N-Heterocyclic Carbene Platinum(IV) as Metallodrug Candidates: Synthesis and 195Pt NMR Chemical Shift Trend

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Abstract: A series of octahedral platinum(IV) complexes functionalized with both N-heterocyclic carbene (NHC) ligands were synthesized according to a straightforward procedure and characterized. The coordination sphere around the metal was varied, investigating the influence of the substituted NHC and the amine ligand in trans position to the NHC. The influence of those structural variations on the chemical shift of the platinum center were evaluated by 195Pt NMR. This spectroscopy provided more insights on the impact of the structural changes on the electronic density at the platinum center. Investigation of the in vitro cytotoxicities of representative complexes were carried on three cancer cell lines and showed IC$_{50}$ values down to the low micromolar range that compare favorably with the benchmark cisplatin or their platinum(II) counterparts bearing NHC ligands.

Keywords: N-heterocyclic carbene; platinum; metal complexes; 195Pt NMR

1. Introduction

In the treatment of solid tumors, platinum-based chemotherapy remains a top-notch drug thanks to its high anticancer efficiency and high remission rates in selected cancers, up to 90% in patients suffering testicular cancer [1]. However, the severe systemic toxicity and poor selectivity for tumors, with only 1% of the injected dose of cisplatin actually reaching their target, stress the importance to explore new strategies to stabilize the platinum center and prevent off-target interactions [2]. Lot of efforts have focused on adjusting the coordination sphere of the platinum or oxidizing the well established Pt(II) center into redox-activable Pt(IV) pro-drugs [3–5]. In particular, platinum complexes functionalized with N-heterocyclic carbenes have appeared as promising alternatives to cisplatin, as possible chemotherapeutics targeting the mitochondria [6–9]. In addition to investigating the redox potential of Pt(IV) complexes, 195Pt NMR is a valuable technique for the fast and standardized characterization of platinum complexes to complement routine characterization [10–15]. Moreover, investigating the chemical shift in 195Pt NMR is a prerequisite to further enable mechanistic and pharmacokinetic investigations of the platinum complex and its metabolites using 195Pt spectroscopy [16], as an alternative to LA-ICP-MS [17] or X-ray-based techniques [18–21]. Of note, Huynh et al. recently suggested the direct correlation of the platinum chemical shift in 195Pt NMR to both the electronic density at the platinum center and the electronic donation of the coordination sphere, in particular in the case of N-heterocyclic carbene (NHC)-platinum complexes [22–24]. Moreover, a linear correlation of the 195Pt NMR chemical shift with the in vitro anticancer activity (IC$_{50}$) has been noted in azido-Pt(IV)

complexes [25]. The chemistry in the solution of cisplatin and its derivatives have been studied by ^{195}Pt NMR spectroscopy. In particular, they have been used to characterize related complexes with aqua, chloro, nitrato, sulfato, acetate, and phosphate ligands [26,27]. Therefore, we report herein a series of NHC-Pt(IV) complexes and a few examples of their Pt(II) metabolites possibly formed in vitro, that were synthesized and characterized using routine techniques. In vitro activities against three cancer cell lines of representative NHC-Pt(IV) complexes are also presented. Moreover, the shift in the platinum resonance signal in ^{195}Pt NMR is investigated and discussed as a function of tuning their oxidation degree and coordination sphere.

2. Results and Discussion

2.1. Synthesis of the Platinum(II) and Platinum(IV) Complexes

All NHC-Pt complexes were prepared using standard synthetic procedures as previously reported. The general scheme for the synthesis of the Pt(II) and Pt(VI) complexes is described in Scheme 1. First, platinum(II) NHC pyridine complexes were synthesized involving the in situ deprotonation of the imidazolium salt with K_2CO_3 and the coordination of the carbene to the $PtCl_2$ precursor in dry amine with excess NaI overnight ((1), first step, Scheme 1) [28]. Chemical variation was then possible by the ligand substitution of the pyridine with various nitrogen-based ligands as shown in (1), second step, Scheme 1. The obtained (NHC)PtI$_2$(pyridine) and (NHC)PtI$_2$(amine) complexes could further be oxidized according to a procedure previously reported by us [9]. The aforementioned Pt(II) complexes were reacted with a 10-fold excess of bromine at 0 °C to obtain the corresponding (NHC)PtBr$_4$(L) complexes ((2), Scheme 1). The reaction proceeded very quickly and cleanly to give the expected corresponding Pt(IV) species after only 5 min of reaction. The chlorinated complexes ((NHC)PtCl$_4$L) were obtained by direct oxidation using a 2-fold excess of freshly prepared hypervalent iodine reagent PhICl$_2$ ((3), Scheme 1). The reaction was complete after 1 h at 0 °C. All the platinum(IV) complexes were easily isolated by precipitation with pentane. They were usually obtained in high chemical yield and were stable under air in the solid state or in chlorinated solvents and showed increasing solubility in organic solvents in respect to the length of alkyl chains on the NHC or amine ligand.
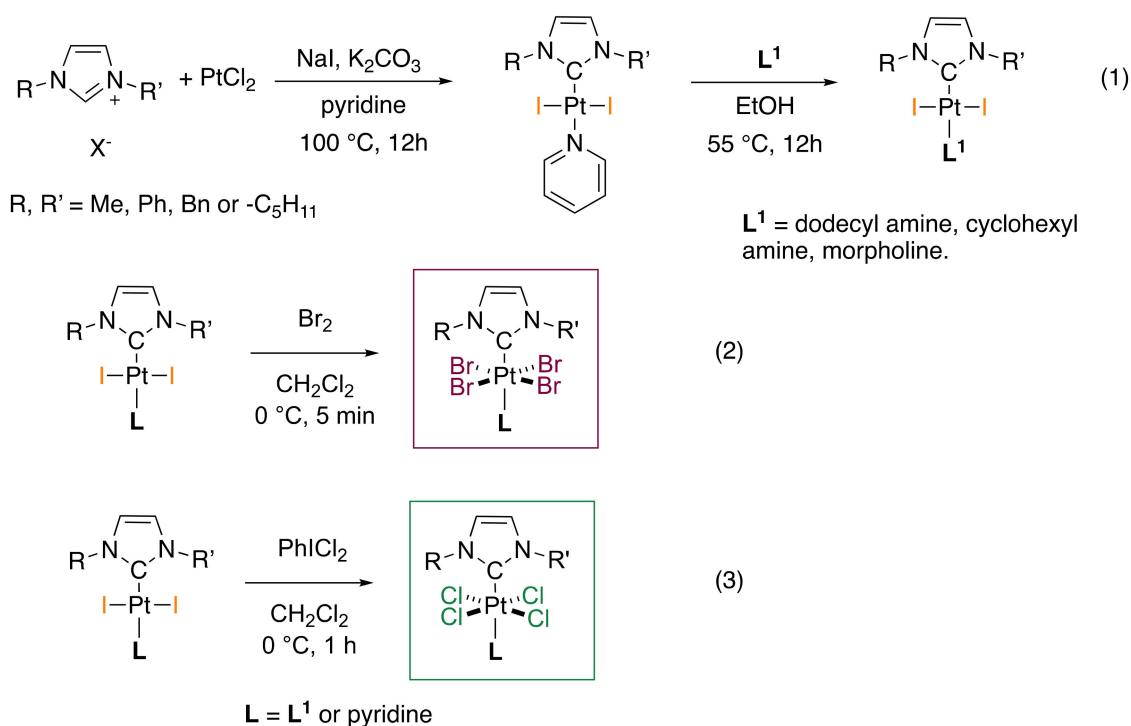

Scheme 1. General synthesis of the platinum (II) and platinum (IV) complexes.

Scheme 2 displays the molecular structures of the five platinum(II) NHC complexes used either as precursors for the Pt(IV) syntheses, or as a reference for the studies discussed here. The (NHC)Pt(II)(DMSO) complexes **3** and **4** were obtained by a transmetallation route from the bis(benzyl)imidazol-2-ylidene silver(I) bromide precursor reacted with platinum salt as previously published by us [7]. The NHC Pt(II) complexes **2** and **5** were obtained using the procedure described in (1), Scheme 1 using the corresponding salt NaBr or NaCl respectively.
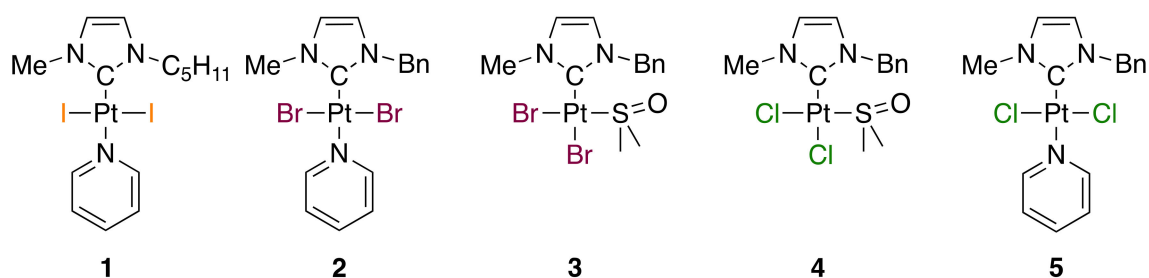
Scheme 2. Molecular structure of the *N*-heterocyclic carbene (NHC)-Pt(II) references.

Scheme 3 displays all the platinum(IV) that were synthesized and characterized. A series of (NHC)PtBr$_4$(amine) complexes bearing a (methyl-, benzyl-)NHC, were obtained in a 99% yield with various trans amine ligands, i.e., dodecylamine, cyclohexylamine, morpholine and pyridine, corresponding to complexes **6**, **8**, **12** and **18**, respectively. Identically, the (NHC)PtCl$_4$(amine) complexes with varying amine ligands were obtained in good yields, the corresponding amine ligand being a cyclohexylamine for **22**, a morpholine for **23** and a pyridine for **26**. The versatile synthesis tolerated the NHC structural variations among the (NHC)PtBr$_4$(amine) family, with *N*-substituents being a CH$_2$-*tert*-butylacetate for **14**, *p*-nitro-benzyl for **15**, *p*-benzaldehyde for **16**, a pentyl for **19**, a cyclopentyl for **20** and a phenyl for **21**, all obtained in 99% yield. The functionalization of the positions 4 and 5 of the NHC ligand did not hamper the oxidation reaction, and the (NHC)PtBr$_4$(amine) complexes **9**, **11**, **13** and **17** were isolated in high yield, corresponding respectively to a benzimidazole, 4-metyl- and 5-aldehyde, 4-methylester, and 4,5-dichloro-NHC. Similarly, the (NHC)PtCl$_4$(amine) complexes **24** bearing a 4,5-dichloro-NHC and **25** functionalized with a pentyl-*N*-substituted NHC were obtained also in a yield up to 99%. The characterization by the ^{1}H NMR showed that all the proton signals displayed a shift to a lower field compared to their imidazolium precursors which proved typical for such complexes. Overall, the NHC-Pt(IV) complexes showed a signal duplication typically observed for all the protons in up to the ^{5}J position to the platinum center, suggesting an enhanced coupling with the ^{195}Pt isotope compared to their NHC-Pt(II) precursors. Of note, the very low solubility of (NHC)PtBr$_4$(pyridine) complexes prevented the successful acquisition of the ^{13}C NMR of complexes **4**, **5**, **11**, **20** and **26**, or rendered the carbenic carbon signal not visible. However, in the case of more lipophilic complexes, coupling between the carbenic carbon and the platinum center was observed in ^{13}C NMR. Such a trend was found typical throughout all the NHC-Pt(IV) complexes, the carbenic carbon signal appearing as a singlet and doublet system, possibly due to the heavy atom effect of platinum [29]. Moreover, chemical shifts to a higher field of the carbenic carbon were also observed by ^{13}C NMR spectroscopy, ca. δ 109–120 ppm in the case of NHC-Pt(IV) complexes, while (NHC)PtI$_2$(amine) complexes previously reported by us [30,31] and others [32,33] typically show a signal shift at least 30 ppm greater.
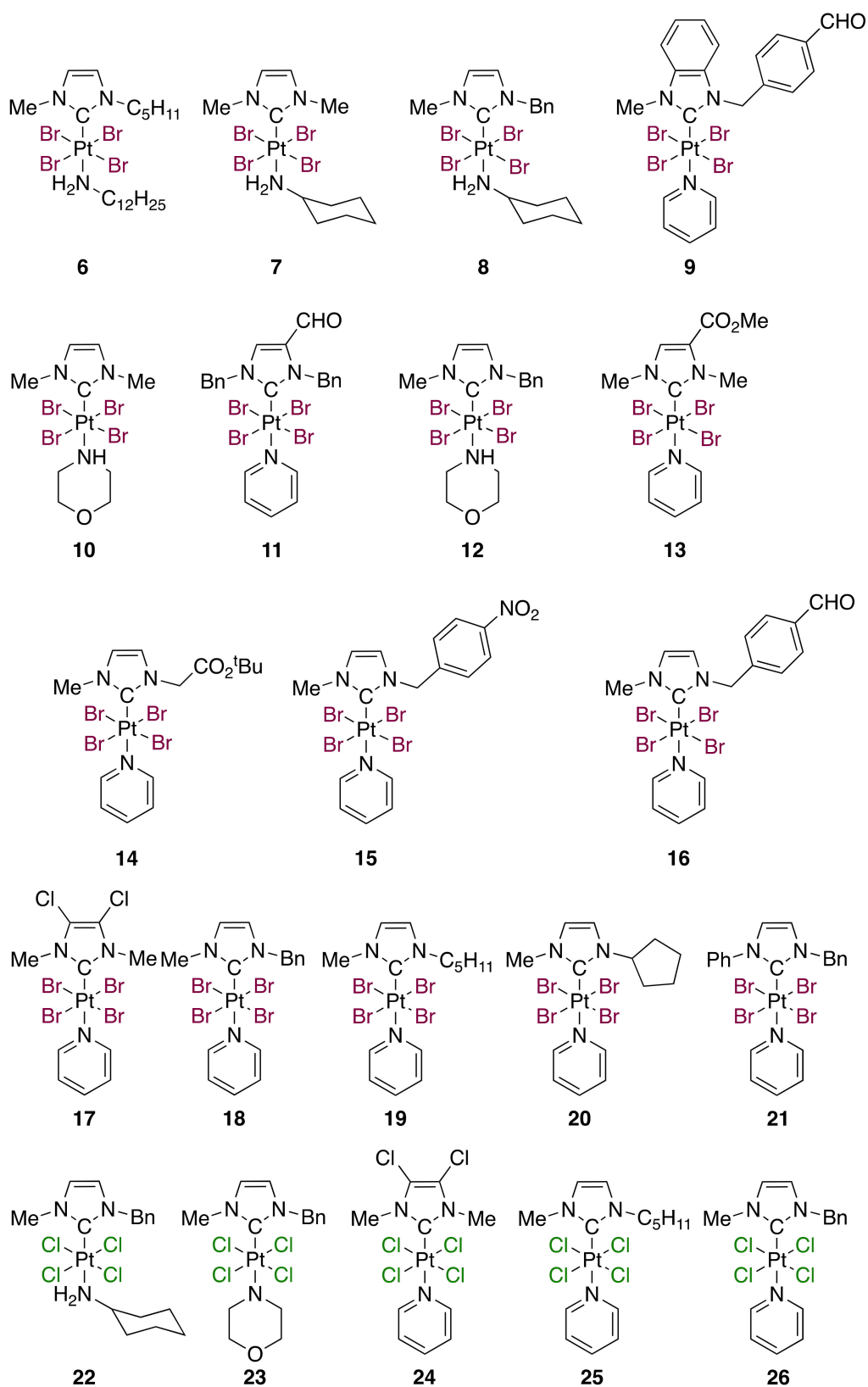
Scheme 3. Molecular structure of the NHC-Pt(IV) complexes.

Among these Pt(IV) complexes, the molecular structure of the (NHC)PtBr$_4$(amine) complex **15** was determined by X-ray diffraction and is presented in Figure 1. The platinum center shows an octahedral geometry with bromine ligands forming a distorted square planar shape in equatorial position,

comparable to other (NHC)PtBr$_4$(amine) complexes previously reported by us [6,7]. The pyridine ligand is located in trans position to the NHC with a platinum-pyridine length of 2.128(6) Å while the NHC-platinum bond is found to be 2.057(8) Å. The molecular structure of the (NHC)PtCl$_4$(amine) complex **23** revealed a comparable geometry with overall shorter bonds between the platinum center and the ligands, reflective of the influence of the coordination sphere on platinum's electronic density, exemplified by the NHC-platinum length of 2.034(3) Å, and the chloride-platinum bonds in the range of 2.327(3)–2.336(3) Å [7].
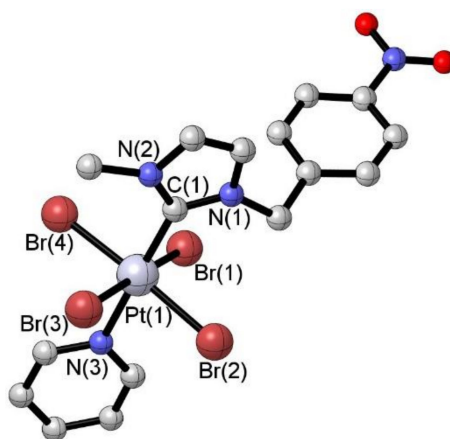

Figure 1. Molecular structure of complex **15**. Selected bond distances (Å) and angles (deg): C(1)-Pt(1), 2.057(8); Br(1)-Pt(1), 2.4882(8); Br(2)-Pt(1), 2.4657(8); Br(3)-Pt(1), 2.4615(8); Br(4)-Pt, 2.4839(8); N(3)-Pt(1), 2.128(6); C(1)-Pt(1)-N(3), 179.2(3); C(1)-Pt(1)-Br(3), 92.9(2); N(3)-Pt(1)-Br(3), 87.10(16); Br(2)-Pt(1)-Br(3), 86.10(3); Br(1)-Pt(1)-Br(4), 177.05(3).

2.2. In Vitro Activities against Cancer Cell Lines

Among the series of NHC-platinum complexes herein, a series of the most soluble complexes were selected for the evaluation of their in vitro anticancer activities. Overall, most NHC-Pt(IV) complexes were found to display comparable IC$_{50}$ values to cisplatin in the range of 0.5–23 μM. Contrastingly, the complex **16** showed disparate anticancer activities depending on the cancer cell line with the IC$_{50}$ values of 5.42 μM and 81.09 μM against the PC3 or HCT116 respectively (Table 1). Of note, the low solubility of this complex in aqueous media might explain the low IC$_{50}$ values observed in this study. The series of the (NHC)PtBr$_4$(amine) complexes **6**, **8**, **12** and **19** show potencies that compare favorably with the NHC-Pt(II) complexes which are expected to be the species released upon their redox activation. Such a result is in line with our previous findings suggesting their rapid reduction and release of the active species [6,7]. Remarkably, the (NHC)PtCl$_4$(amine) complexes **22** and **25** show the most promising in vitro potencies with IC$_{50}$ values in the low micromolar range against the three tested cancer cell lines.

Table 1. Half-inhibitory concentrations IC_{50} (μM) of the selected complexes toward the HCT116, MCF7 and PC3 cancer cells.

Complex Number	Structure	IC_{50} (μM) HCT116 [1]	IC_{50} (μM) MCF7 [1]	IC_{50} (μM) PC3 [1]
Cisplatin	$(NH_3)_2PtCl_2$	3.57 ± 0.1	4.15 ± 0.7	3.10 ± 0.2
2	$(NHC)PtBr_2(pyr)$	5.44 ± 1	7.73 ± 1	5.35 ± 1.6
3	$(NHC)PtBr_2(DMSO)$	>100	>100	>100
4	$(NHC)PtCl_2(DMSO)$	63 ± 5	80 ± 13	65 ± 6
5	$(NHC)PtCl_2(pyr)$	3.78 ± 0.1	3.48 ± 1	4.40 ± 0.9
6		7.5 ± 0.3	23 ± 5	10 ± 1
8		14 ± 2	5 ± 1	5 ± 1
12	$(NHC)PtBr_4(amine)$	11 ± 0.3	3 ± 0.7	2 ± 0.5
16		81.09 ± 2	17.22 ± 1.8	5.42 ± 0.5
19		5 ± 1	4 ± 0.2	5 ± 1
22	$(NHC)PtCl_4(amine)$	0.5 ± 0.03	0.5 ± 0.09	1 ± 0.1
25		1.48 ± 0.2	1.78 ± 0.6	1.31 ± 0.2

[1] HCT116, colon cancer cells; MCF7, breast carcinoma; PC3, prostate adenocarcinoma. (After 72 h of incubation; stock solutions in DMSO for all complexes; stock solution in H_2O for cisplatin).

2.3. ^{195}Pt NMR Spectroscopy

The NHC-platinum complexes were further characterized using a ^1H detection inverse NMR spectroscopy sequence which was preferred to direct the ^{195}Pt measurement in regard of shorter acquisition time and enhanced sensibility. This was supported by a test experiment using complex **8** as a reference, comparing spectra obtained in direct ^{195}Pt NMR or indirect HMQC ^1H-^{195}Pt NMR, and both showed a signal peak at $\delta_{Pt} = -2168$ ppm irrespective of the sequence used. Table 2 displays the ^{195}Pt chemical shift NMR of all the complexes and carbenic carbon signal in the ^{13}C NMR, when observed. The most significant variation in the platinum chemical shift was found as a function of the oxidation state of the platinum center. All the $(NHC)PtBr_4(amine)$ complexes **6–21** displayed a platinum chemical shift in the range of δ_{Pt} −1901 to −2196 ppm while the $(NHC)PtCl_4(amine)$ complexes **22–26** were observed at δ_{Pt} −883 to −795 ppm and all other NHC-Pt(II) complexes **1–5** displayed a chemical shift below −3304 ppm.

Of note, the use of ^1H detection inverse spectroscopy proved of high interest for most complexes to observe the $^4J_{H-Pt}$ long-range couplings between the platinum center and C_3, C_4 protons on the NHC backbone as well as the protons on the *N*-substituents of the NHC. This strong chemical coupling suggests a high electronic delocalization from the platinum center to the substituents of the NHC ligand which yet does not seem to significantly affect the chemical shift in ^{195}Pt NMR. Thus, the series of NHC-Pt(IV) complexes **14–16**, **19** and **20** show a platinum chemical shift decrease from $\delta_{Pt} = -2032$ to −2070 ppm with the *N*-substituents following the trend Cy > C_5H_{11} > Bn > $CH_2CO_2{}^tBu$. Similarly, the functionalization of C_3 and C_4 positions on the NHC backbone of the NHC-Pt(IV) complexes is shown to have a negligible effect on the platinum shift with $\Delta\delta_{Pt} = 2$ ppm between complexes **13** and **11**. Moreover, a large platinum chemical shift variation $\Delta\delta_{Pt} = 64$ ppm was observed between the imidazolin-2-ylidene ligand in **16** (δ_{Pt} −2063 ppm) and the benzimidazolin-2-ylidene ligand in **9** (δ_{Pt} −2127 ppm), which was found to correlate with the $\Delta\delta_C = 23.1$ ppm of their carbenic carbon observed by ^{13}C NMR. Among the series of the NHC-Pt(IV) complexes, the variation of the trans amine ligand shows a trend in the platinum chemical shift that follows the amine's basicity from δ_{Pt} −2040 ppm for complex **18** to δ_{Pt} −2196 ppm for complex **6**. Thus, the trend in the platinum chemical shift is found to be **18** > **12** > **8** > **6**, corresponding to a trans ligand being pyridine > morpholine > cyclohexylamine > dodecylamine. Of note, the same trend is visible while comparing their carbenic carbon shift as complex **18** bearing a pyridine shows a δ_C of 109.3 ppm while its cyclohexylamine counterpart **8** shows a shift up to 115.2 ppm. Moreover, the $(NHC)PtCl_4(amine)$ complexes follow the same trend with platinum chemical shifts being **26** > **23** > **22**, corresponding to the trans amine ligand pyridine > morpholine > cyclohexylamine.

Table 2. Chemical shift evolution of the Pt signal as a function of the metal oxidation state, the coordination sphere of the metal and the NHC substituents (external reference for ^{195}Pt: H_2PtCl_6 in D_2O: δ_{Pt} = 0 ppm).

Complex	Ox. State	δ_{Pt} (ppm) ^{195}Pt NMR	δ_C (ppm) ^{13}C NMR
1	+II	−4313	125.1
2	+II	−3814	138.2
3	+II	−3356	154.7
4	+II	−3351	n.o. [1]
5	+II	−3304	n.o.
6	+IV	−2196	n.o.
7	+IV	−2168	113.4
8	+IV	−2168	115.2
9	+IV	−2167	133.9
10	+IV	−2083	124.6
11	+IV	−2081	n.o.
12	+IV	−2080	112.7
13	+IV	−2079	115.4
14	+IV	−2070	n.o.
15	+IV	−2067	n.o.
16	+IV	−2063	110.8
17	+IV	−2058	110.7
18	+IV	−2048	109.3
19	+IV	−2040	109.2
20	+IV	−2032	n.o.
21	+IV	−1901	n.o.
22	+IV	−883	n.o.
23	+IV	−853	n.o.
24	+IV	−825	112.9
25	+IV	−810	111.5
26	+IV	−795	n.o.

[1] n.o.: not observed.

3. Materials and Methods

All the manipulations of the air- and moisture-sensitive compounds were carried out using standard Schlenk techniques under an argon atmosphere and the solvents were purified and degassed following standard procedures. All the reagents were purchased from commercial chemical suppliers (Acros (Illkirch, France), Alfa Aesar (Lancashire, UK), and TCI Europe (Paris, France)) and used without further purification. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Brucker AVANCE 300 or Bruker AVANCE 500 spectrometer (Bruker, Wissembourg, France) using the residual solvent peak as a reference ($CDCl_3$: δ_H = 7.26 ppm; δ_C = 77.16 ppm) at 295 K. The HMQC ^{1}H-^{195}Pt spectra were recorded on a Bruker AVANCE 600 spectrometer using the residual solvent peak as reference for the ^{1}H calibration and an external reference for the ^{195}Pt (H_2PtCl_6 in D_2O: δ_{Pt} = 0 ppm) at the Institut de Chimie NMR Facility of the University of Strasbourg. Positive mode electrospray ionization mass spectra (ESI-HRMS) analyses were carried out on microTOF, Bruker Daltonics (Bruker, Wissembourg, France).

All the syntheses and characterizations are available in the Supplementary Materials.

4. Conclusions

In the present work, a series of *N*-heterocyclic carbene-coordinated platinum(IV) complexes were synthesized in high yield according to a versatile procedure. All the complexes were found stable in the air and in chlorinated solvents for months. Some representative examples of these NHC-Pt(IV) complexes were selected for the in vitro evaluation of their cancer inhibitory properties and compared

to their possible Pt(II) metabolites formed in the biological environment. Overall, the lipophilic (NHC)PtCl$_4$(amine) complex **22** was found to induce the greater in vitro potencies toward selected cancer cell lines with IC$_{50}$ values in the low micromolar range.

In the development of platinum-based metallodrugs, numerous parameters have to be considered in addition to the apparent electronic density at the platinum center that may be reflected by the ^{195}Pt NMR chemical shift, namely lipophilicity and pharmacological properties and so forth. Moreover, the balance between the stability of the platinum drugs in the blood stream and their ability to form metabolites and interact with DNA is difficult to anticipate by finetuning the coordination sphere of the platinum. However, the ^{195}Pt NMR has proved to be a helpful probe in investigating the biological activity of platinum-based drugs. For example, a recent study involving the monitoring of carboplatin after subcutaneous injection in rats was studied using ^{195}Pt NMR [34]. Thus, all the complexes presented here were characterized with standard techniques and the influence of structural variations, i.e., on one hand the coordination sphere and on the other hand the NHC ligand's functionalization, were correlated to their chemical shift in ^{195}Pt NMR. All the (NHC)PtBr$_4$(amine) complexes displayed platinum chemical shifts in the range of δ_{Pt} −1900 to −2200 ppm while the (NHC)PtCl$_4$(amine) complexes were observed at δ_{Pt} −900 to −800 ppm. All other NHC–Pt(II) complexes displayed a chemical shift below −3304 ppm. The ^{195}Pt NMR spectroscopy could then be used to monitor the kinetics and the mechanism of such platinum complexes with biological substances.

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