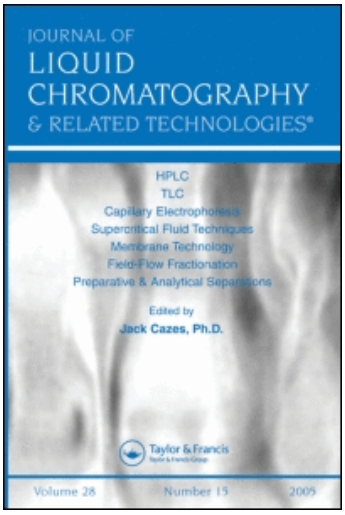

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Development of a Sensitive Indirect Chromatographic Method to Characterize Iodine Monochloride

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DEVELOPMENT OF A SENSITIVE INDIRECT CHROMATOGRAPHIC METHOD TO CHARACTERIZE IODINE MONOCHLORIDE

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ABSTRACT

A highly specific indirect method for the analysis of iodinemonochloride (ICl) has been developed to assess the potential for minor chlorination side reactions when using ICl to iodinate an aniline derivative. The technique offers great advantages over the non-specific thiosulfate titrimetric method commonly used to characterize ICl and differentiates samples previously thought to be identical. The method described in this paper uses a simple and rapid "bench top" analytical laboratory version of the formal iodination reaction as a pre-HPLC sample

derivatization, followed by detection of the chlorinated aniline analogues. The derivatization method mimics the ability of the formal reaction to predict the chlorination potential of ICl samples with varying levels of excess chlorine. The principles used for this specific application should be suitable for related iodination reactions as long as a suitable laboratory derivatization reaction can be developed.

INTRODUCTION

Many quantitative methods are available for the determination of iodine species. Atomic spectroscopy and indirect titrations based on iodometric process which liberate iodine are well documented common techniques.[1, 2] Numerous reports of the use of ion chromatography to determine halogen anions, including iodide, in environmental / biological matrices have been published recently, with various detection schemes employed such as amperometry,[3] post-column reaction,[4] coulometry,[5] and indirect photometric detection[6] to name a few. However, far fewer reports of chromatographic or titrimetric means of determining iodine have been published. A microtitration based on the fluorescence quenching of binaphthyl amphiphiles for trace iodine has been proposed.[7] After derivatization of iodine to 4-iodo-2,6-methylphenol, gas chromatography has been coupled with mass spectrometry (selected-ion monitoring) to determine iodine in drinking water.[8] Iodine was extracted from incinerated food samples and chromatographed on an ion-exchange resin with electrochemical detection.[9] Trace iodine species were determined spectrophotometrically after separation as iodide on a reversed phase column and post-column reaction.[10] In this approach, iodine catalyzes the redox reaction between cerium (IV) in the post column reagent stream and arsenic (III) in the mobile phase. Quantitation of iodine was made indirectly by measuring the fluorescence of the cerium (III) product at 350 nm.

Iodinemonochloride (ICl) has been widely used as an iodinating reagent for aromatic compounds for decades. It is formed via the reaction of iodine and chlorine and is commerically available as a neat liquid or as a solution in aqueous or organic solvents, such as dichloromethane. Aqueous ICl reagent is prepared in the presence of chloride ions (NaCl or HCl) as a solution stabilizer.

$$I_2 + Cl_2 \longleftrightarrow 2\,I^+Cl^- \qquad (1)$$

Reports of iodination procedures which incorporate ICl have been published for phenols,[11-13] (poly)methylbenzenes and (poly)methoxy-

benzenes,[14-17] haloaromatics,[15,18] polyaromatics,[17,19] cyclic tryptophans,[20] and anilines.[14, 21-22] Often, polar solvents are used to promote a reaction mechanism of heterolytic cleavage of ICl, followed by subsequent electrophilic attack of the resulting iodine cations on the aromatic ring system.[12,23] Based upon electronegativities, iodination is the predominant reaction anticipated with an aromatic ring. However, there have been published reports of ring chlorination, especially in solvents of lower dielectric constant such as carbon tetrachloride (CCl_4).[14,24] The chlorination reaction has been attributed to electrophilic substitution by chlorine cations which are generated via homolytic cleavage of ICl to form the trichloroiodine interhalogen compound [ICl_2^- Cl^+].[12,18,23]

$$ICl + Cl_2 \longleftrightarrow ICl_2^-Cl^+ \qquad (2)$$

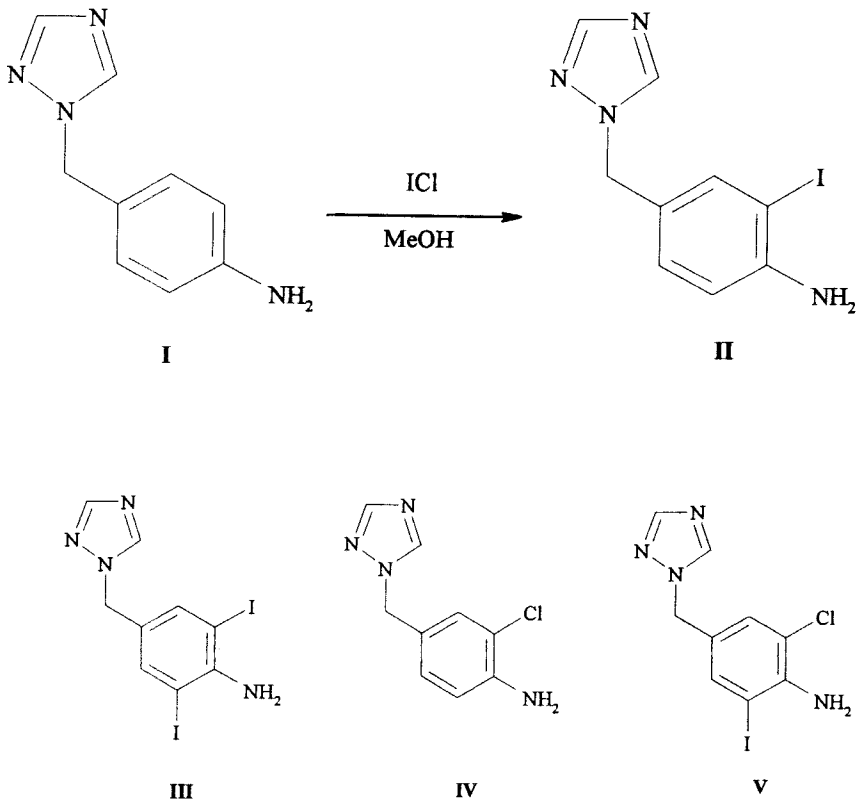
Such an interhalogen iodine compound may also result from a defICIt of iodine relative to chlorine during the manufacturing process.

ICl is soluble in aqueous solutions of NaCl and HCl at concentrations up to approximately 5.5 M; excess iodine levels will result in the precipitation of solid iodine. Aqueous ICl solutions are a deep bromine red color at this concentration, but appear as orange solutions at lower molarities (approximately 3.5 M).[25] Decomposition in aqueous media will produce insoluble I_2 and I_2O_5, which will float on the solution surface:

$$10\ ICl + 5H_2O \longrightarrow 10\ HCl + 4\ I_2\ (s) + I_2O_5\ (s) \qquad (3)$$

Aqueous 5.0 - 5.5 M ICl stabilized by NaCl and HCl (and identified in this paper as ICl) was used to selectively iodinate an aromatic intermediate **I** at the 3-position of the aniline ring system to form intermediate **II** as seen in Scheme 1.[26-27] Compound **III** is an impurity which results from an unavoidable side reaction with the aromatic ring, which proceeds with an initial rate constant that is approximately 3.5 times slower than that of the main reaction.[27]

An effort was made to identify the cause of chlorination in this reaction system to minimize the formation of the undesired chloroderivatives **IV** and **V**. It is apparent from the literature, as described above, that chlorination of **I** should proceed in a solvent of low dielectric constant primarily through the presence of excess chlorine (Equation 2). It, therefore, follows that the quality of the ICl reagent, especially with respect to excess chlorine (iodine undercharge), is the key parameter which controls formation of **IV** and **V** in polar solvent.



Scheme 1. Formal reaction of intermediate I and ICl to form intermediate II, as well as potential impurities III, IV, and V.

Common wet chemical and qualitative analytical techniques for ICl analysis were found to be inadequately selective and sensitive for the determination of undercharge of iodine (or excess chlorine) at the levels required in this application. This paper describes the development of a new indirect technique for ICl analysis in which a large excess of **I** was rapidly derivatized in a polar solvent with ICl (simulating the reaction selectivity) and the product was analyzed by reversed phase HPLC for chlorination products. This approach provides a tool for iodine undercharge (chlorine excess) analysis in ICl with the selectivity and sensitivity of chromatography, and as such, serves as an accurate predictor of the reaction performance of ICl. While the technique is illustrated for this application, it is believed to be applicable to the iodination of substituted anilines in general.

EXPERIMENTAL

Materials Used

Samples of ICl reagent were obtained for testing from Deepwater Iodides (Woodward, OK; 5.1 M; sample 1), Ajay Chemicals (Powder Springs, Georgia; 5.5 M; samples 2 and 3) and DSM Andeno (Baton Rouge, LA; 3.6 M; sample 4). The Ajay and Deepwater solutions were reported to contain 2 wt% HCl and 10 wt% sodium chloride, while the DSM material was reported to contain 13 wt% HCl and 0 wt% NaCl by the respective manufacturers. Sodium thiosulfate pentahydrate (0.1N standard solution), 1% (w/v) starch solution, and citric acid were purchased from Aldrich (Milwaukee, WI).

Development of an HPLC Procedure

An HPLC system consisting of Shimadzu components was used, which included an SIL-10A autoinjector, SCL-10A system controller, LC-10AS gradient pumps, and SPD-10AV UV/VIS detector. The reversed phase HPLC procedure developed to monitor the reaction that forms **II** was also used to evaluate the results of the ICl derivatization procedure. A Zorbax RX C8 column (25 cm x 4.6mm i.d., 5 μm particles) was used with a 5 mM aqueous KH_2PO_4 / acetonitrile mobile phase gradient from 20 to 80% acetonitrile over 15 minutes at ambient column temperature. Detection was performed with a ultraviolet detector at 226 nm. Method flow rate was set at 1.0 mL/min.

Common Techniques for Analysis of ICl

Samples of ICl were characterized by the following common wet chemical and qualitative tests: solution appearance (color and presence of particulates), the USP test for the presence of chloride anion, solution pH to confirm the presence of HCl solution stabilizer, and thiosulfate titration to verify titer and the presence of iodine. The titration is performed as follows. A sample of aqueous ICl is diluted 100 fold in 0.5 N HCl , then diluted 5 fold more in deionized water. To this solution, 1 g of KI is added with vigorous stirring until the KI is completely dissolved. Titration with standardized thiosulfate is immediately commenced until the ICl solution turned pale yellow. At this point, 1 mL of 1% (w/v) starch solution is added to produce an intense dark purple color. Dropwise, thiosulfate addition is continued until the ICl solution returns to a clear color and remains clear for approximately thirty seconds.

Icl Treatment Procedures

Two procedures were used in this work to effect the formation and/or disappearance of free chlorine in samples of ICl reagent as a means of demonstrating the sensitivity of the new analytical test for ICl in detecting slight changes in the ICl. The changes brought about by both of these procedures was found to produce ICl of similar quality as that received from the vendors listed in this paper. Excess chlorine gas was bubbled through ICl sample 2, producing an ICl sample containing 1 wt% chlorine. This sample was termed ICl sample 5. It is known that sufficient exposure of ICl to solid iodine eliminates the free chlorine in ICl. Studies were performed to determine that the addition of 2 wt% iodine to ICl at room temperature, followed by at least 4 hrs of agitation and then filtration, was adequate to remove the excess chlorine in sample 3 ICl (as measured by the detection of **IV**) to undetectable levels by HPLC. Addition of 8 wt% iodine was necessary to remove excess chlorine from sample 4 ICl.

Development of a Lab Derivatization Procedure for the HPLC Analysis of ICl

A simple and rapid laboratory derivatization procedure was developed to mimic the reaction which forms **II** (Scheme 1). In the formal reaction, **I** is nearly consumed upon completion of the ICl addition at sub-ambient temperature.[27] However, the derivatization procedure was developed with two significant changes to further ensure that the reaction would instantaneously be driven to **II**. First, an approximate 30% molar excess of **I** relative to ICl was used to accelerate the reaction kinetics (the reaction is pseudo-first order in **I**) and second, the procedure was performed at ambient temperature. The excess of **I** used results in a significant amount of residual **I** in the derivatization reaction solution which is analyzed by HPLC. For this reason, the chromatographic peak for **I** is not included in the computation of results for any of the derivatization experiments.

The derivatization procedure developed is as follows: approximately 500 mg of **I** and 100 mg of citric acid (pH buffer) were combined in a 50 mL Erlenmeyer flask and dissolved in 20 mL of HPLC grade methanol by gently swirling the flask and its contents. A 200 mL aliquot of ICl was quickly added to the flask and the solution was swirled for 2 min to ensure the reaction was completed. The reaction was then quenched with 100 mL of 40 wt% sodium thiosulfate solution while briefly swirling the reaction mixture. Finally, the reaction mixture is diluted 75x in HPLC grade methanol and analyzed by HPLC.

Table 1

Results of Common Tests for the Analysis of ICl

Test	ICl Sample 1	ICl Sample 2	ICl Sample 3	ICl Sample 4
Identity				
Iodine Chloride	Positive Positive	Positive Positive	Positive Positive	Positive Positive
Thiosulfate Titration	4.04 M	5.51 M	5.46 M	3.60 M
pH	≈0	≈0	≈0	≈0
Appearance	Deep black liquid, free of particulates	Deep black liquid, free of particulates	Deep black liquid, free of particulates	Deep black liquid, free of particulates

RESULTS AND DISCUSSION

Summary of Results from the Analysis of ICl Using Common Techniques

Analytical results using the common techniques for the different samples of ICl used in this work are shown in Table 1. The table includes data for the ICl samples as they were received from the vendor. There is no discernable difference between samples 1 through 3 based upon this set of tests; sample 4 was orange in color and of much lower molarity as per manufacturer's specifications.

However, if the performance of ICl in the formal reaction in question (Scheme 1) is used to compare these samples, significant differences are noticed in the HPLC chromatogram of isolated **II**. Figure 1 shows the impurity profile of compound **II** made using ICl samples 2, 3 and 4.

Under identical reaction conditions, all of the samples listed in Table 1 produce < 3 A% compound **III**. Production of **III** is minimized in the reaction via equimolar charges of compound **I** and ICl, as well as careful control of reaction pH.[26]

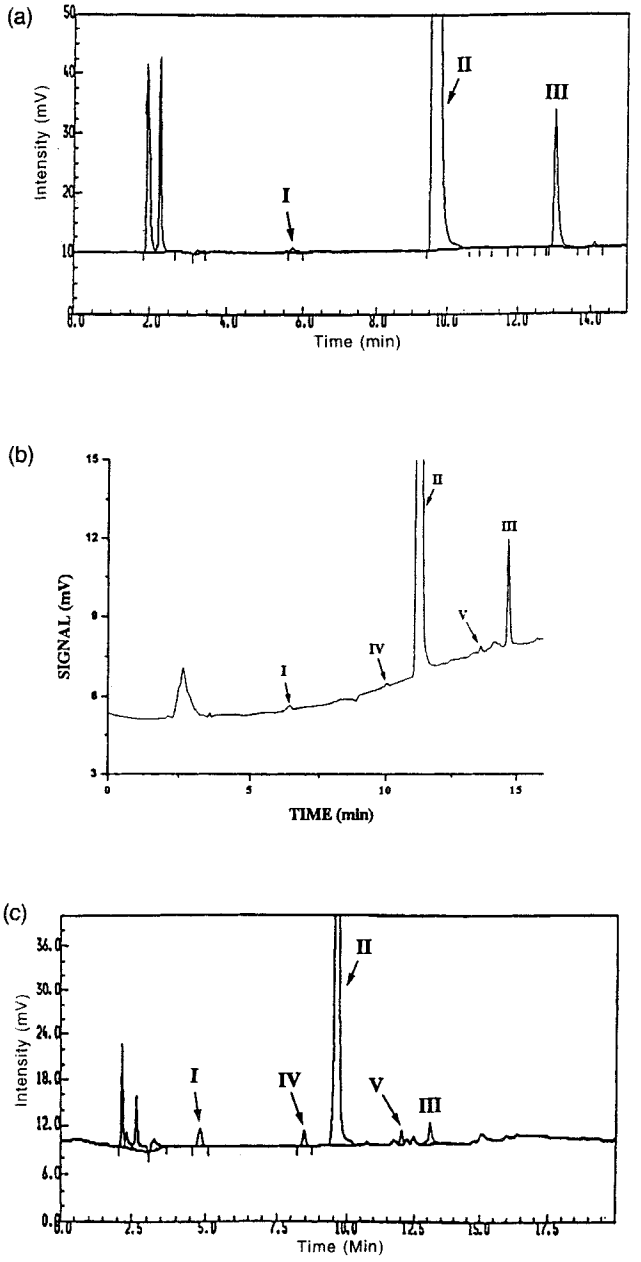


Figure 1. Comparison of impurity profiles of II made via formal reaction with a) ICl sample 2; b) ICl sample 3; and c) ICl sample 4.

While all of the reactions in Table 1 produce some **III**, only samples 3 and 4 produce **IV** and **V** at detectable levels (both impurities were < 0.1% for ICl sample 3 and ≥ 0.5 % for ICl sample 4). The identities of **IV** and **V** were verified by spiking authentic samples of **IV** and **V** into the solutions of **II** used for the chromatographic analysis.

It was postulated that excess chlorine (iodine defICIt) in ICl samples 3 and 4 was responsible for the appearance of **IV** and **V** in the reactions performed. To confirm this, ICl sample 5 (containing 1 wt% chlorine) was used in the reaction described in Scheme 1. It was noted that ICl sample 5 was a dark orange color, similar in appearance to ICl sample 4 (Table 1).[28] Isolated **II** from this reaction was found to contain ≥ 0.3 A% each of both **IV** and **V**, simulating the HPLC results of the reaction with ICl sample 4. This confirms that excess chlorine in the ICl raw material is responsible for the unwanted chlorination observed with samples 3 and 4 ICl. Further, it follows that sample 3 ICl contains less excess chlorine than ICl samples 4 and 5 from the ICl solution appearance and reaction performance. However, solution appearance is not a very sensitive analytical technique and only shows utility for samples with significant chlorine excess, such as ICl samples 4 and 5. For ICl samples with lower chlorine content (smaller iodine defICIt) such as sample 3 ICl, a more sensitive technique for evaluating ICl raw material and predicting reaction performance prior to use had to be developed.

Derivatization Procedure for the Analysis of ICl

The only available method that was adequately sensitive and specific enough to predict the reaction performance of all types of ICl was a formal reaction of the ICl and **I**, followed by HPLC analysis of the reaction product **II**. While this procedure worked, it was very cumbersome for an analytical raw materials laboratory to perform as a routine evaluation of a raw material. Based on this, a simple and rapid "bench-top" version of the formal reaction was developed as described in the experimental section for analyzing ICl.

With this "bench top" procedure, which includes the derivatization of **I** with ICl as a means of analyzing the ICl for chlorination potential, the sensitivity and selectivity of the full formal reaction is maintained while making the test amenable to routine testing in a raw materials evaluation laboratory. In the following discussion, this test is demonstrated with (i) samples of ICl as received from the vendor and (ii) samples of ICl that have been altered via exposure to solid iodine.

Table 2

Comparitive HPLC Results from Samples of II Produced by Formal Reactions and by the Derivatization Procedure

	Formal Reaction		Derivatization Solution	
	A% of IV	A% of V	A% of IV	A% of V
ICl Sample 2	n.d.	n.d.	n.d.	n.d.
ICl Sample 3	0.01	0.03	0.14	0.04
ICl Sample with added iodine	n.d.	n.d.	n.d.	n.d.
ICl Sample 4	0.65	0.50	0.70	0.14
ICl Sample 4 with added iodine	n.d.	n.d.	n.d.	n.d.

Both the derivatization procedure and formal reaction, followed by HPLC analysis, were completed on ICl samples 2, 3, and 4 and the results are summarized in Table 2. The results of both experiments agree in terms of detectability of impurities **IV** and **V** for all ICl samples considered, indicating that the derivatization procedure mimics the results of the formal reaction in this respect. However, due to differences in the reaction and isolation conditions used for the two sample preparation techniques, the levels of **IV** and **V** differ for ICl samples 3 and 4. Therefore, the derivatization test will be used to identify ICl samples with excess chlorine, but not to quantitate the actual amount of excess chlorine via **IV** or **V** that one would expect from a formal reaction. Further, ICl samples 3 and 4 were treated with solid iodine in the manner described in the experimental section to quench the excess chlorine, then were derivatized and chromatographed and the results are also summarized in Table 2.

Once again, the results from the derivatization samples agree with those obtained from the formal reaction samples. This indicates that the derivatization procedure is adequately sensitive to accurately differentiate ICl samples which have chlorine excesses that generate $\leq 0.1\%$ of **IV** and **V**. This represents an improvement over the thiosulfate titration, which was found to have a method precision of 0.1% RSD at the 5 M level, or the same order of magnitude as the estimated excess of chlorine (iodine deficit) in ICl sample 3.[31] Representative chromatograms of the derivatization reaction solution of ICl sample 3 before and after iodine addition are found in Figure 2.

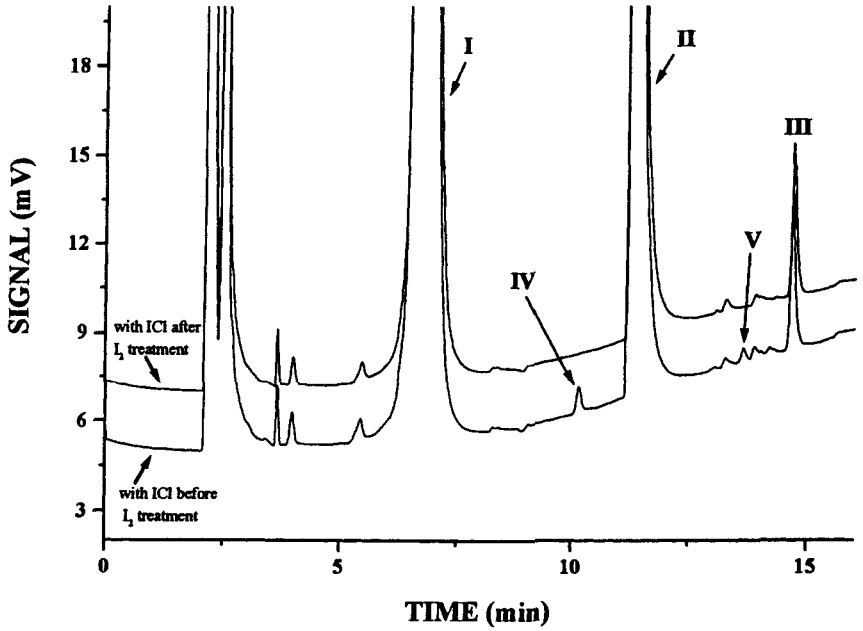


Figure 2. Comparison of impurity profiles of the derivatization solution made with ICl sample 3 before and after iodine treatment.

It is anticipated from the kinetics of the main reaction that **IV** is the predominant chlorination side product of the derivatization reaction, since formation of **II** is greatly favored over **III**. Further, **IV** elutes in a portion of the chromatogram (Figure 2) in which there are no chromatographic interferences from the sample matrix, while **V** elutes near several matrix components. This facilitates routine and unambiguous detection of **IV** by HPLC retention time. For these reasons, detectability of **IV** in the derivatized solution was selected as the marker for ICl quality evaluation and **V** will no longer be discussed.

Validation of the HPLC and Derivatization Methods

The capabilities of the derivatization procedure / HPLC method combination were validated to a level appropriate for the application in accordance with International Conference on Harmonization (ICH) guidelines.[29,30] In addition to the demonstrated method specificity for the compounds of interest (**I**, **II**, **III**, **IV**, and **V**), the chromatographic method was

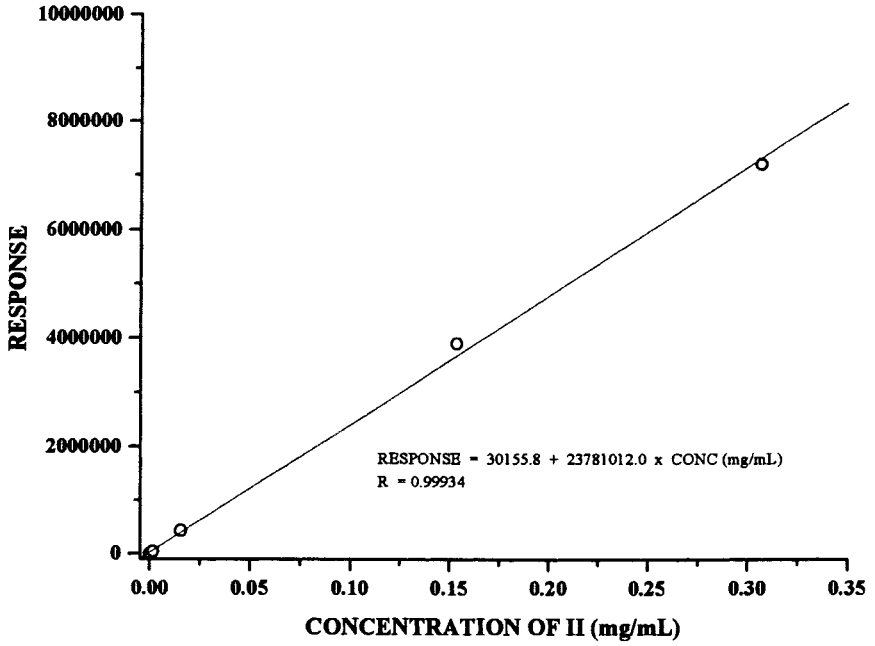


Figure 3. Linearity of the chromatographic method for compound II.

determined to be linear for serial dilutions of **II** in methanol over the concentration range of 0.3066 mg/mL to 3.066E-5 mg/mL, or 200% to 0.02% of the method target concentration of 0.15 mg/mL (R = 0.99934) (Figure 3). The injection precision of **II** was determined from six replicate injections of a single 0.15 mg/mL preparation to be 0.4% RSD.

The method reproducibility for multiple preparations of the derivatization reaction using samples 3 and 2 ICl are provided in Tables 3 and 4, respectively. These experiments represent the worst case scenario for evaluating ICl - the chlorine excess in ICl is small enough to produce levels of **IV** near the method LOD / LOQ. The results for the experiments in Table 3 are all interpreted as "unacceptable ICl" since impurity **IV** was consistently detected. The reproducibilities of quantitation of impurity **IV** for preparations 1 and 2 of **II** were 28.9 % and < 0.1 % RSD, respectively, at the 0.1 % level and the overall reproducibility was 26.1% RSD.

Table 3

Derivatization/HPLC Procedure Reproducibility for Sample 3 ICl

	II	III	IV	Evaluation of ICl
Sample 3 - Preparation 1	99.40	0.48	0.08	unacceptable ICl
Analyst 1	99.34	0.48	0.14	unacceptable ICl
	99.34	0.48	0.14	unacceptable ICl
% RSD - Preparation 1	<0.1%	<0.1%	28.9	
Sample 3 - Preparation 2	99.63	0.19	0.09	unacceptable ICl
Analyst 2	99.62	0.21	0.09	unacceptable ICl
	99.61	0.21	0.09	unacceptable ICl
% RSD - Preparation 2	<0.1%	5.7 %	<0.1%	
% RSD-Overall	0.1%	44.4%	26.1%	

Table 4

Derivatization/HPLC Procedure Reproducibility for Sample 2 ICl

	II	III	IV	Evaluation of ICl
Sample 2 - Preparation 1	99.40	0.60	n.d.	acceptable ICl
Analyst 1	99.38	0.62	n.d.	acceptable ICl
	99.39	0.61	n.d.	acceptable ICl
% RSD - Preparation 1	<0.1%	1.6%	n/a	
Sample 2 - Preparation 2	99.66	0.34	n.d.	acceptable ICl
Analyst 1	99.71	0.29	n.d.	acceptable ICl
	99.71	0.29	n.d.	acceptable ICl
% RSD - Preparation 2	<0.1%	9.4%	n/a	
% RSD - Overall	0.2%	36.4%	n/a	

These results from two different analysts demonstrate that ICl sample 3 will consistently generate both detectable and quantitatable levels of **IV**, suggesting that both the derivatization procedure and HPLC analysis are acceptably robust.

The results in Table 4 obtained from experiments with ICl sample 2 once again demonstrate the reproducibility and robustness of the method for two preparations of an "acceptable ICl" sample. The experimental variability observed in the levels of **III** for the derivatization samples is similar to that observed for numerous formal reactions to **II**, and is therefore not due to errors associated with the HPLC or derivatization methods.[31]

The HPLC method limit of detection (LOD) for **IV** was determined as the lowest concentration for which the signal to noise ratio $\geq$ 3:1, which occurred at 0.01% for a formal reaction sample in Table 2 and 0.08% for an injection of the derivatization solution sample in Table 3. No additional chromatographic interferences with **IV** were observed for derivatization samples vs. formal reaction samples (Figures 1 and 2), hence it is believed 0.01% **IV** would also be detectable in derivatization solutions. The limit of quantitation (LOQ) for **IV** was estimated as 3.3 x LOD or 0.03%. The concentration range of **II** in the derivatization preparation over which **IV** remained detectable (method range) was 300 % to 38% of that described in the experimental section. System suitability requirements include baseline resolution ($R \geq 2.0$) of **II**, **III**, and **IV** and detection of a 0.1% spike of **IV** into a methanolic solution of **II**.

CONCLUSIONS

Trace levels of excess chlorine (iodine deficit) in ICl produce minor, but undesired, chlorination side products **IV** and **V** during the iodination of aromatic aniline compound **II**. Direct means of analysis of ICl raw material are not capable of reproducibly detecting either trace levels of chlorine excess or trace iodine deficits, and as such can not be used as a predictive tool for evaluating ICl raw material prior to use in this type of reaction. To better characterize ICl, an indirect means of assessing the quality of the material has been developed to differentiate ICl samples.

The method described in this paper uses a "bench top" laboratory version of the synthetic reaction in question, followed by HPLC. This new technique was demonstrated to be both adequately specific and sensitive for the application described, while remaining simple and rapid enough to serve as a routine derivatization procedure for an analytical raw materials testing laboratory. The derivatization method was demonstrated to reproducibly identify ICl samples with levels of excess chlorine (iodine deficit) which produce as little as 0.1% of **IV**. The ability to determine the chlorination potential of ICl as a raw materials screening test gives one the option to remediate the raw material before use, thus avoiding removal of various

chlorinated impurities downstream which may be less desirable. The principles used for this specific application should be suitable for related iodination reactions so as long as a suitable laboratory derivatization reaction can be developed.

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REFERENCES

1. S. D. Ingle, S. R. Crouch, **Spectrochemical Analysis**, Prentice Hall, Englewood Cliffs, NJ, 1988, Chapter 8.

2. D. G. Peters, J. M. Hayes, G. M. Hieftje, **Chemical Separations and Measurements: Theory and Practice of Analytical Chemistry**, W.B. Saunders Company, Philadelphia, PA, 1974, Chapter 10.

3. G. A. Sacchetto, G. Favaro, P. Pastore, M. Fiorani, Anal. Chim. Acta, **294 (3)**, 251-260 (1994).

4. A. C. M. Brandao, W. W. Buchberger, E. C. V. Bulter, P. A. Fagan, P. R. Haddad, J. Chromaogr. A, **706 (1-2)**, 271-275 (1995).

5. F. Moussa, M. C. Rauxdemay, F. Veinberg, F. DePasse, R. Gharbi, J. Y. Hautem, J. Chromatogr. B, **667 (1)**, 69-74 (1995).

6. S. Wilson, E. Yeung, Anal. Chim. Acta, **157**, 53-60 (1984).

7. B. Juskowiak, E. Galezowska, Chemia Analityczna, **40 (6)**, 971-977 (1995).

8. H. S. Shin, Y. S. O. Shin, J. H. Kim, J. K. Ryu, J. Chromatogr. A, **732**, 327-333 (1996).

9. H. Kuwahira, Y. Asai, J. Food Hygienic Society of Japan, **35 (3)**, 253-257 (1994).

10. H. Yamada, S. Kajiyama, K. Yonebayashi, Bunseki Kagaku, **44 (12)**, 1027-1032, (1995).

11. G. H. Woolet, W. W. Johnson, **Organic Syntheses (Coll. Vol. 2)**, Wiley, New York, New York, 1943, page 343.

12. F. W. Bennett, A. G. Sharpe, J. Chem. Soc., **284**, 1383-1384 (1950).

13. D. Papa, H. F. Ginsberg, I. Lederman, V. DeCamp, J. Am. Chem. Soc., **75**, 1107 (1953).

14. L. J. Lambourne, P. W. Robertson, J. Chem. Soc., **217**, 1167-1168 (1947).

15. R. M. Keefer, L. J. Andrews, J. Chem. Soc., **72**, 5170 (1950).

16. L. J. Andrews, R. M. Keefer, J. Chem. Soc., **79**, 1412 (1957).

17. B. Jones and E.N. Richardson, J. Chem. Soc., **146**, 713-715 (1953).

18. G. Olah, A. Pavlath, G. Varsanyi, J. Chem. Soc., **79**, 1823 (1957).

19. D. E. Turner, R. F. O'Malley, D. J. Sardella, L. S. Barinelli, P. Kaul, J. Org. Chem., **59**, 7335-7340 (1994).

20. D. E. Zembower, M. M. Ames, Synthesis, **12,** 1433-1436 (1994).

21. R. B. Sandin, W. V. Drake, F. Leger, **Organic Syntheses (Coll. Vol. 2)**, Wiley, New York, New York, 1943, page 196.

22. E. Berliner, J. Am. Chem. Soc., **78**, 3632-3637 (1956).

23. C. W. McCleland, J. S. Pizey editor, **Synthetic Reagents (Vol. 5)**, Wiley, New York, New York, 1983, pages 86-164.

24. R. M. Keefer, L. J. Andrews, J. Org. Chem., **31**, 541-544 (1966).

25. Laboratory observation made of a 3.6 M iodinemonochloride in aqueous HCl solution purchased from DSM Andeno.

26. C. Y. Chen, D. R. Lieberman, R. D. Larsen, R. A. Reamer, T. R. Verhoeven, P. J. Reider, I. F. Cottrell, G. Houghton, Tet. Lett., **35 (38)**, 6981-6984 (1994).

27. Merck and Co., Department of Chemical Engineering, 1997, Unpublished results.

28. Merck and Co., Developmental Laboratories, 1997, Unpublished results.

29. **ICH Harmonized Tripartite Guideline: Text on Validation of Analytical Procedures**, Guidance Q2A, March 1995.

30. **ICH Harmonized Tripartite Guideline: Validation of Analytical Procedures: Methodology**, Guidance Q2B, November 1996.

31. Merck and Co., Department of Analytical Research, 1997, Unpublished results.

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