^{1}H NMR and vibrational spectra of *cis*-dichlorobis(cycloalkylamine)-platinum(II) complexes

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Abstract

The ^{1}H NMR and vibrational spectra of the complexes $PtCl_2(am)_2$, with am = cycloalkylamine ($C_nH_{2n-1}NH_2$, $n = 3, 4, 5, 6, 7, 8$) are reported. The anisotropic effects of the cyclopropylamine ligand on the ^{1}H chemical shifts are discussed. Most of the IR and Raman active modes observed for the complexes are assigned by comparison with the vibrational spectra of the pure amine ligands. Shifts of the internal ligand frequencies are explained by effects resulting from the coordination of the amino group to the Pt atom. The Pt–N stretching frequency is observed to decrease in a non-monotonic manner with increasing cycloalkylamine ring size. The frequencies of the Pt–Cl stretching vibrations do not differ significantly for the different complexes, while the antitumor activity has been found to increase strongly for the complexes with the largest ligands ($n = 7$ and 8). Implications of this finding for the mechanism of cytostatic action by DNA binding are discussed.

Introduction

In 1964 Rosenberg *et al.* first observed that *cis*-diammine dichloro platinum(II) ('cisplatin') causes an inhibition of cell division, and induction of filamentous growth of *Escherichia coli* cells [1, 2]. This discovery led to an increasing number of investigations testing the applicability of platinum compounds in the field of cancer chemotherapy [3–5]. There is general agreement that DNA is an important pharmacological target for the platinum compounds. Intrastrand guanine–guanine cross linking appears to be the preferred binding pattern of cisplatin [6]. The hydrolysis of the Pt–Cl bond appears to be the rate determining step in the reaction of cisplatin with DNA [7]. An understanding of the dependence of the antitumor activity on these mechanistic aspects is a requirement for the development of compounds with higher efficiency.

The title compounds, complexes of *cis*-dichlorobis-(cycloalkylamine)platinum(II), are anti-cancer drugs of the first generation of cisplatin analogues. They were tested against ADJ/PC6A tumor [8, 9] and against L1210 leukemia [10], with strongly different results. A detailed analysis of the drug structure by spectroscopic methods has not been performed in these investigations.

As a basis for discussing the structure–activity relationship, we have synthesized the isomeric pure compounds, and tested them against the MDA-MB231 human breast cancer cell line [11]. Characterization of the complexes was carried out by UV–Vis spectroscopy and X-ray measurements [12]. In this study the ^{1}H NMR, IR and Raman spectra of the *cis*-dichlorobis-(cycloalkylamine)platinum(II) compounds, with the cycloalkylamine ligand varied from cyclopropylamine to cyclooctylamine, are reported (see Table 1).

TABLE 1. Platinum complexes $PtCl_2(C_nH_{2n-1}NH_2)_2$ investigated in this study

Compound (n)	$C_nH_{2n-1}NH_2$	Leaving group	Geometric configuration
3	$C_3H_5NH_2$	Cl	*cis*
4	$C_4H_7NH_2$	Cl	*cis*
5	$C_5H_9NH_2$	Cl	*cis*
6	$C_6H_{11}NH_2$	Cl	*cis*
7	$C_7H_{13}NH_2$	Cl	*cis*
8	$C_8H_{15}NH_2$	Cl	*cis*

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Experimental

Preparation and characterization of the complexes have been described elsewhere [11]. ^{1}H NMR spectra of the platinum complexes were recorded on a 250 MHz instrument (Bruker, model WM250), using dimethylformamide-d_7 as solvent.

IR spectra were acquired on a FT-IR spectrometer (Nicolet, model 60SX); typically, 50 scans have been acquired at a resolution of 4 cm^{-1}. Spectra of the complexes in the 4000–600 cm^{-1} range were obtained using KBr pellets; for recording the 600–150 cm^{-1} range, the powders were pressed into polyethylene pellets. The pure ligands were diluted with CCl_4, and measured in KBr cells in the 4000–600 cm^{-1} range. Thin films ($\sim$200 μm) of the pure ligands between polyethylene plates were used to detect the low energy IR absorptions ($<$600 cm^{-1}).

For the Raman measurements, the crystalline complexes were sealed into glass capillaries. The pure liquid ligands were contained in a quartz cuvette. Raman scattering of the complexes was excited by 0.2–2.5 mW of power at the 514.5 nm line of an argon ion laser. For Raman experiments on the ligands, 30 mW of power at the same wavelength was used. In addition, the ligands $C_4H_7NH_2$, $C_5H_9NH_2$, and $C_6H_{11}NH_2$ were excited with 25 mW of power at 647.1 nm, using a krypton ion laser. Signal integration times are indicated in the respective Figure captions. Raman signals were dispersed and detected in a double monochromator (SPEX, model 14018) equipped with photon counting electronics, or dispersed in a triple spectrograph (SPEX, model 1877 A) and detected by an optical multichannel analyzer based on a cooled photodiode array. Spectral positions were calibrated using a neon spectral lamp. For each sample, two intervals of Raman shifts, i.e. 3400–2500 and 1800–150 cm^{-1}, were recorded in separate experiments. The data were smoothed using a Gaussian linewidth of 3 cm^{-1}.

Semi-empirical calculations of atomic charge densities, molecular orbital populations and vibrational frequencies were performed using the AM1 parametrization of Dewar [13]. The scalar version ('SCAMP') of the VAMP program package [14] implementing the AM1 method was kindly made available by Clark, and run on a UNIX workstation.

Results

^{1}H NMR spectra

The ^{1}H NMR spectra of compounds **3–8**, as well as those of the pure amine ligands, have been recorded. The complete set of ^{1}H chemical shift values, relative intensities, values of the ^{195}Pt–^{1}H coupling constants, and assignments is presented in Table 2 for the Pt(II) complexes, and in Table 3 for the amine ligands. The spectral region containing the amine proton resonances of the complexes is shown in Fig. 1.

Vibrational spectra

IR spectra of the complexes and the ligands were recorded in the range between 4000 and 150 cm^{-1}. For the complexes, the spectral region from 500 to 150 cm^{-1} is presented in Fig. 2; see also 'Supplementary material'.

Raman spectra of the complexes have been recorded as described in 'Experimental'. The two relevant spectral regions, i.e. 3250–2800 and 1600–150 cm^{-1}, are presented in Figs. 3 and 4. Measurement of the Raman scattering of the pure amine ligands is impeded by strong luminescence backgrounds, especially for $C_4H_7NH_2$, $C_5H_9NH_2$ and $C_6H_{11}NH_2$. To alleviate this problem, a wavelength of 647.1 nm was used for excitation. See also 'Supplementary material'.

Assignments have been made using literature data of cycloalkylamines [15–18], the available assignment of complex **3** [19], and tabulated frequencies of compound **4** [20]. Bands related to the vibrations of the ligands relative to the platinum(II) ion have been identified by comparison of the spectra of the complexes and those of the pure ligands. See also 'Supplementary material'. In the following paragraphs, some characteristic group frequencies are mentioned in detail.

TABLE 2. ^{1}H NMR data[a] of *cis*-dichlorobis(cycloalkylamine)platinum(II) complexes

Compound (*n*)	^2J(Pt–H) (Hz)	δ (ppm)		
		NH	CH (methine)	CH (alkyl)
3	66	5.05 (br, 4H)	2.61 (br, 2H)	0.6–0.8 (s, 8H)
4	64	5.13 (br, 4H)	3.68 (br, 2H)	1.5–2.4 (s, 12H)
5	65	4.96 (br, 4H)	3.55 (br, 2H)	1.4–2.2 (s, 16H)
6	66	4.89 (br, 4H)	2.92 (br, 2H)	1.0–2.5 (m, 20H)
7	66	4.87 (br, 4H)	3.14 (br, 2H)	1.3–2.5 (m, 24H)
8	66	4.82 (br, 4H)	3.24 (br, 2H)	1.4–2.4 (m, 28H)

[a]250 MHz, in dimethylformamide-d_7.

TABLE 3. ^{1}H NMR data[a] of cycloalkylamines

Alkyl of compound	δ (ppm)		
	NH	CH (methine)	CH (alkyl)
Propyl	1.89 (br, 2H)	2.21 (s, 1H)	0.1–0.4 (s, 4H)
Butyl	2.44 (br, 2H)	3.29 (m, 1H)	1.4–2.3 (s, 6H)
Pentyl	1.78 (m, 2H)	3.23 (s, 1H)	1.1–2.1 (m, 8H)
Hexyl	1.51[b]	2.52 (s, 1H)	0.9–2.0 (m, 12H)[d]
Heptyl	[c]	2.83 (s, 1H)	1.2–2.0 (m, 14H)[d]
Octyl	[c]	2.86 (s, 1H)	1.3–1.9 (m, 16H)[d]

[a]250 MHz, in dimethylformamide-d_7. [b]Sadtler NMR Spectra, No. 6937 (see ref. 23). [c]Superimposed by CH alkyl protons. [d]Includes NH protons.

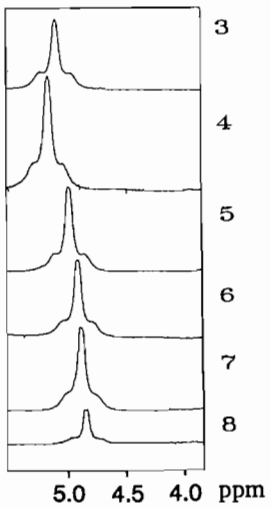

Fig. 1. ^{1}H NMR spectra of compounds **3–8**, recorded at 250 MHz in dimethylformamide-d_7. The spectral region of the NH_2 resonance is shown.

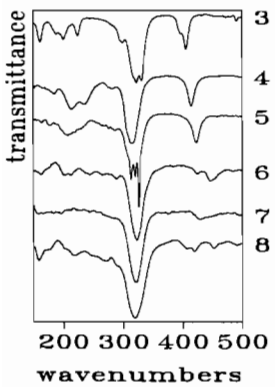

Fig. 2. IR spectra of compounds **3–8** in the 500–150 cm^{-1} range.

Frequencies of the antisymmetric and symmetric NH_2 stretching vibrations of the complexes are observed in the 3300–3400 cm^{-1} range. In the complex compounds, the vibrations are shifted to lower energies, as compared to the pure amines. This red shift has an approximately

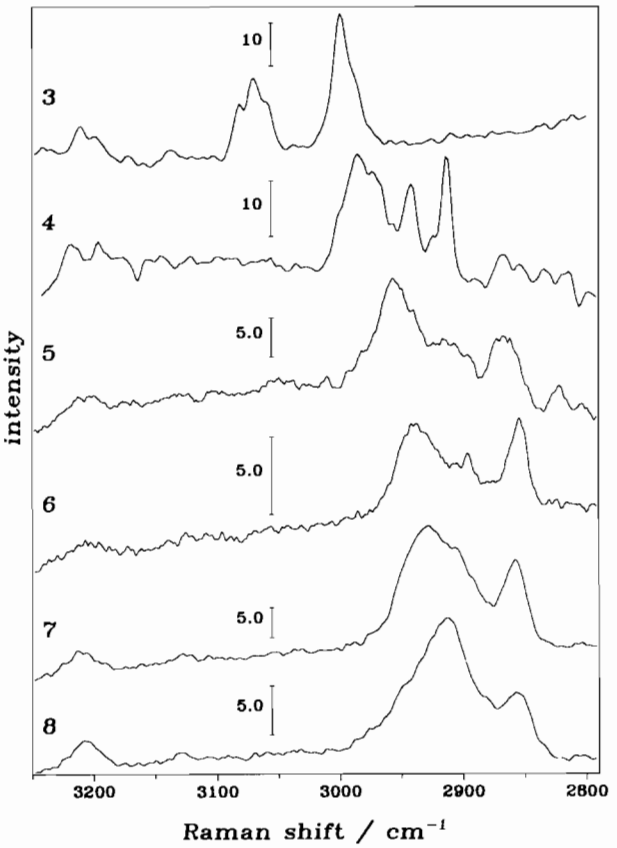

Fig. 3. Raman spectra of the *cis*-dichlorobis(cycloalkylamine)platinum(II) complexes (3250–2800 cm^{-1} range). Compounds **3–5**: photon counting detection, 6 cm^{-1} resolution, 30 s integration per 2 cm^{-1} step. Compounds **6–8**: multichannel detection on triple spectrograph, 8 cm^{-1} resolution; average of 10 spectra, of 200–400 s integration time each. Intensities, as indicated by the calibration bars, are normalized with respect to integration time and laser power, and are given in counts (or digitized bits) per s and mW. Further details of the spectroscopic experiments are described in 'Experimental'.

constant value of ≈ 140 cm^{-1} for all homologue compounds. The NH_2 deformation vibration exhibits typical frequencies of 1600–1620 cm^{-1} for the ligands, and typical values of 1570–1590 cm^{-1} for the complexes. The red shift is again approximately constant for all compounds, and amounts to ≈ 30 cm^{-1}. See also 'Supplementary material'.

In contrast, the asymmetric and symmetric CH_2 stretching vibrations (Tables 4 and 5) as well as the methine (CH) stretching vibration (Table 6) exhibit nearly the same frequencies for the coordinated and free amines of compounds **4–8**. The three-membered ring represents a remarkable exception: here, the symmetric CH_2 stretching vibration is shifted ≈ 50 cm^{-1} to higher energies in the complex, as compared to cyclopropylamine. The C–H stretching vibration shows a similar blue shift of ≈ 30 cm^{-1} in compound **3**, as compared to the pure amine.

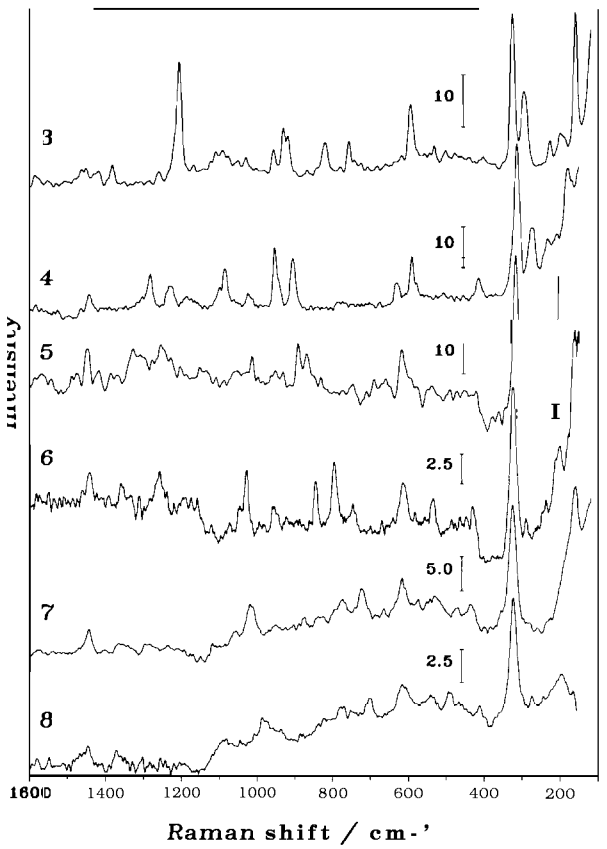

Fig. 4. Raman **spectra of the** *cis*-dichlorobis(cycloalkylamine)platinum(II) **complexes (1600-150 cm-' range). The experimental procedure was the same as in Fig. 4. A monotonically sloping background has been subtracted for compound 5.**

Such an exceptional role of the cyclopropylamine complex is not detected with the CII, deformation vibrations. All complexes exhibit nearly the same frequencies as the pure amines, in the range between 1400 and 1460 cm-'.

The metal-ligand vibrations are expected to be observed in the low wavenumber region. As mentioned above, several important metal-ligand vibrations have been assigned by a comparison of the spectra of the pure amines with those of the complexes. The frequencies of the Pt-N stretching vibration, and of the symmetric and antisymmetric Pt-Cl stretching vibrations of the two chloride ligands, are listed in Tables 7 and 8, respectively. See also 'Supplementary material'.

Discussion

^{1}H NMR spectra

The spectra of the amine ligands match typical spectra of alkylamines [21]. In particular, the spectra of cyclopropylamine and cyclohexylamine agree with those published in the literature [22, 23].

Cyclopropylaminc takcs an cxccptional position in this series of compounds. The CH and CH, resonances show a high field shift of $\approx$ 1.1 ppm, as compared to cyclobutylamine (see Table 3). Lacher *et al.* [24] have reported the anomalous susceptibilities of three-membered ring compounds. The carbon-carbon bonds in cyclopropane exhibit considerable double bond character, as has been analyzed in terms of suitable MO models [25, 26]. The application of an external magnetic field leads to anisotropic ring current effects similar to those observed in benzene. The carbon-proton bonds are oriented at an angle of 60" relative to the plane of the carbon atoms; therefore the protons are located in the area of additional shielding caused by the ring current. This leads to the above-mentioned high field shift of the alkyl proton resonances by $\approx$ 1.1 ppm, as compared to cyclobutylamine. The NH resonances are upshifted by the same mechanism, but the effect is smaller ($\approx$ 0.5 ppm, as compared to cyclobutylamine) due to the larger distance from the ring.

In the sequence from cyclobutylamine to cyclohexylamine, the NH resonances exhibit a high field shift with increasing ring size. This effect could be explained by the electron donating effect of an enlarged number of C atoms.

SCAMP calculations confirm the fact of an increasing charge at the N atom with increasing ring size. For cyclopropylamine, the total charge on the nitrogen atom is calculated to be -0.325 e_0; for cyclobutylamine and cyclopentylamine the calculations yield a value of -0.332 e_0; and for cyclohexyl-, cycloheptyl-, and cyclooctylamine the charge at the N atom has a common value of -0.335 e_0.

Upon coordination of the cycloalkylamines, the deshielding effect of the metal atom causes a low field shift of the NH signals of about 3 ppm (Tables 2 and 3). These signals are broadened by unresolved couplings to the alkyl protons. From the resolved coupling between NH and ^{195}Pt (abundance 33.8%), values of the ^{195}Pt–^{1}H coupling have been determined, and are included in Table 2; these results are in agreement with the value of 66.5 $\pm$ 1.5 Hz rcportcd by Ha *et al.* [27].

Referring to Fig. 1, we note an increasing deshielding of the NH resonance in the series from the cyclooctylamine to the cyclobutylamine complex. One might extrapolate this trend to estimate the chemical shift where the NH resonance would occur in cyclopropylamine in the absence of ring current effects; such an extrapolation yields a value around 5.4 ppm. Thus the anisotropic susceptibility effect described above causes a high field shift of > 0.3 ppm in the complex compound.

The deshielding effect of the metal atom also gives rise to a low field shift of the methine protons. This deshielding amounts to a constant value of $\approx$0.4 ppm for all compounds, and is thus substantially lower than

TABLE 4. Observed and calculated frequencies (cm^{-1}) of the asymmetric CH_2 stretching vibration

Comp. (n)	$PtCl_2(C_nH_{2n-1}NH_2)_2$		$C_nH_{2n-1}NH_2$			Calc. asym./sym.
	IR	Raman	IR	Raman	Lit. (R)	
3	3078m	3082m	3088vs	3079s	3077[a]	3206
					3100[b]	3197
4		2985s	2976vs	2963s	2975[c]	3161–3064
	2977s	2975w	2965vs		2937[d]	
	2943s	2943s	2933vs			
5		2982sh	2956vs	2950vs	2950[e]	3151–3019
	2951	2957m	2941sh	2941vs	2875[e]	
		2939w	2869vs	2870vs		
		≈2916w				
6		2946m	2926vs	2936vs	2922[f]	3098–3001
	2931s	2931m		2923vs		
	2921sh	2899br				
7		2944sh	2925vs	2924vs		3097–2989
	2925s	2925m		2919vs		
		2903m				
8		2948m	2921vs	2916vs		3096–2994
	2920s	2926m				
		2909s				

[a]Ref. 20. [b]Ref. 15, gas phase spectrum. [c]Ref. 16, gas phase spectrum. [d]Ref. 16. [e]Ref. 17. [f]Ref. 18, IR spectrum.

TABLE 5. Observed and calculated frequencies (cm^{-1}) of the symmetric CH_2 stretching vibration

Comp. (n)	$PtCl_2(C_nH_{2n-1}NH_2)_2$		$C_nH_{2n-1}NH_2$			Calc. asym./sym.
	IR	Raman	IR	Raman	Lit. (R)	
3	3063m	3070s	3010vs	3009vs	3005[a]	3162
		3060sh		2979m	3032[b]	3141
					3023[b]	
4	2867s	2868m		2874w	2950[c]	3161–3064
		2854w	2875s	2857m	2872[d]	
		2836vw				
5	2868s	2871m	2869vs	2870vs	2875[e]	3151–3019
		2859m	2858sh	2862sh	2863[e]	
6	2854s	2860m	2854vs	2855vs	2850[f]	3098–3001
		2852m				
7	2856s	2858s	2855vs	2854vs		3097–2989
8	2851s	2855s	2866sh	2855s		3096–2994
			2853vs			

[a]Ref. 20. [b]Ref. 15, gas phase spectrum. [c]Ref. 16, gas phase spectrum. [d]Ref. 16. [e]Ref. 17. [f]Ref. 18, IR spectrum.

TABLE 6. Observed and calculated frequencies (cm^{-1}) of the CH stretching vibration

Comp. (n)	$PtCl_2(C_nH_{2n-1}NH_2)_2$		$C_nH_{2n-1}NH_2$			Calc. asym./sym.
	IR	Raman	IR	Raman	Lit. (R)	
3	2999m	3000vs	2966vs	2969m	2965[a]	3055
					2975[b]	
4	2913sh	2914s		2912s	2910[c]	3014
5	2909sh	2905w	2911s	2923sh	2930[d]	2956
		2894w				
6		2896w	2902sh	2900m		2948
7		≈2880sh	2910sh	2908sh		2930
8		2879sh				2958

[a]Ref. 20. [b]Ref. 15, gas phase spectrum. [c]Ref. 16. [d]Ref. 17.

TABLE 7. Observed frequencies (cm^{-1}) of the Pt–N stretching vibration

Comp. (n)	$PtCl_2(C_nH_{2n-1}NH_2)_2$	
	IR	Raman
3	596s	595s
4	590sh	592s
	580s	580sh
5	542s	580w
6	536m	536m
		520w
7	522m	508m
		484sh
8	492w	494vw

TABLE 8. Observed frequencies (cm^{-1}) of the symmetric and asymmetric Pt–Cl stretching vibrations

Comp. (n)	$PtCl_2(C_nH_{2n-1}NH_2)_2$			
	Symmetric		Asymmetric	
	IR	Raman	IR	Raman
3	332s		301w	
	324s	326vs	296sh	296s
	319sh			
4	315s	314vs	282w	
	307sh		278sh	274s
5	328s		307sh	294vw
	321s	318s	287w	278w
	315s			266vw
6	331sh	338sh	290w	291w
	324s	327m		
		319m		
7	332sh	334m		
	321s	325s		295sh, br
	309sh	315m		
8	333sh		290sh	300sh
	320s	324s		274vw
	310sh			

the shift of ≈3 ppm reported for the NH protons. This is a consequence of the larger distances between the respective methine proton and the platinum central ion. The maxima of the broad resonances of the alkyl protons, and in particular their most deshielded contributions, are also shifted to lower fields in the complexes, as compared to the pure ligands. For compound **3** the shift has nearly the same value (0.5 ppm) as for the methine proton; for complexes with the higher homologous cycloalkylamines the effect is somewhat lowered to ≈0.3 ppm.

Vibrational spectra

Our interpretation of the vibrational spectra is based (i) on the assigned spectra of cyclopropylamine, cyclobutylamine, cyclopentylamine and cyclohexylamine given in the literature [15–18]; (ii) on the assignment of all observed IR and Raman active vibrations of the complex compound **3** given by Howard-Lock *et al.* [19]; and (iii) on the listing of vibrational frequencies for complex **4** reported by Lock and Zvagulis [20].

For the mentioned compounds, the frequencies detected in our IR and Raman spectra are in good agreement with the cited authors. For the remaining ligands (cyclohcptyl- and cyclooctylamine), assignments have been made by carefully monitoring and extrapolating the changes in frequency of the various vibrations over the entire homologous sequence. Spectra of complexes **4–8** have been interpreted, in an analogous fashion, both by a comparison with the ligand spectra, and by extrapolation from the assigned spectrum of complex **3**.

To further support our assignment, vibrational frequencies of the amine ligands have also been calculated using the semiempirical SCAMP program package. Results of these calculations are included in Tables 4–6. Deviations between the theoretical values and the measured frequencies are substantial, as has been noted for calculations using the SCAMP force field [14]; for example, the differences amount to ≈150 cm^{-1} for $\nu_{sym}(CH_2)$. However, within each type of vibration the relative changes in frequency over the entire series of homologous amines are in good agreement with the experiment, as may be seen, for example, for $\nu_{asym}(CH_2)$ in Table 4.

Vibrations involving the amino group

The frequencies observed for the NH_2 stretching and deformation vibrations of the amine ligands agree with typical values [28], expected for this class of compounds. The corresponding vibrations in complexes **3–8** exhibit a red shift both for the NH stretching and deformation modes, as a consequence of the coordination of the nitrogen atom to the platinum central ion. An explanation for this behaviour is given by Nakamoto [29]: the electron density at the coordinated N atom is lowered, and as a consequence the bond strength between N and H is decreased. This effect results in a higher red shift (≈140 cm^{-1}) for the stretching modes, as compared to the deformation modes (≈30 cm^{-1}). Fujita *et al.* [30] have reported similar values for $[M(NH_3)_6]^{3+}$ complexes, with M = cobalt, chromium and nickel. The vibrations involving the amino group apparently do not exhibit a significant dependence on the size of the alkyl ring, both in the platinum complexes and in the pure amine ligands.

C–H stretching vibrations

Frequencies observed for the CH_2 and the CH stretching modes of the pure amines are close to the available literature values [31]. The CH_2 as well as the CH stretching vibrations exhibit essentially the same fre-

quencies in complexes **4–8** as in the corresponding pure ligands (see Tables 4–6). This shows that, as expected, the coordination of the amines to the platinum ion has no effect on the CH_2 or CH stretching modes of the cycloalkyl part of the molecules.

Again, the three-membered ring takes an exceptional role. First, in the pure ligand the positions of the CH and CH_2 vibrations are shifted to higher energies as compared to the homologous amines, in agreement with Kalasinsky *et al.* [15]. Second, the CH stretching vibration further shifts from ≈ 2970 cm^{-1} for the pure amine to ≈ 3000 cm^{-1} in the complex. The symmetric CH_2 stretching vibration (as assigned by Howard-Lock *et al.* [19]) is also blue shifted from ≈ 3010 cm^{-1} for the amine to ≈ 3065 cm^{-1} in the complex.

It is interesting to analyze and compare the effects of complexation of cyclopropylamine on the C–H stretching frequency on the one hand, and on the NH chemical shielding on the other hand. The frequency ν(CH) is observed to *increase* upon complexation, as a consequence of the increased *total* charge at the corresponding carbon atom. On the other hand, the NH protons are *deshielded* as a consequence of a decreased *ring current* density, in addition to the deshielding effect of the metal atom.

We have attempted to analyze these observations in terms of our semiempirical AM1 calculations. As a calculation of the platinum complex is outside the scope of the parametrization used, we had to resort to simple models for representing the changes caused by the bonding of the nitrogen lone pair to the platinum ion. Our way to simulate this effect is to replace the NH_2 group by a substituent without a lone pair, e.g. by a CH_3 group or by a hydrogen atom.

The correlation of the methine C–H stretching frequency with the total charge at the corresponding carbon is illustrated first. The experimental values are $\tilde{\nu} = 2912$, 2969 and 3000 cm^{-1} in cyclobutylamine, cyclopropylamine and complex **3**, respectively. The total charge at the methine carbon is calculated as -0.042 e_0 in cyclobutylamine, -0.106 e_0 in cyclopropylamine, and -0.163 e_0 in methyl-cyclopropane. The calculated stretching frequencies are 3014, 3055 and 3140 cm^{-1}, in the same order.

The ring current in cyclopropane is a consequence of the 60° angles in the three-membered ring, and of the 'bent' carbon–carbon bonds [26]. If the coordinate system is chosen such that the ring coincides with the *xy* plane, the population of the p_x and p_y orbitals is indicative for the number of electrons available for a field induced ring current. The sum of the $2p_x$ and $2p_y$ orbital populations at the methine carbon amounts to 1.969 e_0 in cyclopropylamine and 1.954 e_0 in methylcyclopropane, in line with the deshielding of the amino protons observed upon complexation in compound **3**.

For the CH_2 deformation vibrations (1400–1460 cm^{-1}), no significant changes in band positions are observed upon complexation. A good agreement between experimental and calculated vibrational frequencies, with deviations of 5 to 25 cm^{-1}, has been found, see in 'Supplementary material'.

The 1400–600 cm^{-1} frequency range

This region of the spectra contains a large number of bands due to internal vibrations of the ligands, such as CH_2 deformation motions, CH bending, NH_2 and CH_2 twisting, wagging and rocking, C–N stretching vibrations, and ring deformations. For complex **3**, many of these bands have been assigned by Howard-Lock *et al.* [19]. With respect to the principal features, our spectra agree with those described for **3** [19]; therefore, only a few selected vibrations will be commented.

The breathing vibration of the cycloalkyl rings is characterized by a narrow, intense Raman band; see 'Supplementary material'. This band exhibits a continuous frequency decrease with increasing ring size, i.e. from 1214 cm^{-1} in cyclopropylamine to 696 cm^{-1} in cyclooctylamine. In the complexes, the ring breathing vibrations show an analogous shift from ≈ 1240 cm^{-1} in complex **3** to 700 cm^{-1} in complex **8** (see Fig. 4); other Raman active vibrations exhibit higher intensities in the complexes.

An intense absorption in the IR spectra in the range between 1210 and 1250 cm^{-1} is observed only for the platinum complexes, but not for the pure ligands. This band is assigned [19] to the NH_2 twisting vibration. The corresponding vibration of the pure ligand is a hindered rotation. The pure amines exhibit a broad absorption at ≈ 240 cm^{-1} which is assigned to this motion [16, 17, 19].

Several bands in the mid-frequency range are detected at similar wavenumbers for the complexes as for the ligands. This is due to the fact that the CH_2 group vibrations (twisting, wagging, rocking) should only be slightly influenced by the coordination of the molecule to the platinum ion. A detailed analysis of this frequency range would require deuteration experiments, and a comparison with calculated vibrational frequencies.

Low energy vibrations

For compound **3**, an assignment of the bands observed in this range has been given by Howard-Lock *et al.* [19]. The Pt–N stretching vibration (595 cm^{-1}), the Pt–Cl stretching vibrations (332 an 321 cm^{-1}), as well as the C–N–Pt deformation at 406 cm^{-1}, are observed only for the complex. Cyclopropylamine itself exhibits two absorptions in this range, at 410 and 254 cm^{-1}.

Most of the low energy vibrations have been assigned by a comparison of the spectra of the pure amines and

of the complexes; this is exemplified for cycloheptylamine and complex **7** in Fig. 5. In agreement with the bands assigned for its lower homologues [15–18], cycloheptylamine shows (Fig. 5, upper trace) a broad absorption at ≈ 270 cm^{-1} due to the NH_2 torsion, absorptions at 399 cm^{-1} and 470 cm^{-1} due to out of plane and in plane ring deformation motions involving the nitrogen atom, and further ring deformations at 447, 508 and 549 cm^{-1}. The spectrum of the corresponding complex **7** (Fig. 5, lower trace) is dominated by bands with a high vibrational dipole moment. The Pt–N stretching vibration at 522 cm^{-1} and a C–N–Pt deformation vibration at 427 cm^{-1} are clearly discerned. The ring deformation motions of the ligand are concealed by these strong bands.

The Pt–N stretching frequency (Table 7) exhibits an overall decrease with increasing ring size. However, this decrease is highly non-monotonic: the frequencies of **3** and **4** are very similar, whereas the frequencies of **5** and **6** are lower by ≈ 50 cm^{-1}. On proceeding to complexes **7** and **8**, the frequency further decreases. Obviously, this behavior can not be explained by simple arguments considering only the reduced mass of the ring. If one used complex **4** as a reference, the fact that the frequency for **3** increases less than expected from the masses of the cycloalkylamine rings, would imply that the amine ligands in **3** are less strongly bound.

The variation of the C–N–Pt deformation motion with ring size can be nicely followed in the IR spectra of the complexes in Fig. 2. The frequency first increases, from 407 to 427 cm^{-1}, in the sequence **3** → **7**, to exhibit a slight decrease to 425 cm^{-1} for **8**. A quantitative interpretation of this behavior is difficult: the strength of bonding, the mass of the rings, effects of steric hindrance, the volume of the unit cell, and other solid state effects may all play a role.

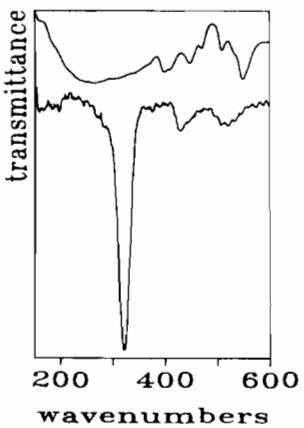

Fig. 5. IR spectra (600–150 cm^{-1} range) of cycloheptylamine (upper trace) and of *cis*-dichlorobis(cycloheptylamine)-platinum(II) (lower trace).

Platinum–chlorine vibrations

The intense absorption observed at ≈ 320 cm^{-1} in Fig. 2, which dominates the spectrum of all complexes in the 600–150 cm^{-1} region, is assigned to the symmetric Pt–Cl stretching vibration. The frequencies of this vibration are nearly constant (Table 8). The considerable width of this band (≈ 25 cm^{-1}) is due to a superposition of the three possible combinations of the two chlorine isotopes. The isotopic splitting is resolved for complex **5**, where three frequencies are clearly seen for the symmetric stretching vibration in Fig. 2 (scc Table 8). The relative band intensities deviate from the 9:6:1 ratio expected from the natural abundance of ^{35}Cl and ^{37}Cl. A similar deviation has been observed for **3** by Howard-Lock *et al.* [19], and has been attributed to the interference of an overtone of the Pt–Cl deformation.

Besides steric influences, the strength of the Pt–Cl bond is important for the rate of the reaction of the complexes with DNA. The hydrolysis of the Pt–Cl bond is the rate determining step of this reaction [7]. However, the Pt–Cl stretching frequency does not exhibit a significant dependence on the ring size of the ligand (Fig. 2). In detail, the frequency of ν_s(Pt–Cl) is highest for **3**; its lowest value, observed with **4**, is only smaller by 10 cm^{-1}. The results in Table 8 are in a good agreement with the frequencies reported for related complexes [32, 33]. For example, in $PtCl_2(NH_3)_2$ ('cisplatin') the symmetric Pt–Cl stretching vibration is observed at 330 and 323 cm^{-1} [32]. This similarity is in agreement with the similar length of the Pt–Cl bonds derived from X-ray diffraction: the bond length amounts to 2.32 ± 0.02 Å in complexes **3**, **4** and **6** [19, 20, 34] and in cisplatin [35]. From this observation, the bond strength between Pt and Cl appears to be similar for all the investigated complexes. The Pt–Cl deformation vibration, around 160 cm^{-1}, exhibits similar values for all compounds as well.

Conclusions

The homologous series of *cis*-dichlorobis-(cycloalkylamine)platinum(II) complexes has been characterized by ^1H NMR and vibrational spectroscopies. From the results, several conclusions on the properties of this class of antitumor compounds can be drawn.

Most of the observed vibrational bands of the complexes have been assigned. Several vibrational frequencies of the ligands are significantly shifted with respect to those of the corresponding pure amines. These shifts have been analyzed and interpreted with the help of semi-empirical AM1 calculations.

Among the ligands investigated, cyclopropylamine takes an exceptional role as a consequence of the strained geometry of the three-membered ring. The

'bent' bonds in the cyclopropane ring give rise to anisotropic ^1H chemical shielding effects, and to unusual values of the vibrational frequencies. Changes in these spectral parameters observed as a consequence of binding of cyclopropylamine to the Pt(II) ion are in good agreement with the predictions from semi-empirical calculations.

The Pt–N stretching frequency exhibits a general decrease with increasing ring size, as expected from the increased reduced mass. However, the decrease is non-monotonic, indicating that other factors (steric hindrance, lower Pt–N bond strength in the cyclopropylamine complex) are important as well.

From the constancy of the observed Pt–Cl stretching frequencies, the platinum–chlorine bond strength appears to be similar within the investigated series of compounds. This observation is interesting in view of the importance of the Pt–Cl bond strength for the binding of the complexes to DNA strands, which in turn is related to their antitumor activity. The latter was established to depend very strongly on the ring size [8–11]. The fact that $\tilde{\nu}$(Pt–Cl) is hardly influenced by the ring size, indicates that other factors have stronger consequences to the pharmacological properties. With increasing ring size, lipophilicity of the complexes increases and may facilitate the transport across the cellular membrane [36]. Steric requirements of the complexes are growing in the same sequence, with the consequence of more severe damage of DNA after formation of the platinum–DNA complex. These effects are consistent with the rise in antitumor activity observed with increasing cycloalkylamine ring size [11].

Additional spectroscopic investigations will be directed towards determining the mobilities of the cycloalkylamine ligands under physiological conditions, i.e. in aqueous media. To further elucidate the mechanisms of antitumor activity of the complexes, a study of the binding of these compounds to oligonucleotides or short DNA fragments is required.

Supplementary material

Infrared spectra of the complexes in the 3500–500 cm^{-1} range and Raman spectra of the ligands in the ranges 3450–2500 and 1500–200 cm^{-1} are available from the authors on request. A complete tabulation of the frequencies and assignments is also available. For the complexes, band positions observed for the C–N–Pt deformation motion {δ(C–N–Pt)}, as well as Pt–N and Pt–Cl deformation vibrations (in-plane and out-of-plane with respect to the plane of the ligands surrounding the platinum ion), are available in tables.

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