Aqueous Lanthanide Shift Reagents. 1. Interaction of the Ethylenediaminetetraacetate Chelates with Carboxylates. pH Dependence, Ionic Medium Effects, and Chelate Structure

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Abstract: The suitability of the ethylenediaminetetraacetate (EDTA) chelates of the trivalent lanthanides as aqueous shift and relaxation reagents for carboxylate substrates has been established in a study of their effects on the proton resonance of acetate. The praseodymium chelate forms mainly a 1:1 acetato complex with a downfield intrinsic shift of 1.83 ppm (at 39 °C) and a dissociation constant of the order of 0.2 M, the latter depending on the ionic medium (LiCl concentration). The useful pH range is between 6 and 10, confined in the acidic side by the formation of acetic acid and on the basic side by the formation of hydroxo complexes of the chelates. Similar behavior is observed with $Yb(EDTA)^-$, which induces upfield shifts (intrinsic shift 3.5 ppm), and with $Gd(EDTA)^-$, which causes line broadenings. A structural change in the EDTA chelates along the lanthanide series manifests itself in the effect of LiCl concentration upon the observed shifts. It appears that the lighter lanthanides are pentachelated, whereas the heavier ones are hexachelated. Yet the acetato complexes are isostructural as judged by the relative magnitude and direction of the shifts induced by $Pr(EDTA)^-$ and by $Yb(EDTA)^-$, which are in good agreement with the theoretical predictions for pseudocontact shifts in lanthanide complexes. Recommendations are given regarding the use of the EDTA chelates or the aquolanthanides as aqueous shift reagents in structural studies as well as for achieving spectral resolution.

The application of lanthanide chelates, that are soluble in organic solvents, as shift reagents in the NMR spectroscopy of organic molecules is now well established.[1] More recently interest is focusing on the use of lanthanide ions as probes in biological systems.[2] Systems of biological interest are normally studied in aqueous solutions and therefore the water soluble aquoions are usually employed as shift reagents.[1,2] The aquolanthanides, however, are stable only on the acidic side of neutral pH, hydrolyzing and precipitating as the hydroxides at higher pH values.[3] It has been suggested that water-soluble chelates of the lanthanides could be employed at the higher pH values.[4] Lanthanides form water soluble chelates of extremely low dissociation constants with a series of aminopolycarboxylates.[3] The ethylenediaminetetraacetates (EDTA), which have been characterized crystallographically,[5] are known to interact with additional ligands in solution.[6] Therefore we embarked on a detailed investigation of the anionic $Ln(EDTA)^-$ chelates as aqueous shift reagents. In the first stages of these studies our attention will be directed toward the characterization of the complex species formed in solution as manifested in the chemical shifts and in the enhanced relaxation rates induced in the NMR spectra of a variety of substrates.[7] In this way the suitability of these chelates as shift reagents should also be revealed.

Presented in this article are the results of our studies on the interaction of carboxylates (mainly acetate) with $Pr(EDTA)^-$, which is a downfield shift reagent, with $Yb(EDTA)^-$, which causes upfield shifts, and with $Gd(EDTA)^-$, which is a relaxation reagent. We were able to elucidate the details of the pH dependence of the induced shifts and line broadenings, to establish the effective stoichiometry, to delineate the structure and structural equilibria of these systems, and to obtain evidence for a structural change of the chelates along the lanthanide series. For comparison some experiments with aquopraseodymium were also carried out.

Experimental Section

Solutions of lanthanide salts were prepared from the corresponding oxides (Research Chemicals, Phoenix, Ariz.) by treatment with analytical grade acids. Concentrations were determined by EDTA titrations using Arsenazo as the end-point indicator. The EDTA solutions were prepared from the free acid by neutralization with four equivalents of lithium hydroxide. Fresh lanthanide-EDTA solutions were prepared in D_2O prior to each set of measurements by mixing stoichiometric amounts of $LnCl_3$ and Li_4EDTA. Note that in this case a threefold molar excess of LiCl is present. In order to keep a constant Li^+ concentration LiCl was added as needed. The pH was adjusted by suitable addition of acid or base. No buffers were employed. All chemicals were analytical grade reagents and were used without further purification.

Proton NMR spectra were recorded on a Varian T-60 spectrometer operating at the ambient probe temperature of 39 ± 1 °C. The pH was measured with an accuracy of 0.01 units using a Metrohm glass electrode. Reported values are meter readings corrected for isotope effects.

Results and Discussion

pH Dependence. In the system composed of acetic acid and $Ln(EDTA)^-$ there are a number of species that may exist in equilibrium with each other with relative concentrations governed in part by the pH. Thus, acetic acid may exist as the free acid or as acetate. Protonation of the $Ln(EDTA)^-$ chelates has been found to occur with p*K* values in the range 2.5-2.8.[8] The existence of hydroxo complexes of the $Ln(EDTA)^-$ chelates has also been surmised.[9] Therefore the effect of hydrogen ion concentration on the chemical shift induced by $Pr(EDTA)^-$ and by $Yb(EDTA)^-$ in the proton resonance of acetate was studied in the pH range 2-12. The results obtained in the presence of $Pr(EDTA)^-$, which induces downfield shifts, are presented in Figure 1. It is seen that the pH profile is bell shaped with a plateau in the range 6-10, and with two apparent p*K*'s, one ca. 5 and the other ca. 11. A qualitatively similar behavior is observed with the upfield shifts induced by $Yb(EDTA)^-$, the results for which are shown in Figure 2. It is clear from these results that a complex is formed between acetate and the $Ln(EDTA)^-$ chelates with the p*K* on the acidic side of the curve corresponding to the formation of acetic acid, which does not complex, and that on the basic side corresponding to the formation of a hydroxo complex of $Ln(EDTA)^-$. It is not immediately obvious, however, whether the decrease of the induced shifts at high pH results from the dissociation of the acetato complex or is due to a much smaller

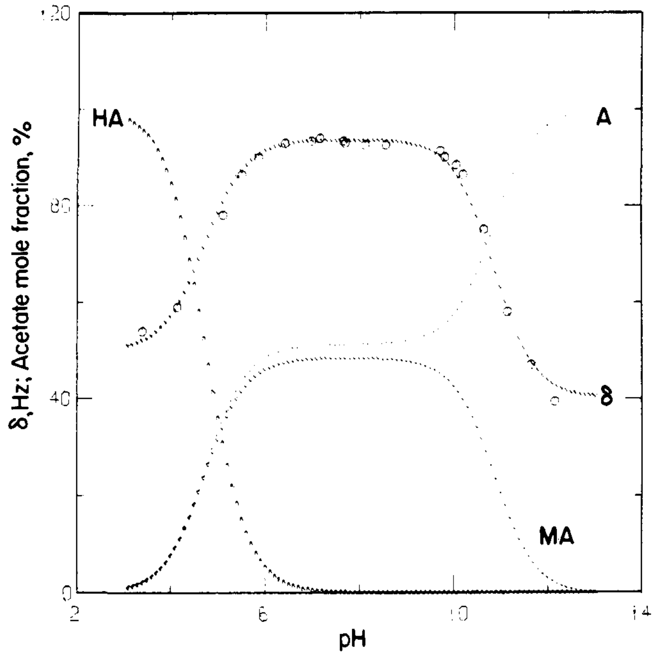

Figure 1. The pH dependence of the acetate shift (downfield relative to *tert*-butyl alcohol) and of the acetate species: acetic acid (HA), free acetate (A), and the acetato complex of Pr(EDTA)$^-$(MA) in solutions containing 0.2 M Pr(EDTA)$^-$ and 0.032 M acetate. The smooth dotted curves are calculated (see text) with the parameters in Table I. The chemical shift between acetic acid and acetate was taken into account.

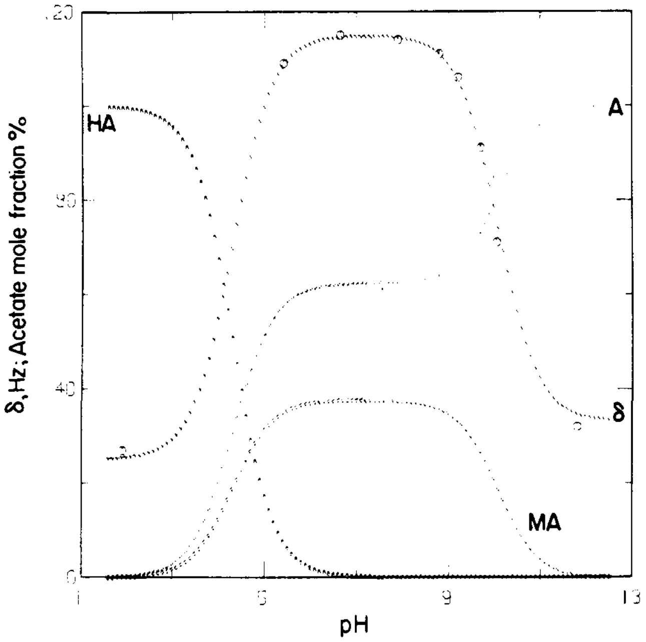

Figure 2. The pH dependence of the acetate shift in solutions containing 0.25 M Yb(EDTA)$^-$, 0.02 M acetate, and 2 M LiCl. Shifts are upfield from an arbitrary point 80 Hz downfield from *tert*-butyl alcohol. Other details as in Figure 1.

shift in a mixed hydroxo-acetato complex in which the orientation of the magnetic axes has changed. The latter possibility should not be ignored since proton shifts in lanthanide complexes obey in general the pseudocontact shift relationship:[1,2]

$$\delta_M = C(3\cos^2\theta - 1)/r^3 \qquad (1)$$

where C is a constant for given lanthanide and temperature, r is the ion-proton distance, and θ is the angle between $\mathbf{r}$ and an axis of effective symmetry which may change upon complex formation. Note that a zero shift will be obtained for $\theta = 54° 44'$.

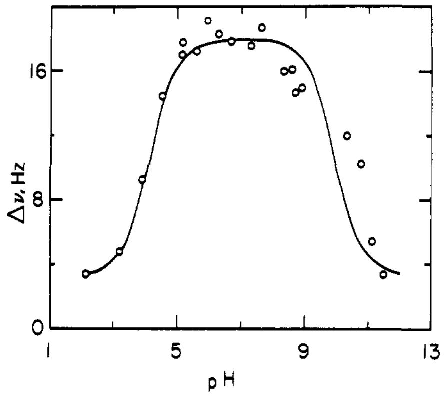

Figure 3. The pH dependence of the acetate line width in a solution containing 2 mM Gd(EDTA)$^-$, 0.12 M acetate, and 2 M LiCl. The smooth curve was calculated with the parameters in Table I, taking into account field inhomogeneity effects as reflected in the line width of *tert*-butyl alcohol (3.3 Hz).

Table I. NMR Parameters and Dissociation Constants of Complexes of Lanthanide Chelates

Chelate	δ_M, Hz	K_{MA}, M	K_{MOH}, M	$K_{MOH}^{(HEDTA)}$, M^a
Pr(EDTA)$^-$	−110	0.19	3×10^{-4}	2×10^{-4}
Gd(EDTA)$^-$	1620^b	0.10	$(2 \pm 0.5) \times 10^{-4}$	1×10^{-4}
Yb(EDTA)$^-$	+210	0.40	3×10^{-5}	6×10^{-5}

[a] These are the dissociation constants of the hydroxo complexes of the lanthanide N'-(2-hydroxyethyl)ethylenediaminetriacetates (HEDTA) calculated from the data in ref 10. [b] This is the intrinsic line width of the acetato-Gd(EDTA)$^-$ complex.

Line broadenings in gadolinium complexes, however, are expected to be mainly a function of r^{-6} and of the fraction of complexed substrate (assuming rapid chemical exchange).[1,2] The pH profile of the line broadenings induced by Gd(EDTA)$^-$ in the resonance of acetate is shown in Figure 3. It is seen that the behavior is qualitatively similar to that observed with the shifts.

The observed shifts and line broadenings were fitted with a model that involves the following equilibria:

$$\mathrm{H} + \mathrm{A} \rightleftarrows \mathrm{HA} \qquad (2)$$

$$\mathrm{M} + \mathrm{A} \rightleftarrows \mathrm{MA} \qquad K_{MA} = [\mathrm{M}][\mathrm{A}]/[\mathrm{MA}] \qquad (3)$$

$$\mathrm{M} + \mathrm{OH} \rightleftarrows \mathrm{MOH} \qquad K_{MOH} = [\mathrm{M}][\mathrm{OH}]/[\mathrm{MOH}] \qquad (4)$$

where A is acetate, M is the Ln(EDTA) chelate, MA is its acetato complex, and MOH its hydroxo complex. The observed shift (or line broadening) is given by

$$\delta = [\mathrm{MA}]\delta_M/([\mathrm{A}] + [\mathrm{HA}] + [\mathrm{MA}]) \qquad (5)$$

where δ_M is the intrinsic shift of the complexed acetate. Equation 5 assumes rapid chemical exchange between the coordinated and noncoordinated acetate. The constants obtained from the fitting procedure are summarized in Table I. They are believed to be accurate within less than (±10%). The smooth dotted curves in Figures 1, 2, and 3 were calculated with these constants. Also shown in Figures 1 and 2 is the relative equilibrium distribution of acetate among its three forms: acetic acid, free acetate, and complexed acetate. The absolute magnitudes of the dissociation constants for the hydroxo complexes, as well as their sequence along the lanthanide series, obtained here for the Ln(EDTA)$^-$ chelates are in good correspondence with the results for the hydroxo complexes of the

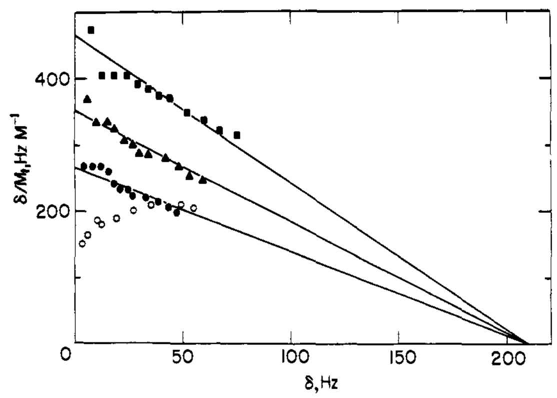

Figure 4. A plot of δ/M_t vs. δ, where δ is the acetate shift upfield from its uncomplexed state and M_t is the concentration of Yb(EDTA)$^-$ in solutions containing 0.02 M acetate and different Li$^+$ concentrations: 3 M, squares; 2 M, triangles; 1 M, filled circles; no addition of LiCl, open circles. The pH was held constant at 7.5 ± 0.2.

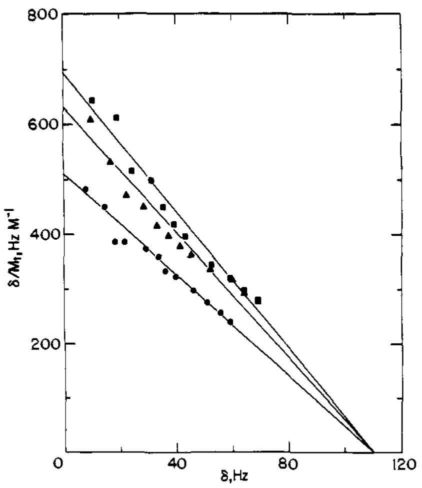

Figure 5. A plot of δ/M_t vs. δ, where δ is the *downfield* shift of acetate relative to its uncomplexed state and M_t is the concentration of Pr(EDTA)$^-$. Other details as in Figure 4.

Ln(HEDTA) chelates (cf. the last column of Table I) obtained by Gupta and Powell[10] from potentiometric measurements.[11]

Ionic Medium Effects and Chelate Structure. It might be intuitively anticipated that the EDTA chelates of the lanthanides, by virtue of their negative charge, would interact with cations in solution. Such interaction was indeed observed by us and further investigated in a study of the suitability of the chelates as aqueous shift reagents for substituted ammonium cations.[12] A striking example of the effect of the interaction between the chelates and Li$^+$ was obtained in a titration of acetate with Yb(EDTA)$^-$, the latter, as mentioned (cf. Experimental Section), being accompanied by a threefold molar excess of LiCl. The upfield shift induced in the acetate resonance was very small at lower concentrations of Yb(EDTA)$^-$ and increased in a sigmoidal fashion as the concentration increased. Titrations of this type were carried out at a pH in the range of the plateau (cf. Figures 1 and 2) and at a constant acetate concentration with the reagent being in large excess throughout most of the concentration range. Since the dissociation constant of the acetato complex is relatively large, the approximation $[M_f] \approx [M_t]$ holds over most of the range (f and t denoting free and total, respectively). With this approximation a combination of eq 3 and 5 gives after proper rearrangement

$$\delta/[M_t] = \delta_M/K_{MA} - \delta/K_{MA} \qquad (6)$$

Thus a plot of $\delta/[M_t]$ vs. δ should be linear with intercepts of δ_M on the abscissa and δ_M/K_{MA} on the ordinate. Such plots for Yb(EDTA)$^-$ are presented in Figure 4. It is seen that only when the total Li$^+$ concentration is held constant are the plots linear. The intercept on the ordinate increases, i.e., the dissociation constant decreases, by a factor of 1.75 on going from 1 to 3 M Li$^+$. Note, however, that the value of δ_M is independent of the ionic medium. With Pr(EDTA)$^-$ the sigmoidal behavior was not observed. Here the effect of the Li$^+$ concentration was less prominent. The results are shown in Figure 5. The intercept on the ordinate increases by a factor of only 1.35 on going from 1 to 3 M Li$^+$. Again δ_M is independent of the ionic medium.

It is clear from these results that between the Ln(EDTA)$^-$ chelate and the Li$^+$ ion there is an interaction which exerts a stabilizing effect upon the acetato complex. This interaction, however, does not alter the structure of the complex as evidenced by the medium independent value of δ_M. For the mere formation of the acetato complex of Pr(EDTA)$^-$ the interaction with Li$^+$ is apparently unnecessary, but it seems to be required for Yb(EDTA)$^-$. The dissociation constant of the latter is larger by a factor of between 3 and 4 than that of the former. By contrast the stability constants of lanthanide complexes normally increase along the series.[3] It seems that the phenomenon observed here arises from a fundamental structural difference between the EDTA chelates of praseodymium and ytterbium. The thermodynamic studies of Geier and Karlen on complex formation between lanthanides and aminopolycarboxylates have indicated that the number of waters of hydration in the chelates decreases by one on going from lanthanum to lutetium.[6a] In the middle of the series the two forms exist in equilibrium as has clearly been revealed in the optical spectrum of Eu(EDTA)$^-$.[13] The hexachelating EDTA has four acetate arms arranged in a hemispherical fashion around the central lanthanide ion leaving space for the coordination of water molecules.[5] We consider this type of Ln(EDTA)$^-$ as noncoordinating toward additional carboxylates and other substrates of this kind. With a pentachelating EDTA, one acetate arm remains free as has in fact been observed at low temperatures in the ^{1}H NMR spectrum of Li-La(EDTA).[2c] In this case rapid exchange with the other arms leads, at higher temperatures, to line broadening and coalescence.[2c,9a] On the other hand the ^{1}H NMR spectrum of Lu(EDTA)$^-$ is sharp,[14] as would be expected for four equivalent acetate arms in a hexachelating EDTA. The chelate is an anion and therefore ion pairing of the free arm with a cation is likely to lower the electrostatic barrier that may otherwise inhibit or altogether preclude the binding of other anionic ligands, e.g., acetate in our case. Judged by the existence of the hexachelated Ln(EDTA)$^-$ species of the heavier lanthanides, it seems likely that only due to steric reasons, associated with the larger size of the lanthanide ion, is the simultaneous coordination of the four EDTA arms less favorable with the lighter lanthanides and thus the accommodation of an outside carboxylate ligand is facilitated. By the same token there is no thermodynamic reason for the binding of an additional fifth carboxylic ligand to the hexachelated lanthanide. This latter type is the predominant species in the case of Yb(EDTA)$^-$ and hence the effect of Li$^+$ in shifting the equilibrium toward the pentachelated type and in enhancing the formation of the acetato complex is more prominent than with Pr(EDTA)$^-$.

It is noteworthy that the ratio between the acetate shift in its complex with Yb(EDTA)$^-$ and that in its complex with Pr(EDTA)$^-$ is −1.91, in excellent agreement with −2.0, which is the theoretically predicted ratio of pseudocontact shifts in *isostructural* complexes of ytterbium and praseodymium.[15] This observation suggests that the acetato complexes of the Ln(EDTA)$^-$ chelates are isostructural along the lanthanide

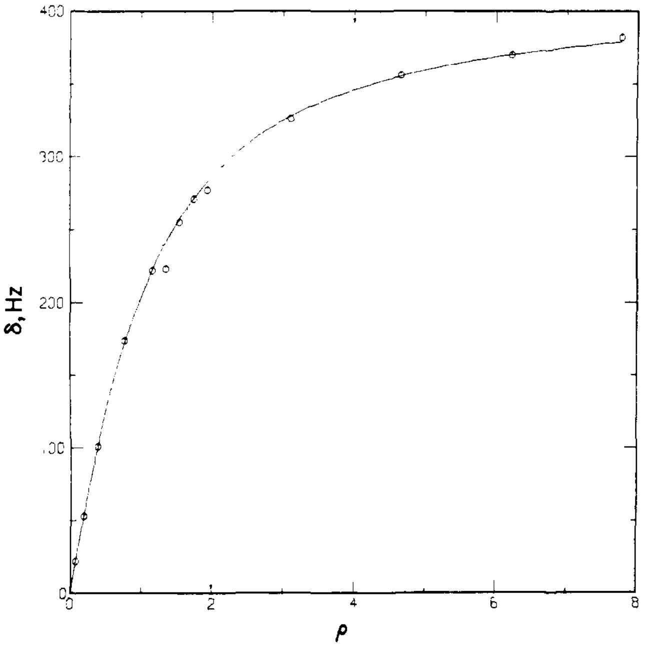

Figure 6. The downfield shift induced by $Pr(ClO_4)_3$ in the proton resonance of acetate (relative to its uncomplexed state) as a function of the Pr^{3+}/acetate ratio, ρ. The acetate concentration was 6.5 mM. The curve is calculated (see text).

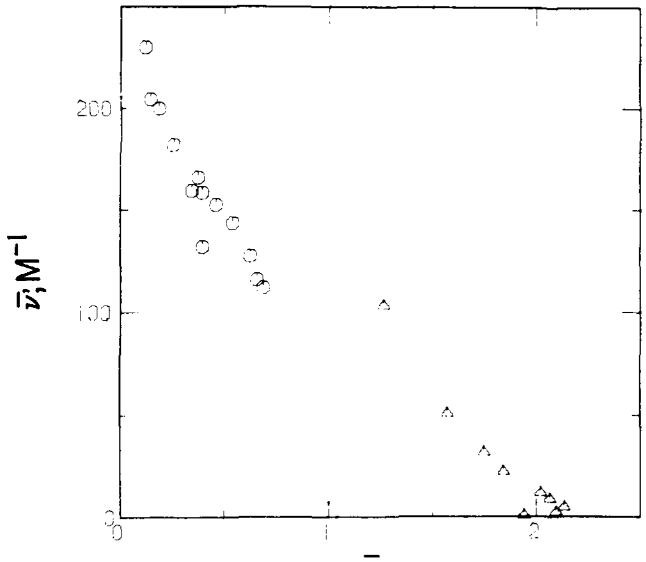

Figure 7. A Scatchard plot, $\bar{\nu}' = \delta/[(\delta_M - \delta)M_t]$ vs. $\bar{\nu} = \delta/(\delta_M\rho)$, for the data in Figure 6 (circles) and data obtained in a titration of 40 mM $Pr(ClO_4)_3$ with acetate in the range 0.03-2.5 M (triangles). A value of δ_M = 360 was used in the calculations.

series. On the other hand ^1H NMR studies have shown that the acetato complexes of the trivalent lanthanide cations exhibit a structural change toward the end of the series.[16] More recently a similar behavior has been reported for the lanthanide complexes of indol-3-ylacetate.[17] Therefore in studies of molecular structure in which the shifts induced by a number of lanthanides are often simultaneously employed[1,2,4,17] the $Ln(EDTA)^-$ chelates should be the shift reagents of choice. Another implication of our findings is that while the structure of the $Ln(EDTA)^-$ chelates in aqueous solution changes along the series the total coordination number of central lanthanide ion probably remains unchanged. This contention, however, deserves further verification.

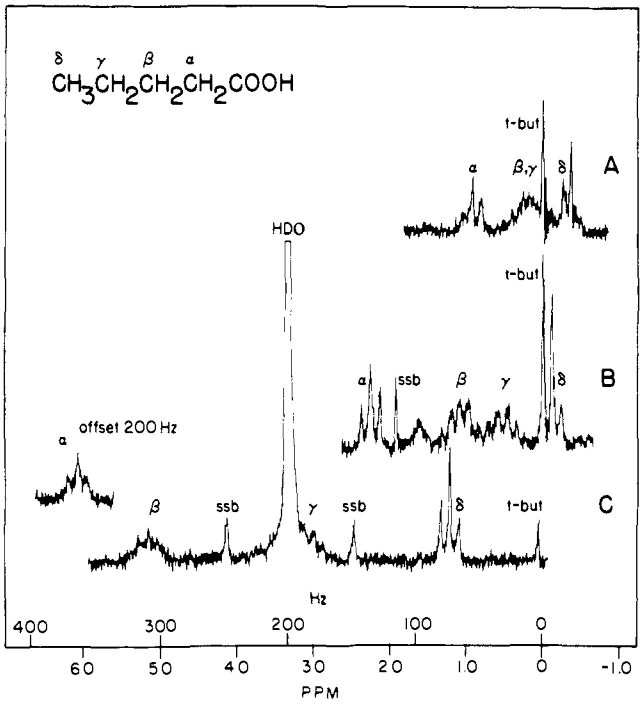

Figure 8. The proton spectrum of 0.09 M *n*-valerate at pH 6.7: A, no additions; B, with 0.36 M $Pr(EDTA)^-$; C, with 0.27 M $Pr(ClO_4)_3$. The broad resonance at 100 Hz in spectrum B belongs to one of the EDTA protons.

Stoichiometry. The lanthanide cations are known to form acetato complexes of higher than 1:1 stoichiometry,[3] the existence of which has been confirmed by NMR.[16] It is instructive, however, to discern the effect this may have on the chemical shift of acetate. The shifts induced by increasing concentrations of Pr^{3+} in the resonance of acetate are presented in Figure 6. Analysis of the data according to previously published procedures[18] reveals that in addition to the 1:1 complex there is a significant contribution of a 2:1 acetate-Pr^{3+} complex. This is more clearly revealed in the Scatchard plot shown in Figure 7, where the quantity $\bar{\nu}' = \delta/[(\delta_M - \delta)M_t]$ is plotted against $\bar{\nu} = \delta A_t/(\delta_M M_t)$.[1a,18] In Scatchard plots the intercept on the abscissa gives the stoichiometry of complex formation. Data obtained at a constant Pr^{3+} concentration with varying acetate concentrations are also included in Figure 7 since it enabled us to cover the range where the 2:1 species is dominant. From the data analysis the stepwise dissociation constants $K_1 = 4 \times 10^{-3}$ M and $K_2 = 3 \times 10^{-2}$ M were obtained with the intrinsic shifts being δ_{M1} = 410 Hz and δ_{M2} = 320 Hz. The smooth curve in Figure 6 is calculated with these constants and it fits the data to within ±3% of the mean shift value. It is clear that the shifts of the 1:1 and 2:1 complexes are different and therefore complications are bound to arise in cases where observed shifts are used for the elucidation of molecular structure. The shifts induced by $Pr(EDTA)^-$ seem to be free of such complications and neither the data of the pH dependence (Figure 1) nor that of the concentration dependence (Figure 5) show indications of the presence of higher than 1:1 species. Even if higher species did exist their concentration would be extremely low due to the large dissociation constant of the acetato complex of $Pr(EDTA)^-$, which is about 50 times as large as that of the corresponding complex of Pr^{3+}.[19] Thus, practically, the acetate-$Pr(EDTA)^-$ system behaves as one with 1:1 stoichiometry.

A comparison between the intrinsic shifts and association constants of the Pr^{3+} and $Pr(EDTA)^-$ complexes of acetate shows that both parameters are much higher for the former complex. Therefore the lanthanide ions are expected to induce much larger shifts in the spectra of carboxylates than would the corresponding EDTA chelates. This is demonstrated with the spectrum of *n*-valerate shown in Figure 8. It is seen that while it is possible to resolve the spectrum with a fourfold molar excess of Pr(EDTA)$^-$, a smaller amount of Pr^{3+} affords a much higher resolution. Thus, if a shift reagent is sought for spectral resolution of a carboxylate in an aqueous medium and below the neutral pH, the aquolanthanides would be the ones of choice.

Conclusions

The EDTA chelates of the lanthanides form effectively 1:1 complexes with acetate inducing chemical shifts in the proton resonance of the latter. The induced shifts are of pseudocontact origin and the complexes of Pr(EDTA)$^-$ and Yb(EDTA)$^-$ are isostructural. Therefore Ln(EDTA)$^-$ chelates would be useful as shift reagents for structural studies of carboxylate substrates in aqueous solution. The practical pH range is between 6 and 10. At higher pH values there is effective competition due to the formation of hydroxo complexes. The usefulness of the aquolanthanides as shift reagents is not only confined to the acidic side of neutral pH but may also be complicated by the formation of higher than 1:1 complexes. They may however by preferred as reagents for spectral resolution.

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(19) By monitoring the change in the chemical shift of one of the EDTA resonances of Pr(EDTA)$^-$ upon successive additions of large excess of acetate, a dissociation constant of 1.2 M was obtained. This seems to indicate that under the conditions of the experiment, i.e., excess of acetate, a complex of higher than 1:1 stoichiometry might be formed.

Synthesis and Structural Characterization of 9-Ethylguaninium Tetrachloroplatinate(II) Dihydrate. A Crystallographic and ^{1}H Nuclear Magnetic Resonance Study

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Abstract: The purine salt 9-ethylguaninium tetrachloroplatinate(II) dihydrate, $(9\text{-EGH})_2[\mathrm{PtCl_4}]\cdot 2\mathrm{H_2O}$, $\mathrm{C_{14}H_{24}Cl_4N_{10}O_4Pt}$, has been synthesized and its molecular structure has been determined by single crystal x-ray diffraction and 100 MHz ^{1}H NMR techniques. The material crystallizes in the triclinic space group $P\bar{1}$ with one formula unit in a cell of dimensions a = 7.916 (8), b = 16.30 (2), c = 9.13 (1) Å, α = 138.25 (5), β = 118.3 (1), and γ = 86.6 (1)°. The observed and calculated densities are 2.02 (3) and 2.037 g cm^{-3}, respectively. The structure has been refined by full-matrix least-squares techniques to a final value of the conventional R factor (on F) of 0.025 based on 2853 independent intensities. The complex consists of 9-EGH$^+$ cations which are hydrogen bonded to $[\mathrm{PtCl_4}]^{2-}$ anions and to water molecules. The purine cation is protonated at N(7), and its geometry is similar to that of other 9-substituted guanine derivatives. The $[\mathrm{PtCl_4}]^{2-}$ anion is planar, with Pt-Cl distances of 2.298 and 2.299 (3) Å and Cl-Pt-Cl angles of 90.0 (2)°. There is extensive intermolecular hydrogen bonding in the crystals. The ^{1}H NMR spectrum in DMSO-d_6 is consistent with the observed solid state structure, but the spectrum suggests that in solution there may be tautomerism in which the acidic proton resides on both N(7) and N(3).

The importance of metal-nucleic acid and peptide–metal–nucleic acid interactions in living systems has stimulated considerable research in the area of metal interactions with nucleic acid constituents.[1-19] This research increased in importance with the discovery that some platinum compounds exhibit carcinostatic properties.[20] Rosenberg's studies with *cis*- and *trans*-dichlorodiammineplatinum(II) indicate that although both forms bind to the purine and pyrimidine bases, only the cis form is effective as an antitumor agent.[21] Roberts and Pascoe have also noted that cross links are formed between