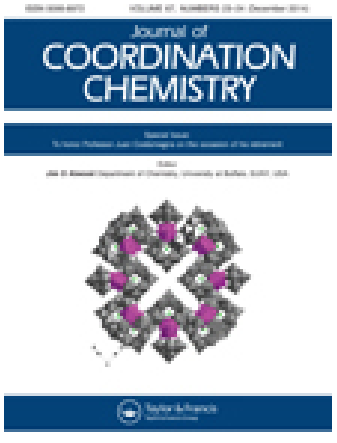

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Towards the water solubilization of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ derivatives by polyether functionalization - a synthetic and mass spectrometric investigation

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Towards the water solubilization of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ derivatives by polyether functionalization – a synthetic and mass spectrometric investigation

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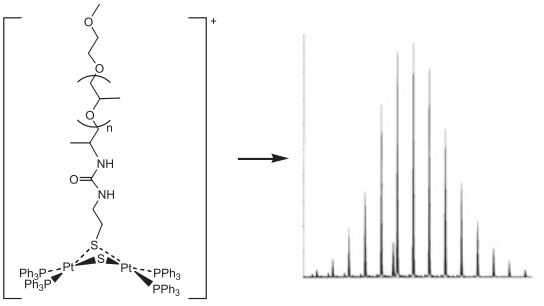

The functionalisation of the platinum(II) sulfide complex $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ with polyether-based alkylating agents, monitored by ESI mass spectrometry, leads to a series of novel polyether-thiolate complexes.

Synthetic methods have been developed to append polyether chains onto the nucleophilic platinum (II) sulfide complex $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ through alkylation reactions of a sulfide ligand. Reaction of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ with $Br(CH_2)_2NHC(O)NH(CH_2)_2OMe$ gave the monoalkylated model complex $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NH(CH_2)_2OMe\}(PPh_3)_4]^+$, isolated as its PF_6^- salt. Extension of this methodology to the polyether-derived alkylating agent $Br(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe$ derived from the polyether amine Jeffamine® M600 gave the cation $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]^+$, isolated as its BPh_4^- salt and characterized by ESI MS and $^{31}P\{^1H\}$ NMR spectroscopy. Reaction of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ with the chloro-PEG $Me(OCH_2CH_2)_nCl$ (derived from MeOPEG 350) in the presence of NaBr in refluxing methanol proceeded slowly, giving $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2CH_2O)_nMe\}(PPh_3)_4]^+$, isolated as its BPh_4^- salt. The aqueous solubility of a selection of compounds was determined.

Keywords: Platinum complexes; Sulfide complexes; Thiolate complexes; Polyether; Electrospray ionization mass spectrometry

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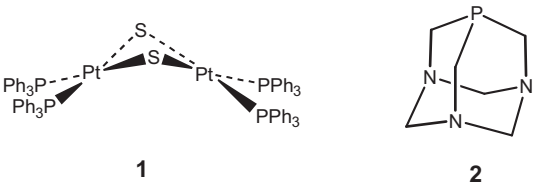
1. Introduction

The platinum(II) sulfide complex $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ **1** (scheme 1) and closely related analogs containing alternative phosphine ligands contain nucleophilic sulfides, and as a consequence have a very extensive chemistry as a nucleophile [1]. By reaction with organic electrophiles, it is possible to convert either one or both bridging sulfides ($\mu\text{-}S^{2-}$) into bridging thiolates ($\mu\text{-}SR^{-}$), allowing a facile methodology for synthesis of a diverse range of functionalized thiolate complexes of platinum(II) [2–4]. Using this chemistry, it has been possible to synthesize a wide range of dinuclear platinum(II) thiolate complexes which include simple alkyl or aryl substituents [5], dithiolates [6], fluorinated groups [7], carbonyl-containing compounds [8], and heterocycles [9]. However, these compounds, as a result of the presence of highly lipophilic PPh_3 (or other aryl phosphines) and the thiolate substituent, are typically soluble only in polar organic solvents such as methanol and dichloromethane. We wished to investigate whether or not such dinuclear thiolate complexes might have interesting biological properties, but their effective insolubility in water precluded such studies. Replacing PPh_3 with a water-soluble phosphine such as phosphatriazaadamantane (PTA, **2** (scheme 1)) offers a possible means to achieve improved water-solubility [10] but the platinum–sulfide derivative of this phosphine has not been prepared. We have therefore explored an alternative methodology through appending water-solubilizing groups onto the thiolate sulfur. Polyether functionalization offered an attractive means to achieve this; polyethers are commercially available with a range of functional groups and are typically inexpensive, of low toxicity, and biocompatible. Attachment of polyether chains (generically termed PEGylation in the case of polyethyleneglycol derivatives) is a widely employed strategy for solubilizing a diverse range of substrates, from therapeutic drugs [11] to inorganic nanoparticles [12] to single-walled carbon nanotubes [13]. Although PEGylation of metal complexes is less well studied, there are sufficient literature precedents [14] to confirm the validity of the approach, including applications to platinum complexes having biological activity [15]. Furthermore, ESI mass spectrometry [16], which we have extensively used in developing the chemistry of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ [17], is a powerful technique for characterization of polyether-containing materials, easily able to characterize the typically complex mixtures of oligomers and cationic adducts thereof [18–20]. Indeed, some of the very earliest studies on ESI MS recognized the power of the technique for characterizing polyethers [21].

2. Results and discussion

2.1. *Synthesis and characterization of the short-chain model complex $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NH(CH_2)_2OMe\}(PPh_3)_4]PF_6$, $4{\cdot}PF_6$*

We have previously used 2-chloroethylurea derivatives to monoalkylate $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ [8]. The reaction between 2-bromoethylisocyanate ($BrCH_2CH_2NCO$) and an amine was an attractive method for converting commercially available, inexpensive polyetheramines (Jeffamines®) into alkylating agents, via the formation of a bromoethylurea derivative. Alkyl bromides are effective alkylating agents towards $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$, showing good reactivity but without the complicating side reactions (from the halide acting as a nucleophile) that can occur with alkyl iodides [3]. The mechanism of alkylation of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ has been studied theoretically, and the effect of the halide of the



1 **2**

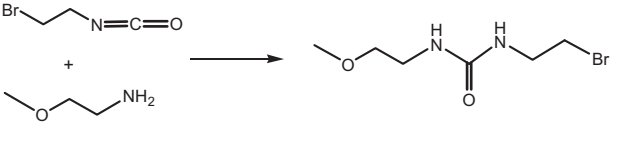
Scheme 1.

alkylating agent, the effect of an excess of alkylating agent, and the effect of solvent polarity have been determined [22].

To extend the methodology to polymeric alkylating agents, a short-chain model alkylating agent was initially synthesized and its reactivity with $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ was investigated. Reaction of $BrCH_2CH_2NCO$ with $H_2NCH_2CH_2OMe$ in diethyl ether proceeded rapidly, giving the white crystalline 2-bromoethylurea product **3**, scheme 2. This compound has not been reported previously, however, several compounds with the $BrCH_2CH_2NHC(O)NHCH_2CH_2$–moiety are known [23]. The positive-ion ESI mass spectrum of **3** showed $[M+H]^+$ (*m/z* 225.020) and $[M-Br]^+$ (*m/z* 145.094) ions, the former having a distinctive isotope pattern as a result of the two Br isotopes (^{79}Br, ^{81}Br). The $[M-Br]^+$ ion was the base peak even at low capillary exit voltages; this is ascribed to a facile cyclization reaction (via loss of HBr) known to occur for 2-haloethylureas to produce a five-membered oxazoline ring [24]. Other minor ions were also observed; these all contain one or two bromines from their distinctive isotope patterns, and include $[2M+H]^+$ (*m/z* 451.029) and $[2M-Br]^+$ (*m/z* 369.106). The compound showed a double melting point, melting to a colorless liquid at 62–64 °C, which then formed colorless crystals melting at 78–80 °C; this is also consistent with the conversion to an oxazoline product on heating [24].

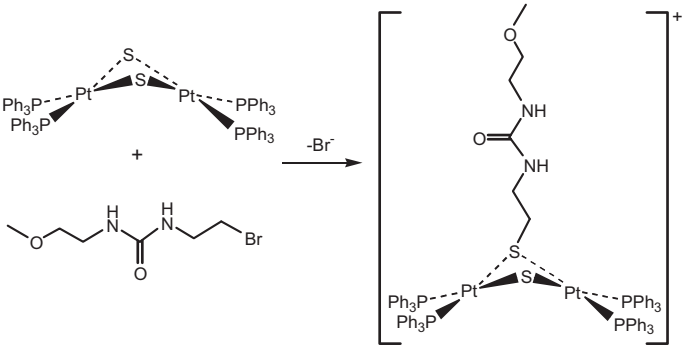
Reaction of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ with **3** proceeded rapidly in refluxing methanol, giving a yellow solution containing $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NH(CH_2)_2OMe\}(PPh_3)_4]^+$, which was isolated as its PF_6^- salt **4**·PF_6, scheme 3. The positive-ion ESI mass spectrum showed a dominant base peak at *m/z* 1648.286 due to the parent cation, with excellent agreement between observed and calculated isotope patterns for the ion (calculated *m/z* 1648.337). A small ion at *m/z* 835.465 was assigned to the sodiated dication $[M+Na]^{2+}$ (calculated *m/z* 835.663) from adventitious sodium ions; this ion gave the signature 0.5 *m/z* separation between adjacent peaks in the isotope pattern. Since simple monoalkylated complexes $[Pt_2(\mu\text{-}S)(\mu\text{-}SR)(PPh_3)_4]^+$ (R = e.g. alkyl, Ph) do not form such sodiated cations, the sodium ion presumably interacts with the C=O or OMe oxygens of the thiolate.

The $^{31}P\{^1H\}$ NMR spectrum of **4**·PF_6 showed a very pure complex, with a single central resonance as a complex multiplet at δ 24.5, with two sets of satellites due to coupling to



3

Scheme 2. Synthesis of the model alkylating agent $Br(CH_2)_2NHC(O)NH(CH_2)_2OMe$ **3**.



4

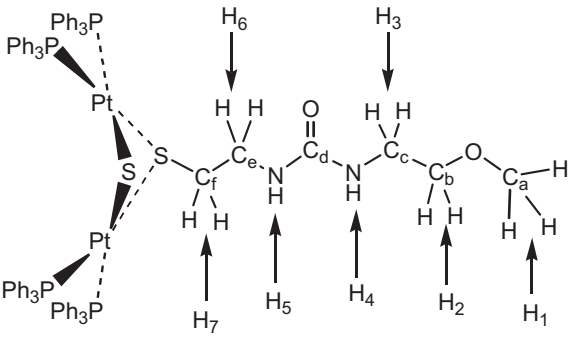
Scheme 3. Synthesis of the model complex $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NH(CH_2)_2OMe\}(PPh_3)_4]^+$ **4**.

^{195}Pt, and ^1J(PtP) coupling constants of 2602 (phosphines *trans* to sulfide) and 3267 Hz (phosphines *trans* to thiolate); ^{31}P NMR data for compounds described in this article are summarized in table 1 and are comparable to other monoalkylated derivatives of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ [8, 25]. In addition to the expected complex set of signals due to PPh_3 ligands, a number of peaks at $\delta < 5$ were observed in the proton NMR spectrum. Scheme 4 shows the NMR atom numbering scheme of **4**. A sharp singlet at δ 3.4 was assigned as the OCH_3 (H_1), and a HSQC spectrum established the connectivity between these protons and the $^{13}C_a$ resonance at δ 58.8, consistent with evidence from the DEPT135 NMR spectrum. The CH_2O methylene (C_bH_2) was subsequently identified as the ^{13}C resonance at δ 72.0 and the multiplet proton signal at δ 3.5. Carbon b showed a ^2J coupling to the multiplet at δ 3.5 (superimposed on the methoxy singlet) indicating the multiplet to be due to methylene protons H_3, subsequently allowing assignment of carbon c at δ 40.1. A ^3J coupling (in both COSY and TOCSY spectra) between hydrogens H_3 and a relatively broad triplet peak at δ 4.4 allowed assignment of the latter as an NH proton (H_4). The other broad resonance at δ 4.9 was therefore easily assigned as the other NH proton, H_5. Similarly, this showed a ^2J coupling in the cozy spectrum to a multiplet at δ 2.9, identifying it as CH_2 protons H_6, and subsequently identifying carbon e at δ 41.5. The urea carbon was observed at δ 157.5 and (as expected) was absent in the DEPT135 spectrum. The remaining two CH_2 groups were assigned using the same methodology, with the thiolate carbon appearing at δ 40.1 in the ^{13}C spectrum (carbon f, overlapping with carbon c), and giving a rather broad ^{1}H NMR signal at δ 2.1, the broadness being ascribed to unresolved ^{31}P and ^{195}Pt couplings, as

Table 1. Summary of $^{31}P\{^1H\}$ NMR data for the monoalkylated complexes $[Pt_2(\mu\text{-}S)(\mu\text{-}SR)(PPh_3)_4]^+$ described herein.

		^1J(PtP) (Hz)	
Complex	R	*Trans* S^{2-}	*Trans* SR^-
4·PF_6	$(CH_2)_2NHC(O)NH(CH_2)_2OMe$	2606	3262
6·BPh_4	$(CH_2)_2NHC(O)NHCHMeCH_2$–$(OCHMeCH_2)_nOCH_2CH_2OMe$	2619	3311
7·BPh_4	$(CH_2CH_2O)_nMe$	2610	3287

Note: For all complexes the PPh_3 chemical shift was δ 24.5.



Scheme 4. NMR atom labeling scheme of [Pt$_2$(μ-S){μ-S(CH$_2$)$_2$NHC(O)NH(CH$_2$)$_2$OMe}(PPh$_3$)$_4$]$^+$ **4**.

observed previously in related compounds [8]. The CH_2 group (H_6) appeared at δ 2.9, which correlated to carbon e at δ 41.5 in the ^{13}C spectrum.

In order to fully characterize the model complex (attempts to obtain single crystals of longer chain polyether derivatives described later in this article were unsuccessful) and identify any interesting structural features (e.g. potential hydrogen bonding involving the urea group), a single-crystal X-ray diffraction study was carried out on **4**·PF_6. However, the structure determination was of very poor quality and only served to confirm the expected connectivity of the complex (figure 1). Subsequent attempts to obtain a crystal of a different salt (**4**·BPh_4) or to grow crystals from other solvents were also unsuccessful.

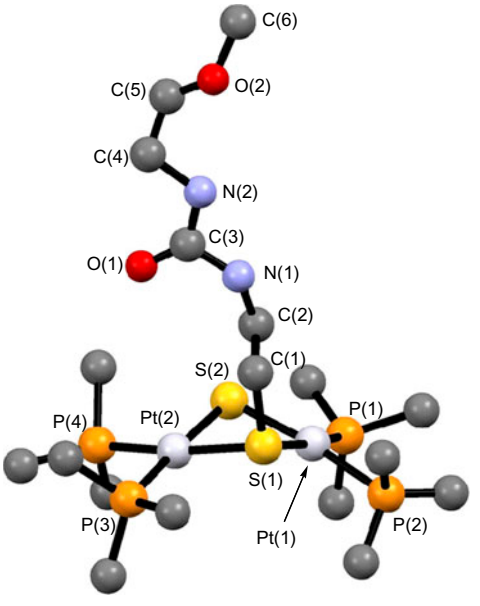
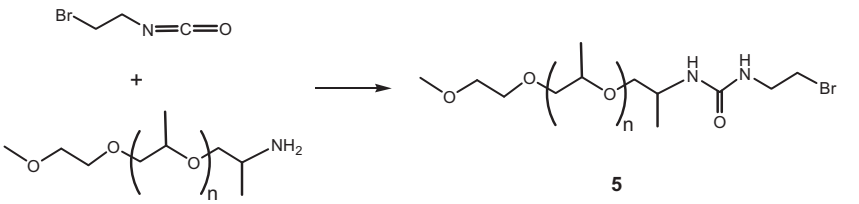


Figure 1. Molecular structure of the core of [Pt$_2$(μ-S){μ-S(CH$_2$)$_2$NHC(O)NH(CH$_2$)$_2$OMe}(PPh$_3$)$_4$]$^+$; only *ipso* carbons of the PPh_3 ligands are shown, and the hydrogen atoms and PF_6^- counteranion are omitted.



Scheme 5. Synthesis of the Jeffamine® M600-derived bromoethylurea alkylating agent $Br(CH_2)_2NHC(O)NHCH-MeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe$ **5**.

2.2. *Synthesis and characterization of the Jeffamine® M600-derived complex $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]^+$ 6*

Following the same methodology described for the model complex (*vide supra*), the commercially available polyether amine Jeffamine® M600, $MeOCH_2CH_2O(CH_2CHMeO)_nCH_2CHMeNH_2$ (a propylene oxide-derived oligomer functionalized with a single primary amine group), was reacted with $Br(CH_2)_2NCO$, giving the 2-bromoethylurea derivative **5**, scheme 5. The reaction was conveniently carried out in hexane, in which both starting materials are readily soluble, but the product is immiscible, forming a viscous lower phase, allowing purification from any unreacted starting materials by washing with hexane. After vacuum drying, the alkylating agent $Br(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe$ **5** was obtained as a viscous, pale yellow oil.

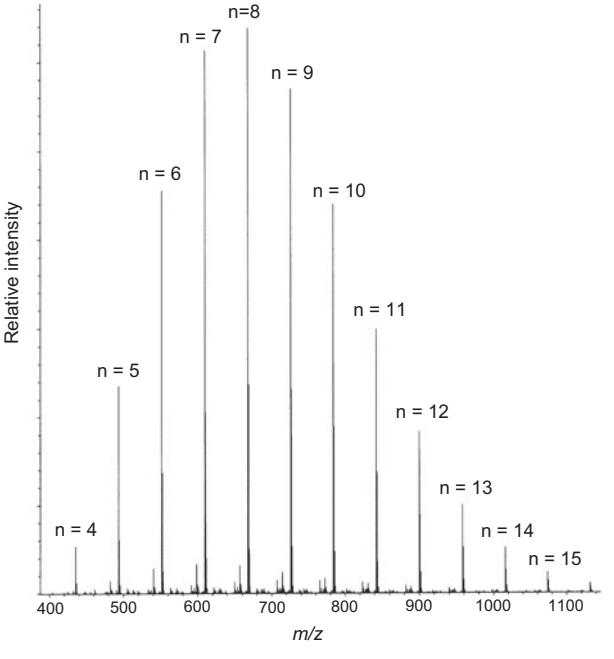


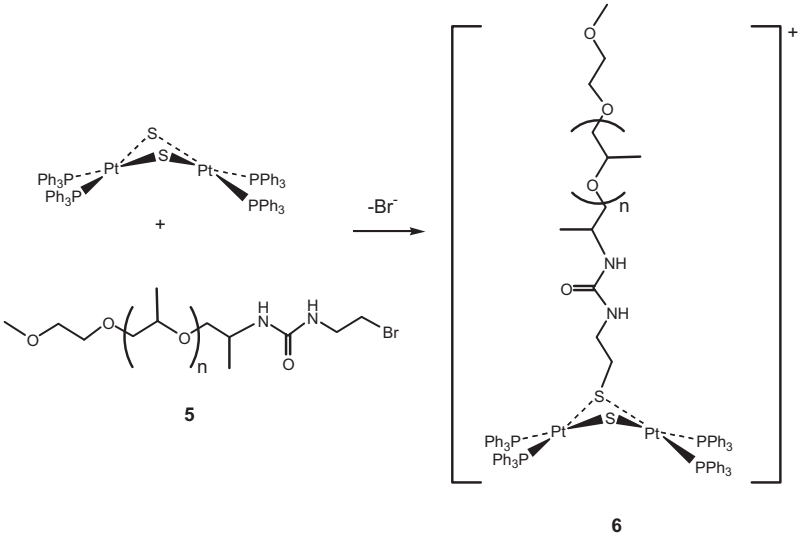
Figure 2. Positive-ion ESI mass spectrum (methanol solvent, capillary exit voltage 190 V) of $Br(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe$ **5** (M), showing the formation of an oligomeric series of $[M - Br]^+$ ions.

Table 2. Mass spectrometric data for the oligomers of Br(CH$_2$)$_2$NHC(O)NHCHMeCH$_2$(OCHMeCH$_2$)$_n$OCH$_2$CH$_2$OMe **5**.

n	Observed *m/z*	Calculated *m/z*
1	–	261.181
2	–	319.223
3	377.202	377.265
4	435.238	435.307
5	493.275	493.348
6	551.313	551.390
7	**609.350**	**609.432**
8	**667.387**	**667.474**
9	725.424	725.516
10	783.461	783.558
11	841.500	841.600
12	899.536	899.641
13	957.573	957.683
14	1015.681	1015.725
15	1073.647	1073.767
16	1131.681	1131.809
17	1189.716	1189.851

Note: Most intense peak in the isotopic envelope of the observed $[M-Br]^+$ ions; most intense oligomers shown in bold.

ESI MS analysis of **5** showed a spectrum characteristic of an oligomeric mixture, with ions assigned as $[M-Br]^+$, analogous to the mass spectrometric behavior of **3**; the observed ions again lacked the distinctive isotopic signature of a Br. The ESI mass spectrum of **5** at a capillary exit voltage of 190 V is shown in figure 2, which gives the oligomeric distribution for the ions $[M-Br]^+$, where M = Br(CH$_2$)$_2$NHC(O)NHCHMeCH$_2$(OCHMeCH$_2$)$_n$OCH$_2$CH$_2$OMe, with $n = 3$ to 17; data are summarized in table 2. The most



Scheme 6. Synthesis of the Jeffamine® M600-functionalized platinum complex [Pt$_2$(μ-S){μ-S(CH$_2$)$_2$NHC(O)NHCHMeCH$_2$(OCHMeCH$_2$)$_n$OCH$_2$CH$_2$OMe}(PPh$_3$)$_4$]$^+$ **6** via the bromoethylurea Br(CH$_2$)$_2$NHC(O)NHCHMeCH$_2$(OCHMeCH$_2$)$_n$OCH$_2$CH$_2$OMe **5**.

abundant ions in the spectrum are at *m/z* 609.35 and 667.39, assigned as the oligomers with $n = 7$ and 8, respectively; this agrees with the approximate composition given by the manufacturer's specifications [26]. The separation between adjacent peaks in the oligomer distribution is 58 Da, characteristic of a propylene oxide (C_3H_6O) unit. On decreasing the capillary exit voltage, the ions formed by **5** vary in relative intensity; for example, at 120 V, the $[M - Br]^+$ oligomers range from $n = 2$ to 11, with the base peak $n = 6$ oligomer at *m/z* 551. However, there is also an additional series of ions assigned to the dications $[M - Br + Na]^{2+}$ centered at *m/z* 374 for the $n = 9$ oligomer, consistent with the expected preference for longer chain oligomers to form dicationic species [21].

Reaction of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ with **5** in refluxing methanol proceeded readily, giving a yellow solution containing the desired alkylated cation $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]^+$ **6** (scheme 6), which was isolated as its BPh_4^- salt **6**·BPh_4. Although the ^1H NMR spectrum provided little useful information, the $^{31}P\{^1H\}$ NMR spectrum of the complex (figure 3) showed similar features to **4**, with a single broad PPh_3 resonance at δ 24.5 showing two different couplings to ^{195}Pt (3311 and 2619 Hz) which agree well with the values for **4**·PF_6 (3267 and 2602 Hz).

The ESI MS spectrum showed two major series of platinum-containing ions centered at *m/z* 2112.42 and 1125.73, with oligomer peak separations of 58 and 29 Da, indicating 1+ and 2+ ion series, respectively. At a capillary exit voltage of 150 V, the 2+ ion series had around two-thirds the intensity of the 1+ series. Data are summarized in table 3. The series centered at *m/z* 2112.42 (figure 4) is assigned as the parent monocations **6**, ranging from *ca. m/z* 1764 ($n = 1$) to *m/z* 2751 ($n = 18$) and centered about the $n = 7$ oligomer, with the isotope pattern for each oligomer (e.g. inset to figure 4) showing the characteristic pattern for a Pt_2 species, with good agreement between observed and calculated parameters. The series of ions centered at *m/z* 1125.73 (figure 5) are assigned as the sodiated dications $[M + Na]^{2+}$, ranging from *ca. m/z* 980 ($n = 4$) to *m/z* 1357 ($n = 17$), centered at the $n = 9$ oligomer. Again, the oligomer distribution of the 2+ cation series appeared to be shifted towards slightly larger oligomers, consistent with the greater preference of these to become doubly charged. A minor series of ions (identified with asterisks in figure 5) are due to the analogous potassium adducts $[M + K]^{2+}$, for example, for the $n = 9$ oligomer, calculated *m/z* 1133.860, observed *m/z* 1133.720. In addition to these series of platinum-containing ions, there were several overlapping series of nonplatinum-containing ions centered around *m/z* 600, which were not further investigated.

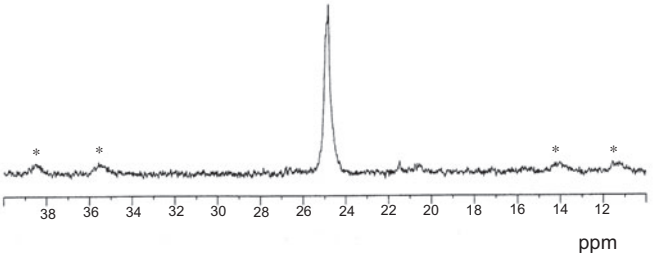


Figure 3. $^{31}P\{^1H\}$ NMR spectrum [in $(CD_3)_2SO$] of $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]BPh_4$ (**6**·BPh_4). Peaks marked with * are due to ^{195}Pt coupling.

Table 3. Mass spectrometric data for the oligomers of $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]^+$ **6**.

	$[M]^+$ cations		$[M + Na]^{2+}$ dications	
n	Observed *m/z*	Calculated *m/z*	Observed *m/z*	Calculated *m/z*
1	1764.204	1764.421	–	893.705
2	1822.244	1822.463	–	922.726
3	1880.277	1880.505	951.628	951.747
4	1938.311	1938.547	981.139	980.768
5	1996.351	1996.588	1009.663	1009.789
6	2054.387	2054.630	1038.681	1038.810
7	**2112.422**	**2112.672**	1067.700	1067.831
8	2170.452	2170.714	**1096.718**	**1096.852**
9	2228.487	2228.756	**1125.735**	**1125.873**
10	2286.519	2286.798	1154.753	1154.894
11	2344.552	2344.840	1183.771	1183.915
12	2402.585	2402.882	1212.791	1212.936
13	2460.614	2460.924	1241.805	1241.957
14	2518.647	2518.966	1270.824	1270.977
15	2576.682	2577.008	1299.839	1299.998
16	2635.712	2635.049	1328.858	1329.019
17	2692.743	2693.091	1358.377	1358.040
18	2750.712	2751.133	1387.889	1387.061

Note: Most intense peak in the isotopic envelope of the observed ions; most intense oligomer(s) shown in bold.

2.3. *Reaction of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ with chloro-functionalized polyethyleneglycol $Me(OCH_2CH_2)_nCl$*

As an alternative strategy, the reactivity of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ towards a chloro-functionalized polyethyleneglycol (Cl-PEG) was also investigated to explore the feasibility of the method with a shorter chain analog. The methoxy-terminated Cl-PEG $Me(OCH_2CH_2)_nCl$ was synthesized from the alcohol $Me(OCH_2CH_2)_nOH$ (MeOPEG350) by reaction with thionyl chloride [27]. The ESI mass spectrum of the alkylating agent showed the expected series of oligomers centered around *m/z* 469.232 for the $n = 9$ oligomer (with *n* ranging from 5 to 13) separated by 44 Da, assigned as $[M + Na]^+$ ions. A weaker set of ions was assigned to the $[M + K]^+$ ions. All ions showed the characteristic isotope pattern resulting from the presence of a chlorine.

Reaction of $Me(OCH_2CH_2)_nCl$ with $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ in refluxing methanol proceeded much slower than the alkylation reactions with the alkyl bromides (*vide supra*). On prolonged refluxing, degradation of the platinum starting material occurred concomitantly with the formation of product. To circumvent these problems, the reaction was carried out in refluxing methanol with added NaBr (to convert alkyl chlorides into more reactive alkyl bromides *in situ*). Under these conditions, reaction was complete after five days, scheme 7. The product was isolated as its BPh_4^- salt, **7**·BPh_4, by addition of excess $NaBPh_4$ to the reaction solution. The ESI mass spectrum in methanol at a capillary exit voltage of 150 V, figure 6, shows a series of oligomers centered around *m/z* 1782.014, assigned to the PEGylated cations $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2CH_2O)_nMe\}(PPh_3)_4]^+$ ($n = 2$ to 11), again with the expected 44 Da separation between oligomers confirming the 1+ charge. Mass spectrometric data are summarized in table 4. Examination of the experimental isotope pattern for the most abundant $n = 6$ oligomer at *m/z* 1782.014 (inset to figure 6) showed good agreement with the calculated pattern. The oligomer distribution for **7** appeared to be shifted towards smaller oligomers compared to the starting $Me(OCH_2CH_2)_nCl$, which might reflect a slightly greater

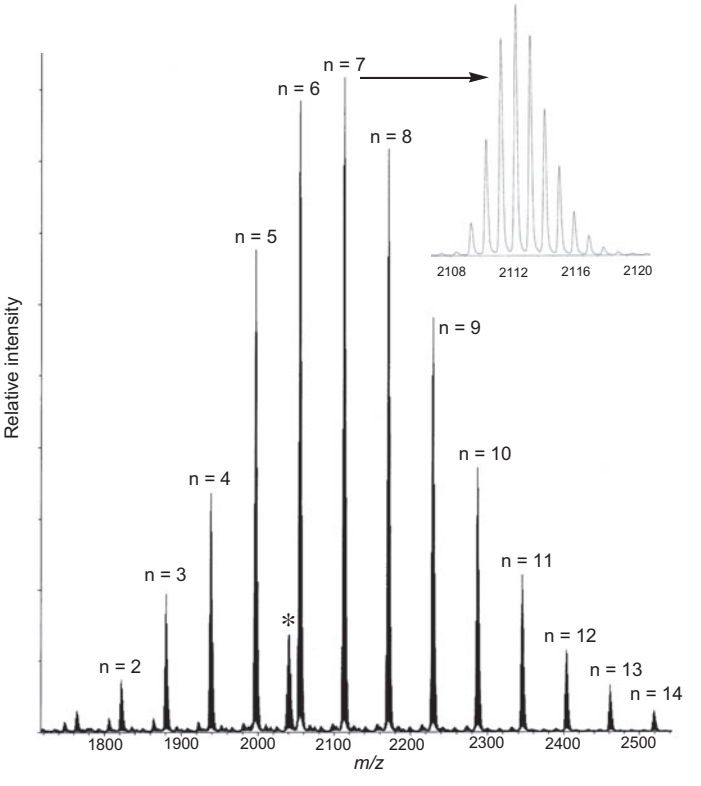


Figure 4. Positive-ion ESI mass spectrum (methanol, capillary exit voltage 150 V) for the series of monocations $[M]^+$ centered at *m/z* 2112 ($n = 7$ oligomer) in the reaction product $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCH\text{-}MeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]^+$ **6** (as its BPh_4^- salt). The inset shows the experimental isotope pattern for the $n = 7$ oligomer. The species marked with an asterisk is unidentified.

reactivity of the shorter chain oligomers. Elemental microanalytical data are also consistent with the shift in oligomer distribution from the alkylating agent to the platinum complex; calculated values of C 62.26; H 5.13% for the $n = 6$ oligomer provide a slightly better match to the experimental data (C 62.53; H 5.17%) when compared to the $n = 9$ oligomer (C 61.82; H 5.37%). $^{31}P\{^1H\}$ NMR data for **7**·BPh_4 again showed similar features to other monoalkylated complexes (table 1), with a single central resonance at δ 24.5, and ^1J(PtP) coupling constants of 3287 and 2611 Hz.

2.4. *Solubility measurements*

A preliminary measurement of the effects of polyether substitution on aqueous solubility has been carried out by the platinum analysis of saturated aqueous solutions of the polyether-appended $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ complexes. Because, the BPh_4^- and PF_6^- salts of the polyether-functionalized Pt complexes were expected to have low solubilities (these anions are widely used in the precipitation of such large cations), the halide salts were prepared by the same alkylation procedures and the products isolated by simply evaporating the solvent, giving yellow oily solids of **6**·Br and **7**·X, where X is a mixture of Cl and Br (from Cl in

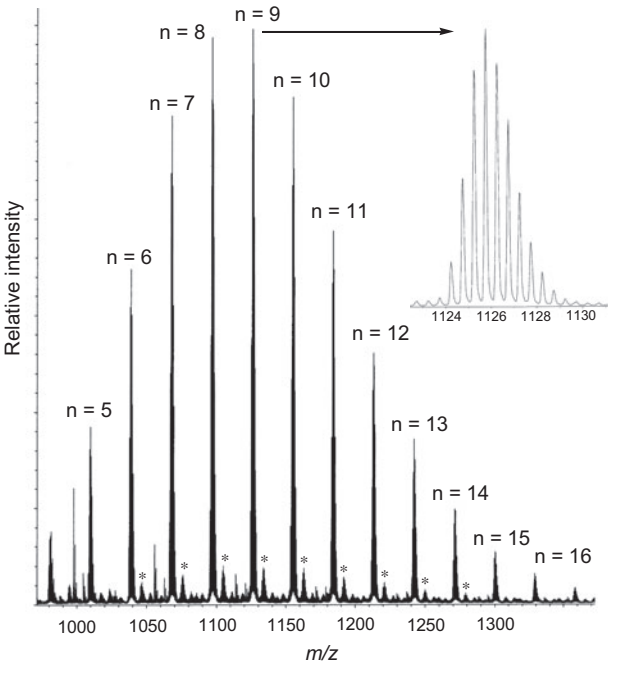
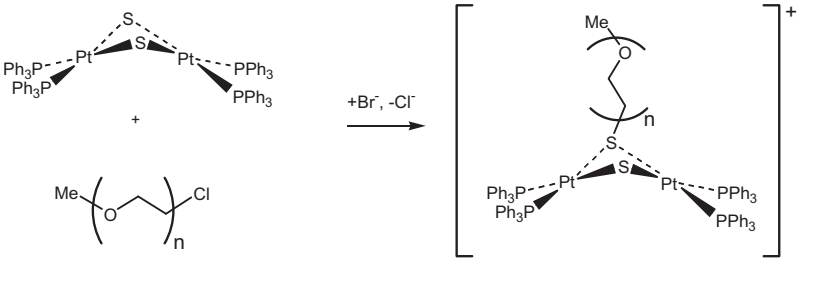


Figure 5. Positive-ion ESI mass spectrum (methanol, capillary exit voltage 150 V) for the series of dications $[M + Na]^{2+}$ centered at *m/z* 1125.73 ($n = 9$ oligomer) in the reaction product $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCH\text{-}MeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]^+$ **6** (as its BPh_4^- salt). The inset shows the experimental isotope pattern for the $n = 9$ oligomer. The series of ions marked with * are the $[M + K]^{2+}$ ions.

the alkylating agent and Br from added NaBr used to promote reaction). While this would not be expected to yield pure complexes, solubility measurements should give a reasonable indication on the overall magnitude of aqueous solubility.

Solubility data are summarized in table 5, where it can be seen that the Jeffamine® M600-derived product **6**·Br produced a considerably higher platinum concentration compared to **7**·X. The results suggest that the use of longer chain Jeffamine® analogs may be the most promising means of imparting significant aqueous solubility.



7

Scheme 7. Synthesis of the polyether-functionalized platinum complex $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2CH_2O)_nMe\}(PPh_3)_4]^+$ **7.**

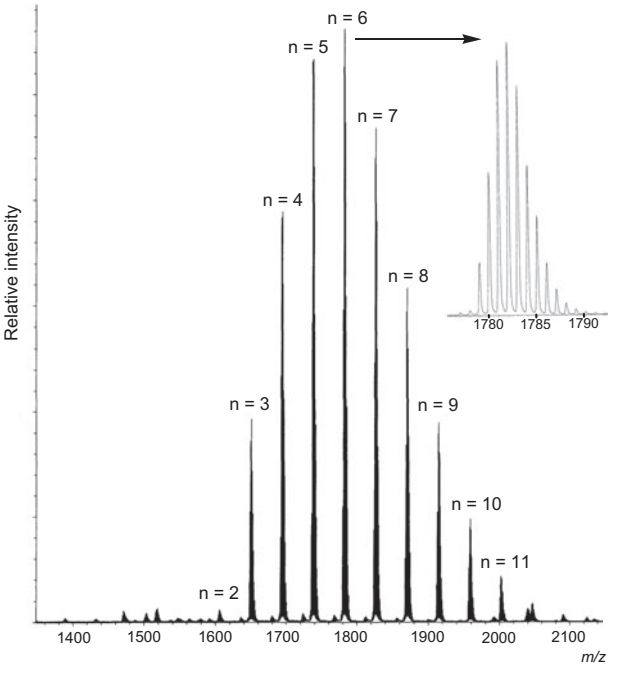


Figure 6. Positive-ion ESI mass spectrum (methanol, capillary exit voltage 150 V) for the complex $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2CH_2O)_nMe\}(PPh_3)_4]BPh_4$ **7**·BPh_4. The inset shows the experimental isotope pattern for the $n = 6$ oligomer at *m/z* 1782.

Table 4. Mass spectrometric data for the oligomers of $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2CH_2O)_nMe\}(PPh_3)_4]^+$ **7**.

n	Observed *m/z*	Calculated *m/z*
1	–	1562.289
2	1605.948	1606.315
3	1649.967	1650.341
4	1693.986	1694.368
5	1738.100	1738.394
6	**1782.014**	**1782.420**
7	1826.029	1826.446
8	1870.045	1870.473
9	1914.060	1914.499
10	1958.076	1958.525
11	2001.092	2002.551

Note: Most intense peak in the isotopic envelope of the ion; most intense oligomer shown in bold.

Table 5. Platinum concentrations in saturated aqueous solutions of some polyether-functionalized complexes $[Pt_2(\mu\text{-}S)(\mu\text{-}SR)(PPh_3)_4]X$.

Complex	X	Approx. average *n* in chain	Pt concentration (ppb)
6	Br	7	12,859
7	Cl/Br	6	1470

Notes: **6** R = $(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe$.
7 R = $(CH_2CH_2O)_nMe$.

3. Conclusion

This current study extends the previous studies on alkylation and arylation reactions of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$, which are well known to lead to platinum(II) thiolate derivatives through derivatization of one or both sulfide ligands. Previously, this methodology has been used to synthesize a diverse range of thiolate complexes, by use of appropriately functionalized alkylating (or arylating) agents. However, water-soluble derivatives of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ are previously undocumented. We have demonstrated that it is possible to append polyether chains onto $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ by alkylation of a sulfide, giving polyether-functionalized μ-thiolate complexes. Due to difficulties in crystallizing such compounds for X-ray crystallographic studies, and complexity of ^1H NMR data, ESI mass spectrometry in association with ^{31}P NMR spectroscopy are the techniques of choice for the investigation of this chemistry. Preliminary studies on the water-solubility suggest that Jeffamine-substituted complexes are likely to show the best solubility, and investigations into the use of longer polyether chains are planned.

4. Experimental setup

All syntheses were carried out under ambient conditions without exclusion of light, air, or water. Solvents were of LR grade and used without purification. $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ was prepared from *cis*-$[PtCl_2(PPh_3)_2]$ to $Na_2S{\cdot}9H_2O$ (Aldrich) in benzene suspension following the literature procedure [28, 29]. The following chemicals were used as supplied from commercial sources: 2-bromoethylisocyanate (Aldrich), 2-methoxyethylamine (Aldrich), sodium bromide (BDH), sodium tetraphenylborate (BDH), methoxypolyethyleneglycol 350 (Sigma-Aldrich), and ammonium hexafluorophosphate (Aldrich). Jeffamine® M600 was a generous donation from Texaco Chemical Company (now marketed by Huntsman).

Electrospray mass spectra were recorded on a Bruker MicrOTOF instrument, typically using a capillary exit voltage of 150 V for routine spectra. The compound (*ca*. 0.5 mg) was dissolved in methanol (1.5 mL), or a few drops of dichloromethane followed by methanol in an Eppendorf tube, and centrifuged prior to analysis. Species assignment was aided by comparison of observed and calculated isotope distribution patterns, the latter obtained using either an Internet-based program [30] or instrument-based software (Bruker Daltonics). ^1H, $^{31}P\{^1H\}$ and $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker Avance spectrometers at 300 or 400 MHz (^1H); coupling constants (*J*) are in Hz. IR spectra were recorded on a Perkin Elmer Spectrum100 FT-IR spectrometer as KBr disks and melting points were recorded on a Reichert Thermopan melting point instrument.

Platinum concentrations were determined on an Elan DRC II Perkin Elmer ICP MS, all samples being run in a 2% nitric acid matrix. The instrument was re-calibrated after every 24 samples using a Pt (100 ppb) calibration standard, a multielement (50 ppb) calibration standard, and a type 1 water calibration blank. The instrument was rinsed for 30 s after each sample and a flush blank was run after every eight samples.

4.1. *Synthesis of $Br(CH_2)_2NHC(O)NH(CH_2)_2OMe$ 3*

$Br(CH_2)_2NCO$ (0.30 mL, 3.32 mM) was added dropwise to a stirred solution of MeO $(CH_2)_2NH_2$ (1 mL, excess) in dry diethyl ether (30 mL), resulting in a vigorous exothermic

reaction giving a white solid. The product was filtered, washed with a small amount of diethyl ether, and dried under vacuum to give **3** (427 mg, 57%) as a white microcrystalline solid. Found: C 31.73; H 5.91; N 12.18. $C_6H_{13}BrN_2O_2$ requires C 32.00; H 5.82; N 12.45%. ESI MS, *m/z* 225 $[M+H]^+$ (20%), 145 $[M-Br]^+$ (100%). ^{1}H NMR (400 MHz), δ 9.51 (1H, s, N**H**CH_2CH_2Br), 9.15 (1H, s, N**H**CH_2CH_2O), 4.80 [2H, t, CH_2, ^3J(HH) 8.6], 3.98 [2H, t, CH_2, ^3J(HH) 8.2], 3.49 (4H, m, CH_2CH_2O) and 3.35 (3H, s, CH_3). IR: ν(C=O) 1703 cm^{-1}. M.p. 62–64 °C followed by resolidifying and re-melting at 78–80 °C.

4.2. *Synthesis of $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NH(CH_2)_2OMe\}(PPh_3)_4]PF_6$ 4·PF_6*

A mixture of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ (293 mg, 0.195 mM) and $Br(CH_2)_2NHC(O)NH(CH_2)_2OMe$ **3** (48 mg, 0.213 mM) in methanol (30 mL) was refluxed for 1 h, giving a clear yellow solution which was then stirred at room temperature for 24 h. The solution was filtered to remove a trace of insoluble matter. Solid NH_4PF_6 (300 mg, excess) was added to the filtrate, followed by dropwise addition of distilled water (10 mL). The resulting yellow precipitate was filtered, washed with water (2 × 10 mL), and dried under vacuum to give **4**·PF_6 (255 mg, 73%). Found: C 51.97; H 4.23; N 1.53. $C_{78}H_{73}F_6N_2O_2P_5Pt_2S_2$ requires C 52.22; H 4.10; N 1.56%. ^{1}H NMR (400 MHz, $CDCl_3$), refer to scheme 4 for atom numbering scheme: δ 7.4–7.1 (60H, m, 12Ph), 4.9 (1H, br m, NH_5), 4.4 (1H, br m, NH_4), 3.5 (2H, m, CH_2 H_2), 3.4 (3H, s, OMe H_1), 3.4 (2H, m, CH_2 H_3), 2.9 (2H, br m, CH_2 H_6) and 2.1 (2H, br m, SCH_2 H_7). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$), δ 157.5 (s, C_d=O), 135–125 (m, PPh_3), 72.0 (s, C_b), 58.8 (s, C_a), 41.5 (s, C_e) and 40.1 (s, C_f and C_c). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$), δ 24.5 [br m, ^1J(PtP) 2602 and 3267]. IR: ν(C=O) 1677 cm^{-1}. M.p. 262–265 °C (decomp.).

4.3. *Synthesis of $Br(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe$ 5*

2-Bromoethylisocyanate (0.83 g, 5.53 mM) was added dropwise with stirring to a solution of Jeffamine® M600 (3.2 g, 5.33 mM) in hexane (20 mL), and the mixture stirred for 10 min, to give a two-phase mixture. The upper organic phase was removed and discarded and the lower product phase washed with two 5 mL portions of hexane. The product phase was then dried under vacuum to give **5** (3.56 g) as a viscous, pale yellow oil. For ESI MS data, refer to table 2.

4.4. *Synthesis of $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe\}(PPh_3)_4]BPh_4$ 6·BPh_4*

A mixture of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ (51.9 mg, 0.0345 mM) and $Br(CH_2)_2NHC(O)NHCHMeCH_2(OCHMeCH_2)_nOCH_2CH_2OMe$ **5** (26 mg, *ca.* 0.041 mM) in methanol (20 mL) was refluxed for 30 min, giving a clear yellow solution. After cooling to room temperature, $NaBPh_4$ (150 mg, 0.439 mM) was added, giving a pale yellow precipitate. Water (20 mL) was added to assist precipitation and the product was filtered, washed with water (3 × 15 mL), and dried under vacuum to give **6**·BPh_4 (68 mg, 83%). Found: C 60.41; H 4.76; N 1.31. $C_{132}H_{153}BN_2O_{12}P_4Pt_2S_2$ requires C 62.21; H 5.95; N 1.12% for the $n=9$ oligomer. ^{31}P{^{1}H} NMR [121.5 MHz, $(CD_3)_2SO$] δ 24.5 [br s, ^1J(PtP) 3311 and 2619]. For ESI MS data, refer to table 3. M.p. softens and gradually melts >80 °C.

4.5. *Synthesis of $Me(OCH_2CH_2)_nCl$*

Methoxypolyethyleneglycol (M_r 350) was refluxed in excess thionyl chloride for 2 h, and the excess thionyl chloride was then removed under vacuum. The crude product was freed from traces of acidic impurities by dissolving in methanol and treating with an excess of calcium carbonate. The mixture was then filtered and evaporated to dryness under vacuum and the product used without purification.

4.6. *Synthesis of $[Pt_2(\mu\text{-}S)\{\mu\text{-}S(CH_2CH_2O)_nMe\}(PPh_3)_4]BPh_4$ 7·BPh_4*

A mixture of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ (73 mg, 0.0484 mM) with $Me(OCH_2CH_2)_nCl$ (107 mg, 0.227 mM) and NaBr (37 mg, 0.356 mM) in methanol (20 mL) was refluxed for five days, monitoring aliquots of the reaction mixture by ESI MS. To the resulting golden-yellow solution, $NaBPh_4$ was added (150 mg, 0.439 mM), giving a yellow precipitate. The product was filtered, washed with water (3 × 15 mL), and dried under vacuum, giving **7**·BPh_4 (83 mg, 83%). Found: C 62.53; H 5.17. $C_{115}H_{119}BO_9P_4Pt_2S_2$ requires C 61.82; H 5.37% for the $n = 9$ oligomer; $C_{109}H_{107}BO_6P_4Pt_2S_2$ requires C 62.26; H 5.13% for the $n = 6$ oligomer. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.5–6.9 (m, Ph) and 3.7–3.3 (m, br, CH_2 and CH_3). ^{31}P $\{^1H\}$ NMR (121.5 MHz, $CDCl_3$), δ 24.5 [^1J(PtP) 2610 and 3287 Hz]. For ESI MS data, refer to table 4. M.p. 106–111 °C.

4.7. *Solubility testing*

Halide salts were prepared for solubility testing by alkylation of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ described earlier Section 4, but the reaction solutions were then evaporated to dryness to give yellow oils, with no addition of BPh_4^- or PF_6^-; conversion of $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ to alkylated products was confirmed by ESI MS. In this way, the complexes **6**·Br and **7**·X were prepared; for **7**, X was a mixture of Cl and Br due to the NaBr used in the synthesis.

Saturated aqueous solutions were prepared in duplicate by stirring distilled water (15 mL) with sufficient solid for 24 h. The solutions were filtered through a 0.45 micron filter and analyzed for Pt by ICP MS.

4.8. *X-ray structure determination*

Yellow block crystals of **4**·PF_6 were obtained by vapor diffusion of diethyl ether into a dichloromethane solution of the complex. This yielded a poor quality structure that served only to confirm atom connectivity (figure 1). Crystal data: monoclinic, space group P_21/c, $a = 21.7157(9)$ Å, $b = 14.3265(7)$ Å, $c = 26.1066(11)$ Å, $\beta = 104.292(3)°$.

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Mercury, used for displaying the X-ray structure diagram in this article and Texaco Chemical Company for a generous donation of Jeffamines®. NJAC thanks the University of Waikato and the Brian Perry Charitable Trust for financial support.

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