

Technical Note

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Abstract

We are demonstrating here the successful development of an ionic liquid device based on affinity ionic liquids AIL 1-6 tailored for chemoselective detection of gaseous chemical warfare agent (CWA) mimics on a quartz crystal microbalance (QCM) as well as on disposable filter papers. In the QCM platform, the negligible vapor pressure of ionic liquids ensures that AILs do not dry out on quartz chips and are used free of leakage during the measurements. This lack of vapor pressure makes these ionic liquid devices highly attractive for gas analysis. In the present study, chemoselective CWA mimics vapor detection by QCM occurs when gas rapidly diffuses into the AIL thin film and accordingly the nucleophilic substitution reaction emerges under the experimental conditions developed. Our initial results give credence to three important conclusions: (i) AILs could be prepared in short synthetic steps and are remarkable in detecting CWA mimics, (ii) the analysis of gaseous CWA mimics on QCM is label-free and chemoselective, and (iii) the detection of CWA mimics vapor by AILs on filter paper discs is colorimetric and portable, and, once used, the paper disc can be disposed. To the best of our knowledge, this is the first report in the literature based upon the CWA mimics vapor detection in ionic liquids on a QCM.

This paper reports our development of a system based on ionic liquids¹ tailored for chemoselective detection of chemical warfare agent (CWA) mimics² by quartz crystal microbalance (QCM),³ on filter paper discs, and in solutions. In the QCM system, the detection of gaseous CWA mimics was achieved by nucleophilic substitution reactions with affinity ionic liquids **AIL 1-6** (Figure 1) thin-coated on quartz chips. The AILs studied in this work are embedded with two unique chemical properties in structures: a nucleophilic pyridyl group responsible for capturing vapor of CWA mimics and, upon reactions, a red-shifted color change in azobenzene chromophore.



Figure 1. Structures of affinity ionic liquids AIL 1-6.

The azobenzene motif likely is one of the most studied and best characterized chromophore groups available to chemists engaged in molecular assembly, and has found a myriad of applications in science and technology such as molecular photoswitches and sensors.⁴⁻⁶ The value of this structural scaffold is widely acknowledged for its facile access to dense structures of defined geometry with targeted properties for specific studies. Here, we are reporting our initial development of **AIL 1-6** for use to investigate reaction-based detections of CWA mimics with these polar ionic liquids.

CWAs are considered the most nefarious and reprehensible manmade chemicals that

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are highly toxic. For exactly that reason, rapid and sensitive methods for rapid and sensitive detection of CWAs are of critical need. Albeit nonportable and expensive GC-MS and NMR-based instrumental techniques are methods of choice for comprehensive detection of CWAs, other sensitive methods such as fluorescence and colorimetric measurements have also been reported and employed.² The development of new sensitive and inexpensive methods for CWA analysis should find applications in forewarning procedure, practice of adequate protection, site mapping of contamination, and during and after decontamination.² To our knowledge, no ionic liquids embedded with azo dyes, such as our AIL 1-6, for detecting CWA mimics on a QCM have been reported in literature. Ionic liquids are made up exclusively of ions and have emerged as versatile solvents for numerous applications in chemistry.¹ They can be further altered, tuned, and controlled by the engineering of cations or anions. In fact, significant progress has been made in exploring functionalized ionic liquids through the incorporation of functional groups to equip novel ionic liquids with tailored properties for targeted applications.^{7,8} Based specifically on azo dye, this work reports our concise synthesis of affinity ionic liquids AIL 1-6 and demonstrates their usefulness in CWA mimics detection by QCM, on portable filter papers discs, and in solutions.

EXPERIMENTAL SECTION

Chemical Synthesis of Affinity Ionic Liquids AIL 1-6. Detailed synthetic procedures and spectral characterization of **AIL 1-6** were given in the Supporting Information. All **AIL 1-6** synthesized are viscous liquid at ambient temperature.

³¹P and ¹H NMR Analysis of AIL Reactions with CWA Mimics in Solution, Gaseous QCM Measurements, and Detection of CWA Mimic Vapor on Paper Discs. Detailed preparation and experimental procedures of AIL reactions with CWA mimics were given in the Supporting Information.

RESULTS AND DISCUSSION

We commenced our syntheses of affinity ionic liquids AIL 1-6 from commercially available starting materials, 4-aminopyridine (for affinity ionic liquids AIL 1, 3, 4, and 6) and aniline (for the control ionic liquids AIL 2 and 5), which were diazotized first and subsequently treated with substituted anilines or phenols in one pot to proceed the electrophilic aromatic substitution reactions to afford the azo alcohols or phenols in 22-73% yields (Schemes 1 and S1). For AIL 4-6, mesylations of the corresponding azo alcohols with methanesulfonyl chloride followed by a nucleophilic substitution with 6.7-dihydro-5H-pyrrolo[1,2-a]imidazole, a bicyclic imidazole, previously developed in our laboratory⁹ and finally the anion metathesis with lithium bis(trifluoromethane)sulfonimide (LiNTf₂) in water readily afforded the desired ionic liquids AIL 4-6 (Scheme 1). The detailed synthesis of AIL 1-3 is illustrated in Scheme S1 (Supporting Information). Our overall syntheses of AIL 1-6 were straightforward and, in our hands, these AILs could be achieved in short synthetic steps (4 steps for AIL 5; 5 steps for AIL 1-4, 6). All AILs obtained are viscous liquid at room temperature. Detailed experimental procedures, spectra and data of AIL 1-6 are summarized in the Supporting Information.



Scheme 1. Synthesis of AIL 4-6.

Analysis of volatile organic compounds (VOCs) emanating from human body, for example, is of immense value for noninvasive medical diagnosis in the form of fingerprints that are disease specific.¹⁰⁻¹² VOCs are typically collected and concentrated using commercial portable gas sampling devices, and then analyzed by GC and identified by MS. Albeit GC-MS often is the method of choice, no one analytical method is suitable for measuring all VOCs. To detect CWA mimics using our AIL-on-QCM technology platform developed in this work, both diethyl chlorophosphate (DCP) as the nerve agent mimic of G-agents (GA, GB, and GD) and 2-chloroethyl ethyl sulfide (CEES) used as a blister sulfur mustard (HD) mimic were studied.¹³ We incorporated reactive azo groups in AILs for reasons that the azopyridine not only acts as a good nucleophile to undergo substitution reactions chemoselectively with vapors of CWA mimics quantitatively measured by QCM, but also can be used to develop colorimetric sensors on test paper discs for rapid qualitative analysis of CWA mimics. Moreover, it is expected that, in comparison to common nonpolar and less polar molecular solvents, polar reactions such as the one studied in this work should proceed with fast rates in inherently polar ionic liquids, owing to its likely stabilization of the polar transition states of the reactions as well as favorable interactions between the Lewis acidic cation of ionic liquids and the P=O (in DCP) and the Cl (in CEES) group of CWA mimics that ultimately promote the reactions.

We first carried out screening by ³¹P NMR to identify the most effective AILs to accelerate the nucleophilic substitution reactions with DCP in deuterated acetonitrile at ambient temperature. ³¹P NMR readily monitors reactions taking place at phosphorus center, often permits detection of reaction intermediates involved, and accordingly can offer insight into mechanism or pathway of reactions studied. The screening results are summarized in Figure 2. These kinetic ³¹P NMR measurements clearly showed that, as expected, more nucleophilic N-linked AILs ($t_{1/2} \sim 33$ min for AIL 4 and $t_{1/2} \sim 48$ min for AIL 6) react faster than the O-linked AILs ($t_{1/2} > 234$ min for AIL 1 and $t_{1/2} \sim 180$ min for AIL 3) toward DCP (Figure 2A). The control O-linked AIL 2 and N-linked AIL 5 ionic liquids were completely inert toward DCP (Figure 2). It was worth noting that, in the presence of an organic base (diisopropylethylamine, DIEA), methoxy-containing AIL 6 ($t_{1/2} = 6$ min) reacts slightly but noticeably faster than AIL 4 ($t_{1/2} = 13 \text{ min}$) with DCP in CD₃CN solution (Figure 2B). Furthermore, the control liquid AIL 5 was inert toward DCP with or without DIEA (85% and 96% DCP remaining after 240 min, respectively; Figure 2). Among all AILs tested, AIL 4 and AIL 6 were found to be two most powerful affinity ionic liquids to accelerate reactions with DCP in solutions.



Figure 2. Kinetic measurements of **AIL 1-6** (30 mM) reactions with diethyl chlorophosphate (DCP, 30 mM; $\delta_{P} = 4.81$ ppm) (A) without and (B) with diisopropylethylamine (DIEA, 30 mM) in CD₃CN solvent at ambient temperature. Trimethyl phosphate (15 mM; $\delta_{P} = 3.67$ ppm) was used as an internal standard in experiments. The progress of the reactions could be readily monitored by the proton-decoupled ³¹P NMR (162 MHz).

To understand the nucleophilic acyl substitution reactions of AILs with DCP, we conducted time course experiments of **AIL 1** reaction with DCP in CD₃CN measured by ³¹P NMR. A less reactive **AIL 1** was used for this study simply because it allowed convenient reaction monitoring. The ³¹P NMR result unambiguously demonstrated the formation of tetraethyl pyrophosphate (TEPP) product (Figure S1). We found that, upon addition of DCP ($\delta_P = 4.81$ ppm) to **AIL 1** in CD₃CN, a new peak at -12.17 ppm was obtained with an identical chemical shift to that of the freshly prepared TEPP.^{14,15} DCP alone did not undergo any detectable hydrolysis when dissolved in CD₃CN. This formation of TEPP from **AIL 1** reaction with DCP could be explained by DCP reaction with its hydrolyzed diethyl phosphoric acid in the presence of adventitious water likely associated with ionic liquid.¹⁵ Scheme S2 shows its proposed mechanism.

Results from both reaction photos and UV-vis spectra further confirmed that the

affinity ionic liquid **AIL 4** dissolved in acetonitrile chemoselectively reacted with DCP at ambient temperature and the control **AIL 5** was not at all reactive (Figure 3). As shown in Figure 3B, the λ_{max} of **AIL 5** remained essentially unaffected upon mixing with DCP (412 nm vs. 414 nm without and with DCP, respectively), clearly indicating that the reaction of **AIL 5** with DCP was negligible, if any, and the reaction of **AIL 4** toward DCP was chemospecific: a large $\Delta \lambda = 100$ nm red-shift was observed; that is, 440 nm vs. 540 nm without and with DCP, respectively (Figure 3A). Reaction photos and corresponding UV-vis spectra for all **AIL 1-6** were given in Figure S2. Among AILs investigated, **AIL 6** produced the largest red shift in wavelength (λ_{max} shifted from 441 nm to 551 nm) upon reaction with DCP in solutions.



Figure 3. UV-vis spectra (1 mm path length) of **AIL 4** (A, 0.1 mM) and **AIL 5** (B, 0.1 mM) (labeled in black), and their reactions (labeled in red) with DCP (0.1 mM) all in acetonitrile (100 μ L). Spectra were obtained using a NanoDrop 2000 spectrophotometer (Thermo Scientific, Waltham, MA, USA). Optical photographic images were for solutions of higher concentration (0.6 mM).

Our gas-phase DCP-AIL 4 reactions were performed at ambient temperatures and monitored on a commercial 9 MHz QCM device.⁸ Results shown in Figure 4 unambiguously demonstrate that, using the same concentration (526 ppb) for all gaseous samples tested, the AIL 4 reacted selectively only with DCP ($\Delta F = -157$ Hz)

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and its analogous, more volatile dimethyl chlorophosphate (DMCP, $\Delta F = -269$ Hz). Under identical experimental conditions, common VOCs such as methanol, acetone, ethyl acetate, hexane, and water were totally inert toward **AIL 4** thin-coated on QCM sensor chips. As expected, the control **AIL 5** was found completely unreactive with all gaseous samples studied. The resonance frequency drops (ΔF) obtained in our QCM measurements from the **AIL 4** reactions with gaseous CWA mimics correlate well with their reactivity (DMCP vs. DCP); that is, the less bulky the dialkyl chlorophosphate is, the greater the reactivity is and accordingly the larger the ΔF results. From the Kanazawa-Gordon study on gas QCM in contact with liquid,¹⁶ these frequency drops likely attribute to an overall change of mass, density and viscosity on **AIL 4**. Our reaction-based QCM system worked well and was totally unreactive to common VOCs, indicating that any residual water present in the gas stream would not interfere with the CWA mimic vapor and, accordingly, the frequency drop in this continuous flow QCM measurement was not at all due to any nonspecific physisorption of gas onto ionic liquid (Figure 4).



Figure 4. Chemoselective detection of methanol, acetone, ethyl acetate, hexane, water, DCP, and dimethyl chlorophosphate (DMCP) gases (526 ppb each) all by a 9 MHz QCM thin-coated with **AIL 4** (2.2 nL, 200 nm thickness). The QCM sensorgrams for gases studied were vertically shifted (20 Hz in between) for clarity. The QCM

responses of DCP and DMCP gas reactions with the control **AIL 5** (2.2 nL, 200 nm thickness) thin-coated on QCM chip were also displayed (vertically shifted by 20 Hz in between). Nitrogen was used as the carrier gas with a flow rate of 3 mL/min, and gaseous samples were injected at 500 s. The resonance frequency drop, ΔF , in Hz is the QCM response on the quartz chip surface.

Figure S3 detailed a quantitative study of the highly reactive **AIL 4** and the control **AIL 5** reactions with DCP gas by QCM and investigated their effectiveness in this CWA mimic gas analysis based on nucleophilic acyl substitution reactions (for all corresponding QCM sensorgrams; see Figure S3A). To our delight, it showed a linear QCM frequency response within the range of concentrations tested (0–1315 ppb). In our hands, the **AIL 4** is highly sensitive to DCP vapor: for DCP at 5 Hz decrease in resonance frequency (i.e., $\Delta F = 5$ Hz), the sensitivity of detection by **AIL 4** was 20 ppb (5/0.24565; Figure S3B). The QCM responses (ΔF) of the control **AIL 5** reactions with DCP gas (0–1315 ppb) were totally negligible.

As we successfully developed AILs for DCP analysis, we next turned our attention to the detection of 2-chloroethyl ethyl sulfide (CEES) as a blister sulfur mustard (HD) mimic and investigated **AIL 4** to demonstrate its effectiveness in CEES analysis based on a nucleophilic substitution (S_N1) reaction.

Results from ¹H NMR analysis, reaction photos, and UV-vis spectra confirmed that the **AIL 4** dissolved in dimethyl sulfoxide chemoselectively reacted with CEES under heated conditions (Figure 5). Using identical experimental conditions, 1-chlorobutane used as the control substrate was totally inert toward **AIL 4**. The ¹H NMR results illustrated in Figure 5B unambiguously demonstrated the formation of **AIL 4**-CEES

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adduct, showing new well defined NMR peaks with all signals down-field shifted on the expected reactive azopyridine motif. The connectivity between **AIL 4** and CEES in the adduct structure could be readily validated by nuclear Overhauser effect measurement (Figure 5A; for nOe spectrum, see Supporting Information). In this reaction, the weak Lewis acidic imidazolium cation¹⁷ of **AIL 4** likely activates the chloro leaving group in CEES to facilitate the formation of a transient but highly reactive sulfonium ion, immediately followed by a S_N1 reaction with the nucleophilic azopyridine in **AIL 4**, finally yielding the **AIL 4**-CEES adduct (Figure 5A). Figure 5C showed that the λ_{max} of **AIL 4** remained essentially unaffected upon reaction with 1-chlorobutane (454 nm vs. 458 nm without and with 1-chlorobutane, respectively), indicating that the reaction of **AIL 4** with 1-chlorobutane was negligible, and the reaction of **AIL 4** toward CEES was clearly chemospecific: 454 nm vs. 558 nm without and with CEES, respectively (Figure 5C).





Figure 5. Chemoselective detection of 2-chloroethyl ethyl sulfide (CEES) by affinity ionic liquid **AIL 4**. (A) Proposed mechanism of **AIL 4** reaction with CEES. (B) ¹H NMR analysis of **AIL 4** (30 mM) reactions with CEES (30 mM) and 1-chlorobutane (30 mM), respectively, at 60 °C for 17 h in DMSO- d_6 solvent, clearly showing the formation of **AIL 4**–CEES adduct. (C) UV-vis spectra (1 mm path length) of **AIL 4** (0.3 mM, labeled in black), and their reactions with CEES (0.3 mM, labeled in red)

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and 1-chlorobutane (0.3 mM, labeled in blue) all in DMSO. Spectra were obtained using a NanoDrop 2000 spectrophotometer. Optical photographic images were obtained with solutions of higher concentration (0.6 mM).

Albeit the mustard and its mimic CEES are known to be poor electrophilic substrates for nucleophilic substitution reactions,^{18,19} we thought that the weak Lewis acidity of **AIL 4** might potentially promote its reaction with CEES and, accordingly, went ahead to investigate its reactions with gaseous CEES by QCM at ambient temperatures. After many trial experiments were tested, including screening of metal triflates and the study of other activated aliphatic chlorides, the **AIL 4** was however found not at all sensitive enough towards capturing CEES gas measured by QCM at ambient temperatures. The rate of reaction appeared to be much limited by the rather slow formation of the cyclic ethylenesulfonium ion, resulting in flowing through without being reacted with **AIL 4** from the continuous flow QCM system.

To illustrate that AILs can be used as a device for rapid analysis of CWA mimics, both **AIL 4** and **AIL 5** in methanol were individually soaked with filter paper discs, dried, placed in sample bottles, and test their ability to capture DCP vapor at room temperature and CEES vapor under heated condition, respectively. We were pleased that, as shown in Figure 6, the color of **AIL 4** on paper discs was intensified and readily visualized by naked eyes upon exposure to CWA mimics vapor in minutes. The control **AIL 5** ionic liquid and 1-chlorobutane substrate were totally unreactive. This initial result demonstrated that **AIL 4** loaded on filter paper can be used as a portable sensor for CWA mimics vapor detection and, potentially, a promising tool for infield detection of CWAs.



Figure 6. Photos of **AIL 4** and **AIL 5** manually printed on ADVANTEC No. 1 filter paper discs (0.3 cm in diameter) upon exposure to (A) DCP, (B) CEES and 1-chlorobutane (as the control) vapors under daylight. For paper disc preparation and detailed experimental conditions, see the Supporting Information.

CONCLUSION

In summary, we demonstrated here the successful development of an ionic liquid device based on **AIL 1-6** tailored for chemoselective detection of CWA mimics by quartz crystal microbalance, on filter paper discs, and in solutions. Since 2010, we have continuously developed the AIL-on-chip technology platforms for reaction-based analysis of targeted gases.^{20,21} In these systems, the negligible vapor pressure of ionic liquids ensures that thin-coated AILs do not dry out on QCM chips and are used free of leakage during the measurements. This lack of vapor pressure makes these AIL devices highly attractive for gas analysis. In this work, chemoselective CWA mimics vapor detection by QCM occurs when gas rapidly diffuses into the AIL thin film and accordingly the nucleophilic substitution reaction emerges under the experimental conditions developed. Our present work on the reaction-based detection and analysis of CWA mimics by AILs lend credence to three important conclusions: (i) AILs prepared in short synthetic steps are superior in detecting CWA mimics in solutions, (ii) the analysis of gaseous CWA mimics on a

QCM is label-free and chemoselective, and (iii), as a promising infield test kit, the detection of CWA mimics by AILs on paper discs is colorimetric, portable, and, once used, the paper disc can be disposed. To the best of our knowledge, this is the first report in the literature based upon the CWA mimics vapor detection in ionic liquids on a QCM. Albeit this ionic liquid device for CWAs analysis is promising and cost-effective, no one analytical method is suitable for measuring all CWAs and our AILs developed here are still preliminary and with no doubt more experimental work is needed.

Supporting Information

Schemes S1-S2; Figures S1-S3; detailed synthetic procedures of **AIL 1-6**; ¹H and ¹³C NMR and HRMS spectra and data of **AIL 1-6**; reactivities of **AIL 1-6** toward DCP without and with DIEA base in CD₃CN measured by ³¹P NMR; **AIL 4** reaction with 2-chloroethyl ethyl sulfide (CEES) and 1-chlorobutane at 60 °C in DMSO- d_6 solvent; time-course ³¹P NMR experiments on DCP conversion to TEPP; color visualization of **AIL 4** and **AIL 5** upon exposure to CWA vapor; QCM measurements.

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