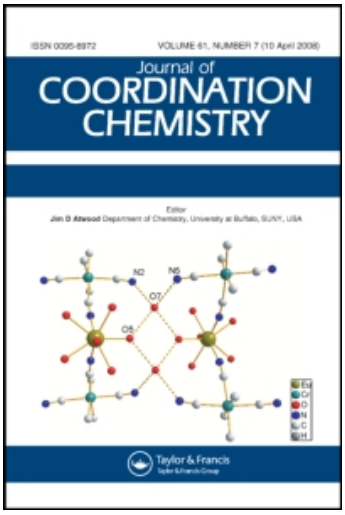

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Synthesis and structure of some mixed *cis*-diamine complexes of platinum(II) containing morpholine and another amine

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SYNTHESIS AND STRUCTURE OF SOME MIXED *cis*-DIAMINE COMPLEXES OF PLATINUM(II) CONTAINING MORPHOLINE AND ANOTHER AMINE

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Fifteen mixed *cis*-diamine complexes *cis*-[Pt(Mor)(Am)Cl_2], Mor: morpholine; Am: aniline, *o*-toluidine, *p*-toluidine, *p*-anisidine, *p*-phenetidine, α-naphthylamine, pyridine, quinoline, 8-oxiquinolinato, benzylamine, 2-phenylethylamine, methylamine, dimethylamine, ethylamine and diethylamine have been prepared. The structures of the complexes have been examined by elemental analysis, molar conductivity, UV, IR, Raman and ^{1}H NMR spectra. Spin–spin splitting patterns of non-equivalent protons H^a_α, H^e_α, H^a_β, H^e_β of morpholine have been designated. The morpholine ring has a chair conformation with nitrogen bound equatorially to Pt. The examined complexes have a *cis*-configuration in which the planes of the aromatic amine and morpholine rings are perpendicular to the coordination plane of Pt(II). The complexes were tested for cytotoxicity: *cis*-[Pt(Mor)($PhCH_2NH_2$)Cl_2], *cis*-[Pt(Mor)($PhCH_2CH_2NH_2$)Cl_2] and *cis*-[Pt(Mor)(OC_9H_6N)Cl] exhibit anticancer activities *in vitro* on human cancer cell Hep-G and RD with $IC_{50} < 5\,\mu g\,cm^{-3}$.

Keywords: *cis*-Diamine Platinum(II); Platinum(II) complexes; Morpholine; ^{1}H NMR

INTRODUCTION

Platinum complexes are now among the most widely used drugs for the treatment of cancers [1,2]. Complexes of platinum(II) containing six-membered heterocyclic amines such as piperidine [3–6] have been well studied but those containing morpholine are rarely synthesized. In 1971, Kukuskin [7] prepared geometric isomers of [Pt(Morpholine)(R_2SO)X_2]. In 1999, the preparations of some complexes of Pt(II) containing morpholine thiourea derivative [8] and *N*-{2-(4-methoxyphenyltelluro)} morpholine [9] were described. The latter ligand bonded with Pt(II) through Te alone. In 2001, the displacement of chloride in coordination of Pt(II) by isosteric pyridines and morpholine, and the reverse process, were carried out in methanol [10].

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In this paper we report the synthesis and structures of a series of mixed *cis*-diamine complexes of platinum(II) containing morpholine (Mor). These complexes are prepared by reaction of $K[Pt(Mor)Cl_3]$ with aliphatic, aromatic or heterocyclic amines. The ^1H NMR data of coordinated morpholine and amines were most informative with respect to the structure of the complexes.

EXPERIMENTAL

Preparation of $K[Pt(Mor)Cl_3]$, (M1)

Morpholine (1 cm^3, 11.5 mmol) was neutralized by 1 N HCl solution to pH 7–8 and added to a solution of 4.15 g (10 mmol) $K_2[PtCl_4]$ in 50 cm^3 water then heated on a water bath at 70–80°C. To the reaction mixture 4 N KOH was added dropwise while stirring to obtain an orange solution which was filtered. The filtrate was cooled and bright yellow-orange crystals were collected by filtration and then dried in vacuum. Yield 2.25 g (52%). Anal. Calcd. for $KPtC_4H_9NOCl_3$(%): ($Pt + K_2SO_4$), 60.38; C, 11.22; H, 2.10; N, 3.27; Cl, 24.49. Found: ($Pt + K_2SO_4$), 59.82; C, 11.49; H, 2.29; N, 3.43; Cl, 25.49.

Preparation of Mixed *cis*-Diamine Complexes

cis-Dichloro(morpholine)(aniline)platinum(II), [*Pt(Mor)*($C_6H_5NH_2$)Cl_2], (*M2*)

$K[Pt(Mor)Cl_3]$ (0.427 g, 1 mmol) was dissolved in 15 cm^3 of 50% (v/v) aqueous EtOH. To this solution aniline (0.140 g, 1.5 mmol in 5 cm^3 EtOH) was added in three portions over 30 min and stirred at 25–30°C for an additional 3–4 h. The mixture was then cooled in an ice-bath. The resulting yellow precipitate was collected, washed with 50% (v/v) aqueous EtOH and recrystallized from 80% (v/v) aqueous EtOH. The light-yellow crystals were dried in vacuum at 50°C for 2 h; yield 0.277 g (62%). Anal. Calcd. for $[PtC_{10}H_{16}OCl_2]$(%): Pt, 44.1; C, 26.90; H, 3.57; N, 6.20; Cl, 15.94. Found: Pt, 43.72; C, 27.40; H, 3.58; N, 6.16; Cl, 16.39.

cis-Dichloro(morpholine)(o-toluidine)platinum(II), [*Pt(Mor)*(*o*-$CH_3C_6H_4NH_2$)Cl_2], (*M3*)

The complex was prepared from 1 mmol $K[Pt(Mor)Cl_3]$ and 1.5 mmol *o*-toluidine, using the procedure for **M2**; yield 0.276 g (60%) of light-yellow crystals. Anal. Calcd. for $[PtC_{11}H_{18}OCl_2]$(%): Pt, 42.34; C, 28.67; H, 3.91; N, 6.09; Cl, 15.43. Found: Pt, 41.30; C, 29.20; H, 4.02; N, 5.96; Cl, 16.65.

cis-Dichloro(morpholine)(p-toluidine)platinum(II), [*Pt(Mor)*(*p*-$CH_3C_6H_4NH_2$)Cl_2], (*M4*)

The complex was prepared from 1 mmol $K[Pt(Mor)Cl_3]$ and 1.5 mmol *p*-toluidine, using the procedure for **M2**; yield 0.336 g (73%), of light-yellow crystals. Anal. Calcd. for $[PtC_{11}H_{18}OCl_2]$(%): Pt, 42.34; C, 28.67; H, 3.91; N, 6.09; Cl, 15.43. Found: Pt, 41.81; C, 29.80; H, 4.20; N, 6.02; Cl, 16.42.

***cis*-Dichloro(*morpholine*)(*p-anisidine*)*platinum*(*II*), [*Pt*(*Mor*)(*p-CH*$_3$*OC*$_6$*H*$_4$*NH*$_2$)*Cl*$_2$], (*M5*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol *p*-anisidine, using the procedure for **M2**; yield 0.336 g (73%) of light-yellow crystals. Anal. Calcd. for [$PtC_{11}H_{18}O_2Cl_2$](%): Pt, 40.96; N, 5.70; Cl, 14.91. Found: Pt, 41.09; N, 4.93; Cl, 15.10.

***cis*-Dichloro(*morpholine*)(*p-phenetidine*)*platinum*(*II*), [*Pt*(*Mor*)(*p-C*$_2$*H*$_5$*OC*$_6$*H*$_4$*NH*$_2$)*Cl*$_2$], (*M6*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol *p*-phenetidine, using the procedure for **M2**; yield 0.255 g (52%) of light-yellow crystals. Anal. Calcd. for [$PtC_{12}H_{20}O_2Cl_2$](%): Pt, 39.95; C, 31.96; H, 4.50; N, 5.74; Cl, 14.55. Found: Pt, 40.72; C, 30.32; H, 4.38; N, 5.81; Cl, 15.96.

***cis*-Dichloro(*morpholine*)(α-*naphthylamine*)*platinum*(*II*), [*Pt*(*Mor*)(*C*$_{10}$*H*$_7$*NH*$_2$)*Cl*$_2$], (*M7*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol naphthylamine, using the procedure for **M2**; yield 0.332 g (67%) of light-yellow crystals. Anal. Calcd. for [$PtC_{14}H_{18}OCl_2$](%): Pt, 39.48; N, 5.66; Cl, 14.37. Found: Pt, 38.44; N, 5.85; Cl, 15.01.

***cis*-Dichloro(*morpholine*)(*pyridine*)*platinum*(*II*), [*Pt*(*Mor*)(*C*$_5$*H*$_5$*N*)*Cl*$_2$], (*M8*)**

K[Pt(Mor)Cl_3] (0.427 g, 1 mmol) was dissolved in 8 cm^3 water. To this solution pyridine (0.119 g, 1.5 mmol in 3 cm^3 water) was added in three portions over 30 min and stirred at room temperature for an additional 3 h. The mixture was then cooled in an ice-bath. The resulting yellow precipitate was collected, washed with cooled water and recrystallized from 80% (v/v) aqueous EtOH. The light-yellow crystals were dried in vacuum at 50°C for 2 h; yield 0.302 g (70%). Anal. Calcd. for [$PtC_9H_{14}OCl_2$](%): Pt, 45.13; C, 25.00; H, 3.22; N, 6.40; Cl, 16.42. Found: Pt, 45.86; C, 25.35; H, 3.33; N, 6.28; Cl, 16.94.

***cis*-Dichloro(*morpholine*)(*quinoline*)*platinum*(*II*), [*Pt*(*Mor*)(*C*$_9$*H*$_7$*N*)*Cl*$_2$], (*M9*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol quinoline, using the procedure for **M2**; yield 0.314 g (65%). Anal. Calcd. for [$PtC_{13}H_{16}OCl_2$](%): Pt, 40.28; N, 5.78; Cl, 14.66. Found: Pt, 39.31; N, 5.03; Cl, 15.12.

***Chloro*(*morpholine*)(*8-oxiquinolinato*)*platinum*(*II*), [*Pt*(*Mor*)(*8-OC*$_9$*H*$_6$*N*)*Cl*], (*M10*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol 8-hydroxyquinoline, using the procedure for **M2**; yield 0.204 g (41%) of yellow crystals. Anal. Calcd. for [$PtC_{13}H_{15}O_2Cl_2$](%): Pt, 42.25; N, 5.63; Cl, 7.14. Found: Pt, 41.75; N, 5.85; Cl, 7.91.

***cis*-Dichloro(morpholine)(benzylamine)platinum(II), [*Pt*(*Mor*)(C_6H_5 CH_2NH_2)Cl_2], (*M11*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol benzylamine, using the procedure for **M8**; yield 0.336 g (71%) of light-yellow crystals. Anal. Calcd. for [$PtC_{11}H_{18}OCl_2$](%): Pt, 42.34; C, 28.67; H, 3.91; N, 6.09; Cl, 15.43. Found: Pt, 41.51; C, 28.89; H, 4.12; N, 6.42; Cl, 16.22.

***cis*-Dichloro(morpholine)(2-phenylethylamine)platinum(II), [*Pt*(*Mor*)($C_6H_5CH_2CH_2NH_2Cl_2$], (*M12*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol 2-phenylethylamine, using the procedure for **M2**; yield 0.322 g (70%) of light-yellow crystals. Anal. Calcd. for [$PtC_{12}H_{20}OCl_2$](%): Pt, 41.14; N, 5.91; Cl, 14.98. Found: Pt, 41.51; N, 6.22; Cl, 15.62.

***cis*-Dichloro(morpholine)(methylamine)platinum(II), [*Pt*(*Mor*)($MeNH_2$)Cl_2], (*M13*)**

A solution of 1 N HCl was added to 0.5 cm^3 3.9 M methylamine solution (2 mmol) to bring the pH to 5. The obtained solution was then added to a solution of 0.427 g (1 mmol) K[Pt(Mor)Cl_3] in 8 cm^3 water. A solution of 2 N KOH was added dropwise during 30 min to bring the pH to 7 and the mixture was stirred for an additional 3 h at room temperature. The resulting yellow precipitate was collected, washed with 1 N HCl solution, water and recrystallized from 80% (v/v) aqueous EtOH. The light-yellow crystals were dried in vacuum at 50°C for 2 h; yield 0.219 g (57%). Anal. Calcd. for [$PtC_5H_{14}N_2OCl_2$](%): Pt, 50.78; C, 15.62; H, 3.65; N, 7.29; Cl, 18.49. Found: Pt, 50.02; C, 15.22; H, 3.87; N, 6.87; Cl, 19.03.

***cis*-Dichloro(morpholine)(dimethylamine)platinum(II), [*Pt*(*Mor*)(Me_2NH)Cl_2], (*M14*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol dimethylamine, using the procedure for **M13**; yield 0.239 g (60%) of light-yellow crystals. Anal. Calcd. for [$PtC_6H_{16}N_2OCl_2$](%): Pt, 48.99; C, 18.09; H, 4.02; N, 7.04; Cl, 17.84. Found: Pt, 49.32; C, 18.45; H, 3.98; N, 6.88; Cl, 18.43.

***cis*-Dichloro(morpholine)(ethylamine)platinum(II), [*Pt*(*Mor*)($EtNH_2$)Cl_2], (*M15*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol ethylamine, using the procedure for **M13**; yield 0.267 g (67%) of light-yellow crystals. Anal. Calcd. for [$PtC_6H_{16}N_2OCl_2$](%): Pt, 48.99; C, 18.09; H, 4.02; N, 7.04; Cl, 17.84. Found: Pt, 48.22; C, 18.81; H, 4.29; N, 7.48; Cl, 18.34.

***cis*-Dichloro(morpholine)(diethylamine)platinum(II), [*Pt*(*Mor*)(Et_2NH)Cl_2], (*M16*)**

The complex was prepared from 1 mmol K[Pt(Mor)Cl_3] and 1.5 mmol diethylamine, using the procedure for **M13**; yield 0.256 g (67%) of light-yellow crystals. Anal. Calcd. for [$PtC_8H_{20}N_2OCl_2$](%): Pt, 45.77; C, 22.53; H, 4.69; N, 6.57; Cl, 16.67. Found: Pt, 45.12; C, 22.85; H, 4.98; N, 6.85; Cl, 17.03.

Physical Measurements

Elemental analysis: Pt was analyzed according to the weight method [11], and C, H, N, Cl analyses were performed at Ho Chi Minh city Center of Analytical Service Experimentation using an automatic elemental analyzer. The molar conductivity was measured using a HI 88119 N conductivity meter. UV spectra were recorded on a 2855 spectrophotometer (GCB Instruments). The Raman spectra were observed on a Micro Raman LABRAM instrument at 4000–100 cm^{-1}, using excitation radiation at 632.8 nm from helium-neon laser. IR spectra were recorded on a IMPACK-410 NICOLET spectrometer in KBr discs at 400–4000 cm^{-1}. ^1H NMR spectra of **M1**, **M3**, **M6**, **M9**, **M10**, **M11**, **M13**, **M14**, **M15** and **M16** were recorded on Bruker AVANCE 500 MHz instrument and of **M2**, **M4**, **M5**, **M7**, **M8** and **M12** on a Bruker AC 200 MHz spectrometer, all at 298–300 K, with TMS as the internal standard in a suitable solvent excluding D_2O.

Biological Test

The cytotoxicity towards cancer cells was tested at the Experimental Biological Laboratory – Institute of Chemistry of natural compounds (in Hanoi), using the method applied by the National Cancer Institute of America (NCI) [17], IC_{50} values were calculated based on OD values taken on an Elisa instrument at 515–540 nm.

RESULTS AND DISCUSSION

In the preparation of the monoamine complex $K[Pt(Mor)Cl_3]$ (**M1**), morpholine was used in the form of $OC_4H_8NH \cdot HCl$, but the formation of a small quantity of the diamine complex $[Pt(Mor)_2Cl_2]$ is unavoidable. As it is neutral, $[Pt(Mor)_2Cl_2]$ precipitated at room temperature and was filtered out.

The mixed *cis*-diamine complexes were prepared by replacement of a Cl from $K[Pt(Mor)Cl_3]$ by an amine Am, according to the *trans*-effect. For amines that are weak donors and insoluble in water, such as aniline, toluidine, *p*-anisidine, *p*-phenetidine, α-naphthylamine, the reaction was carried out with free amine in aqueous EtOH solution:

$$K[Pt(Mor)Cl_3] + Am \rightarrow \textit{cis}\text{-}[Pt(Mor)(Am)Cl_2] + KCl$$

For strong electron donors such as methylamine, dimethylamine, ethylamine and diethylamine, the reaction was carried out with their salts, $Am \cdot HCl$, in aqueous solution:

$$K[Pt(Mor)Cl_3] + Am \cdot HCl + KOH \rightarrow \textit{cis}\text{-}[Pt(Mor)(Am)Cl_2] + 2KCl + HOH$$

The neutral diamine complexes precipitate out and can be easily isolated and purified by recrystallizing from aqueous EtOH solution.

Molar conductivities (μ), electronic spectra (λ_{max} /log ε), IR , Raman spectra (ν) and ^1H NMR spectra (δ, J) of the synthesized complexes are listed in Tables I, II, III and IV.

The molar conductivity (μ) of 10^{-4} M $K[Pt(Mor)Cl_3]$ solution is 91 $\Omega^{-1}cm^2\,mol^{-1}$ and of 5.10^{-5}–10^{-4} M solutions of *cis*-$[Pt(Mor)(Am)Cl_2]$ measured soon after

TABLE I Molar conductivity (μ) and electronic spectra of synthesized complexes

Complex	*Formula*	μ, $\Omega^{-1} cm^2 mol^{-1}$	λ_{max} (nm)/log ε
M1	K[Pt(Mor)Cl_3]	90.8	206/4.08; 300/2.5; 346/1.94; 413/1.60
M2	[Pt(Mor)($C_6H_5NH_2$)Cl_2]	11.8	205/4.55; 221/4.14; 278/3.20
M3	[Pt(Mor)(*o*-$MeC_6H_4NH_2$)Cl_2]	14.5	206/4.35; 229/4.16; 276/3.15
M4	[Pt(Mor)(*p*-$MeC_6H_4NH_2$)Cl_2]	14.0	202/3.99; 225/3.80; 278/3.08
M5	[Pt(Mor)(*p*-$MeOC_6H_4NH_2$)Cl_2]	12.9	205/4.30; 226/4.05; 283/3.55
M6	[Pt(Mor)(*p*-$EtOC_6H_4NH_2$)Cl_2]	15.1	207/4.46; 230/4.10; 283/3.52
M7	[Pt(Mor)(α-$C_{10}H_7NH_2$)Cl_2]	12.5	< 200; 224/4.18; 290/3.28
M8	[Pt(Mor)(C_5H_5N)Cl_2]	11.5	206/3.90; 250/3.30.14; 289/3.10
M9	[Pt(Mor)(C_9H_7N)Cl_2]	13.1	204/4.75; 233/4.65; 318/3.98
M10	[Pt(Mor)(8-OC_9H_6N)Cl]	10.6	< 200; 238/4.09; 270/4.20; 327/3.51
M11	[Pt(Mor)($C_6H_5CH_2NH_2$)Cl_2]	10.4	202/3.86; 262/2.86; 282/2.14
M12	[Pt(Mor)($C_6H_5CH_2CH_2NH_2$)Cl_2]	12.5	206/4.20; 259/2.20; 281/2.10
M13	[Pt(Mor)($MeNH_2$)Cl_2]	13.6	202/3.60
M14	[Pt(Mor)(Me_2NH)Cl_2]	14.5	202/3.61
M15	[Pt(Mor)($EtNH_2$)Cl_2]	10.1	204/3.85
M16	[Pt(Mor)(Et_2NH)Cl_2]	15.8	207/4.30

dissolution is in the range 11–16 $\Omega^{-1}\,cm^2\,mol^{-1}$ indicating their non-electrolytic nature (Table I).

The high solubility in water allowed the electronic spectra of K[Pt(Mor)Cl_3] to be recorded at 10^{-2} and 10^{-4} M. The three weak bands of this complex are assigned to *d–d* transitions. All the [Pt(Mor)(Am)Cl_2] complexes have low solubilities and their spectra were recorded at concentrations $< 10^{-4}$ M in 96% (v/v) aqueous EtOH. Only charge-transfer and ligand spectra were observed (Table I).

The main IR and Raman spectral absorption bands are listed in Table II. The difference in frequency between IR bands and Raman bands is small, but the intensities of ν(NH) and ν(CH) in IR spectra are much stronger than those in Raman spectra. In IR and Raman spectra of [Pt(Mor)(8-OC_9H_6N)Cl] (**M10**) there is no evidence of ν(OH), indicating that 8-hydroxyquinoline has been deprotonated on coordination to Pt(II). The ν(Pt–N) and ν(Pt–Cl) values reported in Table II are in general agreement with those in the literature for *cis*-[Pt(Am)$_2$$Cl_2$] [12].

Figure 1 shows the ^{1}H NMR spectra of two of the complexes, **M13** and **M6**. Figure 2 illustrates the interconversion of the two chair conformations of morpholine and the way in which one of them coordinates with Pt(II).

For non-coordinated morpholine (OC_4H_8NH), eight protons attached to carbon give two resonances at 2.9 ppm ($4H_\alpha$) and 3.6 ppm ($4H_\beta$) [13], while spectra of complexes (coordinated morpholine) give four resonances as illustrated in Fig. 1. There are four multiples characterized for eight coordinated morpholine protons attached to carbon. This is expected since upon coordination to Pt(II), one chair conformation of morpholine (with NH in the axial position) is fixed (Fig. 2b). Thus, resonances of non-equivalent protons H^a_α, H^e_α, H^a_β, H^e_β appear individually.

The assignment of H^a and H^e resonances of coordinated morpholine, in [Pt(Mor)(*p*-$C_2H_5OC_6H_4NH_2$)Cl_2] (**M6**), based on spin–spin splitting patterns is shown in Fig. 3. Because proton H^a_α interacts with H^e_α,H^a_β, H^a_N and H^e_β its resonance appears as *a quartet of doublets* centered at 3.08 ppm with $^2J_{ae} \approx {}^3J_{aa} = 12$–13.5 Hz and $^3J_{ae} = 3.5$ Hz. Proton H^a_β is coupled toH^e_β, H^a_α and H^e_α giving *a triplet of doublets* centered at 3.35 ppm with $^2J_{ae} \approx {}^3J_{aa} = 12.5$–13.5 Hz and $^3J_{ae}$ = 2.5 Hz. Proton H^e_α interacts with germinal proton H^a_α (with $^2J_{ae} = 12.5$ Hz) and with 3 vicinal protons, H^a_β,H^e_β,H^a_N (with smaller

TABLE II The main bands in IR and Raman spectra of *cis*-[Pt(Mor)(Am)Cl_2], cm^{-1}, (ν(IR) is given above, ν(Raman) is given under)

Complex	*ν(NH)*	*ν(CH)*	*ν(Pt–N)*	*ν(Pt–Cl)*
M1	3187	2968, 2870	450	–
	3187	2963, 2869	450	326
M2	3219, 3182, 3130	3026, 2970, 2860	570, 457	–
	3222, 3191, 3135	3055, 2975, 2857	576, 450	331
M3	3204, 3117	3045, 2965, 2850	538, 486	–
	3210, 3130	3048, 2975, 2857	521, 483	325
M4	3200, 3167, 3110	3040, 2964, 2862	567, 455	–
	3207, 3167	3067, 2966, 2865	569, 447	324
M5	3231, 3175, 3142	3055, 2949, 2833	532, 502	–
	3236, 3178, 3149	3060, 2950, 2841	564, 500	334
M6	3200, 3175, 3134	3020, 2974, 2864	548, 503	–
	3217, 3177, 3138	3074, 2972, 2867	568, 500	331
M7	3182, 3092 3187	3060, 2970, 2849	500, 476	–
		3064, 2977, 2850	502, 479	329
M8	3182	3070, 2966, 2858	536, 462	–
	3183	3075, 2963, 2964	535, 450	335
M9	3176	3050, 2950, 2851	513, 480	–
	3168	3052, 2950, 2854	521, 481	327
M10	3192	3065, 2957, 2860	537, 490	–
	3185	3075, 2958, 2867	536, 505	328
M11	3241, 3207, 3185	3030, 2989, 2863	520, 480	–
	3248, 3206, 3185	3053, 2980, 2867	507, 485	329
M12	3232, 3200, 3163	3035, 2960, 2865	550, 491	–
	3228, 3218, 3170	3045, 2957, 2971	559, 492	328
M13	3205, 3146	2957, 2856	520, 450	–
	3207, 3152	2948, 2855	514, 448	319
M14	3187, 3160	2996, 2935	537, 450	–
	3186, 3150	2999, 2942	534, 451	320
M15	3233, 3200, 3156	2990, 2867	535, 450	–
	3240, 3209, 3156	2992, 2878	536, 449	312
M16	3179	2995, 2867	545, 485	–
	3187	2999, 2884	536, 504	324

coupling constants, $^3J_{ae} \approx {}^3J_{ee} = 2.5–3.5$ Hz), therefore its resonance appears as *broadened doublets*. Proton H^e_β interacts with germinal proton H^a_β (with $^2J_{ae} = 12.5$ Hz) and with 2 vicinal protons H^a_α and H^e_α ($^3J_{ae} \approx {}^3J_{ee} = 2.5–3.5$ Hz) giving a *doublet of doublets* (Fig. 3) or *broadened doublets*.

The signals of morpholine protons in the examined complexes have been assigned (Table III). The spectra of **M2**, **M4**, **M5**, **M7**, **M8**, **M12** and **M16** have been recorded using a 200 MHz spectrometer. Some signals overlapped and were not resolved, so some coupling constants were not determined. Spectra of the other complexes have been recorded using a 500 MHz spectrometer, and the coupling constants are determined as illustrated in Fig. 3.

The ^{1}H NMR data given in Table III were most informative with respect to the structure of the examined complexes:

(1) The magnitude of the coupling constants of H^a_α and the proton of NH (12.5 Hz) corresponding to $^3J_{aa}$ in a cyclohexane chair system [13] indicate that the N–H bond is axial and the N–Pt bond is equatorial as shown in Fig. 2b.
(2) Chemical shifts of morpholine protons in the complexes containing aromatic amines (**M2**–**M11**), except H^e_α of **M9** and H^a_α, H^a_β of **M10**, are smaller than

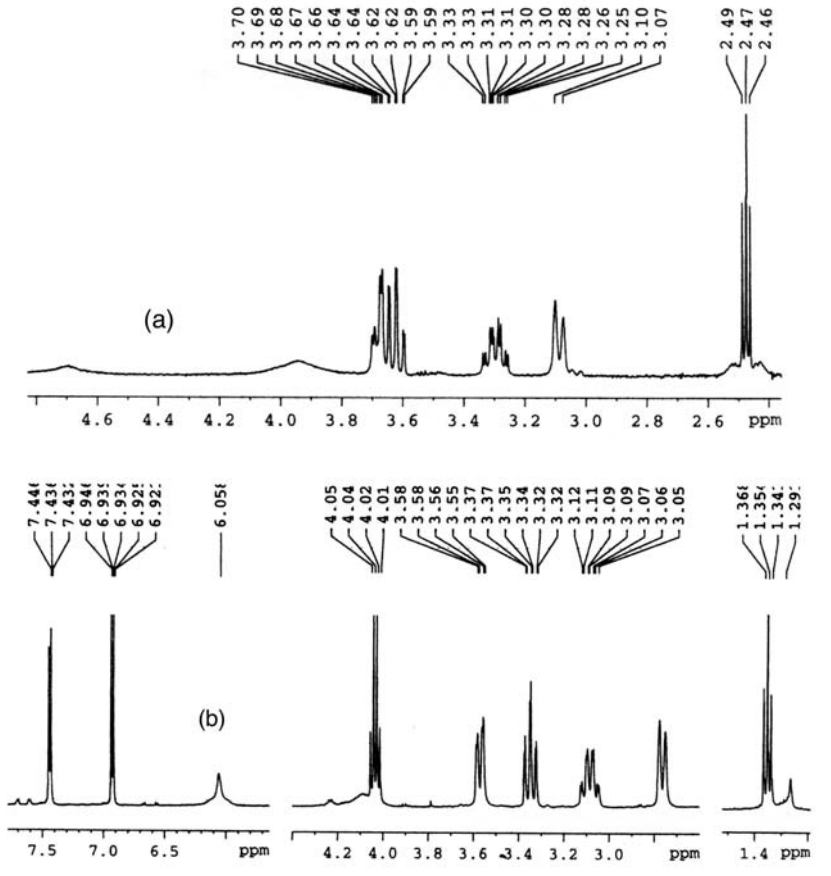


FIGURE 1 ^{1}H NMR spectra of (a) *cis*-[Pt(Mor)(CH_3NH_2)Cl_2] (**M13**); (b) *cis*-[Pt(Mor)(*p*-$C_2H_5OC_6H_4NH_2$)Cl_2] (**M6**).

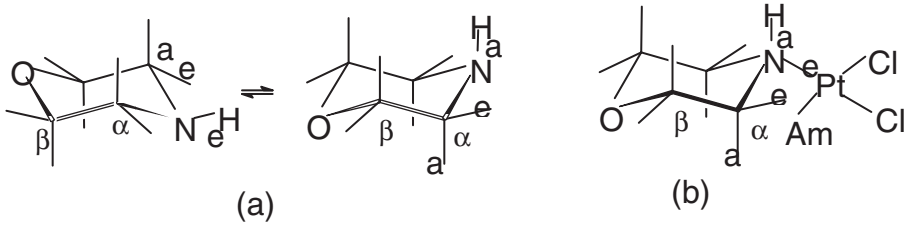


FIGURE 2 (a) Interconversion of the two chair conformations of morpholine; (b) The coordination of morpholine with Pt(II).

those of the analogous complexes without aromatic amines (**M13**–**M16**). In some complexes, these are even smaller than those of non-coordinated morpholine (as expected, the morpholine protons shift downfield upon complexation). The important conclusion to be derived from this anomaly is that in the coordination to Pt(II), morpholine and aromatic amines occupy *cis*-positions, so some morpholine protons fall into the shielding zone of a ring current of the

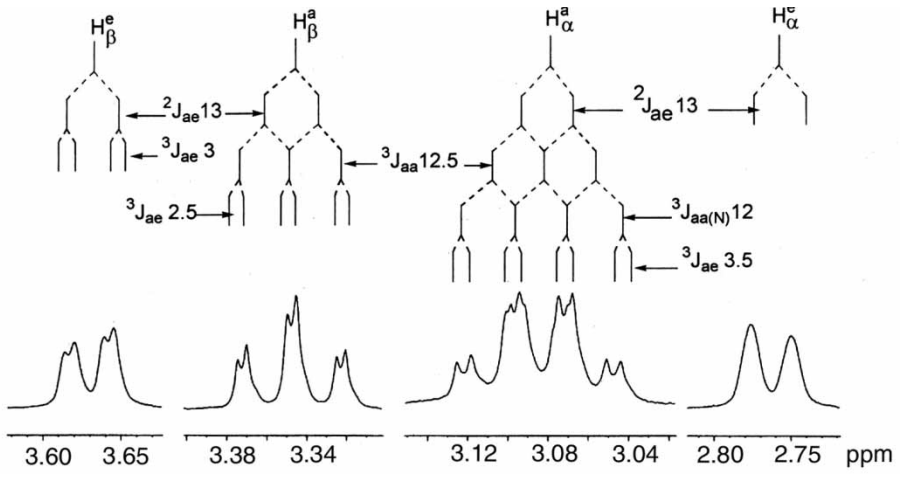


FIGURE 3 The spin–spin splitting patterns of morpholine protons in **M6**.

aromatic amine. For a series of *cis*-[Pt(Pip)(Am)Cl_2] (Pip: piperidine, Am: the same aromatic amine in the reported complexes, *cis*-[Pt(Mor)(Am)Cl_2]) almost all shifts of piperidine protons obey the trend [6]. If dynamic motion of the coordinated morpholine occurs, the signals of H^a_α, H^e_α, H^a_β and H^e_β are not resolved and their splitting patterns cannot be as clear as illustrated in Figs. 1 and 3.

The proton resonances of other amines (Am) are shown in Table IV. It is expected that chemical shifts of protons in coordinated amines are upfield from free amines.

In ^{1}H NMR spectra ^{195}Pt satellites are often broadened beyond detection or are overlapped in wide proton signals. However, in signals from pyridine H2 of [Pt(Mor)(C_5H_5N)Cl_2] (**M8**), from quinoline H2 of [Pt(Mor)(C_9H_7N)Cl_2] (**M9**) and [Pt(Mor)(8-OC_9H_6N)Cl] (**M10**), from benzylamine CH_2 of [Pt(Mor)($C_6H_5CH_2NH_2$)Cl_2] (**M11**), from CH_3 of [Pt(Mor)($MeNH_2$)Cl_2] (**M13**) and [Pt(Mor)(Me_2NH)Cl_2] (**M14**) and from ethylamine CH_2 of [Pt(Mor)($EtNH_2$)Cl_2] (**M15**) the ^{195}Pt satellites are clear (for example, signal at 2.48 ppm in Fig. 1a).

The distance between two satellites, $^3J_{PtH}$, is 41–48 Hz (Table IV) in reasonable agreement with the *cis*-configuration of diamine platinum(II) complexes [14,15].

For all complexes except [Pt(Mor)(C_9H_7N)Cl_2] (**M9**) each pair of $2H^a_\alpha$, $2H^e_\alpha$, $2H^a_\beta$, $2H^e_\beta$ gives rise to one resolved resonance whose splitting pattern is clear (when recorded with a 500 MHz spectrometer). This shows that in complexes of Pt(II) two α-positions of morpholine are equivalent and two β-positions are equivalent. In complexes **M2**, **M4**, **M5**, **M6**, **M8**, **M11** and **M12**, protons H2, H6 are equivalent and H3, H5 are equivalent (Table IV) and their splitting patterns are clear. These equivalences and the shape of the splitting patterns suggest that the plane of the aromatic amine and morpholine rings are perpendicular to the coordination plane of Pt(II) rather than undergoing free rotation. (A rotation about Pt–N in [Pt(quinoline)$_2Cl_2$] does not occur on the NMR time scale, at room temperature [16].) The arrangement is illustrated in Fig. 4a. This arrangement is strongly favored since van der Waals repulsions are minimized.

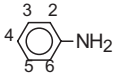
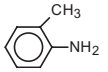
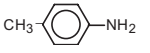
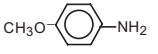
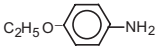
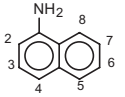
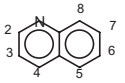
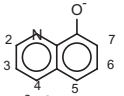
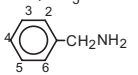
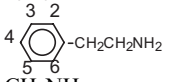
In the spectrum of *cis*-[Pt(Mor)(C_9H_7N)Cl_2] (**M9**) there are two anomalies. The first is that the H_α give rise to four signals: one H^a_α resonates as a quartet of doublets centered at 2.84 ppm (the integrated area was assigned to 1H), another H^a_α resonates

TABLE III ^{1}H-Resonances of the coordinated morpholine, δ (ppm), J (Hz)

Complex (solvent)	H^{e}_{α} *(2H)*	H^{a}_{α} *(2H)*	H^{e}_{β} *(2H)*	H^{a}_{β} *(2H)*	*NH (1H)*
M1 (D_2O)	3.15; br.d $^{2}J_{ae}$ 13	3.38; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 12.5; $^{3}J_{ae}$ 2.0 3.27; q	3.79; br.d (*) $^{2}J_{ae}$ 12.5	3.77; t $^{2}J_{ae}$ $^{3}J_{aa}$ 12.5	5.0
M2 (CD_3OD)	2.82; br.d $^{2}J_{ae}$ 13	$^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 13	3.65; br.d $^{2}J_{ae}$ 12.5	3.40; m $^{2}J_{ae}$ $^{3}J_{aa}$ 12.5	–
M3 (CD_3CN)	2.60; br.d $^{2}J_{ae}$ 12	3.07; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 12.5; $^{3}J_{ae}$ 2.5	3.51; br.d $^{2}J_{ae}$ 11	3.03; t $^{2}J_{ae}$ $^{3}J_{aa}$ 12	4.24
M4 (CD_3OD)	2.72; br.d $^{2}J_{ae}$ 12.5	3.24; m un.	3.63; br.d $^{2}J_{ae}$ 12.2	3.15; m un.	–
M5 (CD_3CN)	2.73; br.d $^{2}J_{ae}$ 13	3.22; m un.	3.63; br.d $^{2}J_{ae}$ 11.2	3.45; m un.	5.48
M6 (CD_3CN)	2.76; br.d $^{2}J_{ae}$ 13	3.08; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 12.5; $^{3}J_{ae}$ 2.5	3.57; d.d $^{2}J_{ae}$12; $^{3}J_{ae}$ 2.5	3.35; t.d; $^{2}J_{ae}$ $^{3}J_{aa}$12; $^{3}J_{ae}$2.5	4.10
M7 (CD_3OD)	2.80; br.d $^{2}J_{ae}$ 12	3.06; m un.	3.67; m un	3.15; m un.	–
M8 (CD_3OD)	2.60; br.d $^{2}J_{ae}$ 12	3.23; m un	3.60; m ov.	3.56; m ov.	–
M9 (CD_3CN)	3.09 (1H) 3.12 (1H) br.d; $^{2}J_{ae}$ 12	2.98(1H); 2.84(1H); q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 12.5; $^{3}J_{ae}$3.5	3.47; br.d $^{2}J_{ae}$ 12.5	3.51; t.d $^{2}J_{ae}$ $^{3}J_{aa}$12.5; $^{3}J_{ae}$3.5	4.25
M10 (CD_3CN)	3.06; br.d $^{2}J_{ae}$ 13	3.44; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 12.5; $^{3}J_{ae}$ 3	3.63;d.d $^{2}J_{ae}$ 12; $^{3}J_{ae}$3	3.78; t.d $^{2}J_{ae}$ $^{3}J_{aa}$12; $^{3}J_{ae}$3	5.86
M11 (CD_3CN)	2.72; br.d $^{2}J_{ae}$ 13.5	3.21; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 13.5; $^{3}J_{ae}$ 4	3.58; d.d $^{2}J_{ae}$ 12.5; $^{3}J_{ae}$4	3.78; t.d $^{2}J_{ae}$ $^{3}J_{aa}$12.5; $^{3}J_{ae}$3	4.75
M12 (CD_3OD)	3.08; br.d $^{2}J_{ae}$ 13	3.15; m un.	3.72; br.d $^{2}J_{ae}$ 12	3.66; t $^{2}J_{ae}$ $^{3}J_{aa}$12.5	–
M13 (CD_3CN)	3.09; br.d $^{2}J_{ae}$ 13.5	3.30; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 13.5; $^{3}J_{ae}$ 3.5	3.68; d.d $^{2}J_{ae}$ 12.5; $^{3}J_{ae}$3	3.62; t.d $^{2}J_{ae}$ $^{3}J_{aa}$12.5; $^{3}J_{ae}$3	4.70
M14 (CD_3CN)	3.07; br.d $^{2}J_{ae}$ 13	3.35; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 13; $^{3}J_{ae}$ 3.5	3.67; d.d $^{2}J_{ae}$ 12.5; $^{3}J_{ae}$3.5	3.65; t.d $^{2}J_{ae}$ $^{3}J_{aa}$12.5; $^{3}J_{ae}$3	4.75
M15 (CD_3CN)	3.06; br.d $^{2}J_{ae}$ 13	3.39; q.d; $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 13; $^{3}J_{ae}$ 3.5	3.67; d.d $^{2}J_{ae}$ 12.5; $^{3}J_{ae}$3.5	3.63; t.d $^{2}J_{ae}$ $^{3}J_{aa}$12.5; $^{3}J_{ae}$3	4.85
M16 (CD_3OD)	3.04; br.d $^{2}J_{ae}$ 13	3.15; q $^{2}J_{ae}$ $^{3}J_{aa(\beta)}$ $^{3}J_{aa(N)}$ 13	3.72; br.d $^{2}J_{ae}$ 13	3.63; m un.	–

(*)br: broadened, d: doublet, m: multiplet, ov: overlapped, q.d: quartet of doublets, q.t: quartet of triplets, s: singlet, un: unresolved.

TABLE IV ^{1}H-Resonances of Am in *cis*-[Pt(Mor)(Am)Cl_2], δ (ppm), J (Hz)

Complex (solvent)	*Am*	*H2*	*H3*	*H4*	*H5*	*H6*	*Other H*
M2 (CD_3OD)		7.56; d(*) J_{23} 7.8	7.47; t $J_{32,}$ J_{34} 7.2	7.33; t J_{45} 7.2	7.47; t $J_{56,}$ J_{54} 7.2	7.56; d J_{65} 7.8	
M3 (CD_3CN)		–	7.36; dd J_{34} 7.5 J_{35} 1.5	7.27; td ^{3}J 7.0 ^{4}J 1.5	7.31; td ^{3}J 7.0 ^{4}J 1.5	7.42; dd J_{65} 7.5 J_{64} 1.5	CH_3:2.66; s NH:5.94; br.s
M4 (CD_3OD)		7.25; d J_{23} 8.5	7.13; d J_{32} 8.2	–	7.13; d J_{56} 8.2	7.25; d J_{65} 8.5	CH_3:2.25; s NH_2:5.60
M5 (CD_3CN)		7.31; d J_{23} 8.8	6.90; d J_{32} 8.8	–	6.90; d J_{56} 8.8	7.31; d J_{65} 8.8	CH_3O:3.73; s NH_2:7.21; br.s
M6 (CD_3CN)		7.44; d J_{23} 8.8	6.93; d J_{32} 8.8	–	6.93; d J_{56} 8.8	7.44; d J_{65} 8.8	–CH_3:1.35; t –CH_2:4.03; q ^{3}J7.0; NH_2:6.06
M7 (CD_3OH)		8.06; d J_{23} 8.0	7.54; dd ^{3}J 7.2	7.98; dd J_{43} 6.6 J_{42} 1.5	7.63; d J_{56} 8.0	7.70; td ^{3}J 8.4 ^{4}J 1.5	H7:7.83; td H8:8.92; dd ^{3}J 8.6; ^{4}J1.5
M8 (CD_3OD)		9.23; d J_{23} 6.0 $^{3}J_{PtH}$ 42	7.41; t ^{3}J 7.0	7.80; t ^{3}J 7.0	7.41; t ^{3}J 7.0	9.23; d J_{65} 6.0	
M9 (CD_3CN)		9.42; dd J_{23} 5.5 ^{4}J1.5 $^{3}J_{PtH}$ 42	7.59; dd J_{34} 8.2 J_{23} 5.5	8.54; d J_{43} 9.0	8.08; d J_{56} 6.5	7.78; td J_{67} 7.4 J_{68} 1.0	H7:8.06; t H8:9.89; d J_{87}: 9.0
M10 (CD_3CN)		8.78; d J_{23} 5.0 $^{3}J_{PtH}$ 42	7.60; q J_{34} 8.5 J_{32} 5.0	8.61; d J_{43} 8.5	7.02; d J_{56} 8.0	7.37; t ^{3}J 8.0	H7:6.83; d $J_{76:}$ 8.0
M11 (CD_3CN)		7.55; dd J_{23}7.0	7.42; dd J_{34}6.5	7.38; tt J_{42}1.5	7.42; dd J_{45} 6.5	7.55; dd J_{56} 7.0	CH_2: 3.98; t ^{3}J 6.5; $^{3}J_{PtH}$ 43 NH_2: 4.50; br.s
M12 (CD_3OD)		7.32; d ^{3}J 7.5	7.36; m un.	7.29; m un.	7.36; m un.	7.32; d ^{3}J 7.5	CH_2:2.96; m CH_2:3.03; m un.
M13 (CD_3CN)	CH_3NH_2	CH_3: 2.48; t; ^{3}J 6.5; $^{3}J_{PtH}$ 46; NH_2: 3.95; br.s					
M14 (CD_3CN)	$(CH_3)_2NH$	CH_3: 2.64; d; ^{3}J 6; $^{3}J_{PtH}$ 42; NH: 4.67; br.s					
M15 (CD_3CN)	$CH_3CH_2NH_2$	CH_3: 1.23; t; ^{3}J 7; CH_2:2.81; q; ^{3}J 7; NH_2: 4.05; br.s					
M16 (CD_3OD)	$(CH_3CH_2)_2NH$	CH_3: 1.62; t; ^{3}J 7; CH_2 :2.84; q; ^{3}J 7					

(*)br: broadened, d: doublet, m: multiplet, t: triplet, dd: doublet of doublets, q: quartet, td: triplet of doublets, s: singlet, un: unresolved, tt: triplet of triplets.

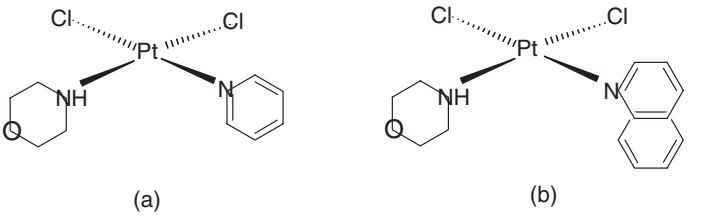


FIGURE 4 Structure of (a) *cis*-[Pt(Mor)(C_5H_5N)Cl_2]; (b) *cis*- [Pt(Mor)(C_9H_7N)Cl_2].

as another quartet of doublets centered at 2.98 ppm (1H); two H_α^e give rise two doublets centered at 3.09 (1H) and 3.12 ppm (1H). The second is that the chemical shifts of H_α^e (3.09, 3.12 ppm) are more downfield than those of H_α^a (2.84, 2.98 ppm), while for the other complexes the shift is reversed. These anomalies may be caused by the difference in spatial relationship of the two α-positions of morpholine in comparison with the quinoline ring, as presented in Fig. 4b. In complex [Pt(Mor)($C_6H_5CH_2CH_2NH_2$)Cl_2] (**M12**) the aromatic ring is far from the morpholine, and thus has small influence on the morpholine. In complex *cis*-[Pt(Mor)(*o*-$CH_3C_6H_4NH_2$)Cl_2] (**M3**) the spatial difference between the two α-positions of the morpholine and the ring current of *o*-toluidine is not significant, thus the two α-positions are still equivalent.

The reported complexes were tested for cell cytotoxicity and *cis*-[Pt(Mor)($PhCH_2NH_2$)Cl_2], *cis*-[Pt(Mor)($PhCH_2CH_2NH_2$)Cl_2] and *cis*-[Pr(Mor)(OC_9H_6N)Cl] exhibit anticancer activities *in vitro* on human cancer cell Hep-G and RD with $IC_{50} < 5\,\mu g\,cm^{-3}$.

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