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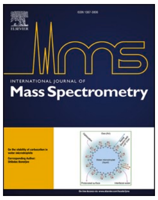

The amenability of different solvents to electrospray ionization mass spectrometry

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ABSTRACT

Electrospray ionization mass spectrometry is capable of transferring ions from solution to the gas phase across a broad range of solvents. A systematic investigation of the relative performance of different solvents has not been previously conducted, and we sought to remedy this situation. Fourteen solvents across a wide range of polarities were investigated for their ability to provide strong signals for four permanently charged ions. We found the best solvents to be acetone, acetonitrile, dichloromethane, tetrahydrofuran, and the previously unused (in an ESI-MS context) trifluorotoluene.

1. Introduction

The electrospray ionization mass spectrometry (ESI-MS) process involves a solution of ions passing through a charged capillary. The solution emerges into an atmospheric pressure chamber filled with warm nitrogen gas, and creates a fine spray of droplets [1]. These droplets carry an excess of one charge or another, dependent on the ion mode under study, and the excess charge is generated through electrochemical processes (oxidation in the positive ion mode, reduction in the negative ion mode) [2,3]. Electrochemistry is favoured in polar solvents [4], which is why ESI-MS is nearly always conducted in such solvents, with water/acetonitrile and methanol being particularly popular. However, a wide range of solvents can be used under appropriate conditions, including even very non-polar solvents such as hexane provided a suitable supporting electrolyte is added [5]. That particular innovation comes with the considerable downside that the last thing most people wish to put in their instrument is a hexane-soluble ionic compound, which tend to have very high surface activity, causing ion suppression and contamination of the source. As such, alternative solvents that support the necessary electrochemistry but do not require the added electrolyte are desirable, and we and others have tried many different options. Some of the more unusual examples involved in successful analyses that we have demonstrated include dimethylformamide [6], fluorobenzene [7], chlorobenzene [8], and 1,2-difluorobenzene [9]. Reasons for avoiding the polar solvents typical of ESI-MS analysis usually concern reactivity, with strongly coordinating and/or protic solvents being incompatible with, for example, reactive organometallic species [9].

As far as we know, no one has systematically investigated different solvents for their amenability to ESI-MS, and so we have tackled this question here, as well as explored an alternative solvent that has not attracted attention in this context before, trifluorotoluene. It drew us due to having some similar solvent properties to dichloromethane, which is an excellent ESI-MS solvent for permanently charged ions. Additionally, trifluorotoluene has the advantages of being less reactive and having a considerably higher boiling point than dichloromethane (104 °C vs. 39 °C), dramatically broadening the range of reaction temperatures that can be employed when conducting real-time ESI-MS reaction analysis [10].

To uncomplicate the experiments, we opted to examine species that carry a permanent charge. This choice partly reflects our own biases - charged tags are how we [11] (and many others) [12–27] go about studying reactions using ESI-MS. We readily concede that the results we obtain will not be entirely representative of the experience of the great majority of analysts who rely on the appearance of quasimolecular ions such as $[M + nH]^{n+}$, $[M - nH]^{n-}$, or $[M + Na]^{+}$. Such solvents need to not only dissolve the analyte and support the electrochemistry, but also need to support the association of a charged species. Protic solvents are good at meeting all of these requirements, and so water/acetonitrile and methanol are very common solvents for ESI-MS.

2. Methodology

A solution of $[N(C_4H_9)_4]^+$ $[PF_6]^-$ and $[Ph_3P(CH_2)_3OH]^+$ $[N(SO_2CF_3)_2]^-$ (see Fig. 1) was made up at a concentration of 5 µmol each in each solvent. We chose different ions because these can exhibit different relative responses in different solvents [28,29]. To encourage dissolution in the more reluctant solvents, solutions were sonicated for 2 min prior to analysis.

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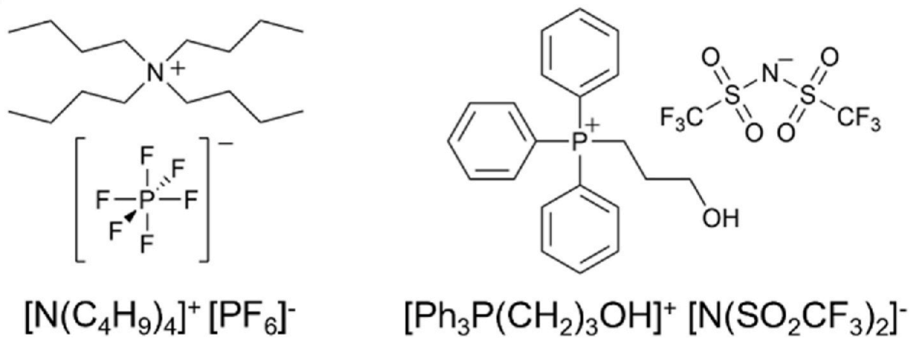


Fig. 1. Structures and pairing of the four ions investigated in this work.

Each solution was infused into a Waters tandem quadrupole detector (TQD) mass spectrometer and the instrument settings optimized against the total ion current using OptiMS [30]. To expedite this process, we did not include source temperature in our optimization, which is very slow to change. Instead we used a rule of thumb that has guided our setting of source temperature prior to the development of OptiMS, namely setting the source temperature to the boiling point of the solvent plus an increment derived from the heat of vaporization of the solvent. The empirical expression we developed for the increment in degrees is boiling point in °C plus heat of vaporization (kJ/ml) × 15 (see supporting information for the calculation spreadsheet). This rule of thumb came about because it did a good job of matching the values that we had established through trial and error, and so we have extrapolated it to the new solvents we investigated in this contribution. Similarly, we did not optimize the cone voltage, because it scales approximately linearly with the TIC [31]. We instead set the cone voltage at 20 V for all experiments, because this setting is enough to efficiently transport ions into the mass spectrometer but not so high as to cause appreciable fragmentation.

Once the settings were optimized, we collected 1 min of data and

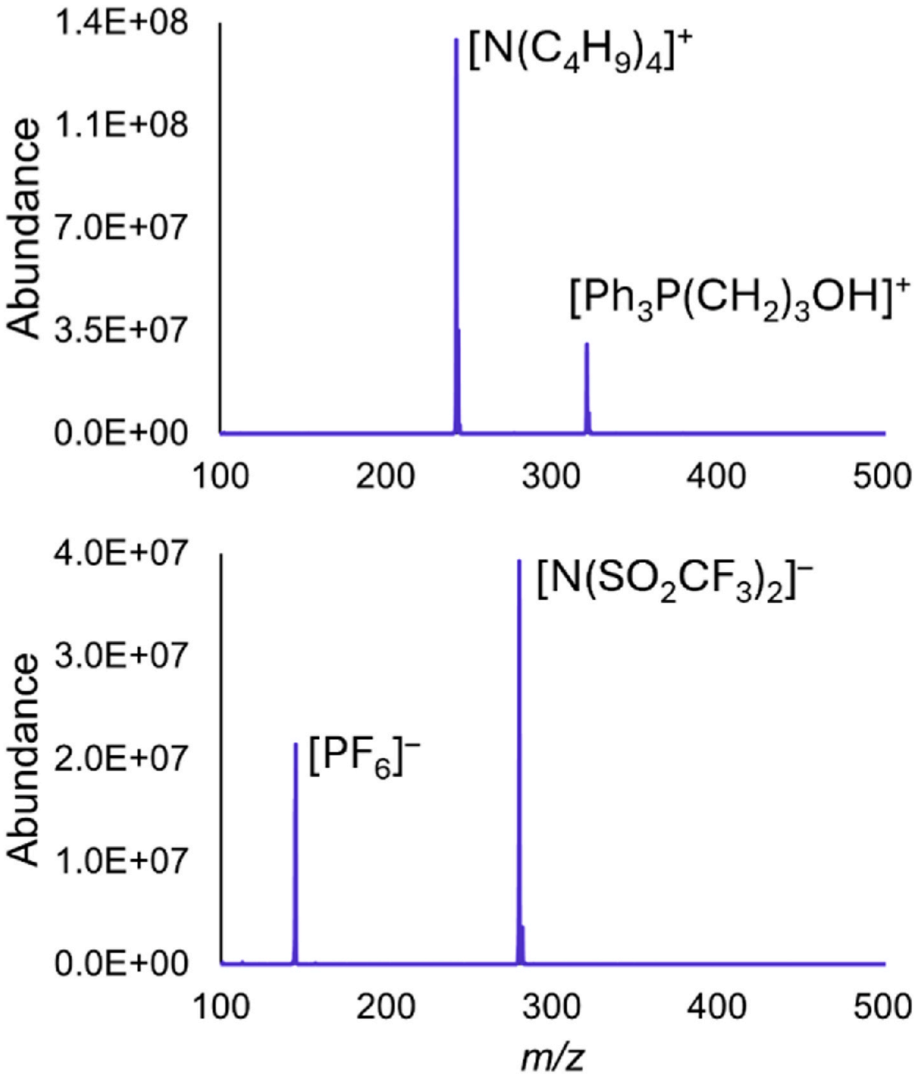


Fig. 2. Positive ion (top) and negative ion (bottom) ESI mass spectra of a 5:5 μmol mixture of $[N(C_4H_9)_4]^+$ $[PF_6]^-$ and $[Ph_3P(CH_2)_3OH]^+$ $[N(SO_2CF_3)_2]^-$ in dichloromethane.

measured the ion intensity for each ion. This process was repeated in the other ion mode. For consistency, we used the optimized settings in the positive ion mode for the negative ion mode as well. All spectra are available in the supporting information, but all resemble the representative spectra shown in Fig. 2 for dichloromethane.

3. Results & discussion

There are many solvent properties that could potentially influence the amenability of a solvent to ESI-MS, and we have collected all that we could think of in Table 1. These include dielectric constant, dipole moment, Hansen solubility parameters [32] (which break down the Hildebrand solubility parameter into components from dispersion, polarity and hydrogen bonding), donor number, boiling point, viscosity, density, and molecular weight. A dynamic spreadsheet including the same data is available in the supporting information, so interested parties can interrogate the data themselves.

There are no clear relationships between any of the solvent parameters and ion intensity (see Table 2). Two selected examples are shown in Fig. 3 using log[average ion intensity] in each case, and the supporting information also contains plots of the remaining solvent parameters against the ion intensity. In these cases, each ion intensity has been separated out, though there is high correlation between ion intensities across different solvents.

Our selected ions are soluble in a wide range of solvents, but minimally so in water or in non-polar solvents such as toluene or hexane. We can safely assume that ion intensities in the non-polar solvents are likely to be very low, so the plots of dipole moment and dielectric constant would in that case be populated by additional points in the bottom left of the plot. It becomes easier then to see the influence of polarity, in that it seems to require dielectric constants >7 and dipole moments >1.7 (the two are of course correlated) in order to unlock maximal ion intensities. Increases beyond these values do not seem to have much of an effect on ion intensity, pointing to polarity having an enabling threshold for ESI-MS analysis.

We can class the 14 solvents we investigated into three groups in terms of their ESI-MS amenability, namely poor, average, and good. We will discuss each of these in turn. Note that some of the solvents that we are investigated are flammable, and so it is important to run nitrogen as the desolvation gas to avoid any issues. Venting systems for the roughing pumps on the mass spectrometer should be made of a material that does not degrade when exposed to organic solvents (i.e. no PVC tubing). In addition, as this work was performed with direct infusion of the analyte solutions into the ESI source, the only limitations on solvent selection we employed were to discount common solvents which are very nonvolatile (e.g. dimethyl sulfoxide), or those likely to result in persistent contaminant ions, such as acetic acid and triethylamine. The practical benefit of the direct infusion approach is avoiding chemical incompatibility with the chromatography columns often used in tandem with ESI-MS; column-specific solvent compatibility should always be confirmed before

Table 1

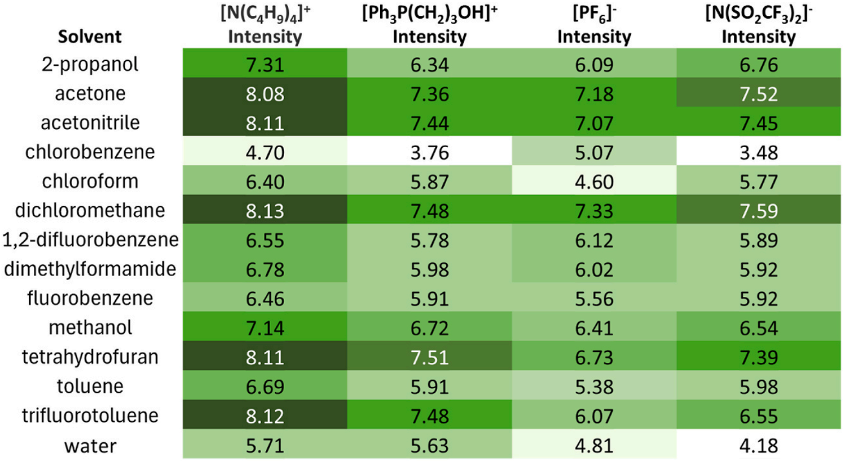
Selected solvent parameters for the solvents used in this study.

a. Hansen solubility parameters (δT, δD, δP, δH) are in Mpa$^{1/2}$.

Solvent	Formula	M.W.	bp (°C)	Density (g/ml)	Dielectric constant	Dipole moment (D)	δT[32], [a]	δD[32]	δP[32]	δH[32]	Donor Number	Viscosity 20 °C (cP)
2-propanol	C_3H_8O	60.1	82.4	0.785	18.3	1.66	23.5	15.8	6.1	16.4	21.1	2.3
Acetone	C_3H_6O	58.079	56.1	0.7845	21.01	2.88	20	15.5	10.4	7	17	0.32
acetonitrile	C_2H_3N	41.052	81.7	0.7857	36.64	3.92	24.4	15.3	18	6.1	14.1	0.36
chlorobenzene	C_6H_5Cl	112.56	131.7	1.1058	5.69	1.5	19.6	19	4.3	2	3.3	0.8
chloroform	$CHCl_3$	119.38	61.2	1.4788	4.81	1.04	19	17.8	3.1	5.7	4	0.57
dichloromethane	CH_2Cl_2	84.93	39.6	1.3266	9.08	2.53	20.3	18.2	6.3	6.1	1	0.43
1,2-difluorobenzene	$C_6H_4F_2$	114.09	92	1.16	13.8	2.8	–	18.0	9.0	1.0	–	–
dimethylformamide	C_3H_7NO	73.09	153	0.9445	38.25	3.82	24.8	17.4	13.7	11.3	26.6	0.85
fluorobenzene	C_6H_5F	96.1	85	1.025	5.42	1.66	–	18.7	6.1	2.0	3	–
Methanol	CH_4O	32.04	64.6	0.791	32.6	1.7	29.6	15.1	12.3	22.3	19	0.55
tetrahydrofuran	C_4H_8O	72.106	65	0.8833	7.52	1.75	19.4	16.8	5.7	8	20	0.55
toluene	C_7H_8	92.14	110.6	0.867	2.38	0.36	18.3	18.0	1.4	2.0	0.1	0.59
trifluorotoluene	$C_7H_5F_3$	146.1	104	1.19	9.18	2.86	–	–	–	–	–	–
water	H_2O	18.02	100	0.998	78.54	1.85	47.8	15.6	16	42.3	18	1

Table 2

Heat map showing logarithmic values of ion response in each solvent tested.



Solvent	$[N(C_4H_9)_4]^+$ Intensity	$[Ph_3P(CH_2)_3OH]^+$ Intensity	$[PF_6]^-$ Intensity	$[N(SO_2CF_3)_2]^-$ Intensity
2-propanol	7.31	6.34	6.09	6.76
acetone	8.08	7.36	7.18	7.52
acetonitrile	8.11	7.44	7.07	7.45
chlorobenzene	4.70	3.76	5.07	3.48
chloroform	6.40	5.87	4.60	5.77
dichloromethane	8.13	7.48	7.33	7.59
1,2-difluorobenzene	6.55	5.78	6.12	5.89
dimethylformamide	6.78	5.98	6.02	5.92
fluorobenzene	6.46	5.91	5.56	5.92
methanol	7.14	6.72	6.41	6.54
tetrahydrofuran	8.11	7.51	6.73	7.39
toluene	6.69	5.91	5.38	5.98
trifluorotoluene	8.12	7.48	6.07	6.55
water	5.71	5.63	4.81	4.18

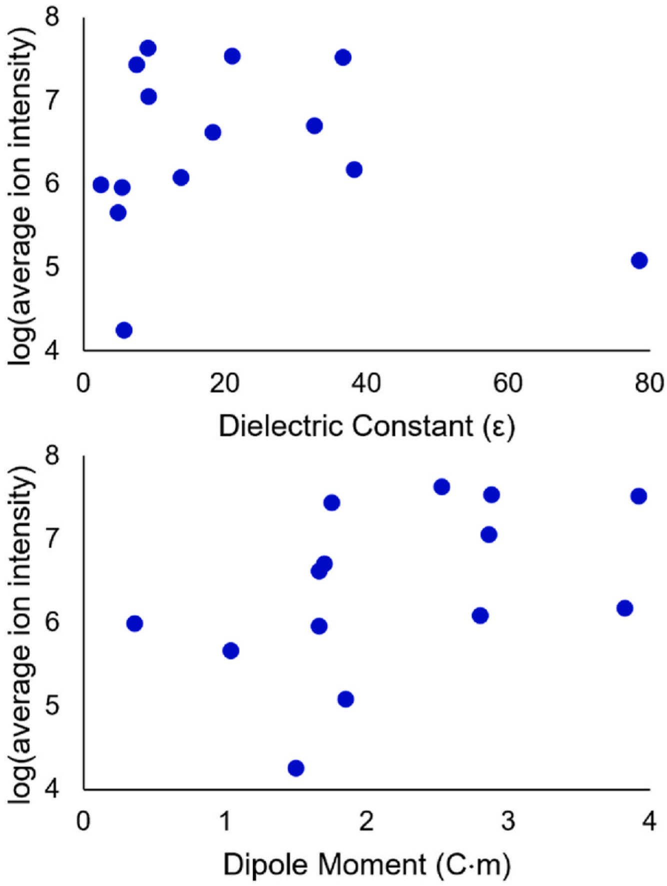


Fig. 3. Plots of log[average ion intensity] vs. dielectric constant (top) and dipole moment (bottom).

new method development.

Outright poor solvents include toluene, chlorobenzene, chloroform, and fluorobenzene. All of these have dielectric constants <7 and dipole moments <1.7, and we strongly suspect any solvent with these characteristics would fall in this class. The main reason for their poor performance is their low polarity which renders them unable to support the necessary electrochemistry to create a sufficient supply of excess charge. We recommend these solvents only when none of the average/good solvents described below are available. Toluene is a sufficiently poor solvent for the ions under study that solubility effects may play an additional role in the low signal observed. Another solvent in this category is water, which of course has a very high dielectric constant and dipole moment. However, the problem in this context is also solubility – neither of the ionic compounds investigated is appreciably soluble in water, and so their low ion intensities (barely competing with background chemical noise) reflect that fact.

Average solvents included isopropanol, methanol, 1,2-difluorobenzene, and dimethylformamide (DMF). All of these have dielectric constants >7 and dipole moments >1.7, so the electrochemistry is not at issue here (though 1,2-difluorobenzene is borderline). Dimethylformamide is complicated by the presence of prominent $[(DMF)_2H]^+$ and $[(DMF)_2Na]^+$ peaks, consistent with the fact that basic solvents also complicate ESI-MS analysis of neutral species that acquire their charge via association of a proton or other cation, as these can be stripped of their charge by the solvent [33]. We see this process happening to a large extent even in the absence of added H^+ or Na^+ (presumably arising from the glassware). Methanol is a very common ESI-MS solvent (isopropanol to a lesser extent), and we were somewhat surprised to see it providing significantly lower ion response than other solvents. We suspect what is going on here is something similar to what we saw for DMF, namely the appearance of solvent-related ions.

Good solvents were acetone, acetonitrile, dichloromethane, tetrahydrofuran (THF), and trifluorotoluene. All of these are polar and aprotic. We were somewhat surprised by the tetrahydrofuran result, as it has a poor reputation in our laboratory for reasons we haven't previously examined in detail. It does get mentioned as being problematic by manufacturers because it attacks the PEEK tubing [34,35]. We investigated this behavior by examining slices of PEEK tubing soaked in THF, but no significant change in PEEK tubing internal diameter could be detected after immersion in THF for 1 h (see SI, Fig. S30). It has been the case that often we were running THF/water mixtures [36], and as these solvents have complicated miscibility especially in the presence of ionic compounds [37], it may be the case that combination of the two was the problem rather than the THF itself. It is reasonable to imagine that tiny droplets of water suspended in the THF may cause instability of the ESI spray.

The high performance of trifluorotoluene was a gratifying result, and puts it firmly into consideration as a promising, previously overlooked ESI-MS solvent. Interestingly, it was also relatively late (2000) to be recognized as a useful solvent for electrochemistry [39]. We will definitely be using it in our laboratory as a replacement for fluorobenzene and 1,2-difluorobenzene, and as a substitute for dichloromethane when we need to access a higher temperature regime (40–100 °C). While we do not believe the ability of the solvents tested herein to support the electrochemistry necessary for ESI would differ much between different electrospray sources, the effects different instrument configurations have on analytes of interest must be considered [38].

4. Experimental

All mass spectrometry experiments were conducted with a Waters Acquity tandem quadrupole detector (TQD) in positive and negative mode with a cone voltage of 20 V, desolvation gas flow of 100 L h^{-1}, cone gas flow of 100 L h^{-1}, and a detector gain of 470 V. Scan time was set to 1 s, with an inter-scan time of 0.1 s. Capillary voltage, extraction voltage, and rf lens voltage were optimized for each solvent in positive mode using OptiMS, with these parameters also used for negative mode data acquisition, except for trifluorotoluene, for which a capillary voltage of 2 kV was used (see Figs. S25 and S26 for comparison). Source temperatures were calculated as boiling point in °C plus (heat of vaporization (kJ/ml) × 15), and desolvation gas temperature was set to source temperature plus 100 °C. All other instrumental parameters were kept constant throughout. A stock solution of both salts was prepared in dichloromethane, with aliquots transferred into vials and concentrated *in vacuo* before subsequent dilution to a final concentration of 5 μmol for each solvent tested. Solutions were infused with a syringe pump at a flow rate of 15 μL per minute.

(3-hydroxypropyl)triphenylphosphonium chloride was prepared according to literature procedure [40]. (3-hydroxypropyl)triphenylphosphonium bis(trifluoromethane)sulfonimide was prepared from the corresponding chloride salt *via* salt metathesis in 5:1 water:methanol with 1.2 equivalents of lithium bis(trifluoromethane)sulfonimide, followed by thorough washing with deionized water and drying under high vacuum.

2-propanol (EMD Millipore, HPLC), acetone (Sigma-Aldrich, ACS, >99.5 %), acetonitrile (Fisher, HPLC), chlorobenzene (Sigma-Aldrich, Anhydrous, >99.8 %), chloroform (Fisher, ACS), dichloromethane (Supelco, HPLC), 1,2-difluorobenzene (Oakwood, 99 %), dimethylformamide (Fisher, ACS), fluorobenzene (Oakwood, 99 %), methanol (Fisher, HPLC), tetrahydrofuran (Sigma-Aldrich, HPLC, >99.9 %), trifluorotoluene (Sigma-Aldrich, Anhydrous, >99 %), 3-chloro-1-propanol (Sigma-Aldrich, 98 %), toluene (Sigma-Aldrich, 99.9 %), triphenylphosphine (Sigma-Aldrich, 99 %), sodium iodide (Sigma-Aldrich, ACS, 99.6 %), lithium bis(trifluoromethane)sulfonimide (Sigma-Aldrich, 97 %), and tetrabutylammonium hexafluorophosphate (MilliporeSigma, >99.0 %) were obtained from commercial suppliers and used without further purification.

5. Conclusions

Electrospray ionization mass spectrometry is amenable to a diverse array of solvents provided the analyte of interest is inherently charged. Factors that contribute to especially good performance (high ion intensity, flat baselines) include: dielectric constants >7 and dipole moments >1.7; no competing ionization pathways for the solvent (e.g. protonation, deprotonation); no gas-phase ion-molecule chemistry available for the solvent; no solvent breakdown products that lead to easily-charged species; and of course, sufficiently good solvating power to fully dissolve the analyte. An especially good candidate for ESI-MS of reactive ionic compounds that has been previously overlooked is trifluorotoluene, PhCF$_3$, uncovered here for its similarity in polarity to dichloromethane (an excellent ESI-MS solvent itself). We see it additionally as a less-expensive, higher-performing substitute for solvents such as fluorobenzene and 1,2-difluorobenzene.

CRediT authorship contribution statement

Charles Killeen: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation. **Antonia Kropp:** Visualization, Investigation. **Ian C. Chagunda:** Methodology. **Emily C. Jackson:** Visualization, Investigation. **J. Scott McIndoe:** Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J. Scott McIndoe reports financial support was provided by Natural Sciences and Engineering Research Council of Canada. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijms.2024.117349.

Data availability

Data will be made available on request.

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