Dextran–Rare Earth Ion Interactions. I. Dynamics in Aqueous Solutions

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ABSTRACT: The interaction of light-lanthanoid cations (La^{3+}, Ce^{3+}, and Nd^{3+}) with dextran in aqueous solutions was studied by viscosimetric, turbidimetric, and conductimetric methods. The effects of the type of the cation and the concentration of the cation on the interaction mechanism were investigated. Viscosity behavior of the solutions was interpreted using the Huggins and Kraemer equations; intrinsic viscosities and the slopes were calculated. The results found from the Huggins and Kraemer approaches accorded well. The order of interaction was determined as $La^{3+} > Ce^{3+} > Nd^{3+}$. In all experimental methods applied, a critical concentration of the Ln^{3+} ion (≈ 0.08 mol Ln^{3+}/L) was noted at which the observed property showed a significant change. Up to this critical concentration, viscosities of the dextran/Ln^{3+} solutions decreased and after making an outstanding turn at this point increased toward higher concentrations. Turbidimetric and precipitation experiments gave opposite results as expected but the same order for the cation and the same value of critical concentration. The results obtained from the application of a mathematical model to the precipitation data verified the conclusions attained by viscosimetry and conductimetry. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 82: 323–329, 2001

Key words: dextran; lanthanoid; viscosimetry; turbidimetry; conductimetry

INTRODUCTION

Interaction of water-soluble polymers with various cations is of importance both from technological aspects and applications. Transition metals as well as rare-earth metals possess the ability to bind to neutral or weakly charged water-soluble polymers. Lanthanide coordination compounds in solution have been used as probes in examining the structure and functions of biosystems. Spectral and chiroptical studies with lanthanoids provide important information about the metal-ion binding sites of polysaccharides.[1,2]

As a cellular macromolecule, dextran is widely used alone or in combination with metals for med-ical purposes, often including drug delivery systems.[3,4] In aqueous solutions, dextran interacts with several metal ions and forms solid complex compounds of therapeutic use.[5,6] However, data on the interaction of dextran with lanthanide ions are very limited and mostly reported as patent formulations.

Dynamic,[7,8] thermodynamic,[9–11] and crosslinking ability[12] of dextran in aqueous and nonaqueous solutions have been under detailed investigation by our group. In the presented study, we report the interaction dynamics of dextran with light-lanthanoid cations (La^{3+}, Ce^{3+}, Nd^{3+}) experimented by different methods.

EXPERIMENTAL

Dextran, T500, used in this study was purchased from Pharmacia Fine Chemicals AB, Uppsala,

Sweden. The molecular weight characteristics were determined by the manufacturer as $\bar{M}_n$ = 191,500 g mol^{-1} and $\bar{M}_w$ = 496,000 g mol^{-1}. It was dried and stored over CaCl$_2$ in a desiccator and used without further purification. The lanthanoid ions were supplied from their laboratory grade, hydrated nitrate salts [La(NO)$_3$ 6H$_2$O and Ce(NO)$_3$ 6H$_2$O from BDH Chemicals Ltd (Poole, UK) and Nd(NO)$_3$ 6H$_2$O from Aldrich Chemical Company (Milwaukee, WI)] and used as received. Complexes were precipitated with 10 mL of methanol (AnalaR). Dextran and lanthanoid solutions were prepared in deionized, bi-distilled water.

Viscosity measurements were performed with freshly prepared polymer/Ln^{3+} solutions at 25°C using an Ubbelohde-type capillary viscometer. The temperature was controlled with a thermostat system within ±0.1°C, the efflux times were reproducible to ±0.2%, and the flow times were measured with an accuracy of ±0.1 s. The effects of concentration and the type of lanthanoid ion on the viscosity of dilute dextran solutions ($c = 0.4–0.2$ g dL^{-1}) were explored by applying the well-known Huggins and Kraemer eqs. (1) and (2), respectively, to experimental data.

$$\eta_{sp/c} = [\eta] + k_H[\eta]^2 c \qquad (1)$$

$$\ln \eta_{r/c} = [\eta] - k_K[\eta]^2 c \qquad (2)$$

The intrinsic viscosities, $[\eta]$, were determined from the average values of the intercepts of the plots of $\eta_{sp/c}$ and $\ln \eta_{r/c}$ versus c.

The conductivities of Ln_{aq}^{3+} solutions (concentration range: $5.0 \times 10^{-3} - 0.3$ mol L^{-1}) and of dextran/Ln^{3+} solutions were measured comparatively by a Siemens WPA CM 35 conductometer at 25.0 ± 0.5°C . The decrease in the conductivities of Ln_{aq}^{3+} solutions were measured twice and the mean values recorded.

Cloud point determinations were performed by turbidimetric titration method by adding methyl alcohol to Ln_{aq}^{3+} and dextran/Ln^{3+} solutions in Pyrex tubes under controlled temperature (25.0 ± 0.5°C) and continuous stirring conditions. The first appearance of cloud formation was noted as the cloud point of the solution during the addition of the alcohol. Reproducibility of the measurements were excellent within the addition of ±0.1 mL of alcohol.

Cloud point experiments were extended to precipitation reactions. The precipitates were ob-
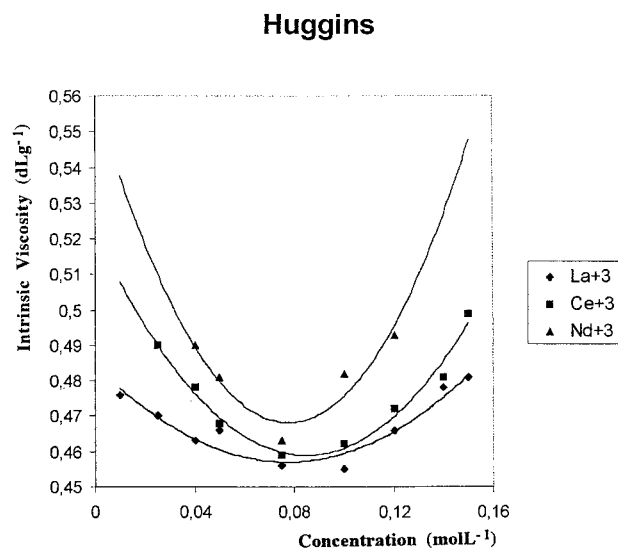
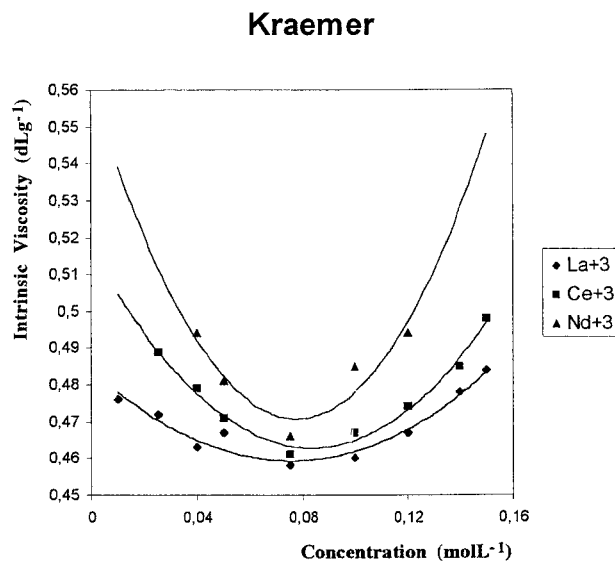**Figure 1** Change in intrinsic viscosity (Huggins) with Ln^{3+} concentration.

tained by adding a constant volume of methanol (10 mL) to dextran and also to dextran/Ln^{3+} solutions and gravimetrically determined.

RESULTS AND DISCUSSION

Intrinsic viscosity is a characteristic property for a polymer molecule in a chosen solvent. It depends on the structure and the conformation of the polymer as well as the solvent power and temperature. The dimension of $[\eta]$ is a measure of the effective hydrodynamic volume of the polymer in the solution. It also reflects the dynamism, hydrogen bonding, dipole–dipole, hydrophobic interactions, and complexation ability of the polymer in the presence of different additives. Generally, the addition of certain organic or inorganic cosolutes to solution affects the dynamism of water-soluble polymer/water systems depending on the nature and the concentration of the additive. Furthermore, some other types of interactions, such as ion–dipole interactions may exist in solution.

The intrinsic viscosity results calculated according to Huggins and Kraemer equations are presented in Figures 1 and 2, respectively. These two Figures can be divided in two regions. Region I represents a decrease in the intrinsic viscosity of dextran + Ln_{aq}^{3+} solutions with increasing Ln^{3+} concentration whereas Region II represents the opposite behavior. The decrease in intrinsic vis-

Kraemer

Figure 2 Change in intrinsic viscosity (Kraemer) with Ln^{3+} concentration.

cosity is due to intramolecular complex formation with the cation added. This interaction is possibly between the hydroxy groups, rather than the etheric oxygen atoms of dextran and the Ln^{3+} ion. Optical rotatory dispersion measurements have shown that the OH groups bound to the C2 and C3 atoms in the monomeric unit of dextran (see Scheme 1) are capable of bidentate complex formation with the lanthanoid ions.[1]

Among the three lanthanoid ions experimented in the viscosimetric studies, the order of interaction with dextran is:

$$La^{3+} > Ce^{3+} > Nd^{3+}$$

A cooperative effect among the adjacent groups of the polymer contributes to a larger Ln^{3+}/dextran interaction as the concentration of the Ln^{3+} ion increases leading to a contraction of the polymer coil in solution and hence a decrease in viscosity. The minima points in the curves indicate almost the same critical concentration which is around 0.08 mol Ln^{3+}/L. The relative positions of the minima points for the three lanthanoid ions are such that La^{3+} and Ce^{3+} have slightly higher values than 0.08 mol Ln^{3+}/L whereas Nd^{3+} slightly shifts to a lower value. Besides, viscosity decreases sharply for Nd^{3+} and a smooth decline is observed for both La^{3+} and Ce^{3+}. Further increase in the lanthanoid ion concentration results in electrostatic repulsions between the metal ions bound to the polymer chain and consequently the

coils expand and viscosity increases. The effectiveness of the ions in Region II is in the same order observed through the viscosity decrement in Region I. The Huggins and Kraemer results accord well as can be realized from Figures 1 and 2.

Such discontinuities in the plots of intrinsic viscosity versus cosolute concentrations have been previously noted with certain polymer/solvent systems. The discontinuity in the curve has been attributed to a probable conformational transition of the polymer chain, the interaction of the polymer with cosolute,[13,14] and/or complex formation dynamism in the polymer/cation system.[15] It is quite plausible that the minima points in Figures 1 and 2 show a transition to the 1:1 complex which is the most favorable stoichiometry for the lanthanide–sugar complexes.[16,17]

The Huggins slope, $k_H [\eta]^2$, is generally considered as a measure of the degree of interaction of the polymer and the solvent.[18] A large slope value indicates more complete solvation of the polymer, thus the presence of a better solvent. In other words, the polymer–solvent interactions (in our system: dextran–Ln^{3+} interactions) are more favored than the polymer–polymer interactions (mostly hydrogen bonding). The Huggins and Kraemer slope results presented in Figures 3 and 4 can also be divided in two regions. The curves show an exponential increase up to approximately 0.08 mol Ln^{3+}/L and then decrease. The intersection points of the exponential increase and exponential decay curves correspond to 0.08 mol Ln^{3+}/L for La^{3+} and Ce^{3+}, and 0.075 mol Ln^{3+}/L for Nd^{3+}. This behavior is the same for Huggins and Kraemer slopes. In both regions, the interaction is significant in the order of $La^{3+} > Ce^{3+} > Nd^{3+}$, as determined by the intrinsic viscosity measurements.

Cloud point is another characteristic property reflecting the transition from the dynamic to thermodynamic behavior of the polymer/solvent and
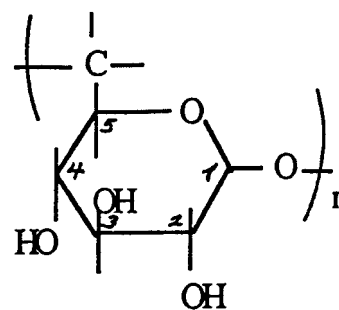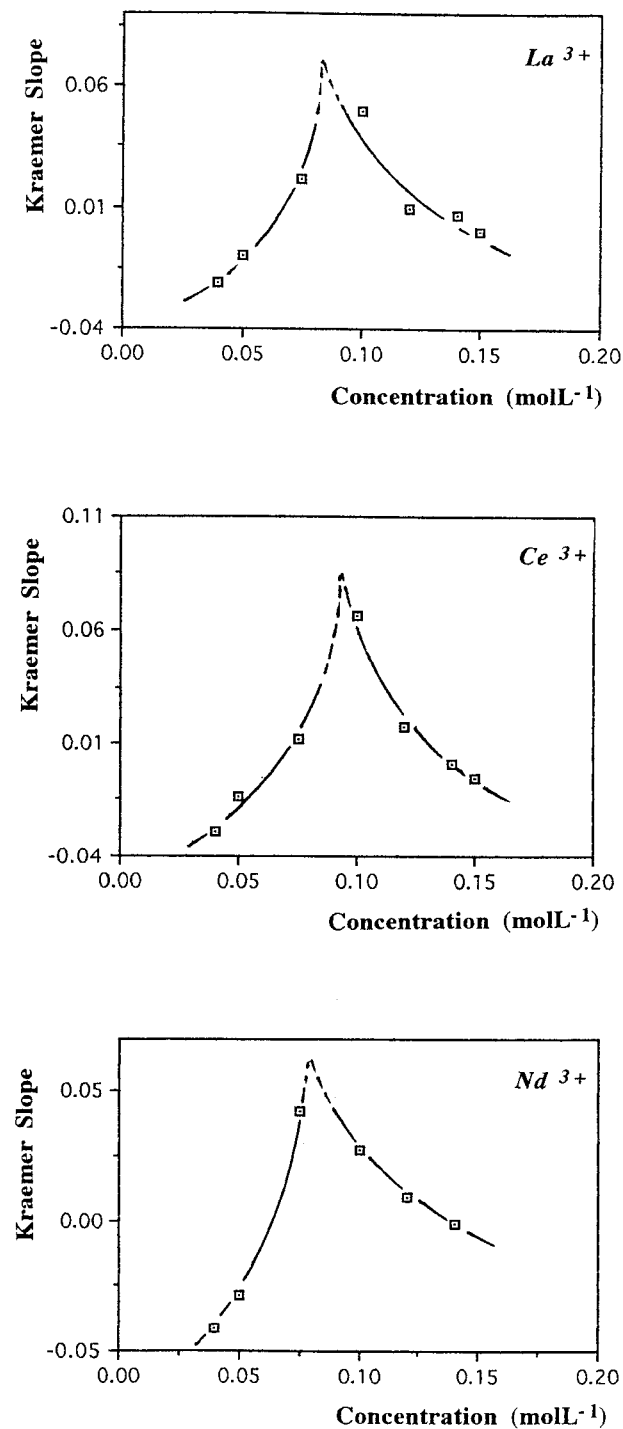

Scheme 1
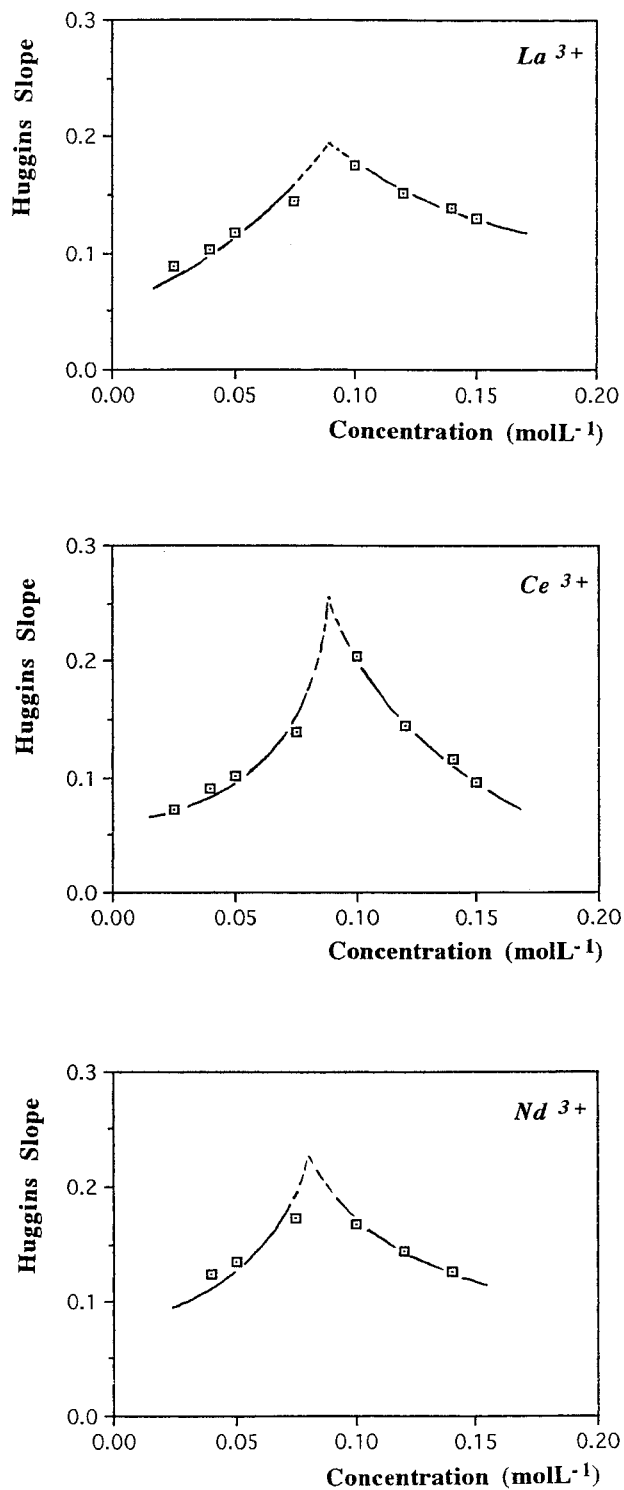
Figure 3   Change in the Huggins slope with Ln^{3+} concentration.

a theta solvent to the system (turbidimetry), as proposed first by Elias. The two methods have a common principle to bring out hydrophobic interactions between polymer segments rather than the hydrophilic interactions between the water-

Figure 4   Change in the Kraemer slope with Ln^{3+} concentration.

polymer/solvent/additive systems which is determined by the polymer solution–temperature relationship[19,20] or more generally by the addition of
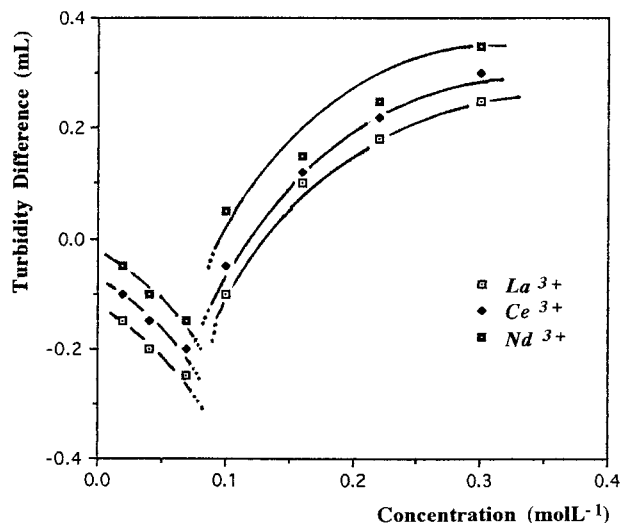
**Figure 5** Change in turbidity difference with Ln^{3+} concentration.

soluble polymer and the solvent. The role of additives is also important in the phase separation through the interaction of the polymer segments.[20–22] The following equation was used to evaluate the turbidity differences:

$$\Delta CP = CP_{dex/Ln} - CP_{dex} \qquad (3)$$

where ΔCP = difference in cloud points, $CP_{dex/Ln}$ = cloud point of the dextran + Ln^{3+} solution, CP_{dex} = cloud point of the dextran solution itself. The changes in the CP values thus calculated with the concentration of the lanthanoid ion are
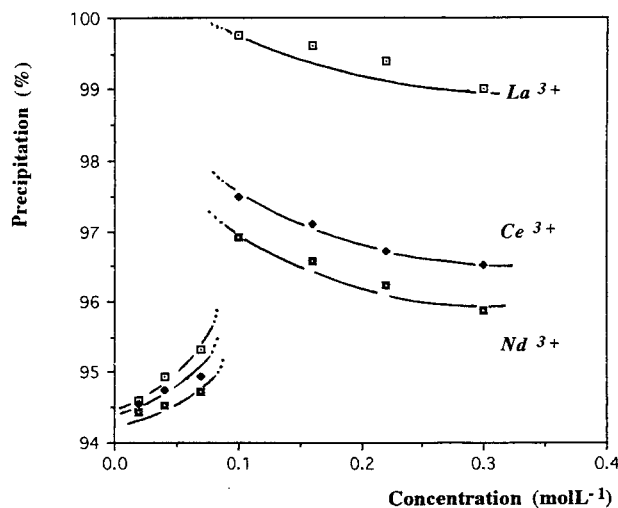
Figure 6 Precipitation–$[Ln^{3+}]$ relationship for dextran/Ln^{3+} solutions.
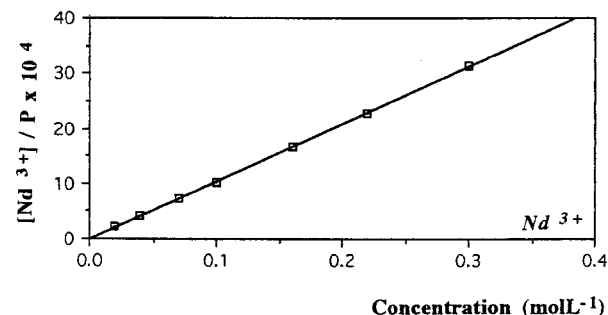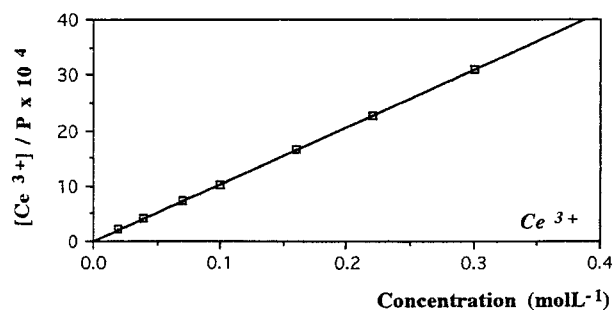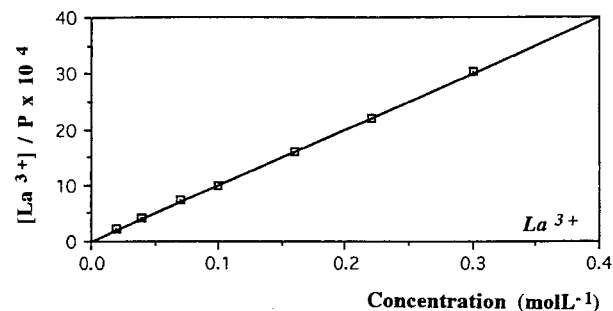
Figure 7 Linear relationship between (Ln^{3+}/P) and $[Ln^{3+}]$ derived from eq. (4).

given in Figure 5. The critical concentration (0.08 mol Ln^{3+}/L) and also the effectiveness of the Ln^{3+} ions ($La^{3+} > Ce^{3+} > Nd^{3+}$) determined by the viscosity measurements have been confirmed here with turbidimetric studies.

Cloud point experiments were extended to precipitation by adding higher values of methanol. Gravimetrical determinations of the precipitates found are given in Figure 6. The same critical concentration stands out again. Before and after this critical concentration, precipitation increases and decreases respectively. The progress in precipitation with respect to the type of the lanth-

Table I   Precipitation from Dextran/Ln^{3+} Solutions

Solution	$P_{\max}$ (%)	k_P (Gram Precipitate mol^{-1} L)
Dextran/La^{3+}	100.0	10.0
Dextran/Ce^{3+}	97.9	21.22
Dextran/Nd^{3+}	96.5	36.06

anoid ion is in the same order as La^{3+} > Ce^{3+} > Nd^{3+}. The interaction between the Ln^{3+} ions and the appropriate groups on the polymer structure leads to a closer contact between the polymer segments, cloud formation, and eventually precipitation. This effect is greatest for La^{3+}.

A mathematical modeling was considered for precipitate formation and the following equation was applied with best fit ($R^2 = 0.998$):

$$[Ln^{3+}]/P = \alpha + \beta[Ln^{3+}] \tag{4}$$

$$P = (P_{dex/Ln} - P_{dex})/P_{dex} \tag{5}$$

$$\alpha = 1/(k_p P_{\max}^2) \tag{6}$$

where P is precipitation, k_p is precipitation rate, $P_{\max}$ is maximum precipitation, and β is the reciprocal of maximum precipitation. [Ln^{3+}]/P versus [Ln^{3+}] graphic is shown in Figure 7. $P_{\max}$ and k_p values calculated by using eq. (4) are given in Table I. A good agreement is observed if one compares the calculated (Table I) and experimental $P_{\max}$ values (Fig. 7). Maximum precipitation reflects the order of effectiveness of the ions, La^{3+} > Ce^{3+} > Nd^{3+}, in complex formation, whereas k_p values indicate the effectiveness of the ion in precipitation rate. Considering the sharp decrease observed in the intrinsic viscosities of dextran/Nd^{3+} solutions, it is possible to conclude that, because of the high charge density of the Nd^{3+}, the rate of interaction is high. However, the thermodynamic stabilities of the various complex forms statistically distributed in aqueous solution apparently are greater with the La^{3+} ions. Although the stabilities of most other lanthanoid complexes increase with the charge density of the lanthanoid ion (decreasing ionic radius as La^{3+} = 117 pm, Ce^{3+} = 115 pm, Nd^{3+} = 112 pm), a similar observation has been noted with polyethylene glycols where the stability constants de-

crease with increase in the atomic number of the lanthanoid.[16]

In the final part of our study, we have performed conductimetric measurements. Ionic conductivities of the solutions are presented in Figure 8. The results are given in terms of the conductivity differences calculated using the following approximation:

$$\text{conductivity difference } (\Delta\mu) = \mu_{Ln(aq)}^{3+} - \mu_{Ln(aq)/dextran}^{3+} \tag{7}$$

The following equilibrium was attained in the solutions:

$$[Ln(H_2O)_n](NO_3)_3 + xD \Leftrightarrow [Ln(H_2O)_{n-x}D_x](NO_3)_3 \tag{8}$$
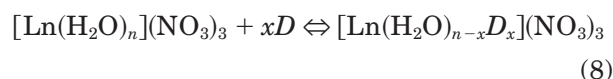
The uncomplexed Ln^{3+} ions together with the NO$_3^-$ ions are responsible for the measured conductivities. The conductivities of Ln$_{(aq)}^{3+}$/dextran solutions diminish in the sequence of La^{3+} > Ce^{3+} > Nd^{3+}, supporting the same order of effectiveness as observed with the other measurements. A careful examination of Figure 8 would display that $\Delta\mu$ varies almost linearly with the lanthanoid concentration in the low concentration range up to about 0.08 mol Ln^{3+}/L. Further points showed deviations from linearity (as established by regression analysis) indicating a change in the
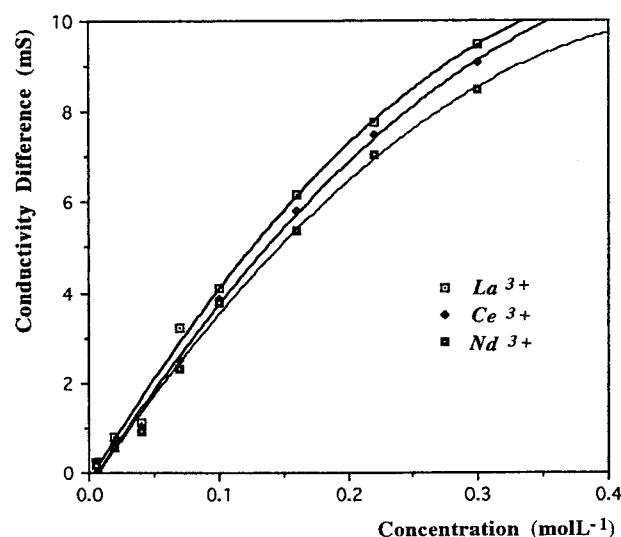
Figure 8 Conductivity differences against [Ln^{3+}] for dextran/Ln^{3+} solutions.

interaction behavior of dextran with the cations after a critical concentration of the cation.

CONCLUSIONS

In aqueous solutions, Ln^{3+} ions interact with dextran and the complexes can be precipitated with the addition of methanol. The type of the lanthanoid ion and its concentration are important in this interaction. The conclusion of our solution phase studies, namely viscosimetric, turbidimetric, and conductimetric, indicate that this interaction is favored in the sequence of $La^{3+} > Ce^{3+} > Nd^{3+}$. Significant changes around a critical Ln^{3+} concentration of ca. 0.08 mol Ln^{3+}/L occur, which may possibly be attributed to the 1:1 complex formation with dextran. The rate of interaction increases with the increasing charge density of the Ln^{3+} ion, reaching a maximum with the Nd^{3+} ion. However, the complexing power of these light-lanthanoid ions with dextran decreases with their atomic numbers. Although it seems contradictory to the general belief that the stability of the lanthanoid complexes with most ligands increases with the decreasing ionic size, this remarkably different behavior may be considered as specific for the dextran/Ln^{3+} system. The fact that polyethylene glycols form complexes with lanthanoids in the same order should be noted.[16]

We have also studied the solid-state properties of the precipitates by spectroscopic and thermal methods and obtained parallel results to our solution studies. The results of the solid-state experiments will be presented in the following report.

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