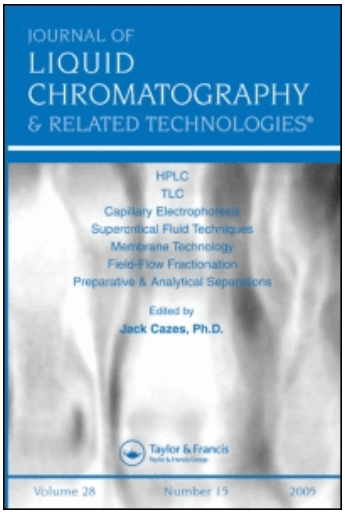

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

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To cite this Article Geise, Robert J. , Machnicki, Nancy I. and Ianneello, Robert M.(1993) 'Determination of Chloride, Sulfate, Nitrate, and Phosphate in N-Methyl-2-Pyrrolidone and γ-Butyrolactone by Capillary Electrophoresis', Journal of Liquid Chromatography & Related Technologies, 16: 17, 3699 — 3712
To link to this Article: DOI: 10.1080/10826079308019662
URL: http://dx.doi.org/10.1080/10826079308019662

JOURNAL OF LIQUID CHROMATOGRAPHY, 16(17), 3699-3712 (1993)

DETERMINATION OF CHLORIDE, SULFATE, NITRATE, AND PHOSPHATE IN N-METHYL-2-PYRROLIDONE AND γ-BUTYROLACTONE BY CAPILLARY ELECTROPHORESIS

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ABSTRACT

N-methyl-2-pyrrolidone (NMP) and γ-butyrolactone (BLO) are important solvents in the semiconductor and electronics industry. These applications demand solvents with low levels (< 0.5 ppm) of anions. Traditionally, analytical methods have not kept pace with the requirements desired by the electronics industry. Recently, ion chromatography (IC) has provided lower detection levels for anions. However, capillary electrophoresis (CE) for anion analysis possesses unparalled resolution and efficiencies, with analysis times reduced by up to a factor of ten over IC. Using the method of standard additions, the concentrations of chloride, sulfate, nitrate and phosphate were determined in 1:20 aqueous dilutions of NMP and BLO. A lower limit of detection for the undiluted solvent sample of 40 ppb (2 ppb limit for 1:20 dilution of sample) was found for each of the four anions of interest.

INTRODUCTION

The quality standards of materials used in the electronics industry are demanding and increasingly stringent. Solvents used must be of the highest purity. They need to be sufficiently

free from trace impurities, such as inorganic anions (chloride, sulfate, nitrate, and phosphate). However, the maximum levels established for these impurities often rely on existent analytical methods, and may be set higher than is truly desired by the industry.

N-methyl-2-pyrrolidone (NMP) is used as a solvent in the manufacturing of integrated circuits. This application demands chemicals free of defect-causing impurities. The level of inorganic ions in electronic grade NMP is critical. SEMI (Semiconductor Equipment and Materials International) has established guidelines for the levels of anions in NMP used in the electronics industry (1). The recommended maximum anion levels are 250 ppb each for sulfate and phosphate, 300 ppb for chloride and 400 ppb for nitrate. Another solvent of interest is γ-butyrolactone (BLO). A high purity grade of BLO is used in liquid capacitors. Although there are no set specifications or guidelines for electronic grade BLO at this time, the maximum levels of anions established should be at least as low as those recommended for NMP.

Ion chromatography (IC) is a powerful separation method and is used to determine anions at the ppb level (2). However, a preconcentration step using an additional column to concentrate anions is needed to achieve this sensitivity. A typical analysis time is ca. 15 minutes with sulfate eluting last. Capillary electrophoresis (CE) can resolve and detect ppb levels of the four anions of interest in ca. 5 minutes. No additional preconcentration step or column is required. Instead, the method of injection is manipulated to "stack" anions at the tip of the capillary, thereby maximizing sensitivity.

The use of capillary electrophoresis for the determination of inorganic and small organic ions has been termed capillary ion electrophoresis or capillary ion analysis (CIA) (3). The use of electrophoresis for the separation of ions was reported prior to the start of CE, usually accepted to begin in 1981 with the pioneering work of Jorgenson and Lukacs (4). In 1967, Hjerten reported separating cations in tubes by electrophoresis (5), and in 1979, separation of anions in small tubes by electrophoresis was reported by Mikkers, *et al.* (6).

Recently, efforts have focused on optimization of the separation by capillary electrophoresis of anions (7-9) and cations (3,10,11). For analysis of cations, "normal polarity"

CE is used. A positive potential is applied at the injection end and cations will migrate past the detector to the negative end, with resolution achieved by differences in the apparent velocities (υ_{app}) of the cations. The electrophoretic velocities, υ_{ep}, of the cations are in the same direction as the electroosmotic flow (EOF), toward the cathode. However, the electrophoretic velocities of the anions oppose "normal" EOF. Therefore, to achieve reasonable analysis times, the EOF needs to be reversed (or eliminated). This can be accomplished by addition of a cationic surfactant to the running buffer.

Chloride, sulfate, nitrate, and phosphate are non-absorbing anions. The addition of a UV-absorbing anion (e.g. benzenetetracarboxylate) to the running buffer allows for indirect detection of these anions (12). The non-absorbing anions will displace the absorbing anions, resulting in a negative absorbance signal peak proportional to concentration of analyte anion. Optimum separation (i.e. resolution, efficiency, etc.) is achieved using an absorbing anion of similar mobility to the analyte anions. Because of matrix interference, the method of standard additions was used. Using electromigration injection and manipulating conditions to maximize the "stacking" of the anions at the capillary/sample solution interface (i.e. tip of capillary), detection limits of less than 10 ppb each of chloride, sulfate, nitrate, and phosphate can be achieved.

Using the method of standard additions to overcome matrix effects and with 1:20 dilutions of the solvent sample with water, detection limits of 2 ppb of each of the anion (40 ppb in undiluted solvent) are achieved. Based on this, capillary ion electrophoresis is a powerful method for determining trace impurities of chloride, sulfate, nitrate, and phosphate well below the recommended SEMI guidelines.

EXPERIMENTAL

Apparatus

All experiments were done using a Dionex Capillary Electrophoresis System I connected to a Dionex 4400 integrator (Dionex, Sunnyvale, CA). The unmodified, fused silica capillary

(Dionex) of 50 μm i.d. was cut to a length of 50 cm. A detector window was obtained by burning off the polyimide coating. The length from injection to detector was 45 cm.

Reagents

Benzenetetracarboxylic acid and triethanolamine were obtained from Aldrich (Milwaukee, WI). Hexamethonium bromide was obtained from Fluka (Ronkonkoma, NY), 1-heptanesulfonic acid, sodium salt was obtained from Alltech. Electronic grade N-methyl-2-pyrrolidone (NMP) and γ-butyrolactone (BLO) were obtained from commercial sources. All water used was purified (> 18 Mohm/cm) with a Milli-Q^{uv}Plus system (Waters, Milford, MA). The water was vacuum filtered, degassed, and stored in a Teflon bottle. All vessels, transfer pipets, and pipet tips were thoroughly rinsed with this water.

Procedure

The capillary was activated by pressure injection of 0.5 N NaOH three times for five minutes per injection. This procedure was repeated with water, followed by running buffer. The running buffer (12) consisted of 2.25 mM benzenetetracarboxylic acid and 0.75 mM hexamethonium hydroxide in a buffer of 6.5 mM NaOH and 1.6 mM triethanolamine (TEA). The pH was between 7.7 - 7.9. The hexamethonium chloride was converted to hexamethonium bromide using an "extract-clean" anion exchange cartridge (Alltech). The buffer was vacuum filtered.

The standard additions sample blank was prepared directly in a sample vial by pipetting 25 μL of undiluted NMP or BLO, 25 μL water, and 450 μL of 50 μM heptanesulfonate. The standard additions samples were prepared as above substituting 25 μL of 500, 250, and 125 ppb

anion working standard, corresponding to additions of 25, 12.5 and 6.25 ppb anion standard. The sample is 5% solvent in 45 μM heptanesulfonate (aqueous).

Anion standards used to verify linearity of response over working range were prepared as the above standard additions samples, substituting 25 μL water for 25 μL of solvent sample.

The following electrophoretic conditions were employed:

Applied voltage:	(-) 30kV
Temperature:	Ambient
Injection:	Electromigration: (-) 5kV for 45 s
Detection:	Indirect at 250 nm

The capillary dimensions and buffer composition are described above. Concentrations of chloride, sulfate, nitrate, and phosphate in the solvent samples were determined from the x-intercept of the fitted standard additions curve for each anion. The values obtained were corrected for dilution (1:20).

RESULTS AND DISCUSSION

Method of injection

The conditions used for injection were selected to maximize the anion "stacking" at the tip of the capillary. A voltage of (-)5 kV was applied for 45 s (electrokinetic injection). The sample vial solution was 50 μM 1-heptanesulfonate and the capillary was filled with running buffer. The conductivity of the sample solution is lower than that of the running buffer inside the capillary. When a voltage is applied, the electric field in the sample solution vial is much greater than that inside the capillary. The result is sample anions rapidly migrating to the capillary tip and "stacking" at this capillary/sample solution interface until the anion zone conductivity matches that of the running buffer inside the capillary (13).

An additional advantage of anion "stacking" is focusing of the analyte anions into very narrow bands, resulting in excellent separations (i.e. efficiencies). The use of a relatively slowly-migrating alkyl sulfonate in the sample solution creates an isotachophoretic effect at the capillary/sample solution junction and contributes to maximizing the "stacking" of the solute anions at the capillary tip. This isotachophoretic effect causes the fast migrating solute anions to move from the relatively slow alkyl sulfonate anion in the sample solution to an area of anions of similar mobility (running buffer inside the capillary). The addition of the alkyl sulfonate also serves to stabilize the sample matrix conductivity (14). All of these above factors contribute to achieving ppb sensitivity of chloride, sulfate, nitrate, and phosphate.

Linearity over working range and recovery

Plots of peak area ($n \geq 3$) vs anion concentration (anion standards in water) were linear ($r > 0.990$) over the range 3.125 - 25 ppb. A typical electropherogram for a 25 ppb anion standard (chloride, sulfate, nitrate, and phosphate) is shown in Figure 1. Chloride, sulfate, and nitrate (in order) elute in < 3 minutes. Nitrite, if detectable, elutes between sulfate and nitrate. Phosphate is later eluting (4.3 min). This represents one-third the typical analysis time for determination of these four anions by ion chromatography (ca. 15 minutes).

Samples of NMP #1, NMP #2 and BLO (1:20 dilution) were spiked with 12.5 ppb of the four anions. Recovery was calculated using the calibration data obtained above for the anion standards in water. Recovery values were very erratic (31% to 220%). Apparently, at a 5% aqueous solution of NMP or BLO, there is a sufficient matrix effect on the electromigration injection. Because of this, the method of standard additions was used to determine the level of the four anions in the NMP and BLO samples.

A matrix effect was also observed when samples were diluted 1:5 and 1:10 with heptanesulfonate and analyzed for anions by standard additions. Precision was very poor and the

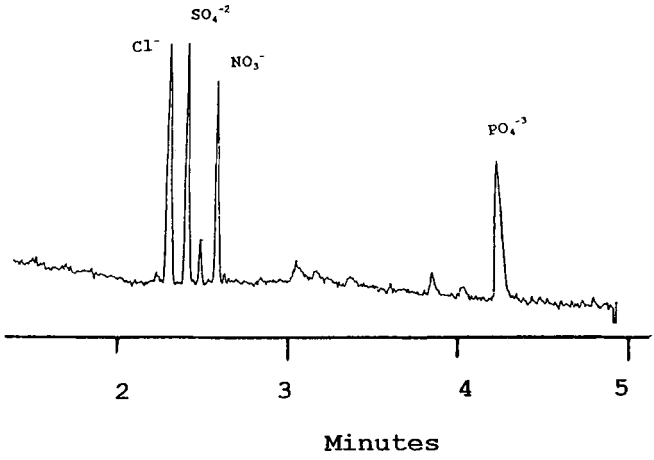

FIGURE 1. Electropherogram of 25 ppb Cl^-, SO_4^{-2}, NO_3, and PO_4^{-3}. Conditions in text.

usually excellent resolution, selectivity and efficiency of CE was badly compromised. For example, single anion peaks were split, peaks were assymetrical and not reproducible. Lack of homogeneity of the sample is a possible factor, however, we found that to sufficiently mix the sample prepared in the sample vial risked contamination.

Determination of anions in NMP and BLO

Figures 2 and 3 are electropherograms for BLO (1:20 dilution) and for BLO (1:20 dilution) spiked with 6.25 ppb of the anions, respectively. In Figure 3, only traces of chloride and sulfate are detected in BLO (1:20 dilution). The large, split peak at ca. 4 minutes could be from the hydrolysis of BLO to hydroxybutyric acid. In Figure 3, spiking with 6.25 ppb of the four anions yields sharp, easily detected peaks.

Figures 4 and 5 are electropherograms for NMP #2 (1:20 dilution) and for NMP #2 (1:20 dilution) spiked with 25 ppb of the anions, respectively. A large sulfate content of sample NMP

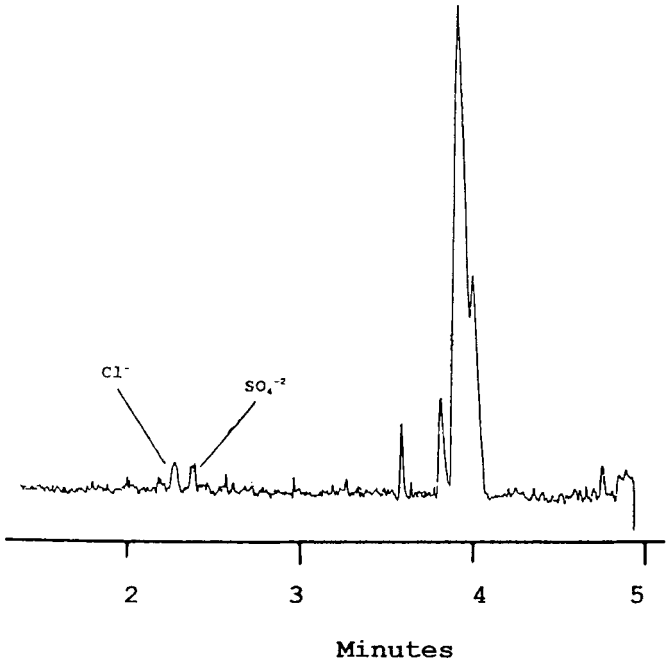

FIGURE 2. Electropherogram of BLO (1:20 dilution with 50 μM 1- heptanesulfonate). Conditions in text.

#2 is seen in Figure 4. Sample NMP #2 represents an experimental sample which was subjected to additional process treatment, resulting in elevated levels of sulfate. There are small peaks due to chloride and nitrate (second of the three small peaks following sulfate), and no detectable phosphate. The two peaks between 4.1 and 4.3 minutes are unknown. The resultant electropherogram from spiking with 25 ppb of the four anions is shown in Figure 5. As stated above, attempts at recovery studies, e.g. of the sulfate spike, produced erratic results.

Standard additions curves of **peak area** ($n \geq 3$) vs **ppb anion added** (0, 6.25, 12.5, and 25 ppb added) were plotted for one sample of BLO and two samples of NMP. The concentrations

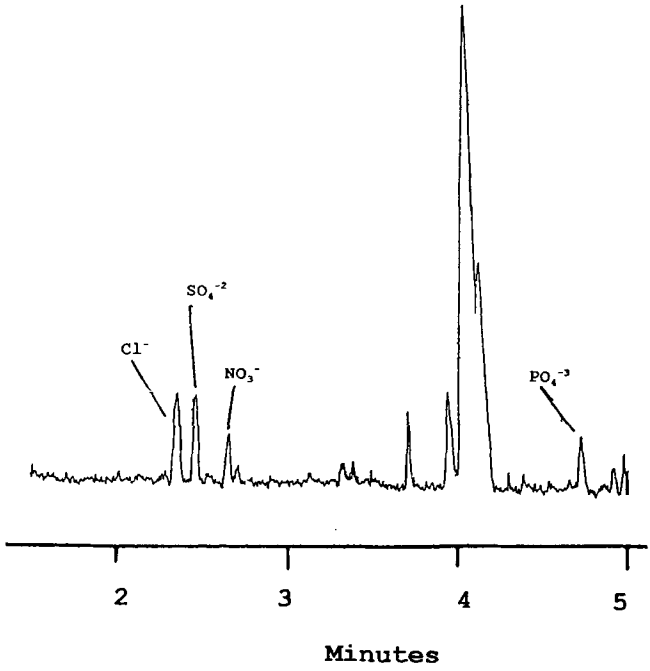

FIGURE 3. Electropherogram of BLO (1:20 dilution with 50 μM 1-heptanesulfonate) spiked with 6 ppb Cl^-, SO_4^{-2}, NO_3^-, and PO_4^{-3}. Conditions in text.

of the four anions of interest found in the solvent samples from the x-intercept (correcting for 1:20 dilution) are summarized in Table 1.

The BLO sample contains < 100 ppb of chloride and sulfate and undetectable (< 40 ppb) nitrate and phosphate. The two NMP samples contain < 100 ppb chloride (89 and 68 ppb) and < 120 ppb nitrate (80 and 116 ppb). These quantified levels are well below the maximum levels of 300 and 400 ppb for chloride and nitrate, respectively, recommended by SEMI (1). Based on the sensitivity of the standard additions curves, a detection limit of 2 ppb for each of the anions in the diluted (1:20) samples of NMP and BLO was achieved. This gives a detection limit of 40 ppb of each of the anions in the undiluted solvent samples.

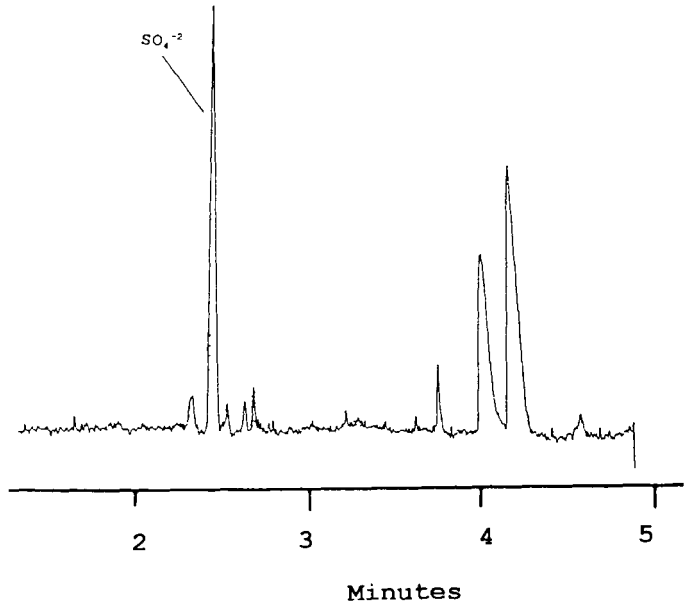

FIGURE 4. Electropherogram of NMP #2 (1:20 dilution with 50 μM 1-heptanesulfonate). Conditions in text.

Precision

Because of the extremely low levels of anions being analyzed and the fact that the method of injection maximized "stacking" of anions at the injection tip of the capillary, only one injection per sample vial was made. Better precision was observed by this method than by multiple injections from a single sample vial.

The precision of the **retention times**, t_r, for the four anions of interest obtained by running the aqueous anion standards (three runs each of 3.125, 6.25, 12.5, and 25 ppb) is summarized in Table 2.

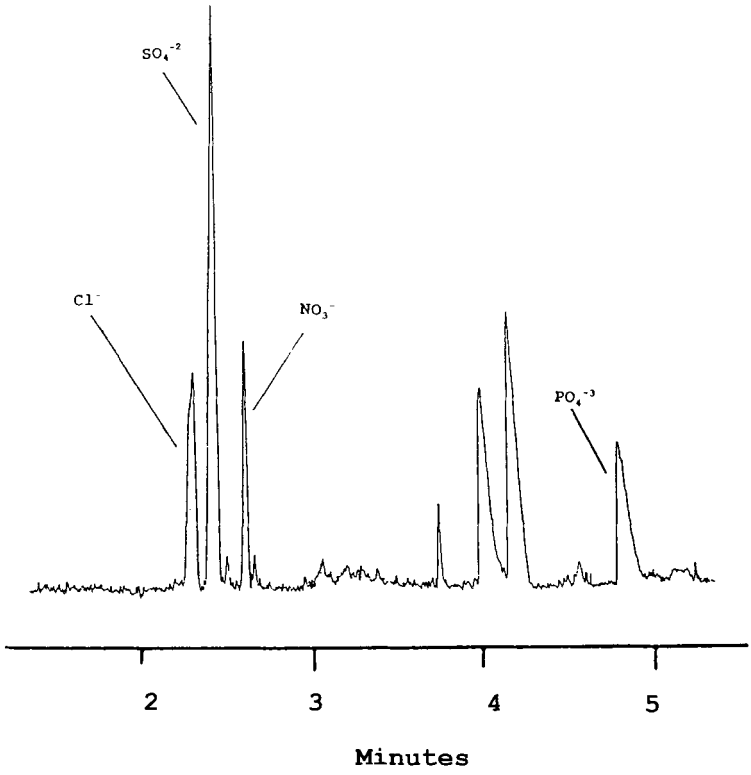

FIGURE 5. Electropherogram of NMP #2 (1:20 dilution with 50 μM 1-heptanesulfonate) spiked with 25 ppb Cl^-, SO_4^{-2}, NO_3^-, and PO_4^{-3}. Conditions in text.

The precision of the peak area for a standard additions sample was investigated. Five injections of BLO sample (1:20 dilution) spiked with 12.5 ppb of the four anions were made. The precision of the five injections is summarized in Table 3.

Efficiency and Resolution

Using $N_{eff} = 16\ (t_r/W_b)^2$ to calculate peak efficiencies, theoretical plates of 100,000 - 200,000 were obtained for sample runs. The resolution, R_s , of the three *early eluting peaks*,

observed in HPLC [1]. Consequently, good separation of SSS and RSS diastereoisomers by HPLC was difficult to achieve.

Recently, micellar electrokinetic capillary chromatography (MECC) has been demonstrated as a highly efficient separation technique [4,5,6]. In the present study, this technique is applied to the separation of lisinopril (**1**) and its RSS diastereoisomer (**2**). More recently, the use of bile salts as surfactants in the electrolytes of MECC has proved very effective for the separation of chiral stereoisomers [7-12]. By using sodium cholate as the surfactant as well as by examining the effects of pH, organic content, and temperature of the electrolyte on resolution, an excellent separation of **1** and **2** (resolution about 2.6) was achieved. A good separation was also obtained by the use of sodium dodecyl sulphate (SDS) as a surfactant. A significant observation is that the RSS compound eluted earlier than the SSS compound when sodium cholate was used, while the elution order was reversed when SDS was used. Difference in the hydrophobic/hydrophilic nature of the micelles formed from these two surfactants is most likely the cause. To the best of our knowledge, this is the first example demonstrating the MECC separation of diastereoisomers possessing cis & trans rotamers. This study serves as an excellent model for the separation of many other important drugs possessing more than one chiral centers and having rotamers (e.g., enalapril, captopril etc.).

The separation of **1** and **2** by bile-salt MECC shows several special features as compared to the separation of planar molecules, which could be significant in the further development of bile-salt MECC. Nishi et al. [9,10] and Sepaniak et al. [11,12] observed that pH of the electrolyte and the rigidity of the solute structures are two important factors which influence the chiral separation in bile-salt MECC. It appears that the bile salts prefer a rigid, planar structure for chiral

TABLE 3

	Chloride	Sulfate	Nitrate	Phosphate
Average peak area	391359	295629	184006	223334
Standard deviation	42267	8573	17481	26130
Coeff. of variation (%)	11	3	9	12

based on the average retention times in Table 2, are given below:

Chloride/sulfate $R_s = 2.9$

Sulfate/nitrate $R_s = 6.5$

If present at detectable levels, nitrite elutes between sulfate and nitrate. Using $R_s \geq 1.5$ as indicating baseline resolution, the above values indicate excellent resolution of the first three anion peaks.

CONCLUSIONS

Capillary electrophoresis has been demonstrated as a powerful separation method for the detection of trace levels of chloride, sulfate, nitrate, and phosphate in electronic grade solvents, such as N-methyl-2-pyrrolidone (NMP). The four anions are eluted in less than 5 minutes, representing a ten minute reduction in analysis time versus ion chromatography. Using standard additions and an electrokinetic injection method which maximizes sample loading and sensitivity, lower detection limits of 40 ppb of the four anions in undiluted NMP and γ-butyrolactone (BLO) are achieved. This level is well below the recommended levels established by Semiconductor Equipment and Materials International (SEMI).

ACKNOWLEDGEMENTS

Support of this work and permission to publish by International Specialty Products is gratefully acknowledged.

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Received: April 17, 1993
Accepted: May 19, 1993