

Unprecedented twofold intramolecular hydroamination in diam(m)ine-dicarboxylatodichloridoplatinum(IV) complexes – ethane-1,2-diamine vs. ammine ligands†

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Reaction of (OC-6-13)-bis(2Z-3-carboxyacrylato)dichlorido-(ethane-1,2-diamine)platinum(IV) and (OC-6-13)-diammine-bis(2Z-3-carboxyacrylato)dichloridoplatinum(IV) with propylamine in the presence of 1,1'-carbonyl diimidazole afforded not the expected amides; instead, beside amide formation, a twofold intramolecular attack of the am(m)ine ligand at the C=C bonds was observed involving either both (ethane-1,2-diamine) or only one (ammine) coordinated nitrogen atom(s).

Square planar platinum(II) complexes such as cisplatin, carboplatin and oxaliplatin are highly effective chemo-therapeutic drugs in world-wide clinical use for the treatment of solid tumors.¹ During the last decade, also octahedrally configured anticancer platinum(IV) complexes were developed, finally resulting in satraplatin, which is now in advanced phase III clinical trials. Platinum agents with the oxidation state +4 are kinetically inert in comparison to their platinum(II) counterparts and therefore of high interest since they show an altered toxicological profile and can be administered orally.

Besides these biological aspects, also the chemistry of platinum(IV) compounds made considerable progress due to their kinetic inertness. Especially axial hydroxido ligands offered the outstanding possibility for carboxylation reactions with the result of a plethora of new bis(carboxylato)platinum(IV) species, among them satraplatin.² Very recently, *trans*-dihydroxidoplatinum(IV) compounds were carboxylated with cyclic anhydrides resulting in analogs with two uncoordinated carboxylic acid groups (besides the two coordinated carboxylato moieties) for further derivatization.^{3–7}

Nevertheless, reports about the reactivity of the inherently available am(m)ine functionality as starting point for further derivatization are extremely rare. This is on the one hand understandable, since bioinorganic platinum chemists traditionally consider am(m)ines coordinated to platinum(IV) as unreactive. On the other hand, it is well documented that the pK_a value of coordinated ammonia in $[\text{Pt}(\text{NH}_3)_6]^{4+}$ is found at

around 7 for the first deprotonation step being in an interesting range and providing useful reactivity.⁸

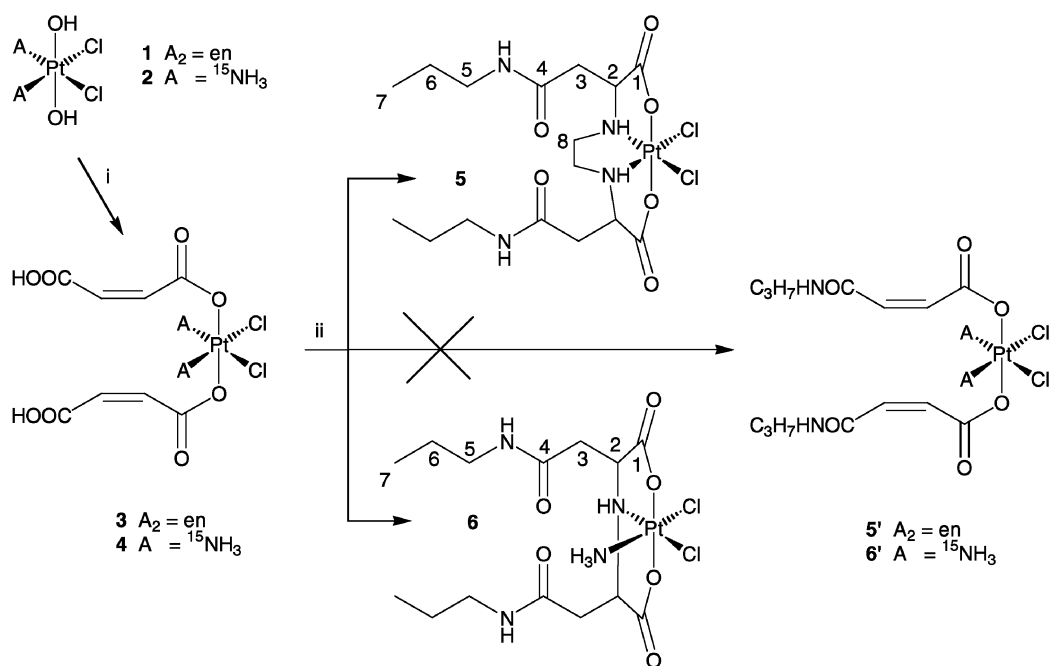
To the best of our knowledge, only four reports were published, dealing with the reaction of am(m)ineplatinum complexes with ketones affording the corresponding ketimines.^{9–12} In addition, an acetoneimineplatinum(II) complex, obtained *via* reaction of coordinated acetone and mono-coordinated ethane-1,2-diamine, was published.¹³ However, coordinated amine ligands intramolecularly attacking C=C bonds in platinum(IV) complexes have not been described so far. Interestingly, this twofold hydroamination involved both or only one am(m)ine moiety depending on the coordinated amine ligand (ethane-1,2-diamine vs. ammine).

The starting compounds **1** and **2**, were synthesized according to standard literature procedures,¹⁴ whereas $^{15}\text{NH}_4\text{Cl}$ was used to label complex **2**. Complexes **3** and **4** were obtained by carboxylation of **1** and **2** in DMF with an excess of maleic anhydride (Scheme 1). Finally, compounds **3** and **4** showing free, uncoordinated carboxylic acid groups were activated with 1,1'-carbonyl diimidazole (CDI) and brought to reaction with propylamine in order to obtain amides **5'** and **6'**. ESI-MS data revealed expected molecular masses of m/z 639.1 ($[\text{M} + \text{H}^+]^+$) and 637.3 ($[\text{M} + \text{Na}^+]^+$), respectively, in principle supporting the chemical structures of **5'** and **6'**. However, in ^1H NMR spectra of the reaction products, resonances for the C=C double bonds could no longer be detected. With the aim to determine the correct structure of the final products **5** and **6**, we extensively studied both complexes by multinuclear (^1H , ^{13}C , ^{15}N and ^{195}Pt) one- and two-dimensional NMR spectroscopy.

In the case of the ethane-1,2-diamine derivative (**5**), amide formation could be proven in the ^1H - ^1H COSY NMR spectrum by detecting the CONH proton signal in a typical region at 8.22 ppm. However, as stated above, the olefinic signals in the region between 6 and 7 ppm were missing. In addition, the Pt–NH resonance shifted significantly from 8.69 ppm in the parent complex **3** to 10.05 ppm; being in a typical range of platinum(IV) complexes, but indicating a reaction at the coordinated nitrogen atoms. In line with these results, the ^{13}C NMR spectra showed no signals in the olefinic region between 120 and 140 ppm. Instead, signals for an additional CH_2 and CH group were detected at 3.51/3.04 and 4.75 ppm, respectively. Therefore, a ^{195}Pt NMR spectrum was measured to judge the coordination sphere as well as the oxidation state of

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Scheme 1 Synthesis of platinum(IV) complexes **5** and **6**, and NMR numbering scheme (i, maleic anhydride; ii, 1. CDI, 2. $CH_3CH_2CH_2NH_2$).

5. The ${}^{195}Pt$ signal was found at 2224 ppm, in comparison to 2610 ppm in **3**. This moderate shift of 386 ppm (${}^{195}Pt$ NMR chemical shifts span a range of several thousands ppm!) is indicative for a distinct but not dramatic change in the coordination sphere; furthermore, it also proves the existence of an octahedrally configured platinum complex with a central platinum atom in the oxidation state +4.

Bond formation between the ethane-1,2-diamine ligand and C-2 could unequivocally be confirmed by 1H - 1H TOCSY and long-range 1H - ${}^{13}C$ HMBC measurements. In the 1H - 1H TOCSY spectrum, cross peaks between the coordinated NH and 2-H and between $Pt-NH$ and one of the diastereotopic protons at C-3 could be detected. In addition, the cross correlation signals in the 1H - ${}^{13}C$ HMBC spectrum between C-2 and 8-H, as well as C-8 and 2-H verified the postulated structure of **5**.

Analogous reaction of the ${}^{15}N$ labeled ammine complex **4** with propylamine in the presence of CDI afforded a product with a 1H NMR spectrum comparable to that of **5**. In contrast to **5**, two $Pt-NH$ resonances in a ratio of 3 : 1 were detected at 6.77 ppm (${}^1J_{H,N} = 74.3$ Hz, ${}^2J_{H,Pt} = 49.5$ Hz) and 9.87 ppm (${}^3J_{H,H} = 8.6$ Hz, ${}^1J_{H,N} = 77.9$ Hz, ${}^2J_{H,Pt} = 55.9$ Hz). The ${}^{195}Pt\{^1H\}$ NMR spectrum of the amide showed a signal at 2302 ppm representing a high field shift of more than 450 ppm compared to the signal of **4**. Beside that expected feature, the ${}^{195}Pt$ nucleus is bound to two non-equivalent ${}^{15}N$ nuclei was proven by measuring a 1H - ${}^{195}Pt$ HMQC spectrum. Shift correlation signals between both NH protons at 6.77 and 9.87 ppm and the platinum atom at 2302 ppm were found, indicating that only one NH_3 group was involved in the hydroamination reaction. The multiplicities of the NH and NH_3 resonances are in line with the chemical structure of complex **6** (Scheme 1).

Besides a 1H - ${}^{15}N$ HSQC NMR spectrum, ${}^{15}N$ chemical shifts were also determined *via* ${}^{15}N\{^1H\}$ NMR spectroscopy and found at 0.3 (NH), and -31.3 ppm (NH_3) flanked by ${}^{195}Pt$ satellites displaying ${}^1J_{N,Pt}$ coupling constants of 215 and 277 Hz, respectively. Measuring the one-dimensional ${}^{15}N$ NMR spectrum without proton decoupling revealed a doublet at 0.3 ppm (${}^1J_{N,H} = 78.1$ Hz) and a quartet at -31.3 ppm (${}^1J_{N,H} = 74.4$ Hz, ${}^{15}N$ trace in Fig. 1).

Attack of $Pt-NH_3$ at the $C=C$ bond and formation of a bond between both C-2 and one coordinated nitrogen atom could undoubtedly be confirmed by two dimensional NMR *via* homonuclear 1H - 1H (COSY and TOCSY) and heteronuclear multiple bond correlation (1H - ${}^{13}C$ HMBC, 1H - ${}^{15}N$ HMBC) experiments. Probably, the most impressive method was the long-range 1H - ${}^{15}N$ HMBC NMR optimized for coupling constants of 10 Hz (Fig. 1). Cross peaks for the NH and the

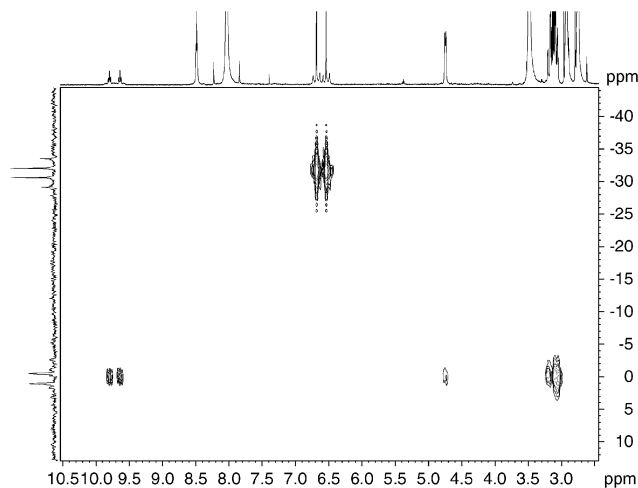


Fig. 1 1H - ${}^{15}N$ HMBC spectrum of complex **6**.

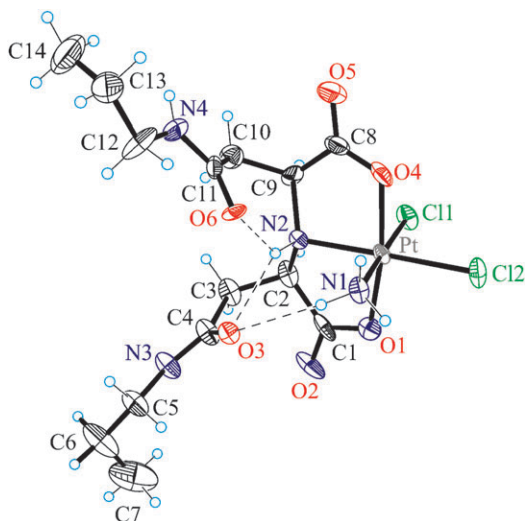


Fig. 2 ORTEP plot of the molecule of **6** with atom-numbering scheme. The thermal ellipsoids are drawn at 50% probability level.

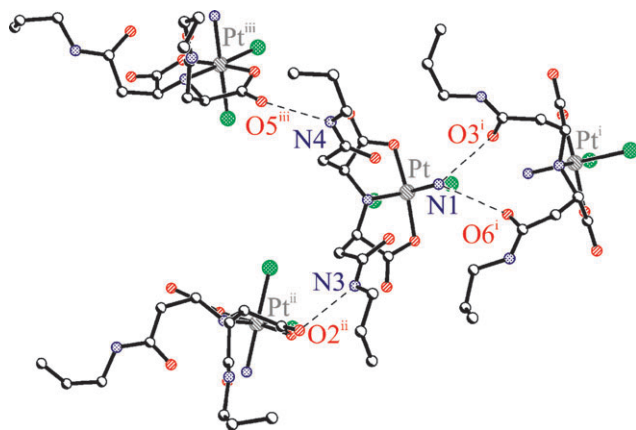


Fig. 3 Portion of the crystal structure of **6**, showing the intermolecular hydrogen bonding interactions. Symmetry codes: (i) $-x + 3/2, -y + 3/2, z - 1/2$, (ii) $-x + 2, y, z + 1/2$, (iii) $x, -y + 1, z + 1/2$.

NH₃ moieties (protons directly bound to nitrogen) were also visible and not completely suppressed. As demonstrated in Fig. 1, the NH₃ group showed only one set of cross peaks, resulting from ¹J_{N,H}. In contrast, the NH group showed, besides the cross peaks for the proton directly bound to nitrogen, three further cross correlation signals, verifying the successful bond formation; correlations *via* ²J_{N,H} and ³J_{N,H} with 2-H and both protons of C-3 were detected. The fact that in the case of **6** only one coordinated nitrogen atom is reproducibly involved in the twofold insertion reaction, results most probably due to pre-organisation after the first hydroamination step favouring the second hydroamination *via* the same coordinated nitrogen atom.

The result of the X-ray diffraction study of **6** is shown in Fig. 2 (‡). The complex crystallized in the orthorhombic space group *Iba*2. The crystal structure consists of molecules of **6**. The coordination geometry of the platinum(IV) atom is octahedral. The template product formed acts as a tridentate ligand and binds to Pt(IV) *via* two oxygen atoms and one

nitrogen atom of the iminodiacetate moiety building up two fused five-membered chelate cycles and one chloride ligand in the equatorial plane with Pt–O1, Pt–O4 and Pt–N2 bond lengths of 1.991(5), 1.994(5) and 2.032(7) Å, respectively. These can be compared to those in [Pt^{IV}Cl(*trans*-DACH)-(*N*-Me-IDA)]Cl (DACH = 1,2-diaminocyclohexane, *N*-Me-IDA = *N*-methyliminodiacetate) of 2.002(13), 2.014(9) and 2.081(14) Å, correspondingly.¹⁵

The Pt–Cl2 interatomic distance is of 2.298(2) Å. Bond lengths for Pt–Cl1 and Pt–N1 were 2.3178(19) and 2.021(6) Å, correspondingly. These are well comparable with those in *mer*-[Pt(NH₃)₂(C₅H₄NO)Cl₃] (C₅H₄NOH = α -pyridone) of 2.326(2) and 2.034(3) Å, respectively.¹⁶

The amine nitrogen N2 is involved in an intramolecular bifurcated hydrogen bond to the oxygen atoms O3 and O6 (Fig. 2). The NH₃ molecule *via* one of its hydrogen atoms acts as a proton donor in both the intramolecular H-bonding to O3 and in the intermolecular H-bonding to Cl2 ($-x + 3/2, -y + 3/2, z + 1/2$) with interatomic separations N1...O3 of 3.449 and N1...Cl2 of 3.183 Å. The two other hydrogen atoms of NH₃, and both CONH groups partake in intermolecular H-bonding to three neighboring molecules of **1** as depicted in Fig. 3 (N1...O3ⁱ 2.840, N1...O6ⁱ 2.943, N3...O2ⁱⁱ 2.864, N4...O5ⁱⁱⁱ 2.929 Å). The symmetry codes are quoted in the legend to Fig. 3.

Notes and references

‡ Crystal data for **1**: C₁₄H_{26.25}Cl₂N₄O_{6.13}Pt, *M_r* = 614.63, orthorhombic, *Iba*2, *a* = 22.1412(9), *b* = 22.6423(8), *c* = 8.5427(3) Å, *V* = 4282.7(3) Å³, *Z* = 8, μ (Mo-K α) = 6.839 mm⁻¹, 61 325 measured reflections, 5339 independent, *R*_{int} = 0.0841, *R*(*F*) = 0.0369, *wR*(*F*²) = 0.0926, Flack parameter 0.006(11). Data collection was performed at 100(2) K on X8 APEXII CCD diffractometer. The structure was solved by direct methods and refined by full-matrix least squares on *F*². CCDC 663532. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b715680d

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