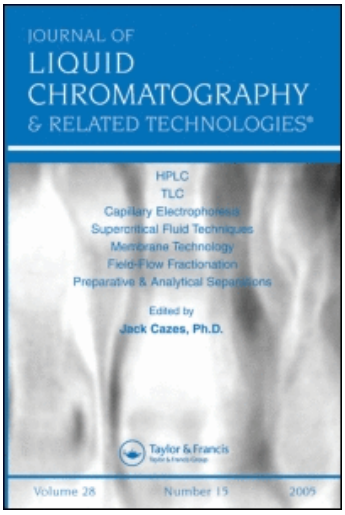

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Metal Cation Speciation via Extraction Reversed Phase HPLC with Refractive Index and/or Inductively Coupled Plasma Emission Detection Methods (HPLC-RI-ICP)

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METAL CATION SPECIATION VIA EXTRACTION REVERSED PHASE HPLC WITH REFRACTIVE INDEX AND/OR INDUCTIVELY COUPLED PLASMA EMISSION DETECTION METHODS (HPLC-RI-ICP)

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ABSTRACT

Conventional high performance liquid chromatography (HPLC) instrumentation and packing materials can be inexpensively and rapidly utilized for the qualitative and quantitative analysis of various metal cations. The final approaches utilize reversed phase HPLC in the form of extraction chromatography. The detection of individually eluted, fully resolved metal cations is then possible via conventional refractive index (RI) and/or inductively coupled plasma (ICP) emission spectroscopic detection. Final data presentation can be in the form of conventional, continuous RI or ICP chromatograms, via pulsed data ICP presentations, and/or via tabular ICP data presentation.

INTRODUCTION (33)

Inorganic metal toxicity has long been an area of intense biological, toxicological, and medical interests. The apparent toxic properties of most, if not all, metals have been elucidated and extensively described for several

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decades (1-4). Unfortunately, the vast majority of published metal toxicity studies have never involved appropriate and complete analytical methodology. Wherein analytical methods have been used as part of the overall biological studies, these have provided total metal concentrations or absolute levels, rather than the more specific and desirable metal speciation profiles for the particular biological, toxicological, or medical samples of interest (5-14). Within recent years it has become apparent to most scientists and some decision makers that partial or complete metal speciation of environmental, biological, toxicological, and/or medical type samples must be undertaken on a regular basis. That is, only when all or most metal species present in any sample are accurately known, can we then appropriately ascribe biological, medical, or toxicological properties to that particular mixture of metals and/or metallic compounds or ions. Many metals can exist as the free metal, various cationic or anionic oxidations states, organically bound chelates/complexes, and/or organometals. Obviously, the final speciation of metals in a complex sample matrix, often in the presence of other metals and their species, must involve some sort of an initial separation process. Within the past few years, a tremendous interest and effort has emerged towards inorganic metal cation/anion analysis, especially in the use of ion chromatography (IC), and/or high performance liquid chromatography using ion exchange packings, together with conductivity and/or electrochemical detection (12, 15-24). It has become obvious that IC, especially via the use of commercially available instrumentation, has become quite popular, very useful, and can be readily utilized in trace environmental and/or toxicological studies. Unfortunately, such commercial instrumentation is often quite expensive ($15,000-$25,000/unit), and must be totally dedicated to the performance of inorganic/organic cation or anion type separations. It does not lend itself to the performance of conventional HPLC separations via liquid-solid, liquid-liquid, reversed phase, paired-ion, and/or gel permeation techniques.

Unfortunately, relatively little non-IC or non-ion-exchange type work has been reported in recent years, especially with regard to using any commercial type HPLC instrumentation and packing materials for performing inorganic metal cation/anion type analyses. Quite obviously, this situation should be remedied, and the work described here, in part, has been designed with this goal in mind. All of this work has utilized conventional reversed phase type packing materials, C_{18}, with extraction reagents in the mobile phase, viz, tributylphosphate (TBP).

Extraction chromatography was developed extensively in the early-mid 1970s, and the work of Horwitz and co-workers is especially relevant (25-27).

The use of organic phosphates for the separation of various radiochemical metal species was quickly extended to a large number of metal cations, but this work almost always involved the use of polymeric or silica gel type packing materials. The usefulness of extraction chromatography with modern, bonded phase packings, especially C_{18}, has not been discussed in depth.

We describe here some initial results in the separation and speciation of various metal cations utilizing extraction chromatography together with reversed phase (RP) type packings, wherein this has now been interfaced with RI and/or ICP detection methods. These methods allow for the successful resolution and speciation of various metal cations, especially when the HPLC methods are combined with ICP detection. Reproducibility studies have been performed using these approaches, both on an intra-day and inter-day basis. In addition, some attempts have been made to compare direct-ICP with HPLC-ICP for cadmium ion limits of detection.

EXPERIMENTAL

Reagents

Inorganic salts, reagent grade, were obtained as Baker analyzed reagent (VWR Scientific, Inc., Boston, Mass.), Fisher ACS certified (Fisher Scientific, Inc., Medford, Mass.), and/or Alfa/Ventron Inorganics, Inc. (Danvers, Mass.). Tributyl phosphate was purchased from Alfa/Ventron, Inc. The mobile phase water was purchased from J.T. Baker Chemical Co. (Phillipsburg, N.J.), or used directly from a Corning Mega-Pure still (Corning Corp., Corning, N.Y.).

Apparatus

We have utilized a number of HPLC instrumentation arrangements for the present work. However, for the extraction chromatography, not all columns proved equally satisfactory. A typical HPLC arrangement consisted of a Laboratory Data Control (LDC) (Riviera Beach, Fla.) Model 711 solvent delivery system, modified with a special pulse dampener, or a newer LDC Constametric III pump, a Rheodyne Model 7125 syringe injection valve (Rheodyne Corp., Cotati, Calif.), an Altex/Beckman variable wavelength UV-VIS detector (Altex/Beckman Corp., Irvine, Calif.), a Waters Model 401 RI detector (Waters Assocs., Milford, Mass.), a modified Instrumentation Laboratory Model Plasma-100 inductively coupled plasma emission spectrometer (Instrumentation Laboratory, Inc., Wilmington, Mass.), and a Linear Corp. (Irvine, Calif.) or

Honeywell Corp. (Minn., Minn.) dual pen recorder. The RI/ICP data was obtained via a dual pen recorder, and/or a separate ICP print-out from the Plasma-100 system. Often, both the recorder ICP chromatogram and the tabular data format from the ICP were obtained at the same time. At other times, the tabular data presentation could be manually used to reconstruct a pulsed type or continuous type HPLC-ICP chromatogram. This was done knowing the timed integration sequence of the tabular data presentation. In later runs, the Plasma-100 system was operated to present both pulsed type chromatograms, as below, and the simultaneous tabular data presentations. This provided additional confirmation of the ICP results for the final metal speciation.

In the work described, the HPLC columns were all of the C_{18} type and usually obtained commercially, as follows: 1) Hibar II RP-18 pre-packed column (4.6mm x 25cm)(MCB Chemicals, Inc., Cinc., Ohio); 1) Alltech C-18 (4.6mm x 25cm)(Alltech Assocs., Inc., Deerfield, Ill.); 3) Altex/Beckman Ultrasphere ODS (4.6mm x 15cm)(Altex/Beckman Corp.); 4) slurry packed in-house columns using Lichrosorb RP-18 (4.6mm x 25cm)(MCB Chemicals, Inc.).

Methods

In extraction chromatography the mobile phase consisted of varying molarities of either NaCl or LiCl, saturated with TBP. The saturation was performed by shaking the salt solution with excess TBP, standing in the presence of the excess TBP overnight, and then separating the aqueous layer from the organic layer in the morning. In some initial studies, inorganic phosphate buffers, 0.1M sodium dihydrogen phosphate/0.1M disodium hydrogen phosphate, were added to the mobile phase, producing a final pH = 3.9-4.2. In the absence of such buffering salts, the final pH was about 6.0. These differences in the pH of the mobile phase did not appear to affect any capacity factors for the metal cations studied. The aqueous mobile phase was de-gassed under vacuum, filtered, and used as quickly as feasible. It appears important that such mobile phases are prepared just prior to actual use, otherwise final retention times can differ greatly. Omission of the TBP altogether, results in all metal cations eluting in the solvent front.

The RP-HPLC columns are equilibrated with the mobile phase for about 1-2 hrs at ambient temperatures, and once the RI or ICP baselines are stable, analyses can begin. It is possible to accelerate the equilibration process by using a special equilibrating solution of TBP in MeOH:HOH (1:1), containing about 20% v/v TBP. This is then used to saturate a brand new C_{18} column. In this way, daily equilibrations with the fresh mobile phase took less time than with the first procedure above. In order to prolong column and component lifetimes, the columns were washed free of all inorganic salts with distilled

water at the end of each day's run. They were then left standing in the presence of the same distilled water. Washing with MeOH or 1:1 MeOH:HOH removed all organic TBP from the packing material, and thus required a much longer equilibration period the next working day. Individual columns used and prepared in this manner have lasted as long as six months before any signs of column degradation or component corrosion began to appear. A mobile phase saturation pre-column, consisting of large particle size silica gel, was used on-line and just before the injection valve. This was designed to extend column lifetime by preventing dissolution of the analytical packing material.

In comparing the sensitivities for direct-ICP analysis vs. HPLC-ICP interfacing for the same metal cation, viz. Cd^{+2}, this was done by injecting a number of identical samples via HPLC-ICP (20ug/20ul), and at the same time determining the ICP response on that same day for a direct-ICP nebulizer uptake analysis of the identical solution. Comparisons of both peak height and peak area responses were then made for the direct-ICP and HPLC-ICP results.

RESULTS AND DISCUSSION

We have now determined retention times and capacity factors (k') for at least three metal cations, all divalent species, of cadmium (Cd^{+2}), zinc (Zn^{+2}), and mercury (Hg^{+2}). Obviously, many other divalent and monovalent cations could be separated using these or similar chromatographic techniques. Initial separation conditions were determined using both RI and ultra-violet (UV) detection, where possible, or RI alone. Two inorganic salts, NaCl and LiCl, were separately added to the mobile phase preparations, in order to "salt-out" the metal cation species and increase or modify retention times. Table I summarizes the overall results obtained in this manner. Changing the NaCl concentrations from 1.0M to 2.0M resulted in a complete reversal of the elution order for Hg and Zn cations. Thus, as others have previously noted in extraction chromatography, retention times and capacity factors, as well as elution orders, can be easily manipulated by varying the salt concentrations and holding all other variables constant. In the case of Cd^{+2}, no NaCl concentration was able to increase the retention time beyond that of the solvent front. However, by going to the use of LiCl, at the 2.0M level, it was possible to obtain a small, but real, retention for the Cd^{+2} ion. These results with 2.0M LiCl are shown in Figure 1, wherein RI alone was used for the detection, and low ug amounts of all three metal cations were injected as a mixture, as well as separately. The total elution time for these three species is under six minutes, with baseline resolution obtained for all cations

TABLE I

TRIBUTYL PHOSPHATE REVERSED PHASE EXTRACTION CHROMATOGRAPHY IN HPLC[a]

RP-HPLC CONDITIONS	METAL CATION	t_r(mins)	k' (capacity factor)
1.0M NaCl[c]	Hg^{+2}	4.8	0.68
	Zn^{+2}	4.4	0.54
	Cd^{+2}	s.f.[b]	s.f.[b]
2.0M NaCl[c]	Hg^{+2}	4.2	0.45
	Zn^{+2}	6.3	1.17
	Cd^{+2}	s.f.	s.f.
1.0M LiCl[d]	Hg^{+2}	4.5	1.3
	Zn^{+2}	2.9	0.51
	Cd^{+2}	s.f.	s.f.
2.0M LiCl[d]	Hg^{+2}	7.6	2.0
	Zn^{+2}	5.7	1.3
	Cd^{+2}	3.3	0.32

a. HPLC conditions: Hibar-II RP-18 column (4.6mm x 25cm)(MCB Chemicals, Inc.), aqueous mobile phase saturated with TBP containing NaCl or LiCl, pH = 4.6-6.0, flow rates 0.65-1.0ml/min, RI/UV detection.
b. s.f. = solvent front; c. mobile phase flow rate = 0.65ml/min; d. mobile phase flow rate = 1.0 ml/min.

present. These same HPLC conditions, Figure 1, were then utilized for subsequent HPLC-RI-ICP studies, as well as for the determination of relative sensitivities for direct-ICP vs. HPLC-ICP.

Figure 2 is a typical HPLC-RI-ICP chromatogram for a single divalent cation, Cd^{+2}, using the same HPLC conditions as in Figure 1, but now with a 50:50 split of the total column eluent to both detectors. In this particular example, Cd^{+2} was injected at a concentration of 36.6ug/20ul, so that about 18ug is reaching each detector. Specific detector operating conditions are indicated in Figure 2. It is apparent from the RI trace that the Cd^{+2} ion is just separated from the solvent front. Also of interest is the fact that the ICP is readily able to provide continuous chromatographic profiles of each peak as these elute from the column. That is, it can function just like any more conventional HPLC detector, be this UV, RI, EC, etc.

Whenever HPLC is interfaced with an initially designed off-line detector, such as the ICP or graphite furnace atomic absorption spectrometer (GFAA), one must expect a certain loss of detection limits and overall sensitivity (28-30). The reasons for this overall loss of detection limits (MDLs) have been

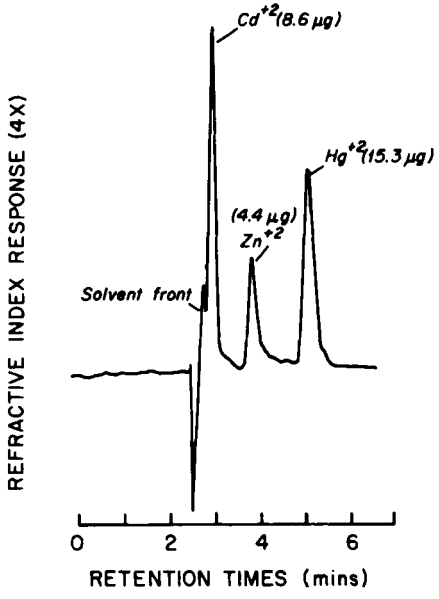

Figure 1. Extraction chromatography of a cation mixture using a 2.0M LiCl-TBP mobile phase at 1.0 ml/min flow rate with RI detection alone.

discussed at length by several workers, but it is a totally general phenomenon whenever HPLC is interfaced with an off-line type detector. We have now tried to determine experimentally the actual differences in overall minimum detection limits (MDLs) for the HPLC system of Figure 2. In reality, we are not actually comparing MDLs nor determining MDLs here, but we are comparing relative responses or sensitivities for these two approaches. These results are summarized in Table II, which compares the ICP peak heights and ICP peak areas for both direct-ICP and HPLC-ICP analyses of a known Cd^{+2} concentration. The direct-ICP values for peak height and peak area were obtained by continuously nebulizing, with a conventional cross-flow type nebulizer, a 1 ppt (parts-per-thousand) solution of Cd^{+2} into the ICP. Peak heights were then measured over several minutes, and an average reading was taken from these peak heights. In the case of direct-ICP peak area measurements, this was done by determining the total emission intensity for Cd^{+2}, via direct nebulization of a 1ppt solution, over a time span representing 20ug total amount (mass) of metal cation. Thus, we can arrive at two methods for directly comparing sensitivities via direct-ICP and HPLC-ICP for Cd^{+2} under these particular HPLC and ICP operating conditions.

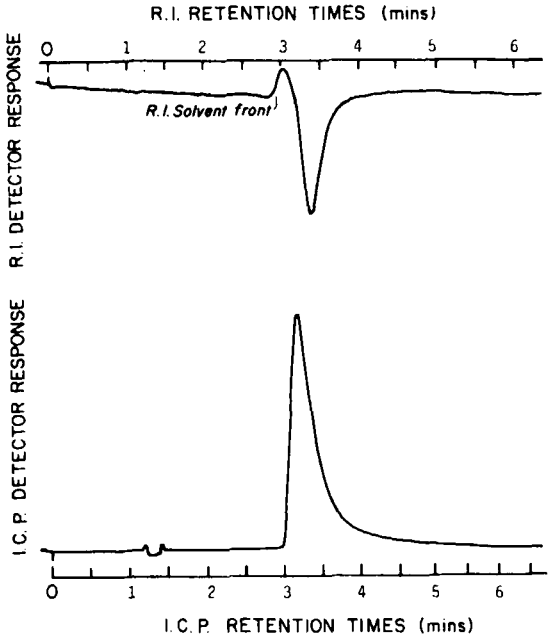

Figure 2. Extraction RP-HPLC of Cd^{+2} (36.6ug/20ul) split 50:50 between RI and ICP detectors. HPLC mobile phase of 2.0M LiCl-TBP at 1.0 ml/min. ICP set at 214.44nm, RI set at 0.10×10^{-3} units.

TABLE II

COMPARISON OF SENSITIVITIES FOR DIRECT-ICP AND HPLC-ICP INTERFACING

METHOD OF COMPARISON	DIRECT-ICP[a]	HPLC-ICP[a,d]	DIRECT-ICP/ HPLC-ICP
ICP PEAK HEIGHTS	10.2, 11.4cm[b]	0.57 ± 0.02cm	18.0
ICP PEAK AREAS	1,037,577-1,198,310[b]	435,587 ± 12,300[c]	2.6

a. Determined by injecting a 1ppt solution (20ug/20ul) of Cd^{+2} onto HPLC-ICP or using a 1ppt solution for direct nebulization into ICP. Peak heights and peak areas were determined from these analyses.
b. Numbers represent two separate runs on same day, average of these results used for final calculations of direct-ICP/HPLC-ICP.
c. Numbers represent the average ± standard deviation for three separate runs on the same day (n=3).
d. HPLC-ICP used extraction RP-HPLC with 2.0M LiCl-TBP mobile phase at 0.5ml/min, no split after column, 20ul injections of 20ug Cd(+2).

In using the ICP peak height measurements alone, the ratio of direct-ICP/HPLC-ICP turns out to be about 18.0. That is, the sensitivity via HPLC-ICP approaches is about 18 times worse than via direct-ICP methods where peak heights are used. Using a comparison of peak area intensities on the ICP, the ratio of direct-ICP/HPLC-ICP comes out to be about 2.6, Table II. Different HPLC conditions, with longer retention times and more peak spreading for Cd^{+2} would tend to produce even larger differences in these overall results. These results suggest that the ICP is acting as a mass sensitive detector in the HPLC mode, rather than as a concentration sensitive type detector. Thus, when the total mass in terms of peak areas is measured and compared for direct-ICP vs. HPLC-ICP, their relative differences tend to cancel out and the ratio approaches a value of 1.0. In fact, in other systems and with other metal cations, we have obtained relative ratios which are between 1.0-1.5 using peak area measurements (31). Using peak area measurements, as opposed to peak heights, the differences in the direct-ICP vs. HPLC-ICP responses for the same mass of cation approach zero (ratio = 1.0). From these measurements and comparisons, one might initially assume that absolute limits of detection via HPLC-ICP could be similar to direct-ICP, and that even if one used peak heights for such measurements, final MDLs might be 15-25 times worse via HPLC-ICP. In fact, wherein we have measured MDLs directly, the HPLC-ICP results are often 2-3 orders of magnitude worse than for the direct mode (31). This is discussed at much greater length elsewhere (32).

In any study involving the interfacing of HPLC with an off-line type detector, it is of interest to determine the overall system reproducibility within any given day, as well as the comparable reproducibilities between days. These overall results are summarized in Table III, for two separate days, wherein we have indicated retention times for Cd^{+2} by ICP and RI detection, ICP maximum intensity less background (tabular print-out), ICP peak heights from chromatograms, and the number of separate analyses performed. Overall retention times by both RI and ICP measurements are extremely reproducible, both intra- and inter-day, with a standard deviation of less than 5%. The ICP peak intensity and peak heights also exhibit a standard deviation of less than 5% within each day, and the inter-day comparisons are also quite close, again less than a 5% overall difference. Thus, from these initial reproducibility studies, it would appear that extraction chromatography can indeed provide a high degree of chromatographic reproducibility both inter- and intra-day. In addition, the ICP interfaced to HPLC seems to provide a high degree of overall reproducibility in the responses obtained, again both intra- and inter-day. The amounts of Cd^{+2} used in these reproducibility studies are quite high,

about 170ug/20ul injections. There is a possibility that with lower amounts and concentrations used, the degree of reproducibility evidenced in Table III may not be fully realized.

One of the major goals of any program which involves the use of ICP as a metal selective detector for HPLC is to demonstrate its true capabilities and potentials. We have therefore applied the above HPLC approaches for the three metal species involved, Cd^{+2}, Zn^{+2}, and Hg^{+2}, using extraction chromatography, Figure 1, for a direct interfacing of both RI and ICP. These overall results are depicted in Figure 3, which is a dual RI/ICP type chromatogram for a split eluent from the extraction chromatographic separation. Indicated in Figure 3 are the specific peak shapes for each metal cation by both RI and ICP, retention times for each cation, specific wavelengths used via ICP, and the absolute amounts of each metal species going to the RI or ICP. The apparent chromatographic peak shapes via ICP are comparable to those observed via RI detection, with an increased band broadening being observed for those metals with longer retention times. We have obtained baseline resolution for each of the three metal cations, as in Figure 1, but we have not yet optimized the final detection limits for each cation on the ICP. Thus, the results given here are not to be construed as MDLs for these species. Work remains to be done with regard to optimizing HPLC peak shapes, emission wavelengths used, nebulizer/interface arrangements and effectiveness, as well as several other parameters of interest in the overall HPLC-ICP system. Nevertheless, these initial results forthe direct interfacing of extraction HPLC with RI and ICP detection appear quite useful and of practical interest/application.

This is not to imply that there are no practical, technical problems with the long term use of extraction HPLC for HPLC-ICP metal cation speciation.

TABLE III

REPRODUCIBILITY STUDIES FOR HPLC-ICP ANALYSIS OF Cd^{+2} VIA EXTRACTION HPLC[a]

PARAMETER MEASURED	DAY ONE[b]	DAY TWO[b]
RETENTION TIME (t_r) BY ICP	3.10 $\pm$ 0.00min	3.03 $\pm$ 0.02min
RETENTION TIME (t_r) BY RI	3.15 $\pm$ 0.01min	3.15 $\pm$ 0.00min
ICP MAXIMUM INTENSITY-BKGRD.	301,410 $\pm$ 11,730	324,451 $\pm$ 9,737
ICP PEAK HEIGHT ON CHROMATOGRAM	15.8 $\pm$ 0.3cm	15.5 $\pm$ 0.3cm
NUMBER OF SEPARATE ANALYSES	4	3

a. Determined using extraction RP-HPLC with a 2.0M LiCl-TBP mobile phase at 1.0ml/min flow rate, eluent split 50:50 to RI:ICP, 20ul injections of 170ug Cd(+2).
b. Numbers represent the averages $\pm$ standard deviations

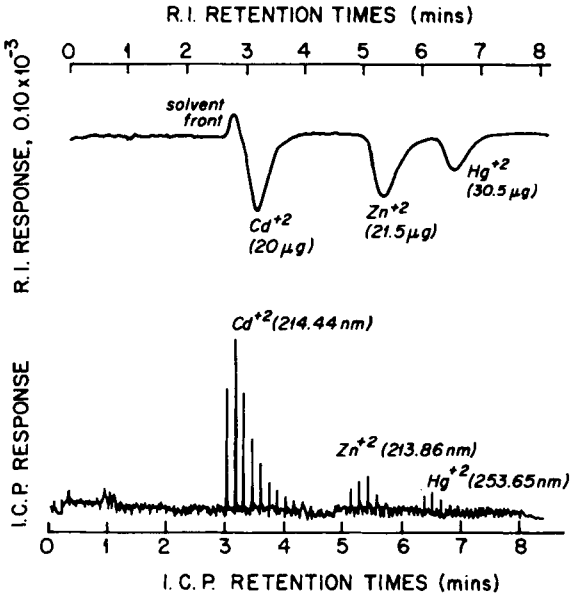

Figure 3. Extraction chromatography of a cation mixture using a 2.0M LiCl-TBP mobile phase. Detection is by RI and ICP simultaneously with a 50:50 eluent split ratio. Amounts indicated are going to each detector.

We have not, as yet, investigated the retention properties of the analogous monovalent cations, and there remains a slight possibility that some metal species may exhibit incomplete resolution of their various cationic valence species. The ICP cannot, by itself, differentiate between two different valences for the same metal species, it must depend on an initial separation prior to their introduction into the ICP system. The separation of one metal cation is apparently easy to realize; however, we have not as yet determined the extraction chromatography separations for different oxidation states of the same metal species via extraction chromatography. In general, we would not expect, for example, Hg^{+1} to interfere with the elution of Hg^{+2}, as described in Figures 1 and 3, but this has not yet been demonstrated.

The use of 1.0-2.0M salt solutions does not appear to create any major problem in the long-term use of the ICP as an HPLC detector, although there is very little in the literature describing such mobile phases in HPLC-ICP. There is no apparent build-up of residual salt onto the plasma tip or surroundings,

and there is no apparent problem of quenching of metal responses or spectral interferences. Thus, at least the ICP itself appears compatible with salt solutions containing 1.0-2.0M NaCl or LiCl. There remains the distinct problem of metal corrosion within the HPLC arrangement, and this is perhaps the greatest concern that one must face in this type of an HPLC-ICP approach. We have not yet attempted to prevent all salt corrosion, such as via the use of glass lined HPLC columns, glass lined connecting lines, Teflon surfaced injection valves, and related hardware modifications, but this is obviously a very desirable goal. The biggest problem that we have faced is that due to rust/corrosion formation in all metal parts contacting the mobile phase, but this is especially a problem within the HPLC columns. This can be somewhat alleviated or prevented using methods described already (Experimental), but eventually corrosion build-up reaches a level that causes severe back pressure in the column, rust eluting with column eluents, and ancillary deterioration of the overall HPLC system. There are known methods of preventing such salt induced problems, and it may develop that such already described approaches would make extraction chromatography an extremely useful and practical approach for performing metal cation/anion type analyses.

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33. Abbreviations used: HPLC = high performance liquid chromatography; RI = refractive index detection; ICP = inductively coupled plasma emission detection; UV = ultraviolet detection; TBP = tributyl phosphate; RP = reversed phase; IC = ion chromatography; MeOH = methanol; HOH = water.