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Development of a new approach for total isocyanate determination using the reagent 9-anthracenylmethyl 1-piperazinecarboxylate

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Diisocyanates and polyisocyanates are widely used in the manufacture of polyurethane materials and coatings. Exposure to airborne isocyanate species is known to cause respiratory disorders. Measurement of isocyanate exposure levels has traditionally involved collection and derivatization of isocyanate species in an air sample followed by reversed-phase HPLC analysis. HPLC analysis of isocyanate samples is complicated for several reasons. Air samples may contain isocyanate species of very different reversed-phase retention (*e.g.*, monomeric and polymeric isocyanates) and some species may not even be chromatographable. Also, pure analytical standards are available only for monomeric isocyanates, so non-monomeric isocyanate species are typically quantified based on the response of monomer standards, which assumes that the non-monomeric species have the same response factor as the monomer. Finally, the analysis of the raw chromatographic data containing many peaks is labor intensive. The method described here would circumvent many of the limitations of traditional methods. In this method, isocyanate species are derivatized with 9-anthracenylmethyl 1-piperazinecarboxylate (PAC) upon collection. At this point, a portion of the sample can be analyzed for individual components of interest (such as monomers) and/or a portion can be treated with a reagent that converts all PAC derivatives to a single analyte. Quantification of this analyte gives a measure of total isocyanate group. This paper examines the reactivity of PAC, the separation of PAC derivatives from excess PAC reagent, the conversion of PAC derivatives to a single analyte and the HPLC determination of this analyte and PAC derivatives of several monomeric isocyanates.

Introduction

Isocyanates are a class of chemicals widely used in the manufacture of polyurethanes, which include such diverse products as rigid foams, flexible foams, durable coatings and adhesives. Exposure to airborne monomeric isocyanates is known to cause a range of respiratory disorders in laboratory animals and humans, most notably occupational asthma.[1–5] Because respiratory disorders may develop after exposure to very low levels of isocyanates, organizations such as the National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have set the exposure standards for several of these compounds at 5 ppb time-weighted average (TWA) for full workshift and 20 ppb TWA for short-term exposure limits (STELS) or ceiling limits.[6–8]

In many workplace environments, exposure to non-monomeric isocyanate species is much greater than exposure to isocyanate monomers. Several studies have indicated that exposure to non-monomeric isocyanate species can give rise to health effects similar to those resulting from exposure to monomeric isocyanates.[9–15] Non-monomeric isocyanate species would include polyisocyanates contained in products that are used to make polyurethane material and also partially reacted isocyanate species generated during production or thermal breakdown of polyurethane. Although non-monomeric isocyanate species are typically not sufficiently volatile to give rise to significant vapor exposure, inhalation exposure can occur when these species are aerosolized through spraying or heating. Concern about the health effects of exposure to non-monomeric isocyanate species has led the UK Health and Safety Executive to create a common exposure standard encompassing all organic isocyanate species based on the number of reactive isocyanate groups (NCO) per unit volume of air. The standard was set at 20 μg NCO m^{-3} for an 8 h TWA and 70 μg NCO m^{-3} for a 10 min TWA.[16] These standards are approximately equivalent to the isocyanate group content of monomers present at 5 and 20 ppb, respectively. At present, there are no OSHA permissible exposure limits (PELs or STELs), no NIOSH recommended exposure limits (RELs) and no ACGIH threshold limit values (TLVs) for non-monomeric isocyanates. One manufacturer (Bayer) recommends a 1 mg m^{-3} STEL and a 0.5 mg m^{-3} 8 h TWA exposure limit for its polyisocyanate products.[17]

There are numerous methods that have been used in the measurement of airborne isocyanate monomers.[18–21] Very few of them are fundamentally conducive to total isocyanate determination. The Marcali method[22] is a colorimetric method developed for the measurement of isocyanate monomer, but other isocyanate species necessarily contribute to the color response. Weaknesses of the Marcali method and its modifications with respect to total isocyanate determination include its limitation to measuring aromatic isocyanates, its susceptibility to interferences, the variability of response factor with isocyanate structure and poor detection sensitivity relative to chromatographic methods. Methods based on colorimetric paper tape technology have the advantage of ease of use, but

suffer from several limitations, including poor performance with isocyanate aerosols, sensitivity to humidity, variability of response factor for different isocyanate species and poor detection sensitivity compared with chromatographic methods.

Several high-performance liquid chromatographic (HPLC) methods have been developed in recent years to measure both monomeric and non-monomeric isocyanate species.[23–36] Because polyisocyanate products are typically complex mixtures of isocyanate species, HPLC methods are difficult and have certain limitations. Isocratic analyses do not provide optimum conditions for either early-eluting monomers or late-eluting polyisocyanates. Gradient elution may provide good chromatography for both monomers and polyisocyanates, but it requires at least two mobile phase components and post-analysis re-equilibration. Even with gradient elution, there is no guarantee that all sample components will be chromatographable. Correct identification of non-monomeric isocyanate species requires either two detectors or a multi-dimensional detector (mass spectrometer or diode array), since identification by retention time can be made with confidence only when pure analytical standards are available. Accurate quantification of non-monomeric isocyanate species based on the monomer calibration curve relies on all the derivatized isocyanate species having the same detector response factor as the derivatized monomer, which, depending on the derivatizing reagent, may not be the case. Finally, although these HPLC methods provide much information to help ensure correct identification and accurate quantification of the potentially numerous species, interpretation of the chromatograms is labor intensive and requires experience.

As HPLC methods for isocyanates have evolved, there has been an attempt to mitigate these chromatographic and detection limitations by the use of elution gradients and improved derivatizing reagents. However, inherent limitations persist and interpretation remains difficult.

There are numerous polyisocyanate products in use, each frequently containing many different molecular species. Although the HPLC methods that measure non-monomeric isocyanate species quantify these species individually, in practice the useful information garnered from these analyses is the summation of all the non-monomeric species. Therefore, it would be simpler if a chromatographic method allowed the measurement of the total isocyanate group through quantification of a single peak. Still, it may be desirable to measure an individual non-monomeric species if, for instance, the toxicity of this species justifies a distinct exposure standard. It is generally desirable that the measurement of the isocyanate monomers be separate because these species are more likely to be covered by specific exposure standards.

The method described here involves derivatization of the isocyanate sample upon collection with 9-anthracenylmethyl 1-piperazinecarboxylate (PAC).[37] After removal of excess PAC reagent, the isocyanate–PAC derivatives are reacted with sodium thiomethoxide to convert them all to 9-anthracenylmethyl methyl sulfide (AMMS). This reaction sequence is shown in Fig. 1. Total isocyanate group is determined by HPLC and quantification of the single AMMS peak. This circumvents many of the disadvantages associated with the current HPLC methods. There are no problems associated with quantifying late-eluting peaks, and analysis times can be very short. A single detector can be used for quantification because a standard of the analyte exists and the retention time can be determined. Since all species are converted to a single analyte, the problem of variability of response factors among different species is averted. Finally, there are no complex chromatograms to interpret. Monomers or other individual species can be measured by analysis of the sample before the individual species are converted to AMMS. This paper describes the laboratory procedure that has been developed to determine PAC-derivatized isocyanate samples. PAC-derivatized isocyanate monomers have been used to develop and evaluate the methodology.

Experimental materials and methods

All solvents were of Burdick and Jackson HPLC grade (Baxter Healthcare, Muskegon, MI, USA). 9-Anthracenemethanol (97%), *p*-nitrophenyl chloroformate (97%), *N*,*N*-dimethylformamide (99.8%), sodium thiomethoxide (95%), phenyl isocyanate (98%), 1,6-hexamethylene diisocyanate (HDI) (98%), phosphoric acid (99.999%) and silica gel (high-purity grade, 70–230 mesh) were purchased from Aldrich (Milwaukee, WI, USA). Toluene-2,4-diisocyanate (2,4-TDI) was obtained from Sigma (St. Louis, MO, USA), 4,4′-diphenylmethane diisocyanate [MDI] from Kodak (Rochester, NY, USA), butyl isocyanate from Pfaltz and Bauer (Waterbury, CT, USA) and triethylamine (99.5%) from Pierce (Rockford, IL, USA). The solid-phase extraction (SPE) tubes were Supelclean LC Si, 3 mL (Supelco, Bellefonte, PA, USA), and the thin layer chromatographic (TLC) plates were silica gel 60 F_{254}, 20 × 20 cm (EM Science, Gibbstown, NJ, USA).

The HPLC system utilized a Waters Model M626 pump and a Waters 717 Plus autosampler (Millipore, Milford, MA, USA). The analytical column was a Waters Nova-Pak C_{18}, 150 × 3.9 mm id, 4 μm particle size (Millipore). The mobile phase consisted of 65% acetonitrile–35% 0.1 M triethylammonium phosphate buffer. The mobile phase buffer was prepared by adding triethylamine to a solution of 0.1 M phosphoric acid in HPLC-grade water until the pH reached 3.0. Detection was accomplished with a Waters 486 tunable absorbance detector (Millipore) set at 254 nm followed by an ABI Analytical Spectroflow 980 programmable fluorescence detector (Applied Biosystems, Ramsey, NJ, USA). The excitation wavelength of the fluorescence detector was set at 254 nm and the emission band was selected using a bandpass filter centered on 425 nm.

Preparation of PAC

p-Nitrophenyl chloroformate (4.89 g, 24 mmol) was dissolved in 100 mL of tetrahydrofuran (THF) and the solution was placed in a two-necked 500 mL round-bottomed flask with a magnetic stirring bar. To this was added dropwise with stirring a solution of 9-anthracenemethanol (3.36 g, 16.2 mmol) and pyridine (2.56 g, 32.4 mmol) in 100 mL of THF. The progress of the

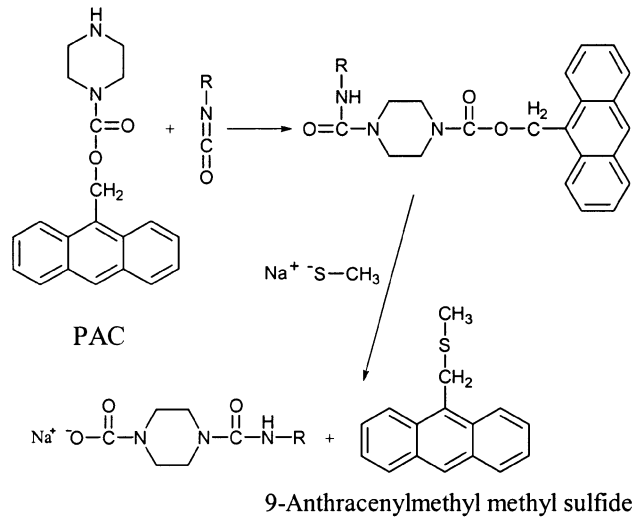
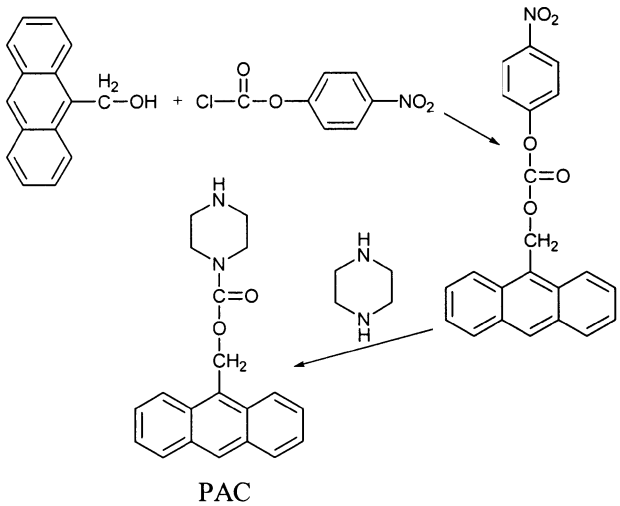


Fig. 1 How the PAC method works.

reaction was monitored by TLC. After allowing the mixture to stir overnight, the solution was decanted to separate it from the white precipitate of pyridine hydrochloride. The THF was removed by rotary evaporation and the residue was dissolved in a small volume of toluene. The toluene solution was separated from a small amount of insoluble material and rotary evaporated to give crude anthrylmethyl *p*-nitrophenyl carbonate containing excess *p*-nitrophenylchloroformate . This crude material was dissolved in 40 mL of DMF. A 10-fold excess of piperazine (14.0 g, 162 mmol) was dissolved in 20 mL of DMF and the solution was placed in a two-necked round-bottomed flask with a magnetic stirring bar. The anthrylmethyl *p*-nitrophenyl carbonate solution was added to the piperazine solution dropwise with stirring and the reaction was monitored by TLC. After 45 min, the reaction mixture was poured into 100 mL of ice–water and extracted with toluene. The toluene extract was washed once with 100 mL of 10% sodium carbonate and twice with 100 mL of water. The toluene solution was then dried through a column of anhydrous sodium sulfate and rotary evaporated to dryness. The residue was recrystallized from toluene–hexane, yielding 3.09 g of PAC (60%). A 1.49 g portion of this product was further purified by dissolving it in 22 mL of toluene and adding this solution to the top of a 500 mL silica gel column packed with toluene. The column was eluted with methanol and 250 mL fractions were collected. Rotary evaporation of fractions 7–10 yielded 1.35 g of purified PAC. The reaction sequence for the preparation of PAC is shown in Fig. 2.

Preparation of isocyanate derivatives of PAC

The following is the procedure used to synthesize the PAC derivative of phenyl isocyanate (Ph–PAC). PAC (0.63 g, 1.96 mmol) was dissolved in 35 mL of toluene and the solution was placed in a two-necked round-bottomed flask with a magnetic stirrer. To this solution was added dropwise with stirring a solution of phenyl isocyanate (0.26 g, 2.2 mmol, 10% excess) dissolved in 10 mL of toluene. The reaction was monitored by TLC. After the phenyl isocyanate solution had been completely added, the reaction mixture was allowed to stir for an additional 20 min. The precipitate was separated by filtration through a fritted glass funnel and washed three times with small volumes of toluene, followed by two washings with small amounts of hexane to remove the residual toluene. After drying, the derivative weighed 0.81 g (94% yield). PAC derivatives of butyl isocyanate (Bu–PAC), HDI (HDI–PAC) 2,4-TDI (TDI–PAC), and MDI (MDI-PAC) were prepared analogously, except that PAC was present in 10% excess during the preparation of derivatives of diisocyanates to ensure complete derivatization of both isocyanate groups.



PAC

Fig. 2 Synthesis of PAC.

Preparation of 9-anthracenylmethyl methyl sulfide (AMMS)

Sodium thiomethoxide (0.474 g, 6.76 mmol) was dissolved in 40 mL of DMF that had been purged with nitrogen. To this was added dropwise with stirring a solution of Ph–PAC (0.404 g, 0.92 mmol) dissolved in 40 mL of nitrogen-purged DMF. The atmosphere above the reaction was continuously purged with nitrogen. The reaction was monitored by TLC. After 60 min, 160 mL of ice-cold 1 M HCl were added to the reaction mixture. The aqueous phase was extracted with 80 mL of toluene, followed by a second extraction with 40 mL of toluene that did not recover substantially more product. These extracts were combined and washed once with 1 M HCl and once with water. The extracts were rotary evaporated to dryness. The crude product was dissolved in 10 mL of toluene and loaded on a 100 mL silica gel column packed with hexane. The column was eluted with 600 mL of hexane, followed by hexane–ethyl acetate (2 + 1), which eluted the product very quickly. The fractions were monitored by TLC and those containing the product were combined and rotary evaporated to yield 0.193 g (88%) of AMMS.

Investigation of the reactivity of PAC with phenyl isocyanate

The reactivity of PAC with phenyl isocyanate was investigated using a procedure similar to that used to compare the reactivity of 1-(9-anthracenylmethyl)piperazine (MAP) with several other reagents.[32] Phenyl isocyanate solutions in acetonitrile at three different concentrations were added to mixtures of MAP and PAC in acetonitrile. The concentrations of phenyl isocyanate after mixing were 20.8, 41.7 and 83.3 nmol mL^{-1}. The concentrations of both MAP and PAC after mixing were 168 nmol mL^{-1} for all experiments. Experiments were carried out in duplicate for each level of phenyl isocyanate. The solutions were allowed to react overnight. Ph–PAC and Ph–MAP standards were run to generate a calibration curve for the quantification of these species in the competitive reactions.

Investigation of the separation of isocyanate-PAC derivatives from excess PAC

Excess PAC can react with sodium thiomethoxide to yield AMMS, analogous to the desired reaction that converts all PAC derivatives of isocyanates to AMMS. Therefore, excess PAC must be quantitatively removed from a sample prior to the cleavage reaction to form AMMS. Solid-phase extraction (SPE) with silica gel cartridges was investigated as a possible means for accomplishing this removal. To determine an appropriate solvent system, TLC with silica gel plates was investigated as a model for the SPE. The degree of separation was judged by comparing the R_F of PAC with the R_F of isocyanate derivatives of PAC for different solvent systems. (R_F is the ratio of the distance traveled by a component to the distance traveled by the solvent front on a TLC plate). Solvent system optimization was conducted using HDI–PAC because it was found to be the model isocyanate–PAC derivative hardest to separate from PAC. The SPE separation was evaluated by loading 1 mL aliquots of a methylene chloride solution containing 1.48 μg mL^{-1} HDI-PAC and 1 mg mL^{-1} PAC on SPE cartridges. The cartridges were eluted with 3 mL of 6% DMF in acetonitrile (the solvent system found to be optimum in the TLC experiments) and analyzed by HPLC to determine the recovery

of the isocyanate–PAC derivatives and the effectiveness of the PAC removal.

Cleavage reaction of isocyanate-PAC derivatives

The cleavage reaction of isocyanate–PAC derivatives with sodium thiomethoxide to form AMMS was investigated for Bu-PAC, Ph–PAC, HDI–PAC, TDI–PAC, and MDI–PAC. The cleavage reaction was carried out in 1 mL of DMF containing 4 mg of sodium thiomethoxide. Also, the cleavage of MDI–PAC in DMF by addition of 20 μL of a 100 mg mL^{-1} solution of sodium thiomethoxide in methanol was examined. The effect of flushing the reaction with nitrogen on the success of the cleavage reaction was investigated. TLC was used to determine when the reactions had gone to completion.

Results and discussion

Determination of monomeric isocyanate–PAC derivatives and AMMS by HPLC-UV-FL

The acetonitrile content in acetonitrile–pH 3.0 triethylammonium phosphate mobile phases was varied to determine the optimum conditions for the determination of both monomeric isocyanate–PAC derivatives and the cleavage product AMMS. A mobile phase containing 65% acetonitrile–35% pH 3.0 triethylammonium phosphate was found to give good separation of monomer derivatives with short analysis times for the three diisocyanate monomer derivatives and for AMMS. It is desirable to have the same mobile phase for the analyses for both the monomer and the total isocyanate (AMMS) to simplify mobile phase preparation and so that the two types of analysis can be run back-to-back without the need for re-equilibration. UV chromatograms of the diisocyanate monomer derivatives and AMMS are shown in Fig. 3.

The detectability of both isocyanate–PAC derivatives and AMMS is attributed to the presence of the anthracene group in these compounds. Other reagents bearing this functional group have been used successfully in isocyanate analysis.[29–32,38–40] The anthracene group absorbs very strongly at 254 nm and also fluoresces very strongly. Therefore, either a variable-wavelength absorbance detector (UV) or a fluorescence (FL) detector provides good sensitivity for the analysis. The FL detector is preferred because of its enhanced selectivity.

Reactivity of PAC with phenyl isocyanate

Experiments were conducted to investigate the kinetics of reaction with isocyanates. Phenyl isocyanate was chosen as a model isocyanate in the competitive kinetic study partly because it is a monofunctional isocyanate, which simplifies the interpretation of results because no mixed derivatives of PAC and the competing reagent MAP could be formed. Also, two previous investigations of the relative reactivities of isocyanate derivatizing reagents used phenyl isocyanate as the model isocyanate.[32,41]

There was excellent agreement between the results obtained in experiments at all phenyl isocyanate concentration levels. The average relative rate factor for MAP/PAC for the low phenyl isocyanate concentration experiments was 12.2, for the medium 12.5 and for the high 12.6. These results indicate that the carbamate carbonyl group of PAC has a significant deactivating effect on the reactivity of PAC. Based on the reactivities of other reagents reported in the previous studies,[32,41] PAC is less reactive than most established reagents toward phenyl isocyanate, but more reactive than at least one widely used reagent, *N*-4-nitrobenzyl-*N*-propylamine (nitro reagent). It is not clear how reactive a reagent must be to be effective. Future experiments must determine the concentration of PAC on a glass-fiber filter necessary to prevent breakthrough of diisocyanate monomer vapor.

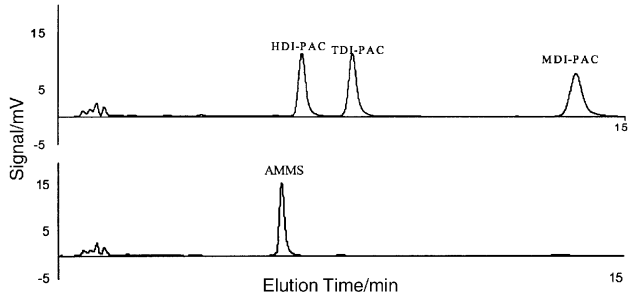


Fig. 3 HPLC chromatogram of PAC monomer derivatives and 9-anthracenylmethyl methyl sulfide with UV detection.

Separation of PAC derivatives of isocyanates from excess PAC

Separation of the five isocyanate–PAC ureas from PAC was investigated by TLC. Solvent systems consisting of mixtures of DMF and acetonitrile were found to be useful mobile phases. In 5% DMF–95% acetonitrile, the five derivatives gave R_F values ranging from 0.47 for HDI–PAC to 0.93 for Ph–PAC. PAC gave an R_F of only 0.03. The degree of separation as measured by the R_F (isocyanate–PAC)–R_F (PAC) ratio for the five isocyanate–PAC ureas was found to be 31 for Ph–PAC, 28 for Bu–PAC, 27 for MDI–PAC, 24 for TDI–PAC and 16 for HDI–PAC. Because HDI–PAC was found to have the poorest separation from PAC, it was chosen as the model compound for further optimization of the elution solvent. The R_F (HDI–PAC)/R_F (PAC) ratio was measured as a function of the percentage of DMF in acetonitrile. The maximum separation was found to occur at 6% DMF. With this elution solvent, HDI–PAC gave an R_F of 0.59 and the R_F (HDI–PAC)/R_F (PAC) ratio was found to be 18. Under these conditions, rapid elution of PAC derivatives with complete removal of excess PAC by SPE was expected. This elution solvent was tested with SPE cartridges loaded with 1.48 μg of HDI–PAC and excess PAC (1 mg). The recoveries for HDI–PAC ranged from 80 to 82%. The analysis indicated that none of the excess PAC had eluted from the SPE cartridge.

Cleavage reaction of isocyanate–PAC derivatives

It was found that quantitative cleavage of Bu–PAC, Ph–PAC, HDI–PAC, TDI–PAC, and MDI–PAC to AMMS could be achieved in less than 10 min in DMF containing 4.0 mg mL^{-1} sodium thiomethoxide. However, it was also determined that flushing the reaction mixture with nitrogen during the course of the reaction was necessary. The reaction was considered complete when no more isocyanate–PAC derivative could be observed by TLC. The cleavage reaction of MDI–PAC with 20 μL of 100 mg mL^{-1} sodium thiomethoxide was analyzed by HPLC and showed quantitative conversion to AMMS.

An important problem was observed when using sodium thiomethoxide solutions to carry out the cleavage reaction. Sodium thiomethoxide is very unstable in air. For maximum stability, sodium thiomethoxide solutions should be prepared and stored under nitrogen. Also, very concentrated solutions have been found to be more readily stored than dilute solutions. Therefore, it is recommended that concentrated sodium thiomethoxide solutions in methanol (100 mg mL^{-1}) be made up and stored in nitrogen. These solutions are stable for at least 1

week. Very small volumes of this solution (20 μL) are needed to cleave the isocyanate–PAC derivatives in a sample.

The cleavage reaction was investigated using only monomeric isocyanate–PAC derivatives. Studies also need to be done with polymeric isocyanate–PAC derivatives. However, because the site of attack of the sodium thiomethoxide on the bound PAC group is several atoms from the point of attachment to the isocyanate, it is possible that the kinetics of the cleavage reaction for a PAC-derivatized polyisocyanate will not be substantially different from that for a PAC-derivatized diisocyanate.

Unique potential application of PAC: surface-bound isocyanate groups

As described previously, there are several potential advantages to using PAC as opposed to conventional analyses for measurement of complex mixtures of isocyanates. However, there are some isocyanate-containing species that cannot be measured at all by conventional HPLC methods. These include isocyanate groups chemically bound to particle surfaces (*e.g.*, dust generated from sawing composites of wood and MDI) or residual isocyanate on polyurethane surfaces. In these cases, SPE would not be used to remove excess PAC. Instead, the excess PAC could be extracted from the insoluble particle or polyurethane with a solvent and the particle or polyurethane could be treated with sodium thiomethoxide solution to generate AMMS from the bound isocyanate groups. The use of PAC in the determination of surface-bound isocyanate groups is depicted in Fig. 4.

Potential limitation of PAC: high blanks from artifacts

The cleavage product AMMS is not specific to isocyanate–PAC derivatives. Other species derived from PAC, such as PAC decomposition products or reaction products of PAC with solvent impurities, may generate AMMS when treated with sodium thiomethoxide. The SPE procedure to remove excess PAC will remove a portion of these artifacts, but some portion will remain to produce a blank level of AMMS. The magnitude of this blank level has been investigated. When a sample containing 0.1 mg of PAC was subjected to the SPE procedure, the yield of AMMS was observed to be 0.044%. Although this is a small percentage, it could be a significant interference when isocyanate levels are low. Moreover, PAC present in impingers or on glass-fiber filters and subjected to air sampling may give higher blank levels. This needs to be investigated further. If it proves to be a serious limitation, ways to reduce the blank levels will be investigated.

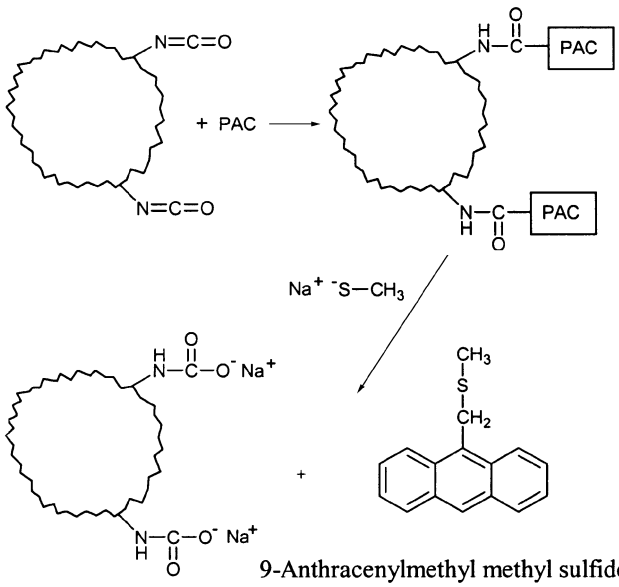


Fig. 4 Unique potential application of PAC: determination of surface-bound isocyanate groups.

Conclusions and future research needs

A new analytical procedure for the measurement of monomeric isocyanates and total isocyanate group in workplaces was investigated. The total isocyanate group determination involves converting all derivatized isocyanate species to a single analyte before analysis. The measurements of monomers and total isocyanate group are achieved in separate HPLC analyses. The HPLC analyses are short, isocratic and require only a single detector, preferably a fluorescence detector. Because total isocyanate measurement is based on quantification of a single peak, data interpretation is minimal.

Laboratory investigations have demonstrated that excess PAC reagent can be satisfactorily removed from PAC-derivatized monomeric isocyanates, a requirement for the success of the analytical procedure. Also, five PAC-derivatized isocyanates were found to be rapidly and quantitatively cleaved to the analyte AMMS when reacted with sodium thiomethoxide.

There are several areas that require further investigation:

(1) Column switching

If the method is used to analyze for individual monomeric isocyanates, then no cleavage reaction is carried out before analysis. The sample may contain late-eluting oligomeric isocyanate derivatives. If analysis times are only long enough to accommodate the elution of the monomers, the late-eluting compounds may interfere in subsequent analyses. To circumvent this problem, the analysis times can be lengthened or a stronger mobile phase can be introduced to accelerate the elution of the highly retained compounds. However, these measures detract from two potential advantages of the PAC methodology: short analysis times and a single mobile phase. Another way to eliminate the problem of late-eluting compounds interfering in subsequent analyses is to employ commercially available column switching equipment. Using this equipment with a guard column and an analytical column would enable the desired monomeric analytes to be quantified while the highly retained oligomeric compounds are back-flushed to waste. This procedure would add almost no additional time to the monomer analyses.

(2) Oligomeric isocyanate products

Monomeric isocyanates were convenient model compounds for the initial evaluation of the PAC methodology because they are available in pure form. However, experiments need to be conducted on oligomeric products to demonstrate that excess PAC can be efficiently removed from their PAC derivatives and to demonstrate that the cleavage reaction proceeds efficiently.

(3) Non-zero blanks

The magnitude of the blank problem in real samples will need to be assessed and ways to minimize the blank response investigated.

(4) Air sampling

Air sampling experiments should be conducted using a volatile monomer with PAC on glass-fiber filters or in an impinger solution. The concentration of reagent in the sampler to prevent breakthrough will need to be established. The use of a non-volatile solvent or a catalyst together with the PAC on a filter might facilitate collection and derivatization of isocyanates.

(5) Stability

The stability of PAC and PAC derivatives on filters or in impinger solutions needs to be evaluated.

(6) Field comparison

Samplers containing PAC should be used side-by-side in the field with samplers for an established method and the analytical results compared.

(7) Surface-bound isocyanate groups

Once it has been determined that the PAC method gives reasonable results compared with a reference method in an environment where the reference method is expected to be accurate, the PAC method should be tested in an environment expected to be problematic for conventional HPLC methods. These environments would include those containing a relatively high proportion of bound isocyanate, such as workplaces generating dust from isocyanate–wood composites or newly cured polyurethane.

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