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Selective mass spectrometric analysis of thiols using charge-tagged disulfides

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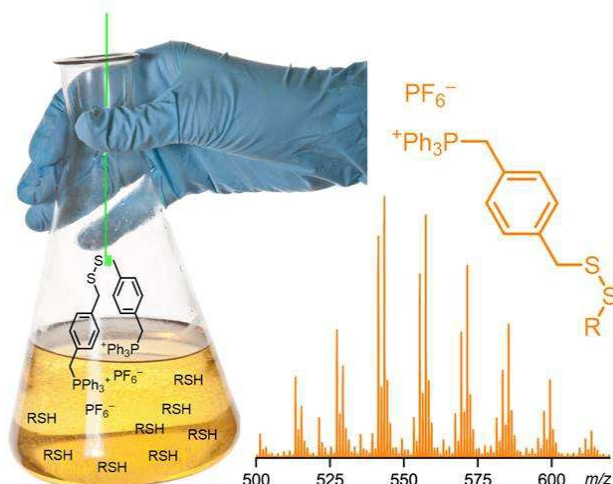*Fax: +1 (519) 339-4436; Tel: +1 (519) 339-5688; E-mail: bryce.mcgarvey@esso.ca*

Abstract

A simple chemical derivatization technique was developed for electrospray ionization mass spectrometry (ESI-MS) in which thiols and disulfides may be selectively analyzed in a complex matrix and easily characterized. These reagents enhance detection of thiols and disulfides solely due to the nature of the charge-tag derivatization agent and therefore does not require an isotopically labelled substrate. The charged disulfides readily and exclusively react with thiols in a complex matrix in a short amount of time. Furthermore, the synthesis of these reagents is simple and results in a highly pure and stable reagent. The efficacy of this reaction was demonstrated using on-line monitoring, while the scope and usefulness of the reaction was demonstrated in petroleum fractions.

Keywords

Electrospray ionization, thiol-disulfide exchange, derivatization, petroleum

Graphical abstract

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Introduction

The need to develop analytical approaches to investigate speciation in petroleum products is well-recognized, whether to enable efficient usage of all the fractions or to establish the extent to which these products may affect the environment. In particular, knowing what contaminating functional groups are present in the finished product is crucial in order to develop effective strategies for their removal. Increasingly elaborate petroleum extraction processes add to the complexity of the petroleum matrix which can complicate refinement. Enhanced oil recovery techniques are employed with increasing frequency especially as displacement techniques such as polymer, microbial and alkaline surfactant flooding become more efficient.[1,2] Unwanted contamination tends to be unavoidable due to the complexity of the petroleum matrix and this problem can be exacerbated partly due to the complicated path petroleum products take from well to refined product.

Sulfur-containing compounds are a major source of contamination in petroleum. Petroleum is a heterogeneous substance and exhibits a range of chemical compositions between wells, or even within the same well. Therefore, the total sulfur content can vary widely from low-sulfur sweet oils to high-sulfur crude oils. [3–8] Refined petroleum products are required to meet strict low-sulfur content standards and are subjected to a variety of treatments in order to meet these standards. At the refinery, distillate fractions of petroleum are refined into several products such as fuels, lubricants, solvents, and primary chemicals. High-sulfur fractions are generally treated downstream with amines for the removal of hydrogen sulfide gas (often referred to as gas-sweetening). [9] Several other sulfur-containing species are removed from petroleum through catalytic desulfurization processes such as SCANfining and catalytic mercaptan oxidation (Merox). [10] Deep desulfurization (less than one part-per-million sulfur) methods must go beyond common hydrodesulfurization processing schemes and adsorbents to economically produce fuel that meets the increasingly strict regulations.[11] Despite advances in desulfurization methods, some deep desulfurization goals (such as the US EPA Tier 3 gasoline sulfur standard) have not yet been met due to the presence of trace quantities of mercaptans. [12]

Modern petroleum characterization techniques include powerful separations using Fourier-transform ion cyclotron resonance mass spectrometry (FT-ICR MS) and two-dimensional gas chromatography (GC×GC). [6,13–19] Analytical techniques that are both accessible and inexpensive are desirable for use in industry, since a rapid and simple analysis with common equipment is the most economically justifiable angle to approach this problem. Functional group specific analyses are valuable since they aid in tracking down problematic species and simplify analysis. Every functional group has unique reactivity, and selective reactions exist that are highly favourable for a particular class of compound while leaving others untouched. We've been partly inspired by bio-conjugate reactions: these are necessarily highly selective, high yielding and easy to execute, and are well-studied. [20] Our approach to characterization of mercaptans in petroleum distillate fractions is the modification of a well-known bio-conjugate reaction, thiol-disulfide exchange, in order to selectively tag thiols for analysis by electrospray ionization mass spectrometry. [21,22]

Electrospray ionization mass spectrometry (ESI-MS) operates by transferring ions from solution into the gas phase through the evaporation of a spray of charged droplets. [23] Neutral species are not detected; therefore, a compound must readily acquire a charge (e.g. through

protonation, deprotonation, or association with a cation such as Na^+) or already contain one. Several notable examples of producing charged compounds for observation by mass spectrometry, notably from the Chen group, are present in the literature. [24–28] Our group has previously employed the addition of a charged tag, such as a phosphonium ($-PR_3^+$), ammonium ($-NR_3^+$) or sulfonate ($-SO_3^-$) group to facilitate the detection of specific analytes. [29–31] As neutrals are not detected with ESI-MS, some form of derivatization is commonly used in order to promote the appearance of target analytes and is typically achieved through adventitious protonation or aggregation (typically involving alkali metals). [32] Solvent adduct and metal ion aggregation has seen use with desorption electrospray ionization in order to promote the detection of polar constituents of petroleum samples. [33] Sulfur compounds have also been detected with some success through methylation and oxidation as alternative chemical derivatization techniques. [34] More exotic chemical derivatization techniques have also enjoyed success in derivatization of thiols including the addition of dansylaziridine, a reagent typically used as a fluorescent probe for proteins. [35] A complimentary soft-ionization technique to ESI-MS is atmospheric pressure photoionization (APPI) mass spectrometry since it specializes in the speciation of nonpolar compounds that are less accessible to typical ESI-MS. [36] When paired with a toluene dopant the technique has been proven useful in the speciation of sulfur compounds in crude oil when paired to an ultrahigh resolution FT-ICR mass spectrometer. [37–39]

We opted to use a charge-tagged phosphonium compound and the thiol-disulfide exchange reaction for the detection of mercaptans in petroleum fractions. Based on the principle of thiol-disulfide exchange a charge-tagged disulfide, R^+SSR^+, will react selectively with RSH to form $RSSR^+$ and R^+SH (see Equation 1). [40,41] The general reaction proceeds by nucleophilic attack of a thiolate anion (RS^-), formed by deprotonation, on one of the two sulfur atoms present in a disulfide (RS-SR). This process "tags" the target functional group for characterization by mass spectrometry resulting in an easily interpretable spectrum of newly tagged thiol species.
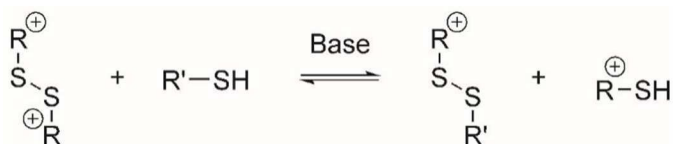
Equation 1. Representation of a thiol-disulfide exchange reaction and the charge-tagging methodology

We were particularly interested in selective thiol speciation since this class of compound promotes odour issues as well as certain types of corrosion in fuel products. For example, thiols contribute to failure of the traditional industrial copper corrosion specification for gasoline. This method will not tag aliphatic or basic sulfur constituents because of the thiol-disulfide exchange mechanism involved; compounds which are greater contributors to high-temperature sulfidation corrosion. Total sulfur analysis of lighter stream petroleum products is typically accomplished via X-ray methods or GCxGC coupled with a sulfur-selective detector. Sulfur analysis of heavier streams and crude petroleum is more easily facilitated by high resolution mass spectrometry. One of the most important benefits of the charge-tagging methodology used

in the present research is the ability to detect low levels of one specific class of compound in a complex matrix using relatively simple techniques.

Experimental

ESI-MS:

All mass spectrometry experiments were collected in the positive ion mode on a Waters Micromass Q-TOF Micro mass spectrometer equipped with a standard Waters Z-spray ESI source. The following parameters were left constant for all experiments: capillary voltage, 3000 V; cone voltage: 15 V; extraction voltage, 0.5 V. Source temperature was set to the boiling point of the solvent used and desolvation temperature was set 100 degrees higher than the source temperature. Cone gas flow rate: 100 L/h. Desolvation gas flow: 200 L/h. Scan time was set to 1 with an inter-scan time of 0.1 s. The MCP detector on the instrument was set to 2.7 kV. A table of complete instrumental parameters, including quadrupole, TOF settings and TDC (time to digital converter) settings, may be found in the supporting information (table S1, S2, and S3).

For PSI experiments, the custom reaction vessel was pressurized using 3 psi of argon gas and solution was fed into the ESI source using 0.178 mm inner diameter PEEK tubing with a length of 50 cm. Mechanical stirring was provided by magnetic stirring hot plate and stir bar. In a typical experiment, a Schlenk flask was charged with a 10% (v/v) solution of a petroleum fraction, and 1-10 eq. of NaOH in 25mL of ethanol. Subsequently, a 100 uL of charged disulfide (4) solution was injected to the mixture, giving a 10-20 µM concentration of (4).

For non-PSI experiments, solutions were fed into the ESI source through the use of a syringe pump and a Hamilton GasTight analytical syringe connected to PEEK tubing (0.1778±0.0127 mm inner diameter, 50 cm length). Prior to each run, instrument cleanliness and stability and was ensured through rinsing with the appropriate solvent and acquisition of stable analyte signal from the subsequent sample solution. After achieving a steady signal, the spray head was moved to a position with optimal intensity and was locked to this position for every experiment.

MS/MS experiments were conducted using the following parameters to acquire structural information. The collision cell energy was set to 32 V, with the high mass and low mass resolution maintained at 15 V each. Argon was used as the collision gas with an internal collision cell pressure of 2.0e-5 psi.

Mass spectrometric interpretation was aided with online tools available from chemcalc.org. [42]

GCMS:

GC-MS data was collected on a PerkinElmer Clarus 680 with a PerkinElmer Axion iQT MS/MS. The injector used was a programmable split/splitless injector with a 0.5 µL injection volume set to 220°C. The analytical column used was a PerkinElmer Elite™-5MS (30m×0.25mmID×0.25µm). Carrier gas flowrate was set to 1 mL/min. The oven was programmed initially to hold at 40°C for 1 minute, with a final ramp of 20°C to 260°C held for one minute. The cold EI source conditions were as follows: GC transfer line was set to 250°C, ion source temperature 200°C, acquisition range m/z 50-500, acquisition time 0.2 s, solvent delay 3.0 mins for split 10, cold EI makeup gas 50 mL/min, and filament set to 5 µA.

NMR:
The ^{1}H and ^{31}P NMR were recorded on a Bruker Avance 300 MHz spectrometer as solutions prepared in CDCl$_3$.

Chemicals, samples and supply:
Solvents and chemicals were purchased from Sigma-Aldrich. All anhydrous and air-free solvents were purified with an MBraun solvent purification system before use unless otherwise noted. Deionized water was obtained from a Millipore Milli-DI water purification system. Petroleum samples "A" and "B" were supplied courtesy of Imperial Oil.

Synthesis of (3) (4-(bromomethyl)benzyl)triphenylphosphonium hexafluorophosphate
Triphenylphosphine (1.58 g, 6.02 mmol) was alkylated with excess α,α′-dibromo-p-xylene (2.00 g, 7.58 mmol) through gentle reflux under argon over 12 hours in 50 mL of toluene in order to generate the phosphonium bromide salt. A white powder was recovered from toluene through filtration and dried under reduced pressure overnight (3.10 g, 5.89 mmol 98% yield). Salt metathesis with sodium hexafluorophosphate improved the solubility of the salt in non-polar solvents, proving helpful for subsequent steps. Several anions were used to substitute the bromide counterion; however, a good mix of cost-effectiveness and increased solubility in polar solvents was achieved through substitution with hexafluorophosphate. The phosphonium salt (3.10 g, 5.89 mmol) was dissolved in a minimum of 85% MeOH and 15% deionized water, by volume. To this, 2.0 equivalents (1.98 g, 11.8 mmol) of sodium hexafluorophosphate were added and stirred for one hour. A white precipitate formed quickly and the powder was recovered through vacuum filtration and, following three washes with 30 mL aliquots of deionized water to remove excess sodium hexafluorophosphate, was recovered and dried under reduced pressure overnight (99% yield). This step also served to greatly increase the purity of the compound as vacuum filtration of the hexafluorophosphate substituted product yielded ionic compounds exclusively.
Little or no double-substitution product was formed in the first step which resulted in a high-yield of a very pure and versatile precursor charge-tag compound which may be used in a variety of applications. [43]

^{1}H NMR (300 MHz, CDCl$_3$): δ$_H$ 4.39 (2H, d, J=0.88 Hz), 4.53 (2H, d, J=14.05 Hz), 6.88 (2H, dd, J=8.34, 2.49 Hz), 7.16 (2H, d, J=7.90 Hz), 7.40-7.88 (15H, m), ^{31}P{^{1}H} NMR (300 MHz, CDCl$_3$): δ$_P$ -144.25 (spt, J_{P-F} = 712.10 Hz), 22.65 (s). QTOF ESI+: m/z: [M]$^+$ 445.3.

Synthesis of Charge-tagged Disulfide (4):
Complete synthesis of the charged disulfide proceeded as shown in Scheme 1. The phosphonium-hexafluorophosphate salt, (4-(bromomethyl)benzyl)triphenylphosphonium hexafluorophosphate, (0.70 g, 1.2 mmol) was dissolved in 25 mL methanol. To this solution, potassium thioacetate was added (0.65 g, 5.7 mmol, 5 eq.) and stirred at gentle reflux for two hours. This solution was initially light tan and developed a deep red colour within 30 minutes of reflux as the compound is thioacetylated. Continued reflux resulted in a subsequent change in colour to a light tan solution indicating formation of the thiol and continued stirring in air provides oxidation to the disulfide. Extended, aggressive reflux at this step resulted in moderate

decomposition and should be avoided for best yield. This step provided transesterification and hydrolysis of the thioester, forming the thiol which oxidizes spontaneously in air to the disulfide. The thiol may be recovered if reflux was done under an inert atmosphere. A variety of oxidants may be used to induce formation of the disulfide from the thiol. Further, the thioester may be recovered if the solution was simply stirred overnight without heat. Reflux of the methanolic solution while exposed to air, or stirring while bubbling air through the solution both provided sufficiently oxidizing conditions to produce the disulfide. The disulfide was recovered from methanol through rotary evaporation under reduced pressure. Excess potassium thioacetate was removed following three washes of deionized water, and the light tan solid was recrystallized from methanol to achieve high purity. The disulfide crystals were dried under vacuum overnight.

^{1}H NMR (300 MHz, CDCl$_3$): δ$_H$ 3.83 (4H, s), 4.53 (4H, d, J=14.30 Hz), 6.81 (8H, s), 7.44-7.85 (30H, m), ^{31}P{^{1}H} NMR (300 MHz, CDCl$_3$): δ$_P$ -144.17 (spt, J_{P-F} = 713.57 Hz), 22.48 (s). QTOF ESI+: m/z: [M]$^{2+}$ 398.1.
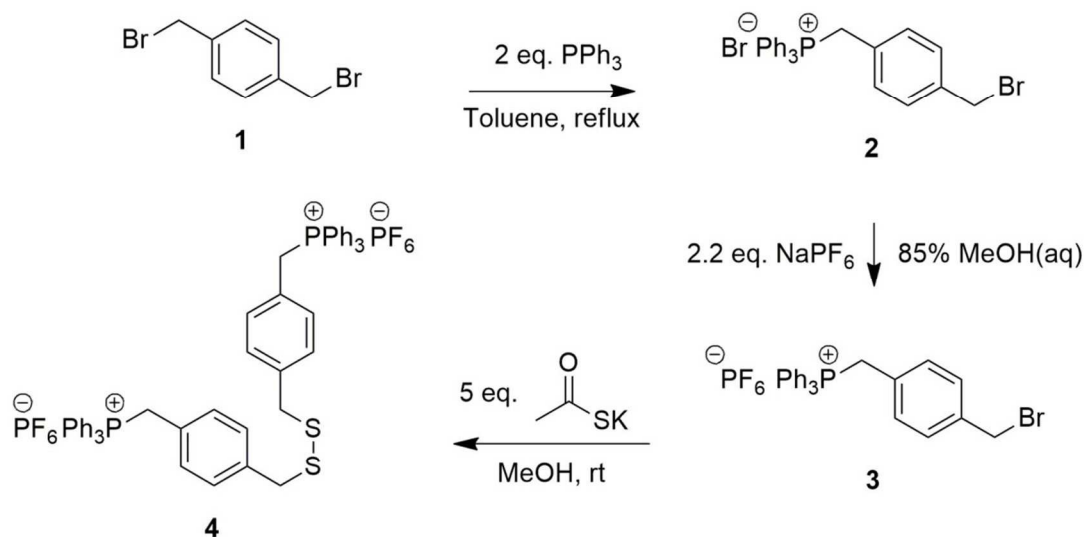
Scheme 1. Charge-tagged disulfide (4) synthetic pathway

Data Processing

    Data and plots were processed using OriginPro 2016. MS and NMR data was exported directly from files acquired using MassLynx 4.1 and TopSpin 3.5, respectively.

Results and Discussion

GC-MS characterization of jet fuel samples

Two of the jet fuel samples that were examined originate from two different points in the refinement process. Sample A is an untreated light distillate stream from the atmospheric distillation of a refinery crude oil blend. It is considered "upstream", that is, this fraction has not been exposed to the treatment processes required of a finished product. Conversely, sample B has been subject to caustic washing, catalytic mercaptan oxidation, water washing, salt drying and clay treating; therefore, it is nearer to finished product. The relative mercaptan concentration of the samples obtained further downstream tends to be consistently diminished when compared to samples retrieved from further upstream. The samples received are acquired in the approximate boiling point range of 150-290°C as judged by the GC-MS chromatographic distribution (Figure 1). Predictably, the complexity of the sample meant much overlap of signals and no thiols could be distinguished from the mixture.
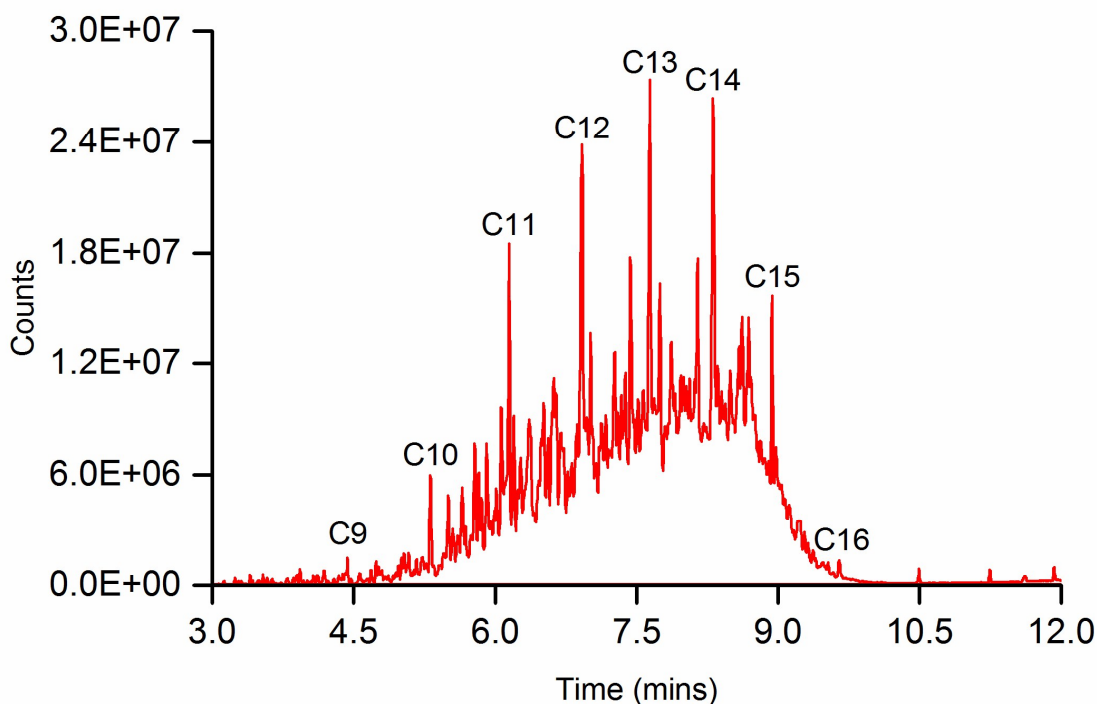

Figure 1. Cold-EI GC-MS chromatogram of jet sample A. Major peaks are labelled with carbon number and correspond to the alkane. Peak assignments were made using library matching. Thiols could not be identified in either sample A or B.

Rate of Thiol-Disulfide Exchange

The rate of thiol-disulfide exchange is well-studied and is considered first-order in both disulfide and thiolate and is therefore catalyzed by base. [44,45] The reaction requires the deprotonated thiolate for the reaction to occur, therefore, the overall rate of the reaction incorporates deprotonation and the thiolate-disulfide S_N2 reaction separately. The rate of reaction for an analysis using the charge-tagging methodology presented is affected primarily, and most simply, by varying solution pH. This ability to moderate rate is important because the amount of charged tag (**4**) added to an unknown sample needs to be limited so as to avoid instrument overloading. In order to evaluate the rate of our charge-tagging methodology via thiol-disulfide exchange, as well as the base-dependence of the reaction, 4-methylbenzenethiol (MBT) standard solutions were prepared. This thiol serves as an exemplary compound considering its boiling point of 195 °C sits in the median of the distillation range for jet fuel (approximately 160-240 °C) and was indeed detected in the jet samples analyzed for the present work (see section on mercaptan-selective derivatization of petroleum fractions). [46] The general reaction for these experiments, along with the results of increasing base concentration, can be seen in Equation 2 and Figure 2, respectively.
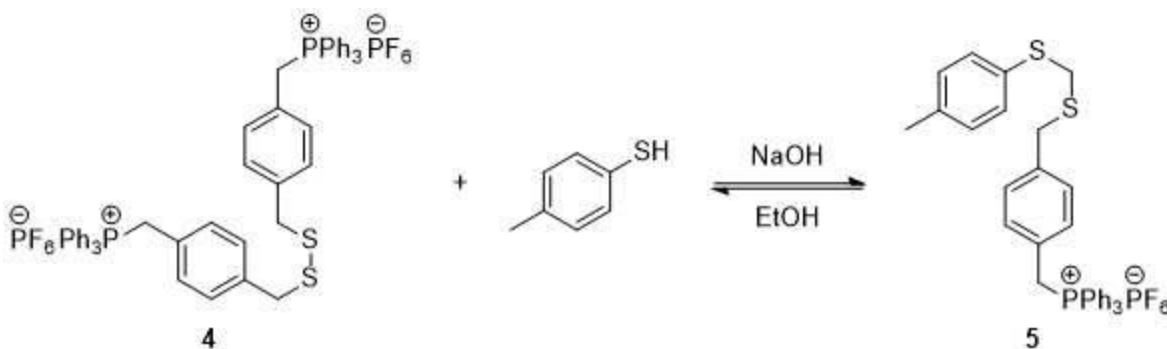
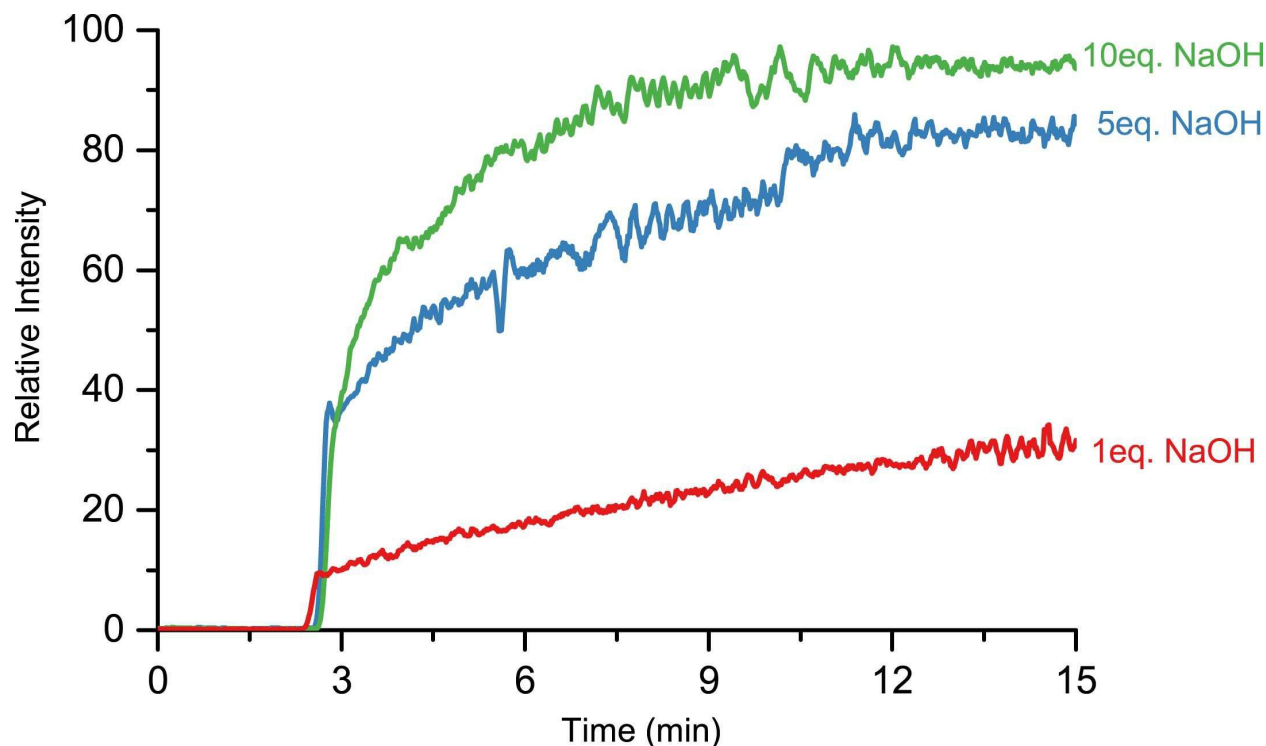Equation 2. Reaction with standard solution of MBT

Figure 2. TDSE reaction dependence on base concentration. Traces show the abundance of the product disulfide (**5**) over time.

For each trial, 20 μM (10 eq.) 4-methylbenzenethiol was injected in to a stirred mixture containing 2.0 μM of disulfide compound (**4**) in ethanol at room temperature and pressure with 1, 5, or 10 equivalents of sodium hydroxide, independently. In addition to the rate of the thiol-disulfide exchange, the degree of conversion of the reaction is largely dependent on the concentration of base. The reaction is sufficiently rapid that information regarding the initial stage of the reaction is lost; however, the equilibrium time is extended to approximately 40 minutes in the case of one equivalent of base. For practical use as a derivatization agent, an elevated concentration of base relative to the expected thiol concentration is recommended to thoroughly deprotonate any thiols present in the sample and expedite analysis time.

Mercaptan-selective derivatization of petroleum fractions

Petroleum fractions were examined to establish the efficacy of the charge-tagged disulfide compound as a mercaptan-selective derivatization agent. Crude oil samples were also investigated using the charge-tagging methodology and were found to be less amenable to straightforward analysis due to the complexity of the matrix and the much larger concentration of thiols present (see supporting information figure S9); therefore, the present research focuses on petroleum fractions rather than crude petroleum. The primary goal of the petroleum fraction experiments was to gather qualitative chemical information about the varieties of mercaptans present in pipeline streams prior to, and following, certain refinery treatments.

Dilute solutions of charge-tagged disulfide (**4**) and sodium hydroxide are prepared separately in ethanol. Each of these reagents are added to a stirring ethanolic solution of 1-10% (v/v) petroleum fraction. The reaction is generally at equilibrium within approximately 10-30 minutes (depending on the analyte concentration present in the sample and base concentration - see reaction kinetics section) and may easily be accelerated through the use of additional base. Extended stirring time on the order of several hours does not yield tag decomposition by-products in this mixture. The reaction is first order in concentration of disulfide and therefore additional charge-tag will expedite the process; however, for direct introduction into the mass spectrometer, the disulfide concentration was generally kept below 20 µM.

The spectra acquired from petroleum fractions prior to derivatization are typically simple and very low intensity as the charged species consist predominantly of adventitiously protonated species and alkali metal adducts. The method detection limit was established based on the noise present in a method blank sample. The derivatization process is limited by the reactivity of target analytes in addition to variation in sample matrix; therefore, this definition for method detection limit is an approximation only and will vary between samples. The limit of detection for 4-methylbenzenethiol was examined and found to be 1.2 ng/L with a limit of quantitation of 4.0 ng/L (see supporting information Figure S11).

Following derivatization with the selective charge-tag the response from thiol species is greatly enhanced since the intrinsic charge from the phosphonium charge tag is independent of ionization efficiency. Spectra of derivatized samples of A and B display a large distribution of mercaptans ranging widely in carbon number and double bond equivalents (DBE).

In sample A a range of charge-tagged thiols from m/z 445-739 is apparent, identifiable as C1 unsaturated (CH_3SH) to C22 thiols ($C_{22}H_{25}SH$) with 0-2 DBE. Within this region is a more obvious Gaussian-like distribution between m/z 520-620. The series starts with C4 unsaturated thiols and ends with C14 (0 DBE) thiols. Within the series, between 0 and 4 DBE are apparent. The exact isomeric forms are not distinguishable mass spectrometrically.

m/z	Thiol C#	DBE	Sample "A" MS Abundance (counts)	Sample "B" MS Abundance (Counts)
487.3	4	0	338	5
501.3	5	0	898	9
513.3	6	1	3037	14
515.3	6	0	1896	9
521.3	7	4	1436	15
525.3	7	2	418	14
527.3	7	1	4689	5
529.3	7	0	3334	7
541.3	8	1	8218	37
543.4	8	0	9703	24
553.4	9	2	1493	6
555.4	9	1	6874	64
557.4	9	0	8976	98
567.4	10	2	1677	38

569.4	10	1	4643	42
571.4	10	0	7069	111
581.4	11	2	1482	83
583.4	11	1	3238	45
585.4	11	0	4928	85
595.4	12	2	731	67
597.4	12	1	1709	30
599.4	12	0	2920	47
607.4	13	3	180	3
609.4	13	2	368	13
611.4	13	1	692	18
613.5	13	0	992	19
621.4	14	3	180	3
623.5	14	2	169	2
625.5	14	1	236	3
627.5	14	0	324	6

Table 1. Thiol derivatives detected in Sample A

The distribution of non-derivatized mercaptans are consistent with the boiling point range of the distillate fraction. The detected thiols in the lower boiling point range are presumably due to derivatization of disulfides (which can react with the charged thiol that is generated after the first thiol-disulfide exchange reaction). Table 1 lists the derivatized mercaptans detectable above the method detection limit in sample A along with the MS abundances of each species in both samples. The method detection limit in complex matrices such as petroleum fractions can vary widely depending on their treatment and source. Very low concentration derivatized thiols may be confirmed via MS/MS (see supporting information) and indeed several derivatives were characterized outside the method detection limit via MS/MS for both samples. The derivatized thiols fragment in a characteristic manner and may therefore be very effectively analyzed using the precursor ion scan mode of a triple-quadrupole mass spectrometer to enhance the sensitivity of the method.

Our derivatization methodology was studied through on-line monitoring using a real sample, jet fuel sample A, (Figure 3). The plot features the rate of appearance of four of the most abundant derivatized thiols present within the sample. To a dilute and mildly basic solution of jet fuel is added 10 µM of compound (4). Shortly following addition of the charged disulfide, several derivatized mercaptans become apparent. This reaction takes longer than the derivatization of MBT (Equation 2) presumably due to the low concentration of thiols in the sample.
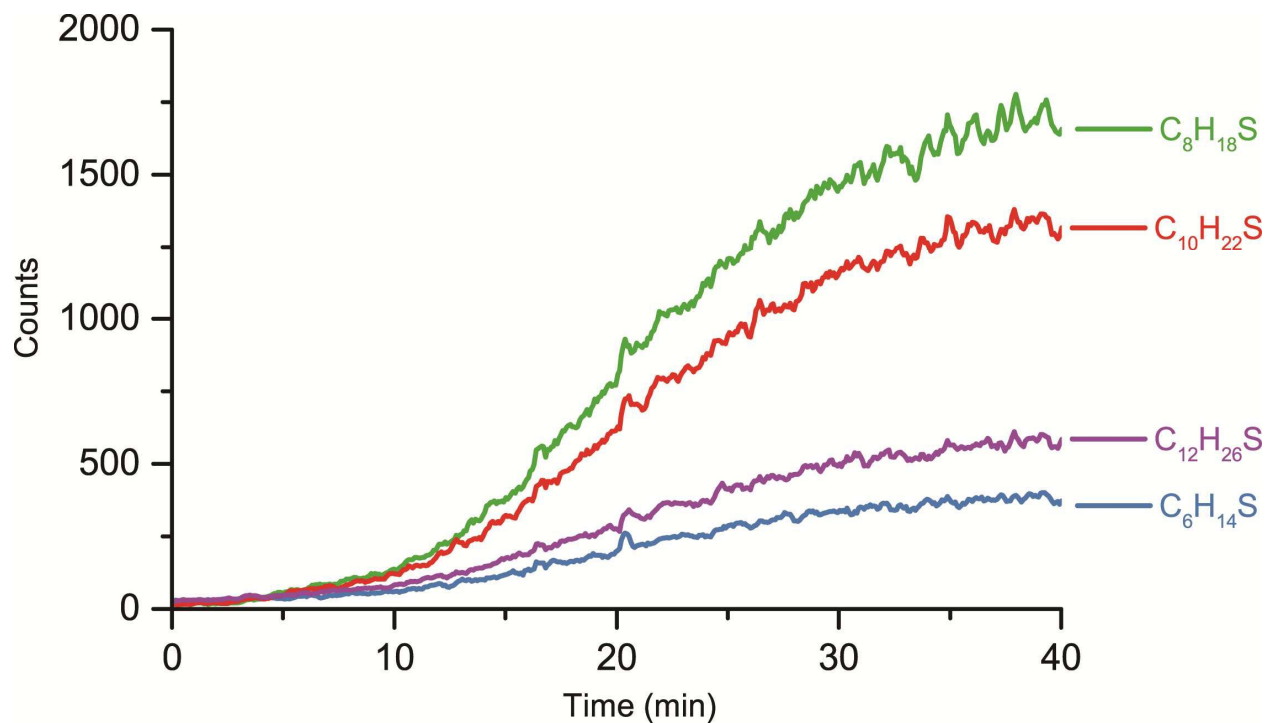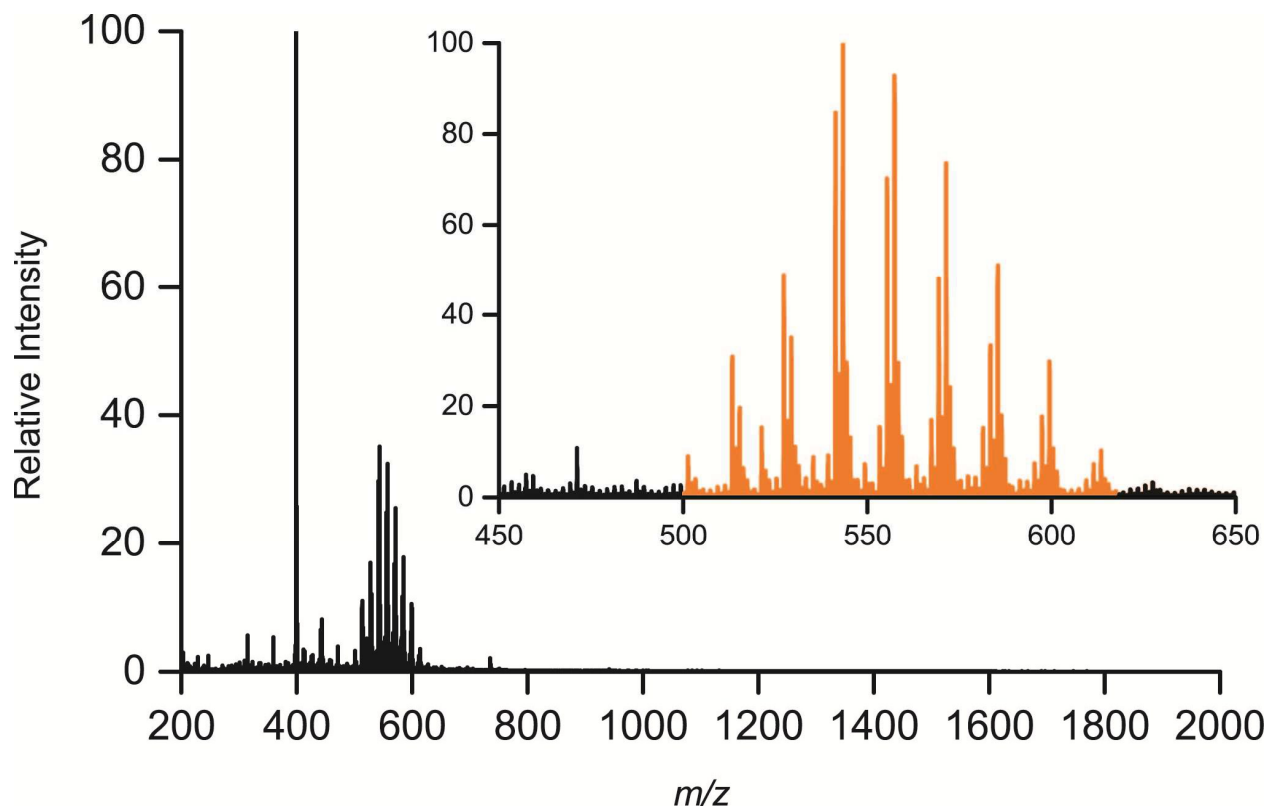
Figure 3. Online derivatization reaction of jet fuel sample A

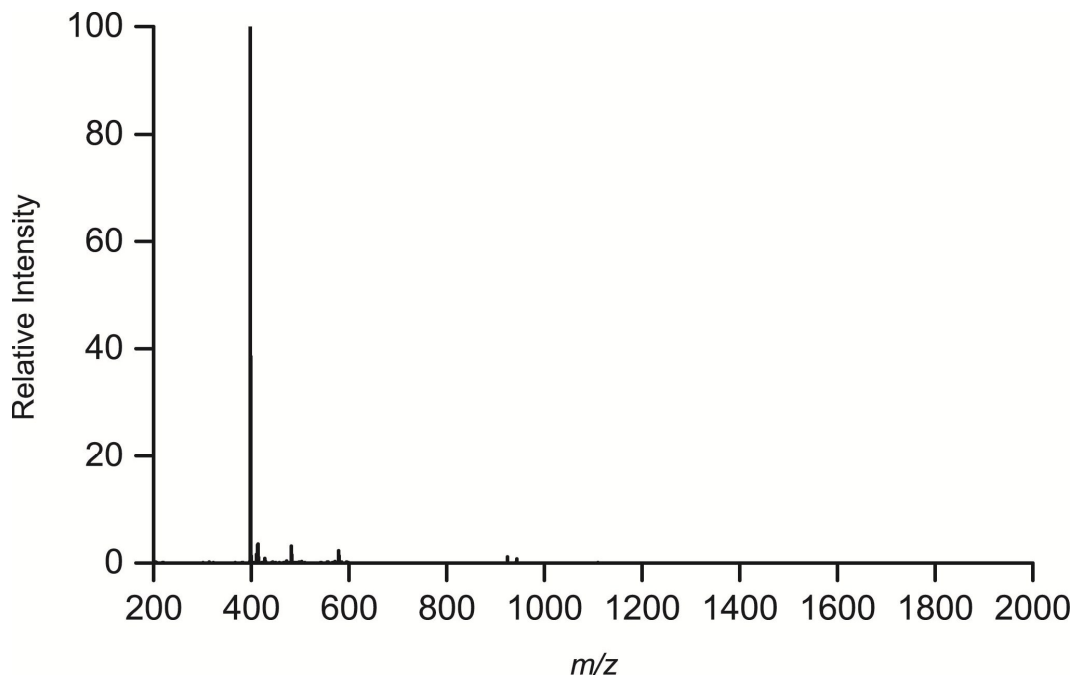Figure 4. Jet fuel sample A (10 µM compound (4), 10%v/v sample in EtOH).

Figure 5. Jet Sample B (10 µM compound (4), 10%v/v sample in EtOH).

As expected, the two samples vary dramatically both in background and detectable thiols, with the relatively "crude" sample A containing far more thiols than the more refined sample, B. A visual comparison between the two samples (Figure 4 and 5) indicates that one or more or all of the treatment processes (caustic washing, Merox treating, water washing, salt drying and clay treating) are demonstrably efficient methods for the removal of mercaptans in jet fuel streams. Derivatized products in sample B are sparse and low in concentration, consisting primarily of short (3-4 carbon) and moderate (8-11 carbon) chain mercaptans.

Conclusions

Electrospray ionization enjoys a wide range of applicability in analyzing complex and often "dirty" samples due to its soft ionization and effective conversion of a solution to gas-phase; however, the softness of ionization can potentially be a problem when the target analyte is not easily ionizable or adventitiously charged in solution. The charge-tagging methodology greatly enhances the utility of ESI-MS in targeting uncharged molecules in a solution and allows the user to explore diverse matrices or follow a reaction without an overly complex spectrum common in less-selective derivatization approaches. The technique is fast, effective, requires no chromatographic steps and can be executed using readily available instrumentation. The strength of the method employed here extends to other areas of research. The successful analysis of petroleum, as a highly complex matrix, provides evidence that this technique is applicable in other matrices such as those derived from biological or environmental samples. In the future we expect to extend the charge-tagging technique toward other molecules of interest in similarly complex matrices.

References

1   A. Muggeridge, A. Cockin, K. Webb, H. Frampton, I. Collins, T. Moulds and P. Salino, *Philos. Trans. A. Math. Phys. Eng. Sci.*, 2014, **372**, 20120320.

2   J. F. B. Pereira, E. J. Gudiña, R. Costa, R. Vitorino, J. A. Teixeira, J. A. P. Coutinho and L. R. Rodrigues, *Fuel*, 2013, **111**, 259–268.

3   R. M. de Souza, A. L. Saraceno, C. L. P. da Silveira and R. Q. Aucélio, *J. Anal. At. Spectrom.*, 2006, **21**, 1345–1349.

4   C. Duyck, N. Miekeley, C. L. Porto da Silveira and P. Szatmari, *Spectrochim. Acta Part B At. Spectrosc.*, 2002, **57**, 1979–1990.

5   E. Ricard, C. Pécheyran, G. Sanabria Ortega, A. Prinzhofer and O. F. X. Donard, *Anal. Bioanal. Chem.*, 2011, **399**, 2153–65.

6   A. G. Marshall and R. P. Rodgers, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 18090–5.

7   Royal Dutch/Shell Group of Companies, *The Petroleum Handbook*, Elsevier, Amsterdam, 6th edn., 1986.

8   J.-P. Wauquier, *Petroleum Refining. Vol. 1 Crude Oil*, Editions OPHRYS, 1995.

9   J. G. Speight, *The Chemistry and Technology of Petroleum, Fifth Edition*, CRC Press, 2014.

10   P. M. Rawson, C.-A. Stansfield, R. L. Webster and D. Evans, *Fuel*, 2015, **139**, 652–658.

11   C. Song, *Catal. Today*, 2003, **86**, 211–263.

12   T. L. Alleman, R. L. McCormick and J. Yanowitz, *Energy & Fuels*, 2015, 150707142503002.

13   H. Müller, J. T. Andersson and W. Schrader, *Anal. Chem.*, 2005, **77**, 2536–43.

14   K. D. Nizio, T. M. McGinitie and J. J. Harynuk, *J. Chromatogr. A*, 2012, **1255**, 12–23.

15   J. J. Harynuk, A. D. Rossé and G. B. McGarvey, *Anal. Bioanal. Chem.*, 2011, **401**, 2415–22.

16   N. E. Oro and C. A. Lucy, *Energy & Fuels*, 2013, **27**, 35–45.

17   G. S. Frysinger and R. B. Gaines, *J. High Resolut. Chromatogr.*, 1999, **22**, 251–255.

18   P. Liu, Q. Shi, N. Pan, Y. Zhang, K. H. Chung, S. Zhao and C. Xu, *Energy & Fuels*, 2011, **25**, 3014–3020.

19   J.-F. Focant, A. Sjödin and D. G. Patterson, *J. Chromatogr. A*, 2004, **1040**, 227–38.

20   H. F. Gilbert, *Adv. Enzymol. Relat. Areas Mol. Biol.*, 1993, **63**, 69.

21   H. F. Gilbert, *Advances in Enzymology and Related Areas of Molecular Biology, Volume 63*, John Wiley & Sons, Houston, 2009.

22   J. McMurry, *Organic Chemistry*, Cengage Learning, 2011.

23   J. B. Fenn, M. Mann, C. K. Meng, S. F. Wong and C. M. Whitehouse, *Mass Spectrom. Rev.*, 1990, **9**, 37–70.

24   C. Hinderling, C. Adlhart and P. Chen, *Angew. Chemie Int. Ed.*, 1998, **37**, 2685–2689.

25   C. Adlhart and P. Chen, *Helv. Chim. Acta*, 2003, **86**, 941–949.

26   W.-Y. Wu, S.-N. Chen and F.-Y. Tsai, *Tetrahedron Lett.*, 2006, **47**, 9267–9270.

27   P. Chen, *Angew. Chemie Int. Ed.*, 2003, **42**, 2832–2847.

28   D. Feichtinger, D. A. Plattner and P. Chen, *J. Am. Chem. Soc.*, 1998, **120**, 7125–7126.

29   A. V. Hesketh, S. Nowicki, K. Baxter, R. L. Stoddard and J. S. McIndoe, *Organometallics*, 2015, **34**, 3816–3819.

30   K. L. Vikse, Z. Ahmadi, J. Luo, N. Van Der Wal, K. Daze, N. Taylor and J. S. McIndoe,

Int. J. Mass Spectrom., 2012, **323-324**, 8–13.

31 M. A. Henderson, J. Luo, A. Oliver and J. S. McIndoe, *Organometallics*, 2011, **30**, 5471–5479.

32 W. Henderson and J. S. McIndoe, *Mass spectrometry of inorganic and organometallic compounds*, J. Wiley, 2005.

33 P. A. Eckert, P. J. Roach, A. Laskin and J. Laskin, *Anal. Chem.*, 2012, **84**, 1517–25.

34 P. Liu, Q. Shi, K. H. Chung, Y. Zhang, N. Pan, S. Zhao and C. Xu, *Energy & Fuels*, 2010, **24**, 5089–5096.

35 J. M. E. Quirke, C. L. Adams and G. J. Van Berkel, *Anal. Chem.*, 1994, **66**, 1302–1315.

36 H. Hayen and U. Karst, *J. Chromatogr. A*, 2003, **1000**, 549–565.

37 J. M. Purcell, P. Juyal, D.-G. Kim, R. P. Rodgers, C. L. Hendrickson and A. G. Marshall, *Energy & Fuels*, 2007, **21**, 2869–2874.

38 J. M. Purcell, C. L. Hendrickson, R. P. Rodgers and A. G. Marshall, *Anal. Chem.*, 2006, **78**, 5906–5912.

39 M. Tubaro, E. Marotta, R. Seraglia and P. Traldi, *Rapid Commun. Mass Spectrom.*, 2003, **17**, 2423–2429.

40 S. P. Black, J. K. M. Sanders and A. R. Stefankiewicz, *Chem. Soc. Rev.*, 2014, **43**, 1861–72.

41 S. Otto, *J. Am. Chem. Soc.*, 12AD, **122**, 12063–12064.

42 L. Patiny and A. Borel, *J. Chem. Inf. Model.*, 2013, **53**, 1223–8.

43 H. Janusson, E.; Luo, J.; McGarvey, B.; McIndoe, J. S.; Oliver, A. G.; Piers, J.; Zhu, *Phenol-selective mass spectrometric analysis of petroleum fractions. Unpublished Manuscript.*, .

44 Z. Shaked, R. P. Szajewski and G. M. Whitesides, *Biochemistry*, 1980, **19**, 4156–66.

45 R. Singh and G. M. Whitesides, *Chem. sulphur-containing Funct. groups. Chichester, Engl. John Wiley Sons*, 1993, 633–658.

46 R. Javadli and A. Klerk, *Appl. Petrochemical Res.*, 2012, **1**, 3–19.

Conflict of Interest Disclosure

The authors declare no competing financial interest.