m}$	$5.63^{n,m}$	5.36 ± 0.23^{m} {2}	
2,9-dimethyl-1,10-phenanthroline	$6.17^{l,m}$	$6.43^{n,m}$	6.15 ± 0.001^{m} {2}	
1,5,9-triazacyclododecane	$7.49^{o,m}$	$14.92^{n,p}$	6.32 ± 0.06^{m} {2}	
	12.60^{p}		12.54 ± 0.05^{p}{2}	

[a] Values given are averages of n individual experiments. Errors given are standard deviations of the mean. [b] Isaacs, N. *Physical Organic Chemistry*, 2nd ed.; Pearson Education Ltd.: Harlow, Great Britain, 1995; pp 238−239. [c] References 14a and 46. [d] References 46a,b,d and 47 [e] Gluck, S. J.; Steele, K. P.; Benko, M. H. *J. Chromatogr. A* **1996**, *745*, 117. [f] Reference 47a,c. [g] *Handbook of Chemistry and Physics*, 48th ed.; CRC Press: Cleveland, *1967−68*; pp D88−89. [h] Reference 7b. [i] References 46a and 48. [j] Andon, R. J. L.; Cox, J. D.; Herington, E. F. G. *Trans. Faraday Soc.* **1954**, *50*, 918. [k] Reference 1d. [l] Schilt, A. A.; Smith, G. F. *J. Phys. Chem.* **1956**, *60*, 1546. [m] ${}^{s}_{s}pK_{a2}$. [n] Reference 39. [o] Bell, T. W.; Choi, H.-J.; Harte, W.; Drew, M. G. B. *J. Am. Chem. Soc.* **2003**, *126*, 12196. [p] ${}^{s}_{s}pK_{a3}$. May be a lower limit since ${}^{s}_{s}pK_a$ is close to solvent ionization.

$La(OTf)_3$ (1×10^{-4} M) or $Zn(OTf)_2$ (2×10^{-4} M), with and without added Bu_4NOH (1 equiv to La^{3+}, 1.5 equiv to Zn^{2+}). Samples were infused at a flow rate of 10 μL/min; the spectrometer was externally calibrated and run in positive-ion mode.

Results and Discussion

Potentiometric Titration of Monobasic Acids. To keep the ionic strength as low as possible, thereby minimizing its effect both on the kinetic reactivity of the ionic species and ion pairing, the concentrations of the acids, aminium ions, and metal ions were held at 1 mM, and an additional 0.5 mM in $HClO_4$ was added to set the initial starting pH for titration to a low value. Titration curves for all the monobasic acids or aminium ions revealed no anomalies in shape, all consuming exactly 1 equiv of titrant per equivalent of titratable proton. In Table 1 are presented the so-determined ${}^{s}_{s}pK_a$ values for each acid, the reported error being the standard deviation in the mean of a set of individual titrations. The literature ${}^{s}_{s}pK_a$ values in Table 1 represent the mean (and standard deviation) of previously reported values excluding extreme outliers. Where the literature values are available, the ${}^{s}_{s}pK_a$ values determined here deviate by no more than 0.15 units, which serves as a measure of the reliability of the present potentiometric methods. The ${}^{s}_{s}pK_a$'s for carboxylic and phenolic (neutral) acids are significantly higher in ethanol than in water or even methanol,[1e,2d,7] consistent with what is expected for the decreasing dielectric constant in passing to ethanol.[3] With the cationic aminium ions the ${}^{s}_{s}pK_a$ does not vary greatly, at least numerically, in passing from water to ethanol, although depending on the structure of the base the acidity in ethanol can be higher or lower than in water. Since neutral ${}^{s}_{s}pH$ in EtOH is 9.55[19,20] while that in methanol and water is 8.39[7] and 7.0, even though a species might have the same numerical ${}^{s}_{s}pK_a$ as in water, it is considerably more acidic in ethanol. The trends in ${}^{s}_{s}pK_a$ in passing from water to the less-polar alcohols can be explained in part by considering the left and right side of the equilibria for carboxylic acid and aminium ion dissociation in alcohol shown in eqs 1 and 2.

$$R_1C(=O)OH + HOR \rightleftharpoons R_1C(O)O^- + {}^{+}H_2OR \quad (1)$$

$$R_2R_3R_4NH^+ + HOR \rightleftharpoons R_2R_3R_4N: + {}^{+}H_2OR \quad (2)$$

Carboxylic acid dissociation creates two opposite charges, while aminium ion dissociation simply relocates (H^+) from the amine to the solvent, which may or may not be better solvated in a given solvent than the aminium ion depending on what the various alkyl groups are. In less-polar solvents, stabilization of charge-separated forms through specific solvation of ions is expected to be poorer than in water, thus accounting for the increased ${}^{s}_{s}pK_a$'s of carboxylic acids and the relative indifference in the ${}^{s}_{s}pK_a$'s of aminium ions. The solvation effects in play comprise more than the dielectric constant and include specific interactions such as hydrogen bonding and ion pairing that can have dramatic effects on the acidity and reactivity. For example, an NMR study by Gold et al.[22] showed that solvation of alkoxide ions becomes weaker in the order MeOH > EtOH > *i*-PrOH > *t*-BuOH, which itself explains the trend in basicity of the corresponding anions. Elliot and Kilpatrick[23] showed that the ${}^{s}_{s}pK_a$ value for benzoic acid in the presence of added salts was lowered in EtOH far more than in MeOH or water, indicating that ionic strength and ion pairing effects stabilize the right-hand side of the equilibrium of eq 1 in a way that depends on the reduced polarity of the medium.

Lanthanide Ions. Shown in Figure 1 are titration profiles for three representative lanthanide ions, La^{3+}, Gd^{3+}, and Tm^{3+}. For each, the titration data show consumption of 2 equiv of base in a narrow ${}^{s}_{s}pH$ range of ∼1 unit followed by continued consumption of another equivalent of base occurring over several ${}^{s}_{s}pH$ units.

This is suggestive of the formation of one or more stable metal/ethoxide species having an [^{-}OEt]/[Ln^{3+}] ratio of 2,

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(22) Gold, V.; Morris, K. P.; Wilcox, C. F. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1615.

(23) Elliott, J. H.; Kilpatrick, M. *J. Phys. Chem.* **1941**, *45*, 466.

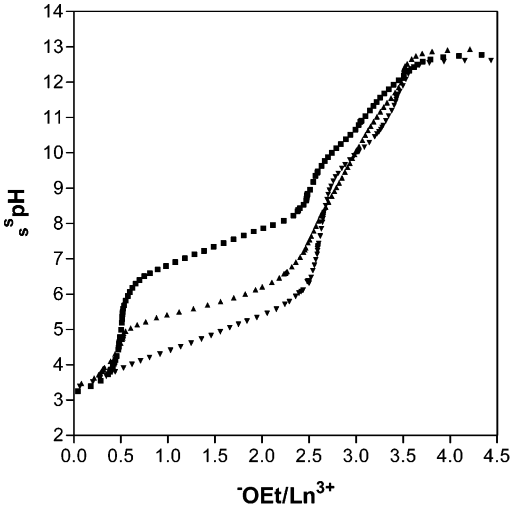
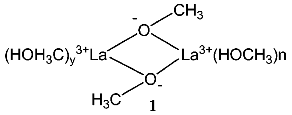


Figure 1. Titration profile for three lanthanide ions, La^{3+}(■), Tm^{3+} (▼) and Gd^{3+} (▲) 1×10^{-3} M in 99.9% anhydrous ethanol. The first consumption of 0.5 equiv of $^{-}$OEt at ${}^{s}_{s}$pH ≤ 4 corresponds to the titration of 5×10^{-4} M added $HClO_4$.

followed by a domain consuming 1 equiv of $^{-}$OEt per Ln^{3+} for which the analysis is far more difficult.

Our previous investigations of metal ion behavior in methanol[1,2,8,9] indicated that lanthanide ions spontaneously form dimeric methoxide complexes $(La^{3+})_2(^{-}OCH_3)_{1-5}$ depending upon the solution ${}^{s}_{s}$pH. The most catalytically active of these for phosphoryl[2a,d] and acyl[1a,f] transfer is $La^{3+}{}_2(^{-}OCH_3)_2$, suggested to be the doubly methoxy bridged form (**1**), the bridging nature of which is supported by



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previous analogous work[11b,24] indicating numerous examples of dimeric metal ion species with bridging hydroxy groups. In addition, structures determined by X-ray diffraction suggest that some lanthanides are capable of forming oligomers of hexameric or higher-order species in alcohol media under certain conditions.[25]

That the gradients $\left(\delta[^{-}OEt]/\delta[{}^{s}_{s}pH]\right)$ of the plots in Figure 1 are steeper than required for two independent ionizations is consistent with the intervention of cooperative processes such as the formation of dimers or higher-order aggregates[24a,26] or a change in the metal ion coordination number[27,28] accompanying addition of the ethoxide to the metal ion. Under favorable conditions, formation of dimers or other oligomers is confirmed by a dependence of the apparent ${}^{s}_{s}pK_a$ values on metal ion concentration,[24a] but for La^{3+} titration in ethanol, we observed no significant difference in this value nor in the appearance of the titration curve over the range 5×10^{-4} M < $[La^{3+}]$ < 3×10^{-3} M. By analogy with our previous observations of the behavior of La^{3+} in methanol, we suggest that dimeric species are more readily formed in the less polar ethanol at these lower concentrations than is the case in methanol, so the monomer ⇌ dimer equilibrium is far to the right for all the concentrations employed in the titration study. Electrospray mass spectrometric measurements (not shown) on 1×10^{-4} M $La(OTf)_3$/ethanol solutions (significantly lower than the concentrations titrated above) containing equimolar Bu_4NOH indicate the presence of peaks analyzing for dimeric $La_2(OEt)_2(OTf)_3$ ($m/z = 860.8$), $La_2(OEt)_3(OTf)_2$ ($m/z = 710.8$), and $La_2(OEt)_4(OTf)$ ($m/z = 607.0$) in addition to three monomeric species $La(OTf)_2(EtOH)$ ($m/z = 482.9$), $La(OEt)(OTf)$ ($m/z = 333.0$), and $La(OEt)_2$ ($m/z = 229.1$) which have comparable intensities.

In view of the above, the first portions of each of the Ln^{3+} titration curves consuming 2 equiv of $^{-}$OEt /Ln^{3+} were analyzed in terms of the dimer model given in eqs 3−6 below using Hyperquad 2000.[18] This analysis gives formation constants for each species in the model from which can be calculated microscopic ${}^{s}_{s}pK_a$'s for individual ionizations, all the computed values for the lanthanides being given in Table 2. From the formation constants can be computed the speciation for the $Ln^{3+}{}_2(^{-}OEt)_{1-4}$ forms by HySS, another program in the Hyperquad[18] suite, those for La^{3+} at 2×10^{-3} M being shown in Figure 2. According to this treatment for La^{3+} the two dominant species have even numbers of attached ethoxides, namely $La^{3+}{}_2(^{-}OEt)_2$ between ${}^{s}_{s}$pH 5.9 and 8.4 (maximum concentration of ∼48% relative to $[La^{3+}{}_2]_{total}$ at ${}^{s}_{s}$pH 7.3), and $La^{3+}{}_2(^{-}OEt)_4$ above ${}^{s}_{s}$pH 7. Species with odd numbers of ethoxides, $La^{3+}{}_2(^{-}OEt)_1$ and $La^{3+}{}_2(^{-}OEt)_3$, are also present to a lesser extent (maximum concentrations of ∼17% and 37% in each reached at respective ${}^{s}_{s}$pH values of 6.7 and 7.8). Of course, the ${}^{s}_{s}$pH's at which the species are at maximum concentration coincide with those where the $^{-}$OEt/La^{3+} ratio from the titration is the same as is present in that species.

$$Ln^{3+}{}_2(HOEt)_x \rightleftharpoons Ln^{3+}{}_2\,(^{-}OEt)(HOEt)_m + H^+ \qquad (3)$$

$$Ln^{3+}{}_2(^{-}OEt)(HOEt\,)_m \rightleftharpoons Ln^{3+}{}_2(^{-}OEt)_2(HOEt)_p + H^+ \qquad (4)$$

$$Ln^{3+}{}_2(^{-}OEt)_2(HOEt)_p \rightleftharpoons Ln^{3+}{}_2(^{-}OEt)_3(HOEt)_q + H^+ \qquad (5)$$

$$Ln^{3+}{}_2(^{-}OEt)_3(HOEt)_q \rightleftharpoons Ln^{3+}{}_2(^{-}OEt)_4(HOEt)_r + H^+ \qquad (6)$$

Also shown in Figure 2 are the observed second-order rate constants (k_2^{obs}) for the La^{3+}-catalyzed ethanolysis of the neutral phosphate triester paraoxon (diethyl *p*-nitrophenyl phosphate) as a function of ${}^{s}_{s}$pH at 25 °C. As was the case for the k_2^{obs} in methanol,[2a] the rate constants correlate very well with the rise and decline of the concentration of the

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(28) (a) Doe, H.; Kitagawa, T. *Inorg. Chem.* **1982**, *21*, 2272. (b) Doe, H.; Shibagaki, A.; Kitagawa, T. *Inorg. Chem.* **1983**, *22*, 1639.

Table 2. Log Formation Constants and Microscopic ${}^{s}_{s}pK_a$'s for the Species $Ln^{3+}{}_2(^{-}OEt)_{1-4}$ as Calculated by Hyperquad as the Mean of Three Independent Potentiometric Titrations of 1×10^{-3} M $Ln^{3+}(^{-}OTf)_3$[a]

metal ion	log β 2,1	log β 2,2	log β 2,3	log β 2,4	${}^{s}_{s}pK_{a2}$	${}^{s}_{s}pK_{a3}$	${}^{s}_{s}pK_{a4}$
La^{3+}	14.85 ± 0.06	27.36 ± 0.08	38.77 ± 0.22	49.84 ± 0.16	6.60 ± 0.03	7.69 ± 0.15	8.03 ± 0.22
Pr^{3+}	15.89 ± 0.09	29.11 ± 0.02	40.86 ± 0.03	52.51 ± 0.08	5.88 ± 0.07	7.35 ± 0.05	7.45 ± 0.09
Nd^{3+}	15.89 ± 0.28	29.09 ± 0.12	41.45 ± 0.33	53.29 ± 0.42	5.90 ± 0.17	6.74 ± 0.21	7.26 ± 0.09
Sm^{3+}	16.21 ± 0.05	29.87 ± 0.06	42.75 ± 0.09	54.83 ± 0.20	5.45 ± 0.11	6.22 ± 0.09	7.02 ± 0.12
Eu^{3+}	16.26 ± 0.40	30.15 ± 0.17	43.26 ± 0.32	55.52 ± 0.41	5.21 ± 0.24	5.99 ± 0.15	6.85 ± 0.12
Gd^{3+}	15.81 ± 0.43	29.74 ± 0.13	43.33 ± 0.23	55.60 ± 0.37	5.17 ± 0.41	5.51 ± 0.32	6.84 ± 0.14
Tb^{3+}	16.83 ± 0.32	30.90 ± 0.04	44.81 ± 0.44	57.58 ± 0.70	5.03 ± 0.29	5.18 ± 0.40	6.33 ± 0.26
Dy^{3+}	17.87 ± 0.26	31.92 ± 0.20	46.11 ± 0.36	59.31 ± 0.63	5.05 ± 0.06	4.91 ± 0.17	5.90 ± 0.28
Ho^{3+}	16.96 ± 0.21	31.63 ± 0.09	45.52 ± 0.09	58.42 ± 0.03	4.44 ± 0.12	5.21 ± 0.01	6.20 ± 0.06
Er^{3+}	17.36 ± 0.29	32.11 ± 0.26	46.16 ± 0.35	59.40 ± 0.54	4.36 ± 0.06	5.05 ± 0.10	5.87 ± 0.20
Tm^{3+}	17.85 ± 0.25	32.92 ± 0.09	46.98 ± 0.12	60.46 ± 0.12	4.03 ± 0.18	5.04 ± 0.04	5.62 ± 0.04
Yb^{3+}	17.80 ± 0.15	33.48 ± 0.06	47.60 ± 0.10	61.26 ± 0.10	3.42 ± 0.16	4.97 ± 0.10	5.44 ± 0.05

[a] For log $\beta(X,Y)$, X and Y refer to the number of Ln^{3+} and the number of ^{-}OEt in the species. β values are defined as equilibrium constants for the process $X(Ln^{3+}) + Y(^{-}OEt) \rightleftharpoons Ln^{3+}{}_X(^{-}OEt)_Y$. ${}^{s}_{s}pK_a$ values are for the processes described by eqs 4−6 for the production of $Ln^{3+}{}_2(^{-}OEt)_{n=2-4}$.

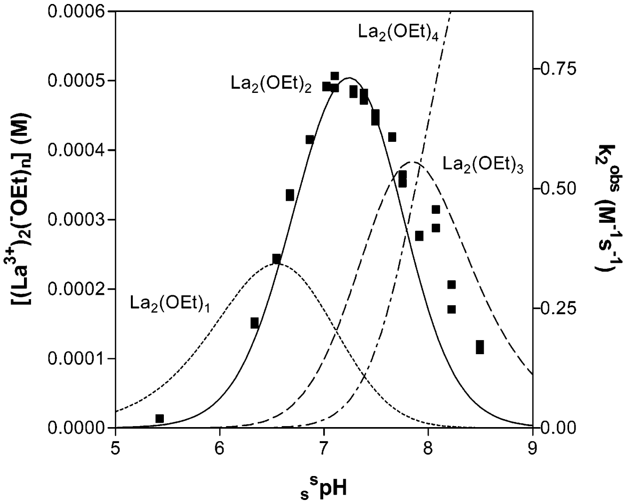

Figure 2. Calculated speciation diagram for $La^{3+}{}_2(^{-}OEt)_n$, $n = 1-4$, total $[La^{3+}] = 2 \times 10^{-3}$ M, computed by Hyperquad fitting of the titration curve shown in Figure 1 to the model given in eqs 3−6. Overlaid are the observed second-order rate constants (k_2^{obs}) for the La^{3+}-catalyzed ethanolysis of paraoxon as a function of ${}^{s}_{s}pH$.

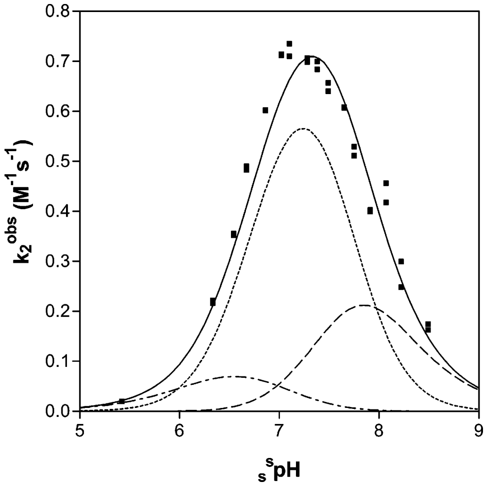

Figure 3. Plot of the contributions of various $La^{3+}{}_2(^{-}OEt)_n$ forms to the k_2^{obs} for La^{3+}-catalyzed ethanolysis of paraoxon as a function of ${}^{s}_{s}pH$. Solid line gives the combined effects of various species; (• − •), contribution of $La^{3+}{}_2(^{-}OEt)_1$; (- - -), contribution of $La^{3+}{}_2(^{-}OEt)_2$; (— — —), contribution of $La^{3+}{}_2(^{-}OEt)_3$; included as (■) are the actual k_2^{obs} kinetic data.

$La^{3+}{}_2(^{-}OEt)_2$ species, implicating it as primarily responsible for the catalysis of the phosphoryl transfer reaction. In fact, the overall observed second-order rate constant in Figure 2 at any given ${}^{s}_{s}pH$ can be calculated as a linear combination of the contributions of each species having its own second-order rate constant associated with its own particular catalytic activity for this reaction. The kinetic data, when fit to the expression given in eq 7 yields the contributions of the relevant ${}^{s}_{s}pH$-dependent La^{3+} dimer species, as shown in Figure 3. The solid line represents the sum of the species contributions and is found to follow the kinetic data reasonably well. As can be seen from the figure, the contributions of the $La^{3+}{}_2(^{-}OEt)$ and $La^{3+}{}_2(^{-}OEt)_3$ species are minor compared to the contribution of $La^{3+}{}_2(^{-}OEt)_2$. From the fit to this curve, the individual species rate constants were determined to be 0.59 ± 0.05, 2.24 ± 0.19, and 1.11 ± 0.09 M^{-1} s^{-1} for $k_2^{2:1}$, $k_2^{2:2}$, and $k_2^{2:3}$, respectively. Note that in this analysis we have not propagated all the errors from the Hyperquad fittings into the analysis of the rate constants, so the error in these rate constants is determined from the average % deviation in the fitted numbers calculated by eq 7 from the actual kinetic data. The k_2^{obs} vs ${}^{s}_{s}pH$ plot for the La^{3+}-catalyzed methanolysis of paraoxon was analyzed previously in the same way for a very similar kinetic profile,[2a] and the species rate constants were determined to be 18.4 ± 5.4, 47.2 ± 2.4, and 110.4 ± 11.8 M^{-1} s^{-1} for $k_2^{2:1}$, $k_2^{2:2}$, and $k_2^{2:3}$, respectively. It was similarly found that the $La^{3+}{}_2(^{-}OCH_3)_2$ was predominantly active with only minor contributions from $La^{3+}{}_2(^{-}OCH_3)$ and $La^{3+}{}_2(^{-}OCH_3)_3$. The $k_2^{2:3}$ value for the methanol system seems considerably higher than that in ethanol, but the abundance of $La^{3+}{}_2(^{-}OCH_3)_3$ in methanol is much lower, thus the contribution of $La^{3+}{}_2(^{-}OR)_3$ is similar in both methanol and ethanol. It is notable that the second-order rate constants for the La^{3+}-catalyzed methanolysis of paraoxon are higher than those for its ethanolysis over the ${}^{s}_{s}pH$ range studied. The exact nature of this decrease in activity passing from methanol to ethanol is not currently understood but may be due to a lower nucleophilicity of a metal-bound alkoxide as a result of increased ion pairing between the metal ion and alkoxide or to the influence of steric effects that are more prominent in the higher-order alcohols. We note that the reaction of ethoxide with paraoxon in ethanol at 5.1×10^{-3} M^{-1} s^{-1} [4b] is roughly a factor of 2 lower than the reaction of methoxide with paraoxon in methanol. Using the former value, we can calculate that the acceleration afforded by a solution 2 mM in total [La^{3+}] which thus contains 1 mM of La_2^{3+} has a maximum rate constant of 7×10^{-4} s^{-1} at a ${}^s_s$pH of 7.3 and accelerates the rate of ethanolysis of paraoxon by a factor of 4.4×10^{11}-fold relative to the ethoxide reaction. By way of comparison, the acceleration afforded by a 1 mM solution of La_2^{3+} for the methanolysis reaction at ${}^s_s$pH 8.3, where rate is maximal in methanol, is 10^9-fold relative to its background methoxide reaction. Although the La_2^{3+} catalyst in ethanol appears to be superior to the La_2^{3+}/methanol system, this stems mostly from from the ${}^s_s$pH ranges considered for the background reactions and the far lower [$^-$OEt] relative to [$^-$OMe] at the ${}^s_s$pH values where the comparisons are made.

$$k_2^{\text{obs}} = \frac{k_2^{2:1}[\text{La}^{3+}{}_2(^-\text{OEt})] + k_2^{2:2}[\text{La}^{3+}{}_2(^-\text{OEt})_2] + k_2^{2:3}[\text{La}^{3+}{}_2(^-\text{OEt})_3]}{[\text{La}(\text{OTf})_3]_t} \quad (7)$$

Fits of the titration data for any of the lanthanides undoubtedly can be mathematically accomplished as easily as for La^{3+}, as this is simply a matter of providing an acceptable model that accounts for the shape of the titration over the ${}^s_s$pH range of interest. As we have not undertaken any kinetic studies at higher ${}^s_s$pH's beyond those set by addition of the first two $^-$OEt/Ln^{3+}, we have decided not to speculate on the species present in this region. Further, we have not undertaken additional fits of any of the data to models that account for the various suspected ion pairing Ln^{3+}/$^-$OTf equilibria because the inclusion of such will inevitably lead to mathematically acceptable results but does not provide reliable chemical insight because one has no additional corroborative information (such as is provided by electrospray MS, UV−vis spectroscopy of kinetic results) to substantiate the models chosen.

Simplification of the Treatment for Ln^{3+} Titrations. An analysis such as presented above for La^{3+} supplies formation constants and ${}^s_s$pK_a data for sequential ionization of the metal-coordinated alcohol if some confirmatory information for the species present in solution can be provided. However, for many purposes, a simpler analysis suffices that is concerned with apparent '${}^s_s$pK_a' values for formation of the metal-bound ethoxides. The simplification is essentially the same as we applied to the titration of metal ions in methanol.[8] Following Simms,[29] we define the titration constants ${}^s_sG_1'$, ${}^s_sG_2'$, ${}^s_sG_3'$, etc. as the half-neutralization points determined for a solution containing monovalent, noninteracting acids. For the hypothetical metal-coordinated ethanolysis process shown in eqs 8−10, the three ${}^s_s$pG_1', ${}^s_s$pG_2', and ${}^s_s$pG_3' values are simply interpreted as the solution ${}^s_s$pH at which the [$^-$OEt]/[M^{x+}]$_t$ ratio is 0.5, 1.5, and 2.5.

$$\text{M}^{x+}(\text{HOEt})_x \rightleftharpoons \text{M}^{x+}(^-\text{OEt})(\text{HOEt})_y + \text{H}^+ \quad (8)$$

$$\text{M}^{x+}(^-\text{OEt})(\text{HOEt})_y \rightleftharpoons \text{M}^{x+}(^-\text{OEt})_2(\text{HOEt})_z + \text{H}^+ \quad (9)$$

$$\text{M}^{x+}(^-\text{OEt})_2(\text{HOEt})_z \rightleftharpoons \text{M}^{x+}(^-\text{OEt})_3(\text{HOEt})_q + \text{H}^+ \quad (10)$$

The ${}^s_sG_n'$ values are related to the individual ${}^s_sK_n'$ values (defined as the dissociation constants of the polyvalent acid, not corrected for activities) pertaining to the three stepwise ionizations by eqs 11−13:

$${}^s_sK_1' = {}^s_sG_1' + {}^s_sG_2' + {}^s_sG_3' \quad (11)$$

$${}^s_sK_1'\,{}^s_sK_2' = {}^s_sG_1'\,{}^s_sG_2' + {}^s_sG_1'\,{}^s_sG_3' + {}^s_sG_2'\,{}^s_sG_3' \quad (12)$$

$${}^s_sK_1'\,{}^s_sK_2'\,{}^s_sK_3' = {}^s_sG_1'\,{}^s_sG_2'\,{}^s_sG_3' \quad (13)$$

The "Simms" method identifies the half-neutralization points, but it cannot fit the overall appearance of a titration curve that is too steep to be explained by sequential, independent ionizations. This is because the method does not allow for situations where there is a cooperativity (usually identified in cases where $pK_{n+1}' - pK_n' < 0.6$), such as is observed where there is dimerization of the metal ions or a change in coordination geometry that accompanies the *n*th ionization which facilitates the subsequent ($n + 1$)th ionization.

Baes and Mesmer[24a] describe the hydrolysis of cations in water according to the simplified process in eq 14.

$$x\text{M}^{z+} + y\text{H}_2\text{O} \rightleftharpoons \text{M}_x\,(\text{OH})_y^{(xz-y)+} + y\text{H}^+ \quad (14)$$

The ligand number, $\bar{n}$, is defined by the mole ratio of metal-ion-bound $^-$OH in the solution and is given as

$$\bar{n} = \sum y[\text{M}_x(\text{OH})_y^{(xz-y)+}]/m_\text{M} \quad (15)$$

where m_M is the total metal ion concentration including nonbound forms or

$$m_\text{M} = \sum x[\text{M}_x(\text{OH})_y^{(xz-y)+}] \quad (16)$$

In principle, it is possible to determine the ligand number, $\bar{n}$, as a function of both the pH and metal ion concentration and thereby determine the formula of each hydroxide complex in eq 14. This is applicable to titrations performed in ethanol, although an exact treatment is not possible at present because of the ion pairing and lack of ionic strength control. However, under the relatively low [M^{x+}], and thus low-ionic-strength conditions as used herein, the titrations can provide conditional constants which pertain to the average number of EtO^-/M^{x+}. The observed ${}^s_s$pH when $\bar{n}$ = 0.5, 1.5, or 2.5 corresponds to the Simms' half-neutralization points ${}^s_s$pG_1', ${}^s_s$pG_2', and ${}^s_s$pG_3', with these values for various Ln^{3+} ions being listed in Table 3.

Over the lanthanides, the general acidity of the $Ln^{3+}(HOEt)_n$ increases with the smaller ions. Shown in Figure 4 is a plot of the apparent "Simms" half-neutralization constants ([$^-$OEt]/[M^{3+}] = 0.5, 1.5, and 2.5) vs the ionic radii for the lanthanide

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(29) Simms, H. S. *J. Am. Chem. Soc.* **1926**, *48*, 1239.

Table 3. Observed Titration Constants (${}^{s}_{s}pG_1'$, ${}^{s}_{s}pG_2'$, ${}^{s}_{s}pG_3'$) Corresponding to Ligand Numbers $\bar{n} = 0.5$, 1.5, or 2.5 for Titrations of 1×10^{-3} M $Ln^{3+}(^{-}OTf)_3$ or $M^{2+}(^{-}OTf)_3$ in Ethanol, $T = 25.0$ °C[a]

metal ion	${}^{s}_{s}pG_1'$	${}^{s}_{s}pG_2'$	${}^{s}_{s}pG_3'$
La^{3+}	6.82 ± 0.07	7.84 ± 0.11	10.60 ± 0.16
Pr^{3+}	6.02 ± 0.03	7.37 ± 0.02	10.29 ± 0.07
Nd^{3+}	5.97 ± 0.05	7.07 ± 0.12	10.58 ± 0.08
Sm^{3+}	5.59 ± 0.02	6.67 ± 0.04	10.28 ± 0.17
Eu^{3+}	5.43 ± 0.08	6.46 ± 0.05	10.15 ± 0.02
Gd^{3+}	5.42 ± 0.05	6.30 ± 0.16	10.03 ± 0.16
Tb^{3+}	4.92 ± 0.07	5.85 ± 0.22	9.75 ± 0.25
Dy^{3+}	4.58 ± 0.04	5.64 ± 0.12	9.47 ± 0.08
Ho^{3+}	4.61 ± 0.02	5.62 ± 0.03	9.99 ± 0.07
Er^{3+}	4.46 ± 0.09	5.42 ± 0.12	10.02 ± 0.17
Tm^{3+}	4.31 ± 0.05	5.35 ± 0.02	9.96 ± 0.00
Yb^{3+}	4.08 ± 0.02	5.25 ± 0.05	9.92 ± 0.05
Zn^{2+}	6.86 ± 0.02	7.38 ± 0.05	NA
Cu^{2+}	4.94 ± 0.10	6.59 ± 0.08	NA

[a] Error is calculated as the mean of values measured in triplicate.

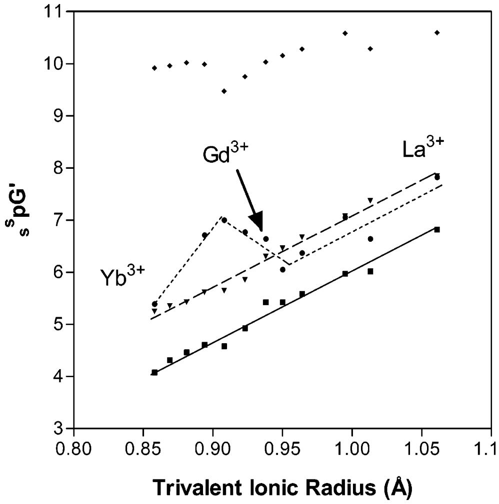

Figure 4. Plot of the "Simms" half-neutralization constants vs ionic radius of the Ln^{3+} ions. In ethanol: ${}^{s}_{s}pG_1'$ (■), ${}^{s}_{s}pG_2'$ (▼), and ${}^{s}_{s}pG_3'$ (◆). The ${}^{s}_{s}pG_1'$ values in methanol (●) are included for comparison.[8] Lines are not fitted curves but rather are included to guide the reader through the data.

ions.[30] A similar trend is evident in methanol (data included in Figure 4 for comparison),[8] but in that solvent, there was a significant rise−fall−rise motif in ${}^{s}_{s}pG_1'$ for the metal ions surrounding gadolinium (the so-called "gadolinium break") that is believed to be related to a change in coordination number from nine to eight in this region.[11a,24a,d,31] The lack of any pronounced break in the plot of ${}^{s}_{s}pG_1'$ or ${}^{s}_{s}pG_2'$ for Ln^{3+} in ethanol in Figure 4 may suggest that coordination number does not change throughout the series, perhaps staying at eight, consistent with the larger size of ethanol relative to methanol making it too crowded to place nine coordinated solvent molecules around the metal ion. A related effect was observed for the solvation of alkoxide anions in alcohol where fewer numbers of coordinating solvent molecules in bulkier alcohols such as *tert*-butanol are the primary cause of the alkoxide's increased basicity.[22]

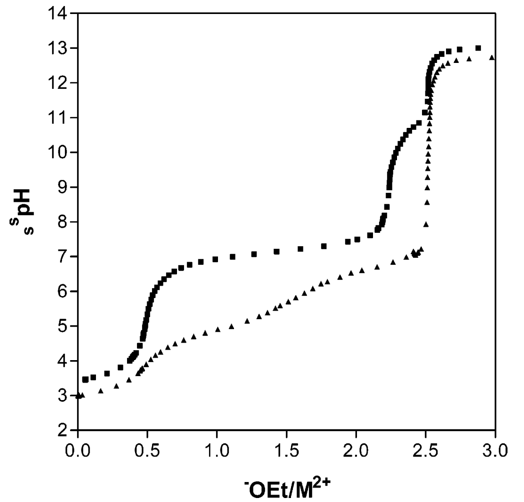

Figure 5. Titration profiles for 1×10^{-3} M $Zn(OTf)_2$ (■) and $Cu(OTf)_2$ (▲) in ethanol.

For the part of the titration curve beyond the first 2 equiv of base, the general inconsistency between the various ions and gradual nature of base consumption indicates a set of relatively undefined species present with changing morphology, possibly the result of oligomerization. Although this part of the titration curve can be fitted reasonably well using the dimer model with five and six attached ethoxides, this model is without further evidence for the existence of such species, and we did not analyze this region since we were not interested in kinetic studies at these high ${}^{s}_{s}pH$ values. The possibility of oligomerization in alcohol receives some literature support and a related process termed "aging" has been described for lanthanides in water over time[32] which may be related to the aggregation of metal ions via bridging hydroxides, an effect amplified at the ${}^{s}_{s}pH$ values in question.

Copper and Zinc Ions. In Figure 5 are presented titration data for 1×10^{-3} M $Cu(OTf)_2$ and $Zn(OTf)_2$ in ethanol. The two are visibly different, save for the total consumption of two ^{-}OEt per M^{2+}. Cu^{2+} consumes these in two distinct steps of 1 equiv each, and the apparent ${}^{s}_{s}pK_a$ of each step does not depend on $[Cu^{2+}]$ over the range 5×10^{-4} M < $[Cu^{2+}] < 3 \times 10^{-3}$ M. While these observations are consistent with a monomeric Cu^{2+} undergoing two sequential deprotonations as in eqs 8 and 9 (a model which fits the data reasonably well), it is nevertheless clear in methanol that an inactive dimeric Cu^{2+} is in equilibrium with an active monomer,[33] and changing the solvent to the less-polar ethanol should favor the formation of dimers and possibly higher-order aggregates. The dimeric model is presented that includes four sequential ionizations to create the forms $Cu^{2+}_2(^{-}OEt)_n$, where $n = 1-4$, which was fit to the titration data with the resulting log formation constants being given in Table 4.

For $5 \times 10^{-4}-3 \times 10^{-3}$ M solutions of Zn^{2+}, the titration curves show consumption of 5/3 equiv of ^{-}OEt in a rather steep step with an apparent ${}^{s}_{s}pK_a$ of ∼7.5 (defined in this case as the ${}^{s}_{s}pH$ corresponding to the midpoint of the

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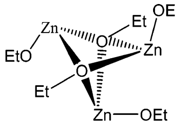
Table 4. Log Formation Constants and Microscopic ${}_{s}^{s}pK_a$'s for the Species $M^{2+}{}_m(^-OEt)_n$ as Calculated by Hyperquad from the Potentiometric Titration of 1×10^{-3} M $M^{2+}(^-OTf)_2$ in Ethanol, $T = 25$ °C[a]

equilibrium	log ${}_{s}^{s}K$	microscopic ${}_{s}^{s}pK_a$[b]
$[Cu_2(^-OEt)_1]/[Cu]^2[^-OEt]$	16.73 ± 0.20	–
$[Cu_2(^-OEt)_2]/[Cu]^2[^-OEt]^2$	31.35 ± 0.04	${}_{s}^{s}pK_{a2} = 4.48 \pm 0.17$
$[Cu_2(^-OEt)_3]/[Cu]^2[^-OEt]^3$	43.75 ± 0.09	${}_{s}^{s}pK_{a3} = 6.71 \pm 0.05$
$[Cu_2(^-OEt)_4]/[Cu]^2[^-OEt]^4$	56.21 ± 0.13	${}_{s}^{s}pK_{a4} = 6.63 \pm 0.14$
$[Zn_3(^-OEt)_2]/[Zn]^3[^-OEt]^2$	30.13 ± 0.17	–
$[Zn_3(^-OEt)_5]/[Zn]^3[^-OEt]^5$	66.38 ± 0.12	–
$[Zn_4(^-OEt)_8]/[Zn]^4[^-OEt]^8$	100.85 ± 0.16	–

[a] Values represent the average of three independent titrations, and errors are calculated as the standard deviation in the mean. [b] Defined as −log ${}_{s}^{s}K_a$ for $M^{2+}{}_m(^-OEt)_n(HOEt)_x \rightleftharpoons M^{2+}{}_m(^-OEt)_{n+1}(HOEt)_y + {}^+H_2OEt$, calculated from data in column 2 as 19.1 − (log ${}_{s}^{s}K_n$ − log ${}_{s}^{s}K_{n-1}$) where 19.1 is the −log of the autoprotolysis constant for pure ethanol.

consumption of base), followed by an additional 1/3 equiv corresponding to an event with an apparent ${}_{s}^{s}pK_a$ of ~11, which becomes slightly lower at the higher $[Zn^{2+}]$. The peculiar 5:3 ratio suggests that a relatively stable species having five ethoxides and three zinc ions (suggested to be **2** or some higher-order species with this ratio) forms readily within the first observed event, but addition of further ethoxide forms a higher-energy species requiring a much greater $[^-OEt]$ to form. It has been noted that zinc alkoxide structures have been very difficult to elucidate due to poor stability,[25b,34] and we can only add some circumstantial corroborative evidence for the presence of $Zn^{2+}{}_3(^-OEt)_5$. A recent kinetic study in our lab on the Zn^{2+}-catalyzed ethanolysis of paraoxon ($(EtO)_2P({=}O)OC_6H_4NO_2$) in the presence of varying Zn^{2+} with a constant $^-OEt/Zn^{2+}$ ratio of 0.25 gives a log/log plot of k_{obs} vs $[Zn^{2+}]$ having a gradient of ~0.3 consistent with the presence of inactive trimeric Zn^{2+} species in equilibrium with a monomeric active form of Zn^{2+}.[35] Furthermore, the electrospray mass spectrum (not shown) of a 2×10^{-4} M solution of $Zn(OTf)_2$ with 1.5 equiv of added Bu_4NOH shows peaks corresponding to $Zn_3(OEt)_5{}^+$ ($m/z = 417.1$) and $Zn_4(OEt)_7{}^+$ ($m/z = 571.0$) in addition to $Zn_2(OEt)_3{}^+$ ($m/z = 263.0$), $Zn(OEt)^+$ ($m/z = 108.7$), and $Zn(OEt)^+ + HOEt$ ($m/z = 155.0$). Although the relative intensities of the former two species are lower than those for the latter three, the $[Zn^{2+}]$ is lower than that titrated. Without added base, the mass spectrum showed mostly monomeric zinc species $Zn(OEt)^+$ and $Zn(OTf)^+$ with one to four associated ethanols depending on cone voltage with minor peaks consistent with the presence of dimeric components.



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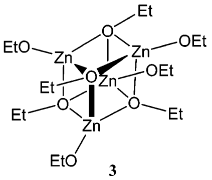

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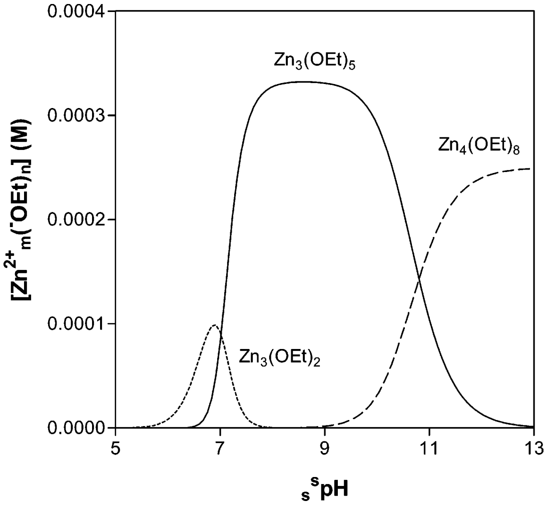
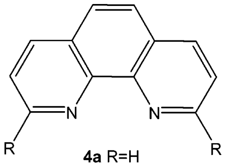


Figure 6. Speciation diagram for 1.0×10^{-3} M Zn^{2+} in ethanol as a function of ${}_{s}^{s}pH$.

That the apparent ${}_{s}^{s}pK_a$ associated with the additional 1/3 equiv of ^-OEt is lower with increasing $[Zn^{2+}]$ suggests a further aggregation of the Zn^{2+} ions, possibly forming a tetrameric species **3** ($[^-OEt]/[Zn^{2+}] = 2$) which is similar to higher-order Zn−alkoxide aggregates suggested in the literature.[36] The titration data for 1×10^{-3} M $Zn^{2+}(^-OTf)_2$ was fitted remarkably well to a model comprising $Zn^{2+}{}_3(^-OEt)_2$, $Zn^{2+}{}_3(^-OEt)_5$, and $Zn^{2+}{}_4(^-OEt)_8$ and yields the log formation constants for these species presented in Table 4; the corresponding speciation diagram is presented as Figure 6.

Metal Ion−Ligand Stability Constants. Competitive binding of a metal ion to a N-donor ligand in solution drops the ${}_{s}^{s}pK_a$ values for $N-H^+$ ionization by an amount related to the strength of the M^{x+} binding, in theory allowing a convenient method to determine K_b binding constants.[10] Presented in panels a, b, and c of Figure 7, respectively, are the titration data for the M^{2+} + ligand titrations for Cu^{2+} and Zn^{2+} with 1,10-phenanthroline (**4a**), 2,9-dimethyl-1,10-phenanthroline (**4b**), and 1,5,9-triazacyclododecane (**5**, 12N3).



4a R=H
4b R=CH_3

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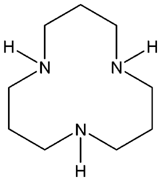

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In these plots, the region below $^-OEt/M^{2+} = 0$ represents ionization for the last ligand $N-H^+$ ionization, where the drop in this ${}_{s}^{s}pK_a$ allows the calculation of the binding constant. The data corresponding to the last ligand $N-H^+$ ${}_{s}^{s}pK_a$ ($^-OEt/M^{2+} < 0$) is clearly seen in the plots to change

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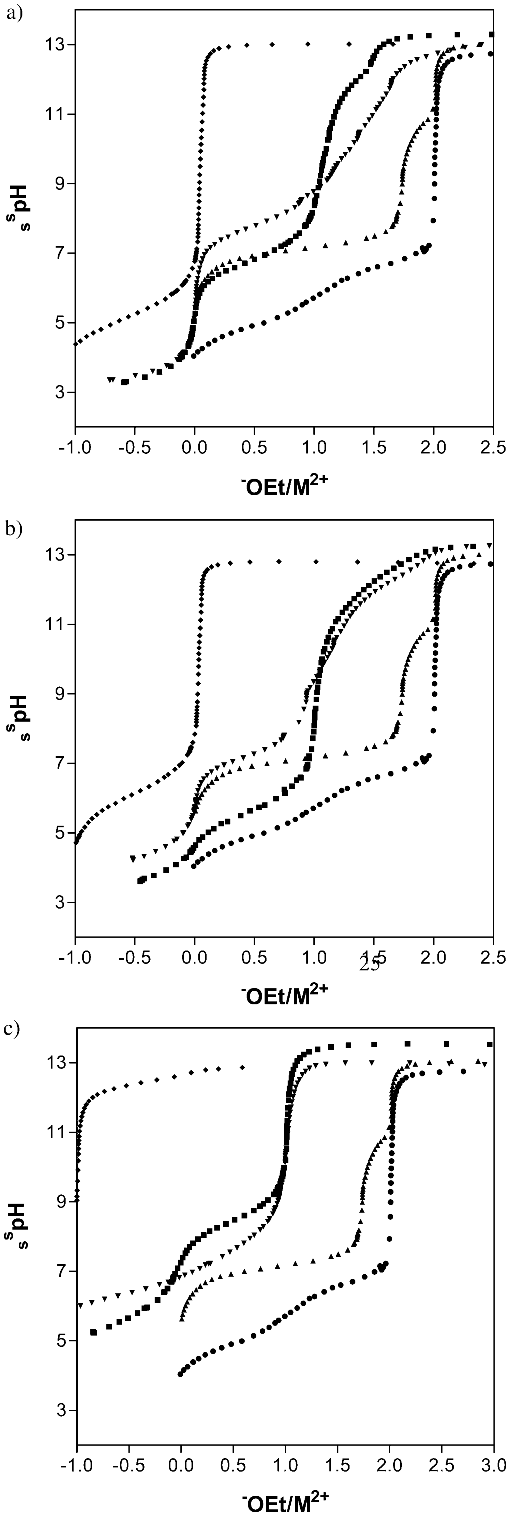

Figure 7. Potentiometric titration profiles for Zn^{2+} (▲), Cu^{2+} (●), and ligand (◆) in ethanol, along with the combinations Zn^{2+} + ligand (▼) and Cu^{2+} + ligand (■), $T = 25$ °C. The last ligand ${}^s_s\mathrm{p}K_a$ is plotted below $^-$OEt/M^{2+} = 0 and M^{2+}-coordinated ethanol titrations are therefore aligned to begin at the origin. In all cases, $[M^{2+}] = [\text{ligand}] = 0.001$ M, with 0.5−1 equiv/M^{2+} added $HClO_4$ to protonate the ligand. (a) ligand is 1,10-phenanthroline; (b) ligand is 2,9-dimethyl-1,10-phenanthroline; (c) ligand is 12N3.

Table 5. Log Stability Constants for the Formation of Complexes of Zn^{2+} and Cu^{2+} with 1,5,9-Triazacyclododecane in 99.9 % Ethanol, $T =$ 25 °C

metal ion	stability constant (log ${}^s_sK_b$, M^{-1})^a{n}	stability constant (log ${}^s_sK_b$, M^{-2})^b{n}	${}^s_s\mathrm{p}K_a{}^c${n}
Zn^{2+}	10.73 ± 0.05 {2}	22.3 ± 0.05 {3}	7.53 ± 0.01 {3} 8.2 ± 0.1 ^{d}
Cu^{2+}	13.33^e {3}	23.93 ± 0.04 {3}	8.58 ± 0.04 {3}

^{a} For the process ligand + M^{x+} ⇌ ligand/M^{2+}. ^{b} For the process ligand + M^{x+} + $^-$OEt ⇌ ligand/M^{2+}/$^-$OEt. ^{c} For the process ligand/M^{2+}/HOEt ⇌ ligand/M^{2+}/$^-$OEt. Obtained from 19.1 − (log stability constant in column 3 − log stability constant in column 2). ^{d} Determined as the ${}^s_s$pH for a solution formulated from 1 mM of ligand **5**, 0.5 mM NaOEt, and 1 mM $Zn(OTf)_2$, added in the indicated order. ^{e} Stability constant fixed since it is heavily correlated with stability constant for process ligand + M^{x+} + $^-$OEt ⇌ ligand:M$^{2+:-}$OEt.

drastically in the presence of metal ion and indicates strong binding of the metal ion. The titration domains above $^-$OEt/M^{2+} = 0 represent the ionizations of M^{2+}-coordinated ethanol molecules, and the shapes of the curves in each plot are very similar to the theoretical ones expected for a monomeric metal ion below $^-$OEt/M^{2+} = 1. This is expected where there is strong binding between the metal ion and ligand but does not allow us to say whether there are aggregated forms present in the absence of other information. Indeed, when we attempted to obtain some corroborative evidence for the speciation of phenanthroline and Zn^{2+} from kinetics, a plot of log k_{obs} vs log [Zn^{2+}= **4a**] gives a slope of 0.27, indicative of a kinetically active monomeric form in equilibrium with kinetically inactive higher-order aggregates such as trimers and/or tetramers. This complexity precludes a detailed analysis of the various stability constants and serves as a warning that simplistic analysis of seemingly informative titration curves can lead to erroneous results unless one is certain that the speciation assumed reflects what is actually in solution. The plot for Zn^{2+} in the presence of 2,9-dimethyl-1,10-phenanthroline has the same general appearance as that with 1,10-phenanthroline but with less perturbation relative to the ligand alone due to weaker binding. With the Cu^{2+}/2,9-dimethylphenanthroline system, potentiometric tritrations in ethanol provide no useful information about the stability constants nor the ${}^s_s\mathrm{p}K_a$ of the metal-coordinated HOEt because there is a rapid replacement of the characteristic blue color of Cu^{2+} by a yellow color, suggesting that this ligand facilitates the reduction of the metal ion to Cu^+ in ethanol.[37] Plots for La^{3+} with these ligands (not shown) do not show near as strong binding, and titration data for the La^{3+}-coordinated ethanol region is poorly defined.

The only system for which accurate stability constant data can be computed is with 1,5,9-triazacyclododecane (**5**) where kinetic plots of k_{obs} for the ethanolysis of paraoxon vs [**5** = Zn^{2+}] are linear and thus consistent with catalysis by a monomer in ethanol solution.[38] The stability constants are collected in Table 5, based on the ligand N−H$^+$ ${}^s_s\mathrm{p}K_a$ values presented in Table 1. Both Zn^{2+} and Cu^{2+} bind **5** with considerable strength, $K_b \approx 10^{9.8}$ M^{-1} for each, which is also consistent with strong binding of Zn^{2+} to **5** in methanol (${}^s_sK_b = 10^{10.11}$)[39] and in water ($K_b = 10^{8.41}$, $10^{8.4}$, and

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$10^{8.75}$).[40-42] Binding to Cu^{2+} is characteristically stronger, as evidenced by the K_b of $10^{12.63}$ with **5** in water,[42] although this cannot be verified to be the case in ethanol due to the fact that the last ${}^{s}_{s}pK_a$ for the triaza ligand is near the solvent ionization domain and may give an artificially low stability constant since the ligand ${}^{s}_{s}pK_a$ may be higher than the value of 12.54 reported in Table 1. The strong binding for the transition metal ions in ethanol indicates that above concentrations of $\sim 10^{-5}$ M in each of metal ion and **5** the complexes will be nearly fully formed, the amount of unbound metal ion in any form being <5%, so that reliable kinetic studies of the catalysis afforded by these can be performed at these and higher concentrations.

The fitting of the potentiometric data also indicate that the ${}^{s}_{s}pK_a$ values for ionization of **5**:M^{2+}(HOEt) are 8.58 for the Cu^{2+} complex and 7.53 for the Zn^{2+} complex, which is 1−2 units lower than the neutral ${}^{s}_{s}pH$ in ethanol (9.55). Both are considerably more acidic in that solvent than are their counterparts in methanol, (**5**/$Zn^{2+}(HOCH_3)$), 9.1[39] and **5**/$Cu^{2+}(HOCH_3)$), 8.75[33]) which are both close to neutrality in that solvent $\left({}^{s}_{s}pH\ 8.4\right)$. This is a likely consequence of the reduced polarity of ethanol which favors charge neutralization through proton loss from the M^{2+}-coordinated HOEt. By way of comparison, in water the ${}^{s}_{s}pK_a$ value for ionization of **5**/Zn^{2+}(HOH) is 7.7[42] while that for **5**/Cu^{2+}(HOH) is 8.36,[42] although this constant is less certain due to the possibility of dimerization of the metal-bound hydroxo complex.[42a,43]

Qualitative Salt Effects. Previous kinetic studies demonstrate that M^{x+}-catalyzed methanolyses of acetyl imidazole and β-lactams are inhibited by the presence of certain counterions such as Cl^-.[1e,44] This requires that subsequent kinetic studies in alcohols must be conducted in the absence of these ions, using as weakly coordinating counterions as possible, namely triflate or perchlorate. The coordinating abilities of anions can be readily judged by titrations by observing the perturbation in the consumption of alkoxide leading to an increase in apparent ${}^{s}_{s}pK_a$ that is proportional to the strength of the anion association. To avoid coordinating effects of added counterions and to approximate as closely as possible the kinetic conditions, titrations in ethanol and methanol[8] were performed using no added salts. Nevertheless, the association effects of added anions can be profound, and a few experiments were done to show which ions were most likely to interfere with the solution chemistry and at what concentrations.

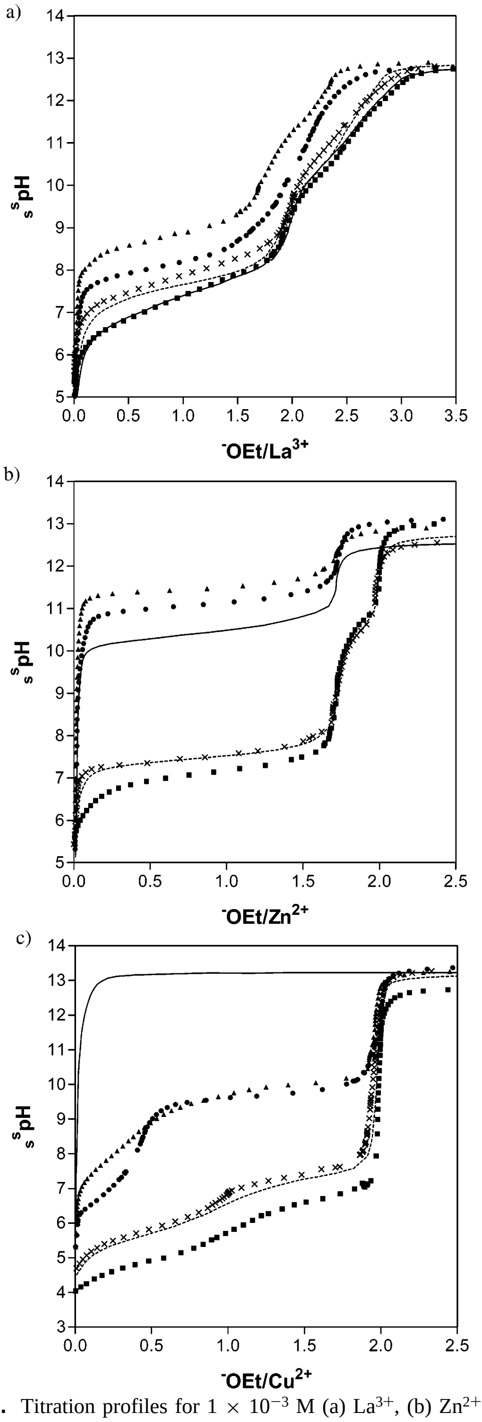

Figure 8. Titration profiles for 1×10^{-3} M (a) La^{3+}, (b) Zn^{2+}, and (c) Cu^{2+} in ethanol (■) in the presence of 0.02 M tetrabutylammonium salts of the counterions (- - -) perchlorate, (×) triflate, (−) iodide, (●) bromide, and (▲) chloride at 25.0 °C.

Presented in Figure 8 are titration data for 1 mM solutions of Cu^{2+}, Zn^{2+}, and La^{3+} in the absence and presence of a 20-fold excess of added anions introduced as their Bu_4N salts. The plots show that added triflate and perchlorate ions cause similar but not insignificantly weak upward perturbations in the titration curves of all three metal ions. For the halides, the order of perturbation is $I^- \ll Br^- < Cl^-$, the latter causing a very large increase in apparent ${}^{s}_{s}pK_a$ of the metal ions in all cases. Although iodide appears to have little coordinating ability with the 'harder' metal ions such as La^{3+} and Zn^{2+}, with Cu^{2+} it produces a rapid discoloration which is due to the well-known reduction of Cu^{2+} to Cu^+ by iodide,[45] leading to a titration curve that shows no consumption of ethoxide until well into the solvent deprotonation region.

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Conclusions

The objective of this study was to determine the titration constants for some metal ions in ethanol solution including the lanthanides and two transition metal ions which have been shown to promote acyl and phosphoryl transfer from various substrates to alcohol solvents. Depending on the level of information required, the titration data can be interpreted in terms of the half-neutralization points corresponding to the solution ${}^{s}_{s}pH$ values where the $[^{-}OEt]/[M^{x+}]$ ratios are 0.5, 1.5, and 2.5, which in most cases are sufficient for setting the solution ${}^{s}_{s}pH$ at a desired value through the addition of known amounts of ethoxide. However, this approach does not reveal the intricate details of the acid/base equilibria involved and the constants are complicated composites of various equilibria including ion-pairing between the M^{x+} and solution counterions and metal dimerizations/oligomerizations that can affect the ionizations of $(M^{x+})_n(HOEt)_m$ forms. For other cases where more detail is required about the nature of the species present in solution, titration data can be computer fit to more or less complicated multi-equilibrium models containing $M^{x+}{}_q(^{-}OEt)_n$ forms whose stoichiometry is suggested by information gained from spectroscopic or kinetic techniques. In the case of La^{3+} in ethanol, we have shown that a detailed analysis can be given for the metal-ion-catalyzed ethanolysis of paraoxon as a function of the solution ${}^{s}_{s}pH$. Further work from these laboratories will be aimed at further applying the titration/kinetic methodology to other metal-ion-catalyzed acyl and phosphoryl transfer processes in ethanol and other reduced dielectric constant media.

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