Metallacrown Ether and Dinuclear Complexes of Platinum

Dissertation

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Contents

Numbering

All compounds retain the numbering used in the publications with the addition of an **a**–**f** depending on the reference in which they are reported (appendix 1 and 2).

Summary of numbering for ligands

Since several of the ligands of the type $Y(CH_2CH_2O)_xCH_2CH_2Y$ (Y is pyrazol-1-yl, pz; imidazol-1-yl, im or benzimidazol-1-yl, bim) are reported in more than one publication some ligands have more than one compound number, as summarized in the table below. 1,8-Bis(pyrazol-1-yl)-*n*-octane and bis[2-(pyrazolyl-1-yl)ethyl]thioether become **L2e** and **L4e**, respectively, herein.

Numbering of non-commercially available ligands of the type $Y(CH_2CH_2O)_xCH_2CH_2Y$ in [**c**–**e**].

Y \ *x*	0	1	2	3	4	5	7
Pyrazol-1-yl	**L1d** **L1e**	**L2d** **L3e**	**L3d**	-	-	-	-
Imidazol-1-yl	**L1c** **L4d**	**L2c** **L5d**	**L3c**	**L4c** **L6d**	**L5c**	**L6c**	**L7c**
Benzimidazol-1-yl	**L8c**	**L9c**	**L10c** **L7d**	-	-	**L11c**	**L12c**

Summary of numbering for complexes

(**1a**) $[PtBr_2Me_2(4,4'\text{-di-Me-}2,2'\text{-bpy})]$

(**2a**) $[PtBr_2Me_2(4,4'\text{-di-}t\text{-Bu-}2,2'\text{-bpy})]$

(**3a**) $[PtBr_2Me_2(2,2'\text{-bpz})]$

(**4a**) $[PtBr_2Me_2(\text{bpym})]$

(**5a**) $[PtBr_2Me_2(\text{H-pz})_2]$

(**6a**) $[PtBr_2Me_2(\text{4-Me-H-pz})_2]$

(**7a**) $[PtBr_2Me_2(H\text{-}idz)_2]$

(**8a**) $[PtBr_2Me_2(H\text{-}im)_2]$

(**9a**) $[PtBr_2Me_2(H\text{-}bim)_2]$

(**10a**) $[PtBr_2Me_2(quaz)_2]$

(**11a**) $[PPh_4][(PtBrMe_2)_2(\mu\text{-}Br)(\mu\text{-}pz)_2]$

(**12a**) $[(PtBr_2Me_2)_2(\mu\text{-}bpym)]$

(**1b**) $[PtBr_2Me_2(py)_2]$

(**1c**) $[(PtBr_2Me_2)_2(\mu\text{-}imCH_2CH_2im)_2]$

(**2c**) $[(PtBr_2Me_2)_2(\mu\text{-}imCH_2CH_2OCH_2CH_2im)_2]$

(**3c**) $[PtBr_2Me_2\{im(CH_2CH_2O)_2CH_2CH_2im\}]$

(**4c**) $[PtBr_2Me_2\{im(CH_2CH_2O)_3CH_2CH_2im\}]$

(**5c**) $[PtBr_2Me_2\{im(CH_2CH_2O)_4CH_2CH_2im\}]$

(**6c**) $[PtBr_2Me_2\{im(CH_2CH_2O)_5CH_2CH_2im\}]$

(**7c**) $[PtBr_2Me_2\{im(CH_2CH_2O)_7CH_2CH_2im\}]$

(**8c**) $[(PtBr_2Me_2)_2(\mu\text{-}bimCH_2CH_2bim)_2]$

(**9c**) $[PtBr_2Me_2(bimCH_2CH_2OCH_2CH_2bim)]$

(**10c**) $[PtBr_2Me_2\{bim(CH_2CH_2O)_2CH_2CH_2bim\}]$

(**11c**) $[PtBr_2Me_2\{bim(CH_2CH_2O)_5CH_2CH_2bim\}]$

(**12c**) $[PtBr_2Me_2\{bim(CH_2CH_2O)_7CH_2CH_2bim\}]$

(**13c**) $[PtI_2Me_2\{im(CH_2CH_2O)_2CH_2CH_2im\}]$

(**1d**) $[PtCl_2(pzCH_2CH_2pz)]$

(**2d**) $[PtCl_2(pzCH_2CH_2OCH_2CH_2pz)]$

(**3d**) $[PtCl_2\{pz(CH_2CH_2O)_2CH_2CH_2pz\}]$

(**4d**) $[\{PtCl_2(imCH_2CH_2im)\}]$

(**5d**) $[PtCl_2(imCH_2CH_2OCH_2CH_2im)]$

(**6d**) $[PtCl_2\{im(CH_2CH_2O)_3CH_2CH_2im\}]$

(**7d**) $[PtCl_2\{bim(CH_2CH_2O)_2CH_2CH_2bim\}]$

(**8d**) $[PtI_2(pzCH_2CH_2pz)]$

(**9d**) $[PtI_2(pzCH_2CH_2OCH_2CH_2pz)]$

(**1e**) $[PtBr_2Me_2(pzCH_2CH_2pz)]$

(**2e**) $[PtBr_2Me_2\{pz(CH_2)_8pz\}]$

(**3e**) $[PtI_2Me_2(pzCH_2CH_2pz)]$

(**4e**) $[PtMe_3(pzCH_2CH_2OCH_2CH_2pz)][BF_4]$

(**5e**) $[PtMe_3(pzCH_2CH_2SCH_2CH_2pz)][CF_3SO_3]$

(**1f**) $[PtBr_2Me_2(4\text{-}CN\text{-}py)_2]$

(**2f**) Tetradeuterated $[PtBr_2Me_2(H\text{-}pz)_2]$

(**3f**) $[PtCl_2\{(Ph)_2P(CH_2CH_2O)_2CH_2CH_2P(Ph)_2\}]$

(**4f**) *cis*-$[PtBr_2(PPh_3)_2]$

(**5f**) [{$PtBr_2Me_2$(4,4'-bipy)}]

Abbreviations

bim: Benzimidazol-1-yl

4,4'-bipy: 4,4'-Bipyridine

bp.: Boiling point

bpym: 2,2'-Bipyrimidine

DMF: Dimethylformamide

DMSO: Dimethylsulphoxide

D. N.: Donor number

dpdo: 1,8-Bis(diphenylphosphino)-3,6-dioxaoctane

CA: Carbonic anhydrase

4-CN-py: 4-Cyanopyridine

cod: Cycloocta-1,5-diene

H-bim: Benzimidazole

H-im: Imidazole

H-pz: Pyrazole

HR-ESI-MS: High resolution-electrospray ionisation-mass spectrometry

IC_{50}: Dose required to reduce the number of living cells by 50%

im: Imidazol-1-yl

K_a: Binding or association constant

mp.: Melting point

μ-pz: Bridging pyrazalato

nbd: Norbornadiene or bicyclo[2.2.1]hepta-2,5-diene

NMR: Nuclear magnetic resonance

NOE: Nuclear Overhauser enhancement

py: Pyridine

pz: Pyrazol-1-yl

$R_{donor,acceptor}$: Sum of the van der Waals radii of donor, acceptor atoms

THF: Tetrahydrofuran

1. Introduction

1.1. Metallacrown ethers

Definitions

Crown ethers are macrocyclic compounds with oligoether, often ethyleneoxy, repeating subunits.[1] Metallacrowns and metallacrown ethers share a number of structural similarities with their organic analogue crown ethers (Fig. 1).

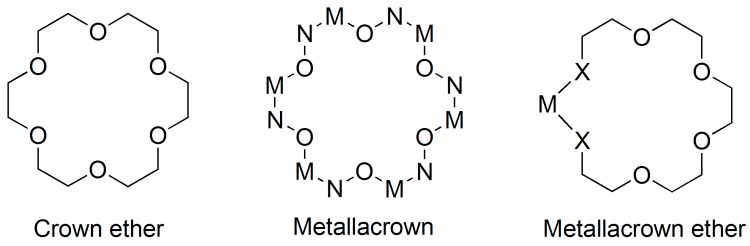


Fig. 1 Analogy between crown ether, metallacrown and metallacrown ether rings. M: transition metal ion fragment. X: ligating atom/moiety.

Metallacrowns are defined as cyclic structures with the ring transition metal ion fragments and nitrogen atoms replacing the methylene carbon atoms of crown ethers thereby giving rise to —(M–O–N)$_n$— repeating subunits.[2] As with crown ethers, metallacrowns can also contain modified subunits, —(M–O–C–N)$_n$— for example. A large number of metallacrowns have been reported over the last decade incorporating a variety of metals and bridging ligands alike.[3] Metallacrowns are often isolated with cationic or anionic guests present in the crown cavity.[2b]

Metallacrown ethers are cyclic structures with metal ion fragments incorporated in the backbone of a polyether macroring such that the metal is connected to the polyether backbone by a ligating moiety at either end of the polyether chain (X in Fig. 1).[4] Metals that have been incorporated in metallacrown ether backbones include Mo(0), Ru(II), Pd(II), Pt(II), Ag(I), Au(I) and Hg(II).[4,5] α,ω-Bis(phosphino) polyether compounds are the most popular choice of polyether ligand to date.[4] Other ligating moieties reported include pyrazol-1-yl and *N*-heterocyclic carbenes (benzimidazolium and imidazolium), although these are less prevalent.[5] The binding capacity of various metallacrown ethers has been examined with a limited range of cationic guests such as Li^+ and Na^+ ions.[4a,d,6]

Host-guest interactions with ammonium ion guests

Host-guest interactions between crown ethers and ammonium ions were studied early on in investigations with crown ethers, although most investigations focused on ammonium or primary ammonium ion guests.[7,8] Hydrogen bonding interactions between primary or some secondary ammonium ion guests and crown ether hosts often leads to the ammonium ion being bound perched above the average plane of the macrocycle,[9] rather than in the ring cavity as is typical for most host-metal-cation guests (Fig. 2a). Dialkylammonium ions may also thread the cavity of suitably sized crown ethers and can subsequently preclude the formation of other interlocking molecules (Fig. 2b).[10]

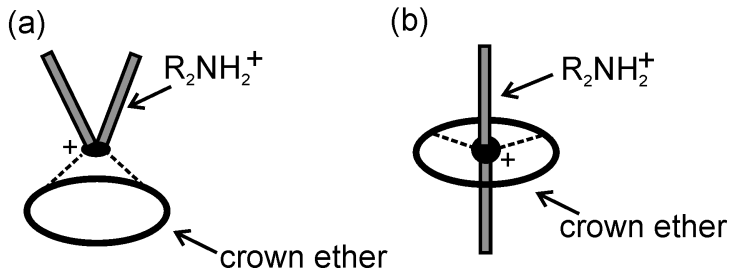


Fig. 2 Perched (a) and threading (b) interactions between dialkylammonium ion guests and crown ether hosts.

Amine bases are often employed in the synthesis of metallacrowns and their ammonium ions are subsequently frequently found in the cavity of the isolated metallacrown.[11] Interactions between ammonium ions and metallacrown ethers are relatively unknown in the literature, only one example between an ammonium ion and a rhenium metallacrown ether has been reported.[6e]

1.2. Complexes with anticancer properties

Platinum complexes with anticancer properties

Since the introduction of cisplatin as a widely used cancerostatic in 1978, two further platinum(II) cancerostatica, carboplatin and oxaplatin (Fig. 3), are in worldwide use for the treatment of cancer. The mechanism of action of cisplatin has been thoroughly studied.[12] It is believed that cisplatin is activated intracellularly on aquation of the chloride leaving groups generating a highly reactive diaqua species that binds to DNA and subsequently activates various signal-transduction pathways.[12,13] While investigation and discussion over the significance of the various binding interactions

of the platinum(II) adduct to the double helix is ongoing, the result of the binding leads to either repair of the damaged DNA or cell death.[12,13]

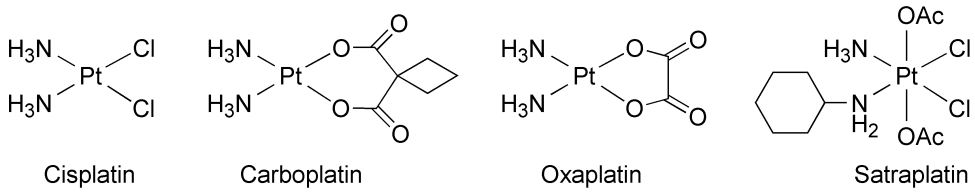


Fig. 3 Widely used platinum(II) anticancer drugs and satraplatin.

The success of cisplatin in the clinic has lead to testing of new platinum compounds that have sought to improve upon the drawbacks and side effects associated with cisplatin.[14] Platinum(IV) complexes are kinetically inert to ligand substitution relative to platinum(II) complexes and the design of platinum(IV) anticancer drugs has been encouraged by their potential as drugs that may be administered orally, a feature arising from their inherent inertness.[15] However, to date, of the three platinum(IV) complexes to have entered clinical trials, iproplatin, ormaplatin/tetraplatin and satraplatin/JM216, only satraplatin remains in clinical trials (Fig. 3).[14,15]

The design of new platinum(II) drugs has been dominated by a number of structure-activity 'rules', all of which are satisfied by the neutral cisplatin (Fig. 4a).[16] The carrier ligand is any ligand inert to ligand substitution and is often an amine with at least one N–H bond. The anionic leaving groups X^-, often chloro ligands, generally undergo hydrolysis in the cell. It has, on the other hand, been shown that some platinum(IV) drugs, for example satraplatin,[17] are reduced to platinum(II) complexes by common intra- and extracellular reductants.[18] Reduction to what is generally believed to be an active platinum(II) complex has been shown to often result from the elimination of the axial ligands (in accordance with the discussion in the literature: plane with *N*-donor carrier ligand 'equatorial' and ligands above and below this plane are 'axial').[19,20] Thus there is no set of structure-activity rules for the design of platinum(IV) drugs but the vast majority are designed such that the resulting reduced platinum(II) species is active and thereby in accord with the platinum(II) structure-activity rules (Fig. 4b). Furthermore, the axial ligands are often used as a means to alter the overall solubility/lipophilicity and reduction potential of the platinum(IV) complex in addition to acting as an extra site for the incorporation of bioactive molecules.[21–23]

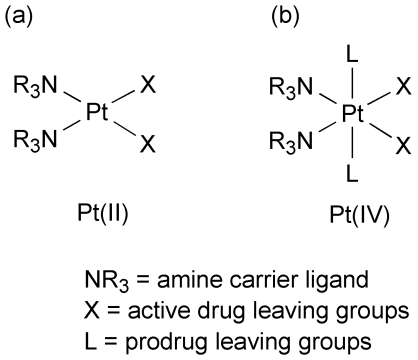


Fig. 4 Generic structures of typical (a) platinum(II) and (b) platinum(IV) drugs.

Bioorganometallics

Recently bioorganometallic chemistry has emerged as a new field distinct from bioinorganic chemistry.[24] Within the scope of this field, and encouraged by the widespread usage of platinum cancerostatica, the design of new anticancer drugs based on metallocenes of titanium (Fig. 5a) and iron (Fig. 5b) has attracted significant attention.[25]

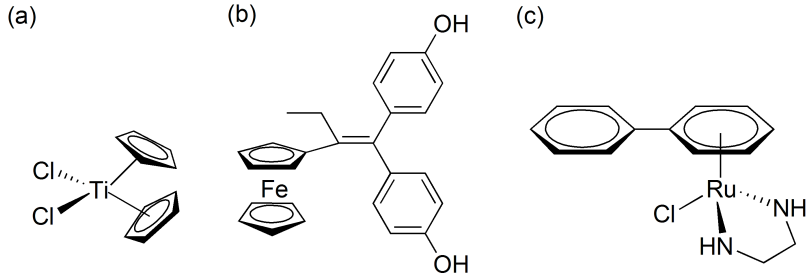


Fig. 5 Anticancer bioorganometallic (a) titanium, (b) iron and (c) ruthenium complexes.

In addition, ruthenium complexes with arene ligands (Fig. 5c) have been shown to possess remarkable activity *in vitro* and *in vivo*, are water soluble and, through variation of the different ligand types, show a wide range of activity.[26] To date however no bioorganometallic complex has undergone successful clinical trials.

1.3. Aims of the thesis

Macrocyclic inorganic molecular structures related to crown ethers have received significant attention in recent years.[2–6] Metallacrown ethers are a relatively small area among metallamacrocycles. Complexes consisting of molybdenum(0) with α,ω-bis(phosphino) polyether ligands are the most frequent type of metallacrown ether

reported and to date the properties of only a few other types of metallacrown ethers have been investigated.[4–6] The pairing of platinum(II)/(IV) precursor complexes with α,ω-bis(azolyl) polyether ligands should afford a route to the preparation of a new family of platinum metallacrown ethers. Host properties of the platinum(IV) metallacrown ethers with guest ions such as dialkylammonium ions would extend the small range of guest ions commonly employed in metallacrown ether receptor studies.[4a,d,6] The cancerostatic behavior of these platinum(IV) metallacrown ether complexes would be of interest since along with the known anticancer activity of platinum complexes, the polyether chain of the ligand may impart a degree of hydrophilicity to the complex overall, thus making it more amenable to biological media.

The results discussed herein can be partitioned into three main themes:

- The extent of the reactivity of $[(PtBr_2Me_2)_n]$ with *N*-heteroaromatic compounds with at least two potential ligating nitrogen atoms and the propensity to form dinuclear complexes from mononuclear building blocks using these types of ligand.
- Examination of the reactivity of α,ω-bis(azol-1-yl) polyether ligands (azol-1-yl: pyrazol-1-yl, imidazol-1-yl or benzimidazol-1-yl) with platinum precursors and the preparation of metallacrown ethers with α,ω-bis(azol-1-yl) polyether ligands.
- To investigate the properties of these metallacrown ethers with α,ω-bis(azol-1-yl) polyether ligands, particularly their host properties and their potential as cancerostatica.

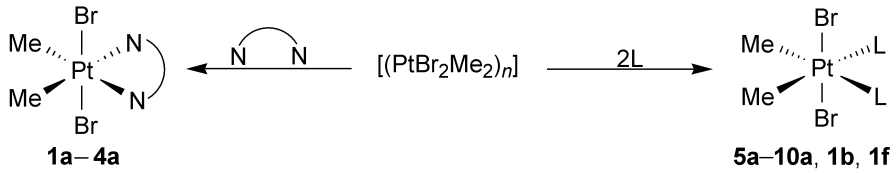
2. Results and discussion

2.1. Mononuclear platinum(II)/(IV) complexes

2.1.1. With N-heteroaromatic donors

Synthesis

The preparation of dibromodimethylplatinum(IV) complexes from the precursor complex $[(PtBr_2Me_2)_n]$ in chloroform proved a simple and efficient means of preparing complexes of the type $[PtBr_2Me_2(N\frown N)]$ (N⌢N is a bidentate *N*-donor ligand) **1a**–**4a** and $[PtBr_2Me_2(L)_2]$ (L is a *N*-heterocyclic monodentate ligand) **5a**–**10a**, **1b** and **1f** (Scheme 1) [**a**,**b**].



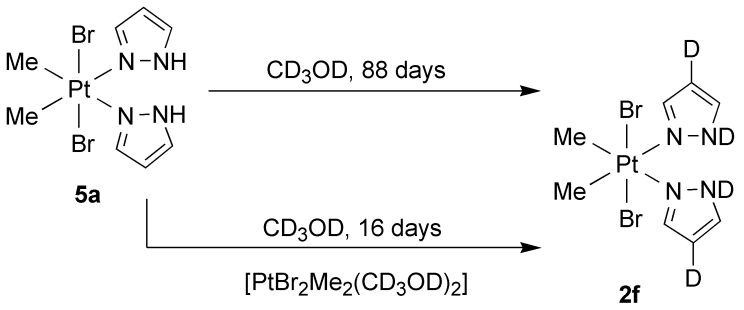
Scheme 1 Preparation of **1a**–**4a** with bidentate N⌢N donors: 4,4'-dimethyl-2,2'-bipyridine (**1a**), 4,4'-di-*t*-butyl-2,2'-bipyridine (**2a**), 2,2'-bipyrazine (**3a**) and 2,2'-bipyrimidine (**4a**). Preparation of **5a**–**10a**, **1b** and **1f** using L: pyrazole (**5a**), 4-methyl-pyrazole (**6a**), indazole (**7a**), imidazole (**8a**), benzimidazole (**9a**), quinazoline (**10a**), pyridine (**1b**) and 4-cyano-pyridine (**1f**).

From the mononuclear complexes **1a**–**10a**, **1b** and **1f** a preference for the *trans* configuration of the *N*-donor ligands to the methyl ligands and mutual *trans* coordination of the bromo ligands is apparent. While the reactivity of $[(PtBr_2Me_2)_n]$ with various donor ligands has been described here the range and nature of the *N*-heterocyclic donor ligands has been extended.[27]

Proton exchange on the pyrazole ligand

It was found that the proton bound to C^4 on the coordinated pyrazole ligands of $[PtBr_2Me_2(H\text{-}pz)_2]$ (**5a**) is completely substituted (spectroscopic yield 100%) in a methanol-d4 solution by a deuteron (Scheme 2). While the N^1–H proton is substituted in free and coordinated pyrazole in CD_3OD, no observable deuteration of the C^4 hydrogen was noted for the free ligand in CD_3OD. Increased reactivity at the C^4 position of coordinated pyrazole ligands has also been observed for other complexes with pyrazole ligands.[28] Substitution of **5a** occurs faster in the presence of

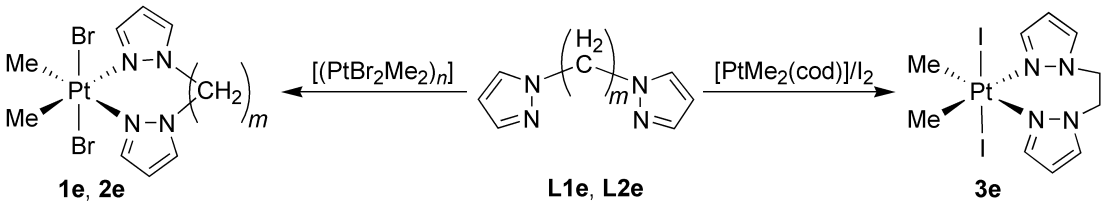
$[PtBr_2Me_2(CD_3OD)_2]$, indicating that intermediately formed $[PtBr_2Me_2(CD_3OD)(H\text{-}pz)]$ may increase the reactivity at the C^4 position.



Scheme 2 Tetradeuteration of the pyrazole ligands of **5a**.

2.1.2. With α,ω-bis(azol-1-yl) alkanediyl ligands

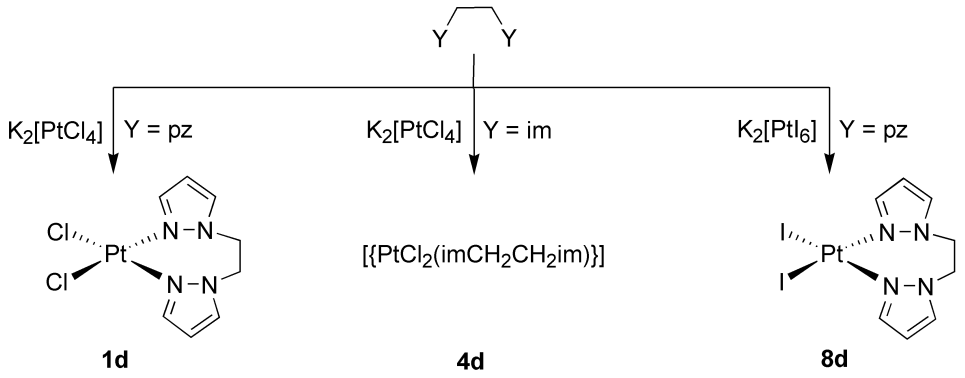
Alkanediyl linked bis(phosphino) ligands can act as *trans* spanning bidentate ligands.[29] Although alkanediyl bridged bis(pyrazol-1-yl) ligands have been reported for some time, investigations of their behavior as ligands is relatively limited.[30] Complexes **1e** and **3e** afforded from the reaction of **L1e** with $[(PtBr_2Me_2)_n]$ and $[(PtMe_2(cod)]/I_2$, respectively, are in accord with the coordination modes of various other alkanediyl linked bis(pyrazol-1-yl) compounds (Scheme 3).[30c–g]



Complex	**1e**	**2e**	**3e**
Ligand	**L1e**	**L2e**	**L1e**
m	2	8	2

Scheme 3 Platinum(IV) complexes **1e**–**3e** with alkanediyl linked ligands **L1e** or **L2e**.

As with **L1e**, 1,8-bis(pyrazol-1-yl)-*n*-octane (**L2e**) reacted with $[(PtBr_2Me_2)_n]$ to give $[PtBr_2Me_2\{pz(CH_2)_8pz\}]$ (**2e**). In addition, dichloroplatinum(II) and diiodoplatinum(II) complexes (**1d**, **4d** and **8d**) were prepared according to the conditions described in [**d**] (Scheme 4). Without X-ray crystal analysis or mass spectrometry it was not possible to determine the exact nuclearity of **4d**.

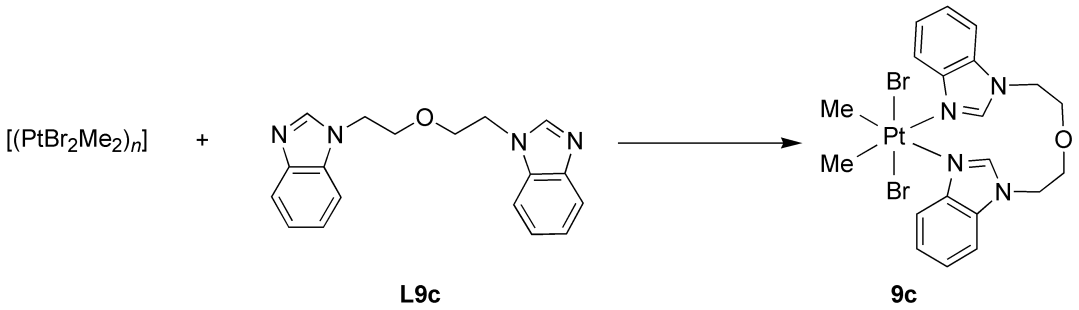


Scheme 4 Preparation of dichloroplatinum(II) and diiodoplatinum(II) complexes **1d**, **4d** and **8d**.

2.1.3. With bis[2-(azol-1-yl)ethyl] ether/thioether ligands

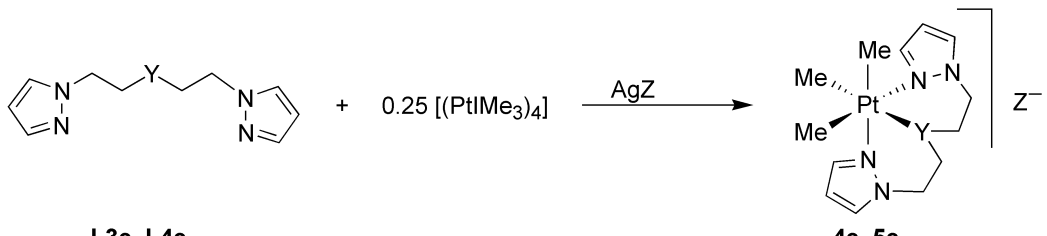
Synthesis

The bis[2-(benzimidazol-1-yl)ethyl] ether ligand **L9c** reacted with $[(PtBr_2Me_2)_n]$ to afford **9c** (Scheme 5).



Scheme 5 Preparation of **9c** with bis[2-(benzimidazol-1-yl)ethyl] ether **L9c**.

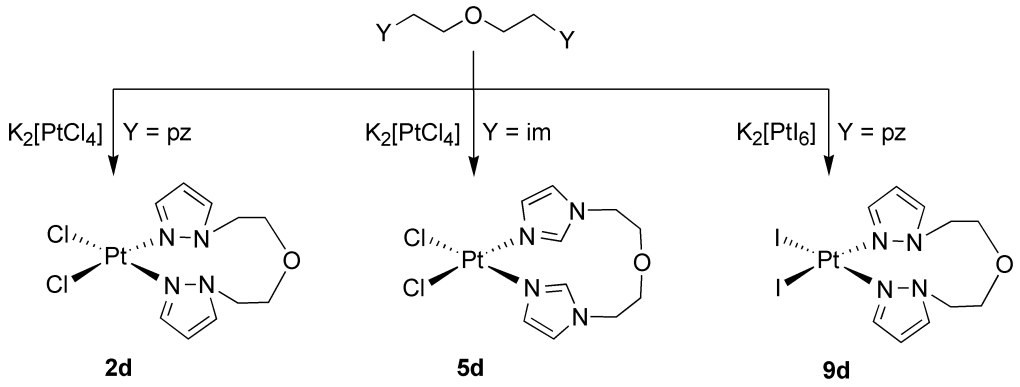
The reaction of bis[2-(pyrazol-1-yl)ethyl] ether/thioether (**L3e**/**L4e**) with platinum(IV) precursors is described in [**e**] (Scheme 6).



Complex	**4e**	**5e**
Ligand	**L3e**	**L4e**
Y	O	S
Z^-	$[BF_4]^-$	$[CF_3SO_3]^-$

Scheme 6 Preparation of **4e** and **5e** with bis[2-(pyrazol-1-yl)ethyl] ether/thioether compounds.

The preparation of **4e** and **5e** shows the ease with which the neutral tridentate κ^2*N,N',*κ*O* or κ^2*N,N',*κ*S* donor set can coordinate to platinum(IV). Bis[2-(3,5-dialkylpyrazol-1-yl)ethyl] ether analogues of **L3e** have also been found to adopt versatile coordination modes.[31] However, structures with neutral tridentate κ^2*N,N',*κ*O* ligands in platinum(IV) complexes or any hexacoordinated *d*-block element are unknown. Thus the solid state structure of **4e** with a facial coordination of the tridentate ligand **L3e** is of interest. As was found for selected bis(azol-1-yl) complexes **1d**, **4d** and **8d** (Scheme 4) above, diethyl ether linked derivatives of the bis(pyrazol-1-yl) and bis(imidazol-1-yl) ligands also reacted with $K_2[PtCl_4]$ and $K_2[PtI_6]$ to yield the respective platinum(II) complexes (Scheme 7).

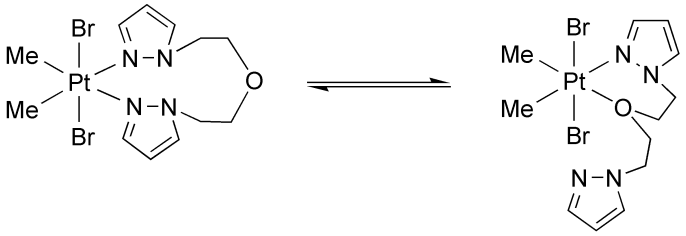


Scheme 7 Preparation of dichloroplatinum(II) and diiodoplatinum(II) complexes **2d**, **5d** and **9d**.

Linkage isomers

Bis[2-(pyrazol-1-yl)ethyl] ether and longer polyether chained derivatives of **L3e** reacted with $[(PtBr_2Me_2)_n]$ to yield yellow oily residues that were difficult to characterize owing to a broadening of all resonances in the ^{1}H, ^{13}C and ^{195}Pt NMR spectra. This is in contrast to spectra of complexes **1c**–**13c**. An equilibrium between the possible bidentate coordination modes of **L3e**, namely κ*N*,κ*O* or κ^2*N*,*N*' coordination, would be expected to result in broadening of both methyl and **L3e** resonances if the equilibrium was sufficiently slow on an NMR timescale (Scheme 8). The formation of other species in solution yielded from a bridging rather than chelating mode of the ligand may also cause broadening, as discussed for **7c** and **12c** below. However low temperature ^{1}H NMR of solutions of **L3e** with $[(PtBr_2Me_2)_n]$ did not reveal signal coalescence and the shortness of the flexible spacer in **L3e** as

well as the κ^2*N,N',*κ*O* coordination mode of **L3e** in **4e** supports the formation of linkage isomers as a cause for broadening in the NMR spectra. Structurally similar ligands have also demonstrated the capacity of the ethereal oxygen atom to ligate.[4d,31]

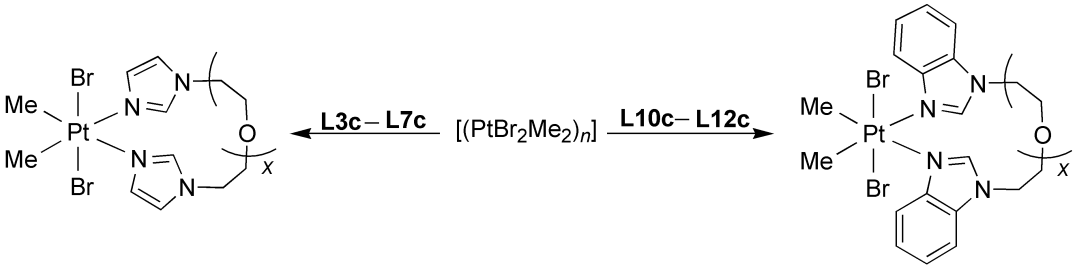


Scheme 8 Possible equilibrium between linkage isomers with the **L3e** ligand.

2.1.4 With α,ω-bis(imidazol-1-yl) or α,ω-bis(benzimidazol-1-yl) polyether ligands

Synthesis

The preparation of platinum(IV) metallacrown ethers using either α,ω-bis(imidazol-1-yl) or α,ω-bis(benzimidazol-1-yl) compounds was readily accomplished under mild reaction conditions (Scheme 9) [**c**].

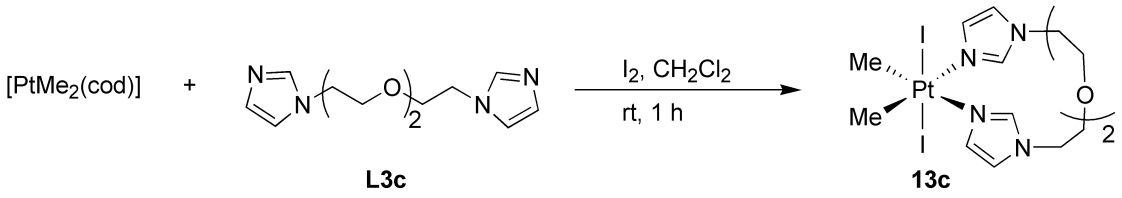


3c–**7c** **10c**–**12c**

Complex	**3c**	**4c**	**5c**	**6c**	**7c**	**10c**	**11c**	**12c**
Ligand	**L3c**	**L4c**	**L5c**	**L6c**	**L7c**	**L10c**	**L11c**	**L12c**
Ligating moiety	im	im	im	im	im	bim	bim	bim
x	2	3	4	5	7	2	5	7

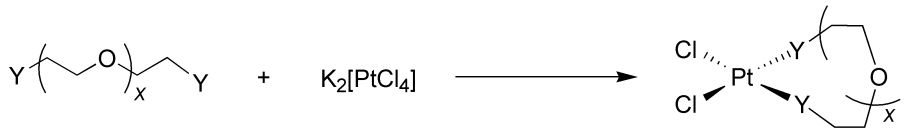
Scheme 9 The preparation of platinum(IV) complexes with (i) α,ω-bis(imidazol-1-yl) and (ii) α,ω-bis(benzimidazol-1-yl) polyether ligands.

This series of complexes represents a new family of metallacrown ethers bearing α,ω-bis(azol-1-yl) polyether ligands rather than the more commonly employed α,ω-bis(phosphino) polyether ligands. The α,ω-bis(imidazol-1-yl) polyether **L3c** also reacted in a fashion similar to **L1e** described above (section 2.1.2.) to yield the diiodo complex **13c** (Scheme 10).



Scheme 10 Preparation of **13c** from $[PtMe_2(cod)]/I_2$ and **L3c**.

Platinum(II) metallacrown ether complexes bearing α,ω-bis(phosphino) polyether ligands have been described, although their complexation chemistry with Li^+ and Na^+ is not straight forward.[4d] As with **1d**, **2d**, **4d** and **5d** the preparation of dichloroplatinum(II) complexes with bis(azol-1-yl) polyether ligands was accomplished under mild reaction conditions (Scheme 11) [**d**].



L3d, **L6d**, **L7d**

3d, **6d**, **7d**

Complex	**3d**	**6d**	**7d**
Ligand	**L3d**	**L6d**	**L7d**
Y	pz	im	bim
x	2	3	2

Scheme 11 Preparation of dichloroplatinum(II) bis(azolyl) polyether complexes.

α,ω-Bis(pyrazol-1-yl) polyether compounds with *x* = 3 to 5 ethyleneoxy groups on the polyether backbone were found to react with $K_2[PtCl_4]$ yielding oily residues. These residues appear to be a mixture of two major and a number of minor unidentified products (^{1}H NMR spectroscopy). The preparation of larger platinum(II) metallacrown ethers would be necessary to examine the host properties of these complexes since fewer than four ethyleneoxy groups are not expected to be sufficient for complexation in the metallacrown ether cavity.

Additionally it was also found that the α,ω-bis(imidazol-1-yl) polyether compounds with more than three ethyleneoxy groups did not react with $K_2[PtCl_4]$, while none of the α,ω-bis(imidazol-1-yl) compounds were found to react with $K_2[PtI_6]$ under the conditions that yielded **8d** and **9d**. The reasons for this unexpected inertness of the respective α,ω-bis(imidazol-1-yl) polyether compounds with $K_2[PtCl_4]$ and $K_2[PtI_6]$ is not clear, particularly since the α,ω-bis(pyrazol-1-yl) derivatives behave differently.

Monomer/dimer(oligomer) equilibrium in solution

In solutions of **7c** and **12c** a second set of resonances was observed in the ^{1}H, ^{13}C and ^{195}Pt NMR spectra as the concentration of the solution was increased above ca. 0.04 mol/l. This behavior was not observed at similar concentrations in solutions of the smaller metallacrown ethers. Increasing the concentration of a solution of either **7c** or **12c** above ca. 0.04 mol/l increased the intensity of the second set of resonances (Fig. 6). The formation of *trans* spanning isomers, as was found for Pd(II) metallacrown ethers having α,ω-bis(phosphino) polyether ligands,[32] is considerably unlikely for the hexacoordinated complexes of **7c** and **12c** due to the steric requirements of the platinum coordination sphere and aromatic ligating imidazol-1-yl and benzimidazol-1-yl moieties.

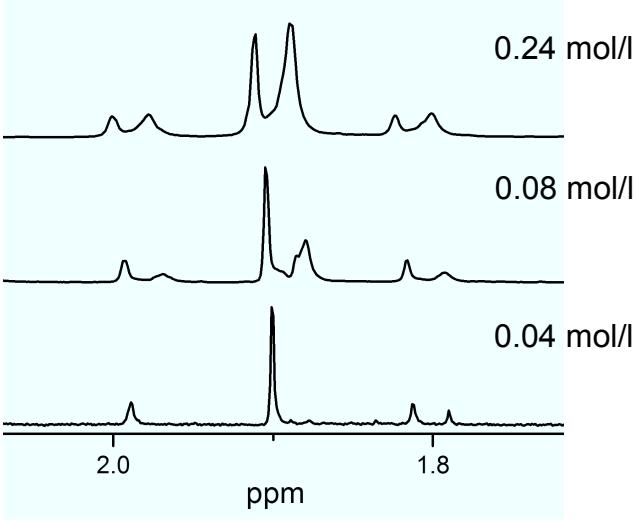
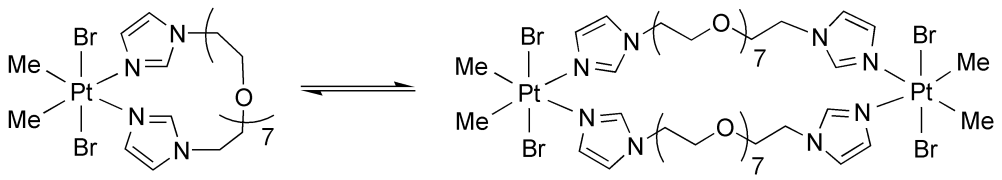


Fig. 6 Partial ^{1}H spectrum of **7c** in $CDCl_3$ showing the Pt–CH_3 singlet with ^{195}Pt satellites in solutions of ca. 0.24 mol/l (top), 0.08 mol/l (middle) and 0.04 mol/l (bottom).

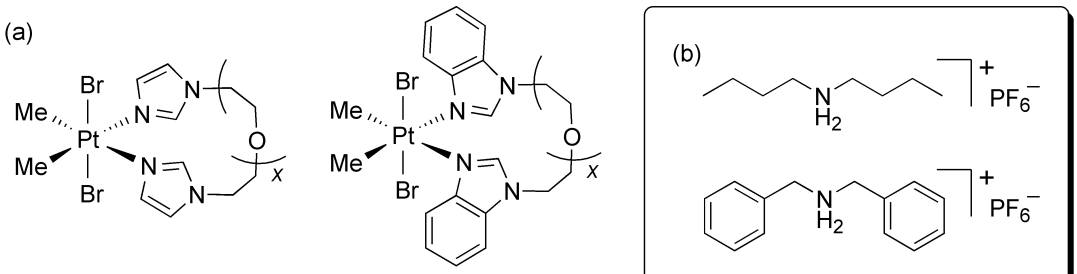
In addition, if *trans* isomers were formed a distinctly different set of resonances may be expected in the methyl region of the ^{1}H NMR spectrum (i.e. methyl ligand *trans* configured to methyl ligand would result in a substantial decrease in $^{2}J_{Pt,H}$ coupling). However this is not found to be the case and the configuration at the platinum atom is the same for both species (methyl ligand *trans* configured to nitrogen donor ligands). Thus, this concentration dependent equilibrium is attributed to the formation of oligomeric, probably dimeric, species in solution (Scheme 12). In addition, the similarity of the species in solution is apparent from the relatively few changes in the respective ^{1}H or ^{13}C NMR spectra.



Scheme 12 Monomer and dimer concentration dependent equilibrium of **7c**.

Metallacrown ether binding studies

The complexation chemistry of dialkylammonium salts has undergone renewed attention over the last number of years owing to the interesting pseudo-rotaxane and rotaxane structures yielded in combination with crown ether cavities of suitable dimensions.[10] Starting with metallacrown ether **5c** (21-membered cavity ring) the complexation of di-*n*-butylammonium and dibenzylammonium hexafluorophosphate salts was investigated (Fig. 7a,b). Binding studies with these ammonium salts were conducted mostly in methylene chloride (studies with **11** in chloroform). In more polar solvents such as acetonitrile and acetone no evidence of any interaction was observed, indicating the relative strength of the interaction between the ammonium ions and the metallacrown ethers.



5c–**7c**				**11c**, **12c**	
Complex	**5c**	**6c**	**7c**	**11c**	**12c**
Ligating moiety	im	im	im	bim	bim
x	4	5	7	5	7

Fig. 7 Complexes (a) and diorganyl ammonium salts (b) used in the binding studies.

Evidence of an interaction between the metallacrown ethers and the ammonium ions was apparent from the respective NMR spectra and was supported by NOE experiments and HR-ESI-MS investigations. In addition, the metallacrown ethers (**5c**–**7c**, **11c** and **12c**) significantly enhanced the solubility of the respective ammonium salts. Furthermore, mixing of **7** and $[Bu_2NH_2][PF_6]$ at room temperature revealed that the complexation-decomplexation equilibrium was reached quickly on a

laboratory timescale (no difference in ^{1}H NMR measured after 15 min and again after 1 day).

Although the resonances of the ethereal backbone experience only very slight changes in shift on binding, these signals are generally broadened and increased in complexity. Broadening of resonances is observed in other binding studies and is largely attributed to rapid complexation-decomplexation of the host-guest species on an NMR timescale or a decrease in the longitudinal relaxation time (T_1) of the molecule.[33] However, variable temperature NMR experiments with selected metallacrown ether/ammonium salt combinations did not reveal coalescence (cooling down the sample) or narrowing (heating up the sample) of the broadened resonances within the temperature range possible with the solvent (CD_2Cl_2 mp. –97 °C; bp. 39.8 °C).

In addition to the broadening of the signals, only a slight complexation induced shift was observed for what appears to be a rapid exchange on an NMR timescale and determination of binding constants was not possible. The exception to this behavior was slow exchange observed for complexation between **12c** and the dibenzylammonium ion. Determination by single point methods disclosed a relatively weak binding constant (K_a = 5 l/mol in CD_2Cl_2 at 27 °C). Although no numerical value was established, Bélanger *et al*. also reported weak binding between their rhenium metallacrown ether and the ammonium ion.[6e]

The type of interaction, a face-to-face or a threading of the macroring by the ammonium ion can only be speculated in the absence of solid state structure analysis (Fig. 8).

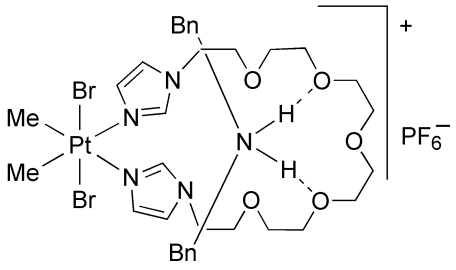


Fig. 8 Possible threading of the metallacrown ether cavity.

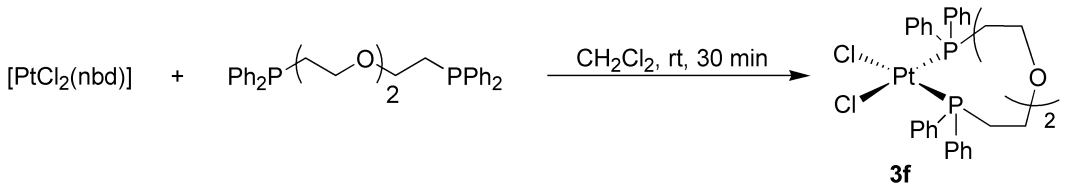
However the cavity of the metallacrown ethers are of comparable ring size (21-membered and greater) to crown ethers that have been used as host molecules in pseudo-rotaxane interactions with these ammonium ions.[10a,b] While the improved

solubility of the ammonium salts and ESI-MS spectra indicate a 1:1 interaction in all cases, NOE experiments may hint at the type of interactions. NOE experiments involved irridation of the proton resonances of the polyether backbone on the metallacrown ether. The resulting spectra were examined for intensity enhancement of the resonance attributed to the α-protons of the ammonium ion $[(RC^{\alpha}H_2)_2NH_2]^+$. From the NOE experiments it was found that the smaller metallacrown ethers of each series (**5c** and **11c**) did not give any intensity enhancement of the $C^{\alpha}H_2$ resonance of the dibenzylammonium ion. In addition, no intensity enhancement was found for the $C^{\alpha}H_2$ resonance of the di-*n*-butylammonium ion in solution with **11c**. The lack of intensity enhancement for the various experiments with **5c** and **11c** may be interpreted as an indication of an interaction differing from those of the larger metallacrown ethers (**6c**, **7c** and **12c**) where intensity enhancements were observed. The pseudo-rotaxane interactions resulting from the threading of dialkylammonium ions with crown ethers of generally 24-membered (or greater) rings is well investigated, while smaller crown ethers facilitate a face-to-face interaction.[10,34] It is therefore quite possible that **5c**, a 21-membered metallacrown ether, may be too small to allow threading of the larger ammonium ion, if perhaps even the less bulkier di-*n*-butylammonium ion. The larger macrorings of **6c** and **11c** (24-memebered) and **7c** and **12c** (30-memebered) are of sufficient size in this respect to facilitate threading. It may also be expected that the bulkier benzimidazol-1-yl moiety may increase crowding at the cavity of the metallacrown ether and thereby prevent threading of the dibenzylammonium ion through the cavity of **11c**. Thus a face-to-face type interaction may result and remove the $C^{\alpha}H_2$ protons from the vicinity of the metallacrown ether ring protons, thereby causing no intensity enhancement in the NOE experiments.

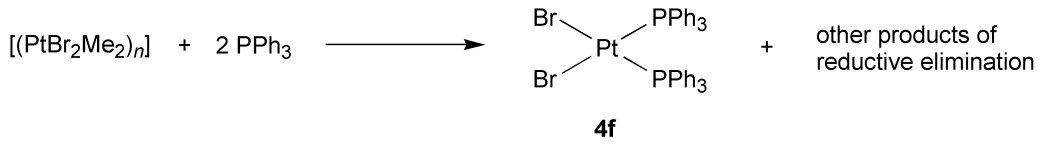
2.1.5. With phosphino ligands

By analogy to a procedure using similar ligands and $[PtCl_2(cod)]$,[4d] 1,8-bis(diphenylphosphino)-3,6-dioxaoctane (dpdo) was reacted with $[PtCl_2(nbd)]$ to yield $[PtCl_2(dpdo)]$ (**3f**), a known complex previously isolated from a refluxing reaction mixture of dpdo with $K_2[PtCl_4]$ (Scheme 13 and appendix 2).[35] The reaction of dpdo with $[(PtBr_2Me_2)_n]$ yields mixtures of inseparable products, probably due to reductive

elimination reactions.[36] Similarly, several products were observed (^{1}H NMR) in the reaction of triphenylphosphine with [($PtBr_2Me_2)_n$] (Scheme 14 and appendix 2).



Scheme 13 Preparation of **3f** from [$PtCl_2$(nbd)] and dpdo.



Scheme 14 Preparation of **4f** from PPh_3 and [($PtBr_2Me_2)_n$].

One of these products, *cis*-[$PtBr_2(PPh_3)_2$] (**4f**) is insoluble in benzene and was isolated from the reaction mixture by filtration. Both *cis*- and *trans*-[$PtBr_2(PPh_3)_2$] are known in the literature, although the X-ray crystal structure analysis of *cis*-[$PtBr_2(PPh_3)_2$] is not described (Fig. 9 and appendix 2).[37]

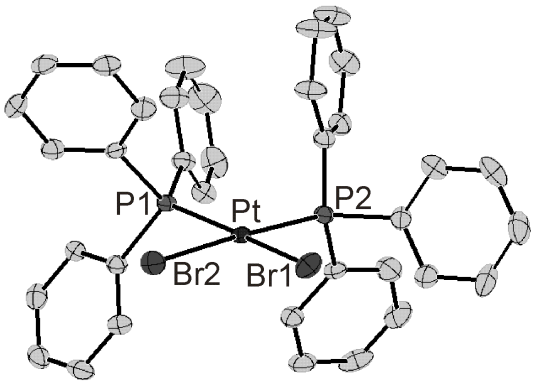


Fig. 9 Molecular structure of *cis*-[$PtBr_2(PPh_3)_2$]·$CHCl_3$, $CHCl_3$ and hydrogen atoms omitted for clarity. Displacement ellipsoids at 30% probability.

Resonances in the ^{1}H NMR attributed to alkanes, mainly ethane and propane, were also among the products of the reaction between triphenylphosphine and [($PtBr_2Me_2)_n$]. These alkanes are consistent with reductive elimination of the methyl ligands from platinum(IV), a process observed for many other platinum(IV) complexes with alkyl and phosphine ligands.[36]

2.2. Platinum(IV) complexes of higher nuclearity

2.2.1. Strategies for dinuclear complexes

The dinuclear complexes obtained herein were prepared by two main strategies. The first involved the use of *N*-heteroaromatic ligands that can present at least two ligating nitrogen donor atoms. Deprotonation of the pyrazole ligand of **5a** allowed coordination through the second nitrogen atom of this *N*-heteroaromatic ligand. Other ligands such as 2,2'-bipyrimidine and 4,4'-bipyridine present a second set of nitrogen donors without deprotonation. With these *N*-heteroaromatic ligands the bridging moiety is rigid owing to the aromaticity of the bridging entity. In addition the metal centers are in relative close proximity (**11a**: Pt···Pt 3.593(1) Å).

The second strategy involved the use of ligands with flexible spacers such as 1,2-bis(benzimidazol-1-yl)ethane (**L8**). Although connected by a flexible ethylene or, as was the case for **2c**, diethyl ether spacer, the formation of a complex with a chelating mode of the respective ligand is disfavored due to the relative positioning of the nitrogen donors on the bis(azol-1-yl) moieties. Hence the difference in coordination mode between 1,2-bis(pyrazol-1-yl)ethane a chelating ligand in **1e**, and **L8**, a bridging ligand in $[(PtBr_2Me_2)_2(\mu\text{-bim}CH_2CH_2\text{bim})_2]$ (**8c**). The distance between the platinum atoms in the resulting dinuclear complexes is increased relative to the dinuclear complexes obtained by the strategy described above, (**8c**: Pt···Pt 9.4730(4) Å). As the length of the chain increases between the bis(azol-1-yl) moieties the chelate effect prevails, as may be expected.

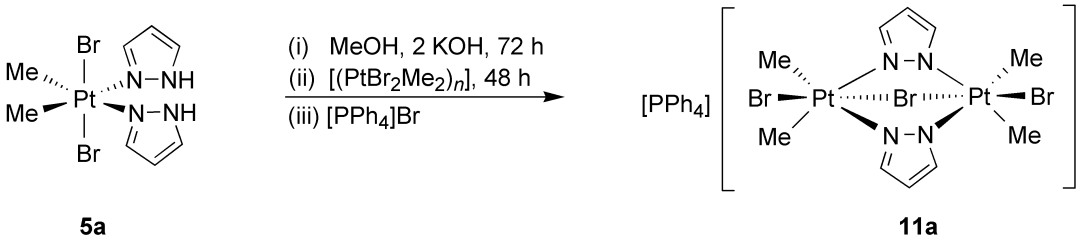
Collectively both strategies belong to the so-called “molecular library” model applied in the self-assembly of metallamacrocycles.[38]

2.2.2. With N-heteroaromatic donors

Bridging pyrazolato

Deprotonation of the *N*-heterocyclic ligands of **5a**, $[PtBr_2Me_2(4\text{-Me-H-pz})_2]$ (**6a**), $[PtBr_2Me_2(H\text{-im})_2]$ (**8a**) and $[PtBr_2Me_2(H\text{-bim})_2]$ (**9a**) was expected to lead to a second ligating nitrogen donor site free to facilitate a bridging coordination mode of the respective ligand. A number of structures with bridging pyrazolato ligands between two group 8–10 organometallic fragments are known.[39] Bridging modes of imidazolato moieties, particularly of dibenzimidazolato ligands, in the construction of multinuclear complexes are also of interest owing, among other features, to their

electronic coupling properties between two metal atoms.[40] Deprotonation of **5a** allowed the formation of the dinuclear complex $[PPh_4][(PtBrMe_2)_2(\mu\text{-}Br)(\mu\text{-}pz)_2]$ (**11a**) (Scheme 15).



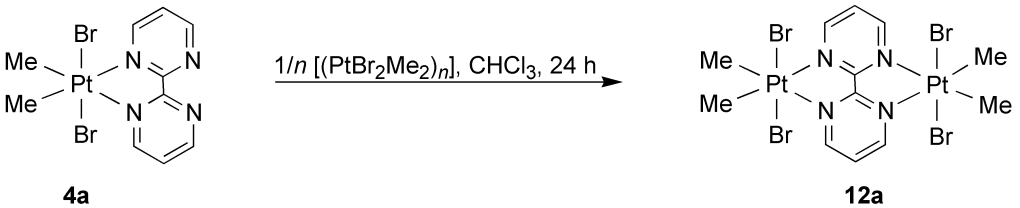
5a **11a**

Scheme 15 Preparation of **11a** from **5a**.

Similar reactions with **6a**, **8a** and **9a** gave multiple products that could not be separated. The bridging mode of the pyrazolato ligand of **11a** was anticipated since although chelating pyrazolato ligands are known,[41] dinuclear complexes with bridging pyrazolato ligands are extremely prevelent.[39,42] The stability of **11a** was demonstrated by its inertness towards substitution of the bridging bromo ligand in the presence of silver salts, a reaction found to be successful for similar dinuclear platinum(IV) complexes with bridging iodo ligands.[42]

Bridging 2,2'-bipyrimidine

Bridging modes of bipyrimidine ligands have been shown to yield dinuclear complexes, of which only a small proportion have been characterized in solution.[43,44] Mononuclear $[PtBr_2Me_2(bpym)]$ (**4a**) was used as a starting complex for the preparation of $[(PtBr_2Me_2)_2(\mu\text{-}bpym)]$ (**12a**) (Scheme 16).



4a **12a**

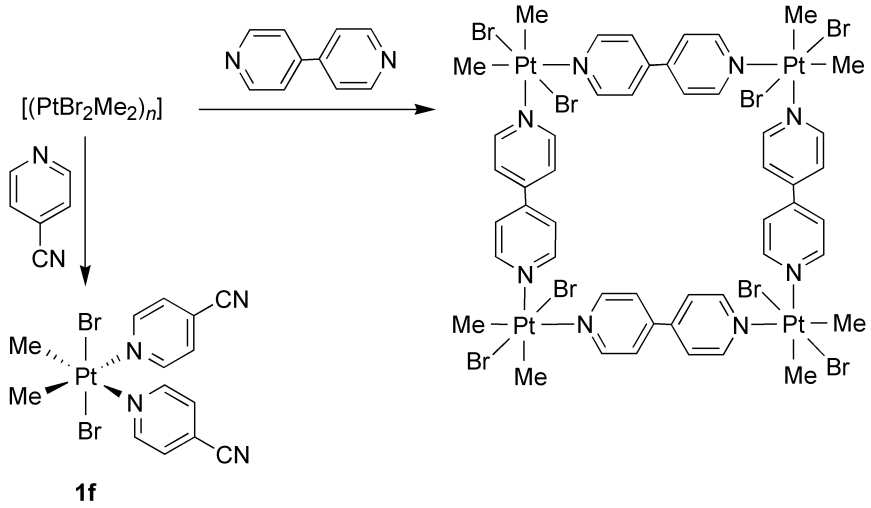
Scheme 16 Preparation of dinuclear **12a** from **4a**.

Complex **12a** dissolves only slowly in DMF (donor number (D. N.) = 26.6)[45] and in doing so yields mononuclear **4a** and $[PtBr_2Me_2(DMF)_2]$ in an equilibrium process. The stability of mononuclear **4a** may act as a driving force in this process since only **4a** is presence in solution (^{1}H NMR) after one month, presumably accompanied by

degradation of **12a** and $[PtBr_2Me_2(DMF)_2]$. Similar sets of signals were observed when DMSO (D. N. = 29.8) was used as the solvent system but the spectrum of **12a** in weaker donor solvents such as THF (D. N. = 20) is featureless, indicating the relative stability of the bridging bipyrimidine complex.

4,4'-Bipyridine – possible tetranuclear complex

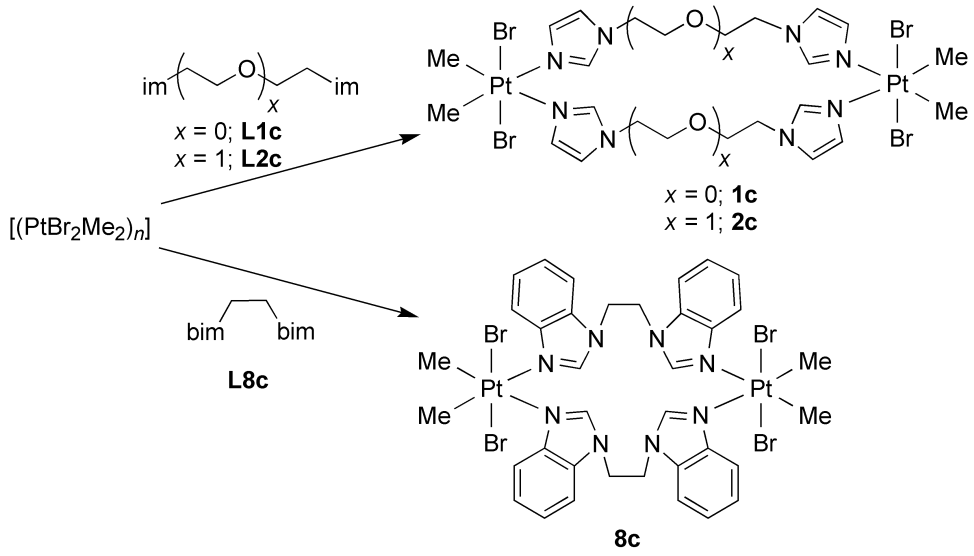
The product of the reaction between 4,4'-bipyridine and the $[(PtBr_2Me_2)_n]$ precursor, $[\{PtBr_2Me_2(4,4'\text{-bipy})\}]$ (**5f**), demonstrates a 4,4'-bipyridine ligand to $PtBr_2Me_2$ ratio of 1 by NMR spectroscopy (^1H and ^{13}C) and microanalysis. Furthermore, NMR spectroscopy is in accord with the presence of one platinum species (δ_{Pt} –2343 ppm) and, from ^1H and ^{13}C NMR spectroscopy, the coordination of both nitrogen donors of the ligand in identical surroundings. The formation of the molecular square $[\{PtBr_2Me_2(4,4'\text{-bipy})\}_4]$ although not proved conclusively, agrees with these results (Scheme 17). Mass spectrometry and X-ray crystal diffraction were not possible and thus the formation of polymeric entities cannot be ruled out, although a molecular square satisfies geometrical and thermodynamic considerations. The linear 4,4'-bipyridine ligand has been shown to form molecular squares with metal ion fragments meeting the correct geometrical requirements.[46] In contrast to this reaction with 4,4'-bipyridine, the linear ligand 4-cyano-pyridine, also an appropriate ligand for self-assembly of molecular squares,[47] yielded only the mononuclear complex $[PtBr_2Me_2(4\text{-CN-py})]$ (**1f**) (Scheme 17 and appendix 1).



Scheme 17 The reaction yielding **1f** and the proposed product of the reaction between 4,4'-bipyridine and $[(PtBr_2Me_2)_n]$.

2.2.3. With bis(azol-1-yl) ligands

As discussed above bis(imidazol-1-yl) and bis(benzimidazol-1-yl) polyether compounds in combination with [($PtBr_2Me_2$)$_n$] yielded mononuclear platinum(IV) metallacrown ethers. Compounds **L1c**, **L2c** and **L8c** reacted with [($PtBr_2Me_2$)$_n$] to yield dinuclear complexes (Scheme 18). Unlike the rigid *N*-heterocyclic bridging ligands described in the previous section above, these bis(azol-1-yl) ligands are relatively flexible due to the spacer between the azol-1-yl groups. This in turn reduces the directionality of the ligand and the orientation of the vacant coordination sites at the platinum atom becomes the principal source of directionality.



Scheme 18 The preparation of dinuclear platinum(IV) complexes with bis(imidazol-1-yl) and bis(benzimidazol-1-yl) ligands. Imidazol-1-yl: im. Benzimidazol-1-yl: bim.

The two ethylene-bridged complexes [($PtBr_2Me_2$)$_2$(μ-**L1c**)$_2$] (**1c**) and [($PtBr_2Me_2$)$_2$(μ-**L9c**)$_2$] (**9c**) are assigned as dinuclear. Since **9c** is completely insoluble characterization of **9c** is eluded from its solid state structure and microanalysis only. Although **1c** was of sufficient solubility to allow NMR spectroscopy, determinative assignment via mass spectrometry or X-ray crystal diffraction analyses was not possible. Nevertheless, due to the structural similarities of the ligands **L1c** and **L8c** and the known propensity of **L1c** to adopt bridging rather than chelating coordination modes,[48] **1c** is more than likely dinuclear.

It was somewhat unexpected that [($PtBr_2Me_2$)$_2$(μ-**L2c**)$_2$] (**2c**) was dinuclear since the analogous benzimidazolyl ligand **L9c** yielded the mononuclear complex [$PtBr_2Me_2$(**L9c**)] (**9c**) under the same reaction conditions. In addition, X-ray crystal

structure analysis of the platinum(II) complex [$PtCl_2$(**L5d/L2c**)] (**5d**) (Section 2.1.3.) shows that the ligand can chelate in a bidentate fashion. The reason for the bridging mode of **L2c** in **2c** is not clear since the bulkier ligating benzimidazolyls of **L9c** were expected to be the most likely of the two analogues **L2c** and **L9c** to yield a dinuclear complex with [$(PtBr_2Me_2)_n$]. Complexes **2c** and **9c** have distinctly different solubilities. While **9c** has some solubility in the $CHCl_3$ (reaction solvent) and CH_2Cl_2, **2c** appears completely insoluble in both solvents. If we assume an equilibrium process between mononuclear and dinuclear species in each reaction it may be that **2c** and **9c** are the least soluble species from each respective pair and the equilibria shift accordingly to the least soluble product.

2.3. Spectroscopic and structural investigations

2.3.1. Spectroscopic data

Where solubility allowed all complexes isolated during the course of these investigations were characterized by NMR spectroscopy (^{1}H, ^{13}C and ^{195}Pt). The ^{1}H NMR spectra of the dimethyl and trimethyl platinum(IV) complexes **1a**–**12a**, **1c**–**13c**, **1e**–**5e**, **1f**, **2f** and **5f** showed a singlet plus doublet resonance pattern shifted between 0.95–2.66 ppm assignable to the methyl ligands (Table 1).

Table 1 Selected NMR data (^{1}H and ^{13}C) representative of the range of chemical shift and couplings associated with the methyl ligand resonances (δ in ppm, *J* in Hz) [**a**–**f**].

Complex	Solvent	H_3C–Pt–*X*	δ(Pt–CH_3) ($^2J_{Pt,H}$)	δ(Pt–CH_3) ($^1J_{Pt,C}$)
4a	$(CD_3)_2NCDO$	*N*	2.20 (72.8)	–5.9 (529.9)
6a	$CDCl_3$	*N*	1.86 (72.2)	–10.8 (501.4)
11a	$CDCl_3$	*N*[a]	1.72 (66.6)	–12.6
12a	$(CD_3)_2NCDO$	*N*[b]	2.25 (74.7)	[c]
13c	$CDCl_3$	*N*[d]	2.32 (72.6)	–19.3
3e	$(CD_3)_2CO$	*N*[d]	2.66 (75.5)	–13.5
4e	$(CD_3)_2CO$	*N*	1.02 (69.9)	–6.7 (692.5)
		O	1.50 (80.7)	–7.1 (773.3)
5e	$(CD_3)_2CO$	*N*	0.95 (70.9)	–7.8 (669.5)
		S	1.33 (66.8)	9.3 (662.0)

[a] *N*-donor of bridging pyrazolato. [b] *N*-donor of bridging bipyrimidine. [c] ^{13}C NMR not possible. [d] Iodo ligands in axial position.

The $^{2}J_{Pt,H}$ coupling of the methyl protons range between 66.6 and 80.7 Hz, depending on the donor atom coordinated *trans* to the methyl ligands. The ^{13}C NMR spectra of the same dimethyl and trimethyl platinum(IV) complexes showed a similar pattern assignable to the methyl ligands shifted in a range between –19.3 and 9.3 ppm. Where observed the $^{1}J_{Pt,C}$ coupling of the carbon atoms of the methyl ligands lie between 501.4 and 773.3 Hz again depending on the donor atom coordinated *trans* to the methyl ligands. The ^{195}Pt NMR spectra of the complexes reported in **a**–**f** show that all values fall in a relatively narrow range regardless of the oxidation state (–1991 to –3409 ppm). This narrow range of values is consistent with those found in the literature for similar platinum(II) and platinum(IV) complex types.[27a,49] High-field chemical shifts of complexes with iodo rather than bromo ligands (**3c**/**13c** δ_{Pt} –2362/–2738 ppm and **1e**/**3e** –2319/–3409ppm) are consistent with the trend observed for platinum complexes of many types where bromo ligands are substituted by iodo ligands.[49a]

2.3.2. Structural investigations

Structure types

Single crystals of several of the complexes from these investigations reported in [**a**–**e**] were characterized by X-ray crystal diffraction. These complexes can be grouped according to the respective donor sets around the central platinum atom, namely $[Br_2C_2N_2]$, $[C_3N_2O]$, $[Br(\mu\text{-}Br)C_2(\mu\text{-}N)_2]$ and $[Cl_2N_2]$. The structures of the platinum(IV) complexes show a roughly octahedral arrangement of the ligating atoms around the central platinum atom, with the nitrogen donor ligands configured *trans* to the methyl ligands. Where bromo ligands are present these are configured mutually *trans* to one another. The vast majority of the structures discussed in [**a**–**e**] have the dibromodimethylplatinum(IV) entity and collectively represent the most substantial body of structural data related to this moiety.[50] Structures of **5d** and **6d** show a square planar arrangement of the ligating atoms around the platinum(II) atom. The individual features of the solid state structures are discussed in the relevant reference [**a**–**f**].

Weak interactions in the solid state

Collectively, a number of intermolecular and intramolecular interactions are observed within the crystal structures. A prevalent intramolecular and intermolecular interaction found is the weak hydrogen bond (<16 kJ/mol).[51] These hydrogen bonding interactions are characterized by three main parameters: (i) the distance between the donor-acceptor pair, (ii) the distance between the hydrogen atom and the acceptor and (iii) the donor-hydrogen atom-acceptor angle. Table 2 collects some of the (i) and (iii) parameters found for the intramolecular hydrogen bonding interactions of **5a**, **6a**, **1b**, **6d** and **1f** and the intermolecular hydrogen bonding and interionic hydrogen bonding interactions found for **7a** and **4e**, respectively.

Table 2 Summary of parameters indicating weak hydrogen bonding interactions.

Complex	Donor···Acceptor Distance [Å]		Estimated* Donor–H···Acceptor Angle [°]	
5a	N···Br	3.23(1); 3.32(1)	N–H···Br	125; 117
6a	N···Br	3.30(1)	N–H···Br	113
7a	N···Br	3.38(1)	N–H···Br	146
1b	C···Br	3.41(1)	C–H···Br	115
6d	C···Cl	3.18(1)	C–H···Cl	104
4e	C···F	3.01; 3.15	C–H···F	116; 137
1f	C···Br	3.42(1); 3.38(1)	C–H···Br	113; 129
		3.36(1)		125

*Positions of hydrogen atoms calculated and angle estimated from these positions.

Most weak hydrogen bonding interactions present in the structures (exception **4e** and **7a**) were found between the hydrogen atom on the aromatic carbon/nitrogen atom (donor) neighboring the ligating nitrogen atom ($^{\alpha}$C/$^{\alpha}$N) and halo ligands of the same molecule (acceptors). The range of angles and lengths typically found in structures believed to exhibit these interactions in complexes with acceptor halo ligands has been reviewed.[52] In all structures reported in [**a**–**f**] where hydrogen bonding is observed the hydrogen atoms were added to the structures using the 'Riding Model' and thus the distance between the hydrogen atom and acceptor atom and the angle given by donor-hydrogen atom-acceptor atoms must not be overestimated. However,

a donor-acceptor distance less than the sum of the van der Waals radii ($R_{donor,acceptor}$) is taken as a strong indicator of hydrogen bonding in these complexes (van der Waals radi: R_{CBr} = 3.55 Å; R_{NBr} = 3.40 Å; R_{CCl} = 3.45 Å; R_{CF} = 3.17 Å).

In addition to weak hydrogen bonding interactions involving Br, Cl and F acceptors, aromatic-aromatic interactions (<15 kJ/mol) are also present in many of the solid state structures reported in [**a**–**e**]. These interactions are divided into three main types depending on the geometry of the interaction: edge-face, offset stacked and face-to-face (Fig. 12a–c). Such interactions are ubiquitous in nature and have been utilized by chemists in the assembly of supramolecular entities.[53] Although there is ongoing discussion as to the contribution of each, aromatic-aromatic interactions consist of van der Waals, hydrophobic and electrostatic forces. Since π-deficient-π-deficient aromatic systems have been shown to be more stable then π-deficient-π-rich and π-rich-π-rich systems, heterocyclic nitrogen ligands are favorable systems for π-π interactions due to their low π-electron density.[54] The geometrical parameters indicating offset stacked and face-to-face interactions are given by the distance between two parallel ring systems, the distance between their centroids and the displacement angle. Several of the solid state structures reported in [**a**–**d**] demonstrate interactions corresponding to the more stable (minimized π electron repulsion and maximized σ framework attraction to the π electron density) offset stacked arrangement, as is apparent from the parameters in Table 3. These parameters are consistent with the findings of other studies reporting such interactions. [54a]

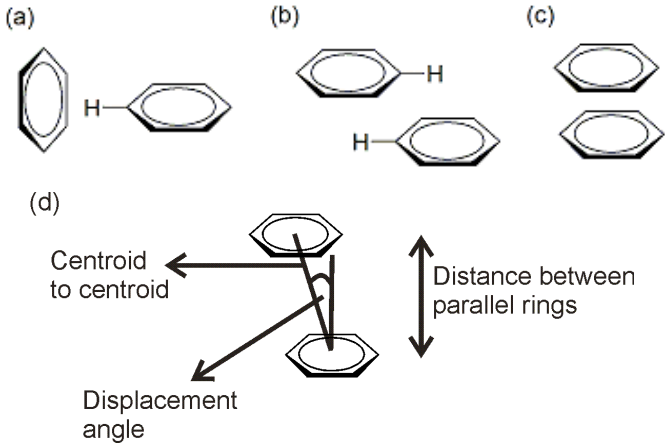


Fig. 10 Types of aromatic-aromatic interactions (a) face-to-edge (b) offset stacked (c) face-to-face. (d) Parameters defining offset stacked and face-to-face arrangements.[53a,54a]

Table 3 Parameters between parallel aromatic rings indicating aromatic-aromatic interactions.

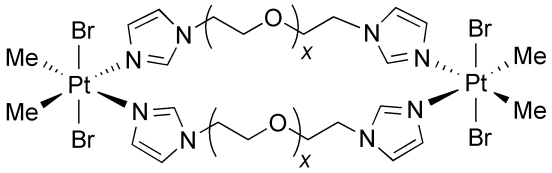
Complex	Heteroaromatic Ligand	Plane···Plane Distance [Å]	Centroid···Centroid Distance [Å]	Displacement Angle [°]
5a	pyrazole	3.22	3.60	24.7
7a	indazole[a,b]	3.49	3.67	18.2
10a	quinazoline[a,b]	3.49	3.67	24.7
8c	benzimidazol-1-yl[b]	3.41	3.66	20.6
		3.46	3.77	23.4
		3.35	3.63	22.5
10c	benzimidazol-1-yl[b]	3.42	3.76	23.2
5d	imidazol-1-yl	3.45	3.76	27.1
		3.29	3.63	24.7
6d	imidazol-1-yl	3.32	3.43	14.3

[a] Both rings of the molecule interact, by symmetry parameters are the same. [b] Closest interaction given.

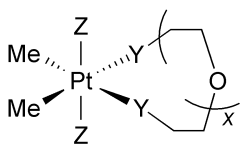
2.4. Anticancer evaluation

Structure-activity relationship

As described in [**c**] the *in vitro* antitumor activity of selected compounds from the series **1c**–**13c** was assessed on the tumor cell lines lipocarcoma, A549 (non-small-cell lung carcinoma) and 518A2 (melanoma). The compounds investigated by cytotoxicity assay were selected with the aim of examining the structure-activity relationship (Fig. 11).



1c, **2c**



3c, **6c**, **10c**, **13c**

Complex	**1c**	**2c**	**3c**	**6c**	**10c**	**13c**
Ligand	**L1c**	**L2c**	**L3c**	**L6c**	**L10c**	**L3c**
Y	-	-	im	im	bim	im
x	0	1	2	5	2	2
Z	-	-	Br	Br	Br	I

Fig. 11 Complexes tested for anticancer activity.

Free ligands **L1c** ($imCH_2CH_2im$) and **L6c** ($imCH_2CH_2(OCH_2CH_2)_5im$) and the solvated starting complex $[PtBr_2Me_2(DMF)_2]$ were included as indicators of the activity of the individual moieties of the corresponding complexes. Table 4 shows a summary of the cytotoxicity data where the IC_{50} represents the dose required to reduce the number of living cells by 50%.

Table 4 IC_{50} values [µM] from the cytotoxicity assay on liposarcoma, A549 (lung carcinoma) and 518A2 (melanoma). Evaluation of cisplatin is under similar conditions. *x* = number of ethyleneoxy groups [**c**].

Compound	IC_{50} [µM]		
	Liposarcoma	A549	518A2
1c	38.8±18.4	9.7±1.8	20.9±5.2
2c	7.8±0.3	5.3±0.3	6.7±0.4
3c	8.6±0.0	7.2±0.1	8.9±0.0
6c	4.0±0.3	7.4±0.2	7.1±0.2
10c	9.5±7.0	12.8±1.4	8.0±3.6
13c	13.7±5.4	4.7±3.1	9.5±6.9
L1c (*x* = 0)	42.3±21.5	37.6±3.2	54.3±24.2
L6c (*x* = 5)	>150	>150	>150
$[PtBr_2Me_2(DMF)_2]$	85.3±35.2	94.9±29.8	94.4±37.6
cisplatin	0.130	0.163	0.179

Although **L6c** exceeded the measurement range, **L1c** showed a measure of activity similar to that of its corresponding platinum(IV) complex. It is known that simple substituted *N*-heterocyclic compounds such as **L1c** can act as activators of carbonic anhydrases.[55] Carbonic anhydrases (CA) are a family of zinc(II) isoenzymes responsible for the catalytic conversion of carbon dioxide to bicarbonate ions and are found in many tissues and organs in humans (α-CA).[56] Some of these isoenzymes, for example CA IX and CA XII, are overexpressed in many tumors and lead to acidification of the tumor tissue.[57] Although *in vitro* experiments do not simulate the hypoxia conditions found in tumor tissue it is nevertheless of interest to note the moderate activity of **L1c**, a carbonic anhydrase activator, and its corresponding complex **1c**. In general, the higher activity of all complexes relative to the solvated

starting complex indicates only that the activity is improved by the polyether ligands, possibly due to the more inert nature of the polyether ligands relative to the DMF ligand.

Although investigations on the mode of action of platinum(IV) anticancer complexes such as satraplatin are ongoing, reduction and reduction rates are of interest since the active species can be platinum(II) metabolites.[19] If platinum(II) metabolites are the active species derived from the platinum(IV) complexes tested in [**c**] (**1c**–**13c**), then reductive elimination of both axial ligands (halide), both methyl ligands or a halide and a methyl ligand may generate the active species. Replacing the bromo ligands with iodo ligands (**3c**→**13c**) or the introduction of benzimidazol-1-yl rather than imidazol-1-yl moieties (**3c**→**11c**) did not appear to influence the activity substantially. Increasing the number of ethyleneoxy units on the ligand backbone from two to five (**3c**→**6c**) caused little change in the cyctoxicity on any of the cell lines. Nevertheless, these complexes are examples of active dibromo (**2c**, **3c**, **6c** and **10c**)/diiodo (**13c**) platinum(IV) complexes, both of which are much less reported than the traditional anticancer platinum complexes with chloro ligands.[19b,58] Furthermore, reports on the anticancer properties of compounds with platinum-carbon bonds are scarce in the literature and this series expands on the small number already reported.[19a,42,59]

Cell death

Platinum drugs can induce one of two modes of cell death, apoptosis (programmed cell death) or necrosis (accidental cell death). Trypan-blue staining tests demonstrate that apoptosis is induced preferentially by the complexes **1c**–**3c**, **6c**, **10c** and **13c**. The test is a primary indicator of cell death and further tests are required to confirm the induced mode of cell death. Nonetheless, breakdown of the cell membrane is an indicator of necrosis and exclusion of the dye for a significant period of time in the presence of cytototoxic quantities of the drugs is consistent with apoptosis. In addition it was noted that the melanoma cell line 518A2 was sensitive to the dibromo bis(imidazolyl) complexes **1c**–**3c** and **6c**, as observed by the quick onset of secondary necrosis.

Platinum-uptake

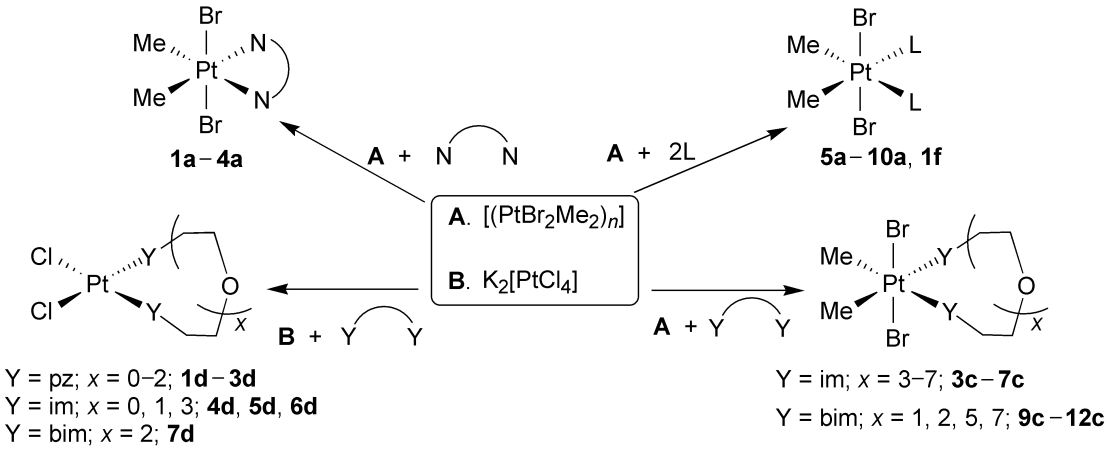
Platinum-uptake is a quantitative measure of the amount of platinum entering the cell. This is of interest since uptake may be correlated with cytotoxicity. The platinum-uptake of **1c**–**3c**, **6c**, **10c** and **13c** showed little evidence of any correlation with cytotoxicity. The uptake of most compounds was higher than cisplatin on cell lines A549 and 518A2, while uptake in liposarcoma was higher than cisplatin for **1c**, **10c** and **13c** only. It has been shown *in vitro* that platinum(IV) complexes often demonstrate significantly better lipophilicity than commercial platinum(II) drugs.[21] Such platinum(IV) complexes can effectively cross the cell membrane by passive diffusion and consequently an increased accumulation of platinum can be observed in the cells. This may also be the reason for the drastic increase in platinum-uptake observe for **1c** relative to the other polyether type complexes and cisplatin.

While at best the activity of the polyether complexes was ca. 40 times less than that of cisplatin the platinum(IV) complexes tested from the series **1c**–**13c**, can still be regarded as moderately active on all three cell lines. There is in most cases no evidence of selectivity between the various tumor cell lines, as is evident from the IC_{50} values. The only exception to this lack of selectivity is the marginally better performance of **6c** on the liposarcoma tumor cell line which is approximately twice as high as the activity found on the A549 and 518A2 cell lines.

3. Summary

The construction of supramolecular entities via the self-assembly approach has been an area of significant interest in recent years. With the growth of this area new classifications for metallasupramolecules have emerged including metal molecular polygons and metallacrown ethers. The search for improved metal based anticancer drugs continues to be a major area of research within inorganic chemistry. While initially focused on a relatively narrow range of platinum(II) complexes, interest in the anticancer properties of platinum(IV) complexes has intensified over the last 15 years owing to the small number of platinum(IV) complexes to have reached clinical trials.

Within the scope of the work herein platinum(II)/(IV) complexes with a range of nitrogen donor ligands were prepared and characterized. These included both mononuclear and dinuclear species. Chief among the mononuclear complexes is a family of metallacrown ethers, inorganic analogues of crown ethers. Different properties including reactivity, binding propensity and anticancer behavior were evaluated for the complexes described herein. The overall results reported in this work may be summarized as follows:

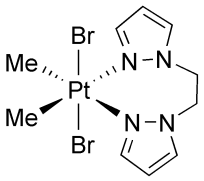


1. The reaction of $[(PtBr_2Me_2)_n]$ (**A**) with *N*-heteroaromatic donors yielding $[PtBr_2Me_2(N⌒N)]$ (N⌒N: bidentate *N*-donor ligand such as bipyrimidine; **1a**–**4a**) and $[PtBr_2Me_2(L)_2]$ (L: *N*-heterocyclic monodentate ligand such as pyrazole; **5a**–**10a** and **1f**) type complexes proved a simple and efficient synthesis of dibromodimethylplatinum(IV) complexes with *N*-donors.

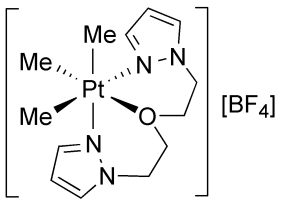
2. A number of platinum(II) complexes with alkanediyl, diethyl ether and polyether linked bis(azol-1-yl) ligands (azol-1-yl: pyrazol-1-yl (pz), imidazol-1-yl (im),

benzimidazol-1-yl (bim)) were also prepared. Reactions of ethylene or diethyl ether linked bis(pyrazol-1-yl) ligands with $K_2[PtI_6]$ yielded $[PtI_2\{pz(CH_2CH_2O)_xCH_2CH_2pz\}]$ (*x* = 0, **8d**; *x* = 1, **9d**). A broad spectrum of compounds reacted with $K_2[PtCl_4]$ to yield complexes of the generic type $[PtCl_2\{Y(CH_2CH_2O)_xCH_2CH_2Y\}]$ (Y: pyrazol-1-yl (**1d**–**3d**), imidazol-1-yl (**4d**–**6d**) or benzimidazol-1-yl (**7d**); *x* = 0–3; see scheme above). Although this series included **6d**, a complex with a 16-membered ring, isolation of larger platinum(II) metallacrown ethers with these ligands requires further investigation since reactivity with the longer α,ω-bis(azol-1-yl) polyether compounds differs from that of the shorter chained compounds.

3. Bis(pyrazol-1-yl) compounds proved flexible bidentate and tridentate ligands in platinum(IV) complexes. 1,2-Bis(pyrazol-1-yl)ethane reacted with $[PtMe_2(cod)]/I_2$ and $[(PtBr_2Me_2)_n]$ to yield platinum(IV) complexes with seven-membered chelate rings, $[PtI_2Me_2(pzCH_2CH_2pz)]$ (**3e**) and **1e**, respectively. 1,8-Bis(pyrazol-1-yl)-*n*-octane also reacted with $[(PtBr_2Me_2)_n]$ to yield $[PtBr_2Me_2\{pz(CH_2)_8pz\}]$ (**2e**). Bis[2-(pyrazol-1-yl)ethyl] ether/thioether ligands reacted with $[(PtIMe_3)_4]$ in the presence of a silver salt (e.g. $AgBF_4$) to yield **4e** and $[PtMe_3(pzCH_2CH_2SCH_2CH_2pz)][CF_3SO_3]$ (**5e**), with $\kappa^2N,N',\kappa O$ and $\kappa^2N,N',\kappa S$ coordination, respectively. Thus, the bis(pyrazol-1-yl) compounds examined here facilitate the formation of platinum(IV) complexes with chelating bi- or tridentate modes of the ligand, depending on the requirements at the metal centre.

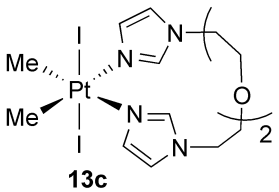


1e



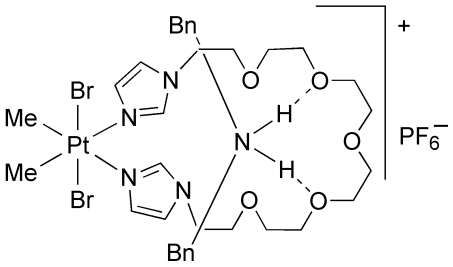
4e

4. A range of α,ω-bis(azol-1-yl) polyether compounds (azol-1-yl: imidazol-1-yl or benzimidazol-1-yl) reacted with precursor **A** to afford a series of platinum(IV) metallacrown ethers (**3c**–**7c** and **9c**–**12c**, see scheme above). In addition, a diiodo analogue of these metallacrown ethers, **13c**, was prepared by combining $[PtMe_2(cod)]/I_2$ with the appropriate α,ω-bis(imidazol-1-yl) ligand. These platinum(IV) metallacrown ethers represent a departure from the more common type of metallacrown ethers prepared with α,ω-bis(phosphino) polyether compounds.

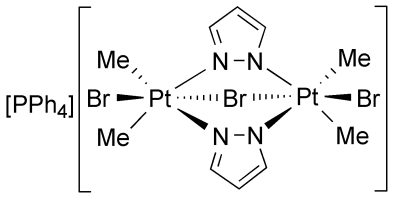


13c

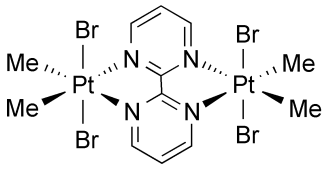
5. The host properties of the larger members of this series of metallacrown ethers (**5c**–**7c**, **11c** and **12c**) were investigated with di-*n*-butylammonium and dibenzylammonium ion guests, respectively. NMR investigation, NOE experiments, HR-ESI-MS analysis and a visual enhancement in the solubility of the ammonium salts in chlorinated hydrocarbons verified the presence of host-guest interactions. Fast complexation-decomplexation equilibria and weak binding interactions predominate between these host/guest species in solution.



6. Starting from the mononuclear building blocks $[PtBr_2Me_2(H\text{-}pz)_2]$ (**5a**) and $[PtBr_2Me_2(bpym)]$ (**4a**) the dinuclear complexes $[PPh_4][(PtBrMe_2)_2(\mu\text{-}Br)(\mu\text{-}pz)_2]$ (**11a**) and $[(PtBr_2Me_2)_2(\mu\text{-}bpym)]$ (**12a**) could be prepared and isolated.

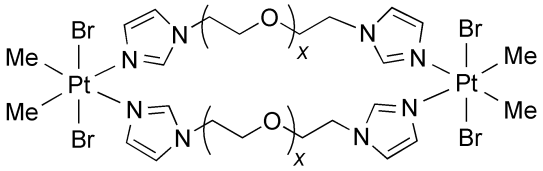


11a

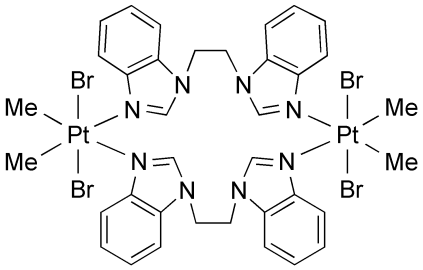


12a

α,ω-Bis(imidazol-1-yl/benzimidazol-1-yl) compounds with short ligand spacers resulted in dinuclear complexes in combination with $[(PtBr_2Me_2)_n]$ (**1c**, **2c** and **8c**).



x = 0; **1c**
x = 1; **2c**



8c

Although the steric requirements of the ethylene bridged ligands in **1c** and **8c** were expected to lead to dinuclear complexes, the formation of **2c** was somewhat unexpected, particularly since the same α,ω-bis(imidazol-1-yl) ligand adopted a bidentate mode with a platinum(II) precursor (**2d**) and the α,ω-bis(benzimidazol-1-yl) derivative of this ligand was also bidentate in **9c**.

7. The majority of the platinum(IV) complexes reported herein have a *trans* configuration of a methyl ligand to a nitrogen donor atom (Me–Pt–N). Thus a range of chemical shift and coupling data characteristic of these methyl resonances was observed for such an arrangement. A number of solid state structures were determined during these investigations and many of these were found to exhibit weak intra- and intermolecular interactions such as aromatic-aromatic interactions and weak hydrogen bonding involving mostly metal bound halo ligands as acceptors. The parameters associated with these interactions are consistent with those in the literature.

8. *In vitro* studies of the cancerostatic properties of selected members of the metallacrown ether series (**1c**–**3c**, **6c**, **10c** and **13c**) showed that these organometallic platinum(IV) complexes possess moderate activity on liposarcoma, lung carcinoma (A549) and melanoma (518A2) tumor cell lines. Despite the structural variation of **3c** (two versus five ethyleneoxy groups, **3c**/**6c**; imidazolyl versus benzimidazolyl, **3c**/**10c**; bromo versus iodo, **3c**/**13c**) a clear relationship between either the structure of the complexes and their activity or indeed between the platinum-uptake and the overall activity was not established. However the complexes generally showed improved activity relative to their free ligands and primary testing indicated apoptotic cell death (programmed cell death) is induced in all cell lines on exposure to cytotoxic quantities of the complexes.

Within the scope of this work a range of platinum(II)/(IV) mononuclear and platinum(IV) dinuclear complexes were described. α,ω-Bis(azol-1-yl) compounds with flexible spacers proved versatile ligands affording mononuclear (bidentate and tridentate) and dinuclear complexes, depending on the initial platinum precursor complex. The platinum metallacrown ethers prepared using these α,ω-bis(azol-1-yl) ligands represent a new family of metallacrown ether complexes. The weak interaction between these metallacrown ether hosts and the dialkylammonium ion guests studied herein may provide a basis for the assembly of more complicated interlocking molecules such as rotaxanes and catenanes, although further investigation is required. The moderate anticancer activity of these organometallic

platinum(IV) metallacrown ether complexes is a new departure from the traditional inorganic platinum(II) complexes tested for such properties and contributes to a growing number of bioorganometallic complexes. Taken with the receptor studies, the cancerostatic activity of these metallacrown ethers demonstrates the versatile properties of these complexes.

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Appendix 1: Published results [a–e]

Reference [**a**]: Studies of mononuclear and dinuclear complexes of dibromodimethylplatinum(IV): Preparation, characterization and crystal structures. Kelly, M. E.; Gómez-Ruiz, S.; Kluge, R.; Merzweiler, K.; Steinborn, D.; Wagner, Ch.; Schmidt, H. *Inorg. Chim. Acta* **2008** in press.

Reference [**b**]: Dibromodimethylbis(pyridine)platinum(IV). Kelly, M. E.; Wagner, Ch.; Schmidt, H. *Acta Cryst.* **2008**, *E64*, m1385.

Reference [**c**]: Platinum(IV) Metallacrown Ethers: Synthesis, Structures, Host Properties and Anticancer Evaluation. Kelly, M. E.; Dietrich, A.; Gómez-Ruiz, S.; Kalinowski, B.; Kaluđerović, G. N.; Müller, T.; Paschke, R.; Schmidt, J.; Steinborn, D.; Wagner, Ch.; Schmidt, H. *Organometallics* **2008**, 27, 4917.

Reference [**d**]: Synthesis, characterization and X-ray crystal structures of polyether and ethylene bridged bis(azolyl) platinum(II) complexes. Kelly, M. E.; Gómez-Ruiz, S.; Steinborn, D.; Wagner, Ch.; Schmidt, H. *Transition Met. Chem.* **2008**, *33*, 721.

Reference [**e**]: Platinum(IV) complexes with α,ω-bis(pyrazol-1-yl) alkanediyl and diethyl ether/thioether ligands. Crystal structures of dibromodimethyl[1,2-bis(pyrazol-1-yl)ethane]platinum(IV) and trimethyl-bis[2-(pyrazol-1-yl)ethyl]etherplatinum(IV) tetrafluoroborate. Kelly, M. E.; Gómez-Ruiz, S.; Schmidt, J.; Wagner, Ch.; Schmidt, H. *Polyhedron* **2008**, *27*, 3091.

Appendix 2: Unpublished results [f]

Crystal structure of $[PtBr_2Me_2(4\text{-}CN\text{-}py)_2]$, **1f**

Crystal structure of *cis*-$[PtBr_2(PPh_3)_2]\cdot CHCl_3$, **4f**·$CHCl_3$

Experimental

Preparation of tetradeuterated $[PtBr_2Me_2(H\text{-}pz)_2]$ (**2f**)

Preparation of $[PtCl_2\{(Ph)_2P(CH_2CH_2O)_2CH_2CH_2P(Ph)_2\}]$ (**3f**)

Preparation of *cis*-$[PtBr_2(PPh_3)_2]$ (**4f**)

Preparation of $[\{PtBr_2Me_2(4,4'\text{-}bipy)\}]$ (**5f**)

*Crystal data and structure refinement for **1f***

*Crystal data and structure refinement for **4f**·$CHCl_3$*

*Crystal structure of [$PtBr_2Me_2$(4-CN-py)$_2$], **1f***

Compound **1f** crystallized in the triclinic space group $P\bar{1}$ and contains two similar symmetry independent molecules per asymmetric unit. The arrangement of the ligating atoms around the respective platinum(IV) atoms is approximately octahedral. The Br1–Pt1–Br2 angle (175.8(1)°) deviates significantly from the expected range of values for similar complexes with mutually *trans* bromo ligands bound to a hexacoordinated platinum (median 178.9°; lower/upper quartile 177.5/180.0°; *n* = 48; *n* = number of observations).[60] The Pt1–N3 bond length (2.273(8) Å) is slightly longer than expected for Pt(IV)–N bonds *trans* configured to a ligating carbon atom (median 2.156 Å; lower/upper quartile 2.135/2.194 Å; *n* = 402).[60] The Pt–Br bond lengths (2.449(1)–2.454(1) Å) and Pt–C bond lengths (2.05(1)–2.07(1) Å) are typical for bonds of these types [**a**–**c**,**e**].[50,61]

Selected bond angles [°] and bond lengths [Å] of **1f**.

C1–Pt1–N1	179.2(4)	Pt1–C	2.05(1); 2.07(1)
C2–Pt1–N3	179.1(4)	Pt2–C	2.07(1); 2.060(9)
C15–Pt2–N5	179.1(4)	Pt1–N	2.202(8); 2.273(8)
C16–Pt2–N7	179.1(4)	Pt2–N	2.204(8); 2.220(8)
Br1–Pt1–Br2	175.8(1)	Pt1–Br	2.453(1); 2.451(1)
Br3–Pt2–Br4	177.6(1)	Pt2–Br	2.454(1); 2.449(1)

The 4-cyanopyridine ligands of both molecules are bend out of the C–Pt–N axes as given by the Pt–N···*para*-C angles. In the most extreme case the Pt1–N1···C5 angle is 165.9(5)° while the Pt1–N3···C11 angle is 173.7(4)° (178.8 (5) and 174.4(5)°, respectively, in the second molecule). The Cambridge Structural Database (CSD) reveals a median of 175.8° (lower/upper quartile 173.1/177.9°; *n* = 104) occurs for this angle between any transition metal and a non-bridging 4-cyanopyridine ligand.[60] Only a small number of structures are known with angles of 168° or less and bending in these structures is generally attributed to packing within the crystal or electron repulsions between ligands on the same molecule.[62]

Crystal structure of cis-*[PtBr$_2$(PPh$_3$)$_2$]·CHCl$_3$*, **4f**·CHCl$_3$

cis-[PtBr$_2$(PPh$_3$)$_2$]·CHCl$_3$ crystallized in the triclinic space group $P\bar{1}$ with no evidence of any unusual intra- or intermolecular contacts. A search of the CSD reveals Pt–P bond lengths with a median of 2.243 Å (lower/upper quartile 2.232/2.255 Å; *n* = 36) and non-bridging Pt–Br bond lengths with a median of 2.479 Å (lower/upper quartile 2.469/2.490 Å; *n* = 36) in tetracoordinated platinum(II) complexes.[60] Thus, the Pt–P and Pt–Br bond lengths of **3f**·CHCl$_3$ are close to these ranges. In addition, bond angles surrounding the central platinum atom deviate from the ideal values somewhat more so than the angles in the *trans*-[PtBr$_2$(PPh$_3$)$_2$].[37b]

Selected bond angles [°] and bond lengths [Å] of **4f**·CHCl$_3$.

P2–Pt–P1	97.9(1)	Pt–P1	2.275(2)
P1–Pt–Br1	169.8(1)	Pt–P2	2.264(2)
P2–Pt–Br2	176.4(1)	Pt–Br1	2.474(1)
Br1–Pt–Br2	85.8(1)	Pt–Br2	2.497(1)

Experimental

[PtBr$_2$Me$_2$(4-CN-py)$_2$] (**1f**)

4-Cyanopyridine (11.5 mg, 0.11 mmol), [(PtBr$_2$Me$_2$)$_n$] (21.0 mg, 0.055 mmol) and CHCl$_3$ (5 ml) were stirred under anaerobic conditions in a Schlenk vessel. After stirring for 8 h the solvent was reduced (ca 1 ml) and a yellow powder was precipitated on addition of pentane (ca 10 ml). Single crystals suitable for X-ray analysis were obtained by slow evaporation of a chloroform solution. Yield: 27 mg (82%). T_{dec}: 148 °C; Anal. Calc. for $C_{14}H_{14}Br_2N_4Pt$, %: C, 28.35; H, 2.38; N, 9.45. Found, % C, 27.82; H, 2.67; N, 9.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s+d, $^2J_{Pt,H}$ = 72.2 Hz, 6H, C*H*$_3$), 7.65 (d, $^3J_{H,H}$ = 6.4 Hz, 4H, C^3*H*), 9.22 (d+dd, $^3J_{H,H}$ = 6.4 Hz, $^3J_{Pt,H}$ = 11.8 Hz, 4H, C^2*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ −8.1 (s+d, $^1J_{Pt,C}$ = 518.9 Hz, *C*H$_3$), 115.1 (s, *C*N), 123.0 (s, *C*^{4}), 127.5 (s+d, $^3J_{Pt,C}$ = 10.5 Hz, *C*^{3}H), 152.0 (s+d, $^2J_{Pt,C}$ = 6.0 Hz, *C*^{2}H). ^{195}Pt NMR (107 MHz, $CDCl_3$): δ −2377 (s).

*Tetradeuterated [$PtBr_2Me_2(H\text{-}pz)_2$] (**2f**)*

Complex **2f** was observed by adding a 1:1 mole ratio of [$(PtBr_2Me_2)_n$] (14 mg, 0.03 mmol) and pyrazole (2 mg, 0.03 mmol) to CD_3OD (0.7 ml) for 88 days or alternatively by addition of a 1:1 mole ratio of [$PtBr_2Me_2(H\text{-}pz)_2$] (**5a**) (16 mg, 0.03 mmol) and [$(PtBr_2Me_2)_n$] (12 mg, 0.03 mmol) to CD_3OD (0.7 ml) for 16 days. By either approach spectra show a mixture of **2f**, [$PtBr_2Me_2(CD_3OD)_2$] and **5a** but eventually only **2f**. Signals from **2f**, ^{1}H NMR (400 MHz, CD_3OD): δ 1.84 (s+d, $^2J_{Pt,H}$ = 72.6 Hz, 6H, CH_3), 7.69 (m, 2H, C^5H), 8.00 (m, 2H, C^3H). ^{13}C NMR (125 MHz, CD_3OD): δ –10.4 (s, CH_3), 107.0 (s, $^1J_{C,D}$ = 27.4 Hz, C^4H), 131.5 (s, C^5H), 140.5 (s, C^3H). Signals for [$PtBr_2Me_2(CD_3OD)_2$], ^{1}H NMR (400 MHz, CD_3OD): δ 2.02 (s, $^2J_{Pt,H}$ = 80.9 Hz, 6H, CH_3). Signals from **5a**, ^{1}H NMR (400 MHz, CD_3OD): δ 1.84 (s+d, $^2J_{Pt,H}$ = 72.6 Hz, 6H, CH_3), 6.37 (m, 2H, C^4H), 7.69 (m, 2H, C^5H), 8.00 (m, 2H, C^3H). ^{13}C NMR (125 MHz, CD_3OD): δ –10.4 (s, CH_3), 107.0 (s, C^4H), 131.5 (s, C^5H), 140.5 (s, C^3H). Mass spectrum: calc. *m/z* for ([$C_8H_{10}Br_2D_4N_4Pt]^{\cdot+}$) 525.9; found 525.9; *m/z* (Intensity calcd/found) for cationic radical [$C_8H_{10}Br_2\ D_4N_4Pt]^{\cdot+}$, %) 522 (37/59), 523 (40/81), 524 (99/95), 525 (79/100), 526 (100/72), 527 (44/47), 528 (29/44).

*Preparation of [$PtCl_2${$(Ph)_2P(CH_2CH_2O)_2CH_2CH_2P(Ph)_2$}] (**3f**)*[35]

By analogy to a procedure with [$PtCl_2$(cod)] and longer α,ω-bis(phosphino) polyether ligands.[4d] In brief, [$PtCl_2$(nbd)] (55 mg, 0.15 mmol), $(Ph)_2P(CH_2CH_2O)_2CH_2CH_2P(Ph)_2$ (76 mg, 0.16 mmol) and distilled methylene chloride (10 ml) were added to a Schlenk under anaerobic conditions. After stirring 30 min the volume of the transparent reaction mixture was reduced (2 ml) and the product, a white powder, precipitated upon addition of methanol (6 ml) at 0 °C. Yield 69 mg (61%). As per literature except ^{31}P NMR (202 MHz, $CDCl_3$): δ 11.5 (s+d, $^1J_{Pt,P}$ = 3712 Hz).

*Preparation of cis-[$PtBr_2(PPh_3)_2$] (**4f**)*[37a]

[$(PtBr_2Me_2)_n$] (15 mg, 0.04 mmol), PPh_3 (20 mg, 0.08 mmol) and C_6D_6 were added to an NMR tube and the tube was secured and sealed. After shaking for 48 h the undissolved pale yellow powder was filtered off and washed with benzene (5 ml) and methanol (5 ml). Single crystals suitable for X-ray diffraction were obtained by slow

evaporation of a chloroform solution. ^{31}P NMR (202 MHz, $CDCl_3$) δ 14.7 (s+d, $^1J_{Pt,P}$ = 3605 Hz).

Preparation of [{$PtBr_2Me_2$(4,4'-bipy)}](**5f**)

[$(PtBr_2Me_2)_n$] (54 mg, 0.14 mmol), 4,4'-bipyridine (23 mg, 0.14 mmol) and chloroform (ca. 10 ml) were added to a flask. The reaction mixture was gently refluxed for approximately 16 h before the mixture was cooled and filtered in air. The powder was washed with MeOH (10 ml) and $CHCl_3$ (10 ml). The finely divided yellow product was dried in air. Yield 76 mg (75%) T_{dec}: 158 °C. Anal. Calc. for $C_{12}H_{14}Br_2N_2Pt$, %: C, 26.63; H, 2.61; N, 5.18. Found, % C, 26.60, H, 2.83, N, 4.84. ^{1}H NMR (400 MHz, $(CD_3)_2NCOD$): δ 2.06 (s+d, $^2J_{Pt,H}$ = 70.8 Hz, 6H, CH_3), 8.17 (m, 4H, C^3H), 9.06 (d, $^3J_{H,H}$ = 6.6 Hz, 4H, C^2H). ^{13}C NMR (125 MHz, $(CD_3)_2NCOD$): δ –8.1 (s+d, $^1J_{Pt,C}$ = 516.6 Hz, CH_3), 124.7 (s(br), C^3H), 146.9 (s, C^1), 152.6 (s(br), CH^3). ^{195}Pt NMR (107 MHz, C_4D_8O): δ –2343 (s). IR: ν (cm^{-1}) 3442(s), 3072(w), 2981(w), 2910(m), 2813(w), 1608(s), 1533(w), 1489(w), 1414(s), 1216(s), 1070(m), 1013(w), 812(s), 638(s), 505(w).

Crystal data and structure refinement for **1f** (STADI997).

Empirical formula	$C_{14}H_{14}Br_2N_4Pt$
Formula weight	593.20
Temperature	220(2) K
Wavelength	71.073 pm
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 964.4(2) pm α = 94.75 (2)°
	b = 1217.4(2) pm β = 105.04 (2)º
	c = 1547.2(3) pm γ = 95.05 (2)º
Volume	1.737 (6) nm^3
Z	4
Density (calculated)	2.268 mg/m^3
Absorption coefficient	12.68 mm^{-1}
F(000)	1096
Theta range for data collection	1.7 to 25.1°.
Index ranges	-11<=h<=11, -14<=k<=14,
	-18<=l<=18
Reflections collected	9997
Independent reflections	6530 [R_{int} = 0.0584]
Completeness to theta = 24.49°	98.1 %
Absorption correction	psi-scans
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6057/0/383
Goodness-of-fit on F^2	1.107
Final *R* indices [I>2σ(*I*)]	R_1 = 0.0518, wR^2 = 0.1322
R indices (all data)	R_1 = 0.0673, wR^2 = 0.1468
Largest diff. peak and hole	2.032 and –2.066 e.$Å^{-3}$

Crystal data and structure refinement for **4f**·$CHCl_3$ (ipds2796).

Empirical formula	$C_{37}H_{31}Br_2Cl_3P_2Pt$	
Formula weight	998.82	
Temperature	220(2) K	
Wavelength	71.073 pm	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 1124.6(3) pm	α= 90.89(2)°
	b = 1177.6(2) pm	β= 98.29(3)°
	c = 1437.7(3) pm	γ =106.53(3)°
Volume	1.8031(7) nm^3	
Z	2	
Density (calculated)	1.840 mg/m^3	
Absorption coefficient	6.444 mm^{-1}	
F(000)	964	
Theta range for data collection	2.25 to 25.85°.	
Index ranges	-13<=h<=13, -13<=k<=13,	
	-17<=l<=17	
Reflections collected	14132	
Independent reflections	6530 [R_{int} = 0.0962]	
Completeness to theta = 25.85°	93.0 %	
Absorption correction	Numerical	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	6530/0/407	
Goodness-of-fit on F^2	1.034	
Final *R* indices [I>2σ(*I*)]	R_1 = 0.0545, wR^2 = 0.1317	
R indices (all data)	R_1 = 0.0653, wR^2 = 0.1365	
Largest diff. peak and hole	2.235 and -3.646 $e.Å^{-3}$	

Curriculum Vitae

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Eidesstattliche Erklärung

Hiermit erkläre in an Eides statt, dass ich die vorliegende Arbeit selbständig verfasst und keine anderen Hilfsmittel als die angegebenen verwendet habe. Ich habe die Arbeit an keiner anderen Hochschule vorgelegt und mich zu keinem früheren Zeitpunkt um den Doktorgrad beworben.

Mairéad Eilís Kelly

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