PREPARATION AND PROPERTIES OF (1,2-DIAMINOCYCLOHEXANE)-DICHLOROPLATINUM(II) COMPLEXES CONTAINING *cis* OR *trans* 1,2-DIAMINOCYCLOHEXANE

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The preparation and properties of (1,2-diaminocyclohexane)dichloroplatinum(II) complexes containing *cis* and *trans* 1,2-diaminocyclohexane were studied, and the separation of the isomers from their mixture was investigated. Separation in the form of the nickel(II) complexes was chosen with regard to its efficiency and to the possibility of obtaining directly the corresponding 1,2-diaminocyclohexane hydrochloride. Good quality products were obtained in a yield of more than 90% by reacting 1,2-diaminocyclohexane dihydrochloride with $K_2[PtCl_4]$ in aqueous solution, pH $\approx$ 10, in dark at room temperature.

(1,2-Diaminocyclohexane)dichloroplatinum(II), $[Pt(DACH)Cl_2]$ (DACH is 1,2- diaminocyclohexane), exhibits pronounced antitumor activity[1], and is frequently used as an intermediate in the preparation of similar platinum complexes containing various anionic ligands. The antitumor activity of this complex inspired the study[2] of a whole group of cytostatics containing 1,2-diaminocyclohexane. Moreover, our interest in the study of platinum complexes with *cis* and/or *trans* 1,2-diaminocyclohexane as neutral ligands, particularly of $[Pt(cis\text{-}DACH)Cl_2]$ and $[Pt(trans\text{-}DACH)Cl_2]$, was stimulated by the marked stereospecific effect of the DACH stereoisomers[3,4]. The purity of the complexes is a basic constraint in the obtaining of high-quality products from sequential synthesis. This is why our attention was directed to seeking for optimum conditions for the synthesis of the two complexes, including the separation of *cis* and *trans* DACH from their mixture.

The $[Pt(DACH)Cl_2]$ complexes can be prepared[5] at room temperature by reacting liquid DACH with $K_2[PtCl_4]$ in aqueous solution. However, the necessity to perform the experiments in dark using inert atmosphere (argon or nitrogen), relatively low yields (about 80%) obtained from time-consuming procedures (5 to 7 h), and a relatively low quality of the products are drawbacks. In the present paper we report on a method of preparation in which most of the drawbacks are eliminated[6].

EXPERIMENTAL

Chemicals. Potassium tetrachloroplatinate(II) was a commercial product of the LACHEMA Research Institute of Pure Chemicals in Brno. 1,2-Diaminocyclohexane, whose *cis*-DACH/*trans*-DACH ratio was 30/70 according to the manufacturer (Strem Chemicals), was distilled prior to use (b.t. 71·5—74·5°C at approximately 1·5 kPa). All the other analytical grade reagents (KOH, NaOH, HCl, K_2CO_3, $NiCl_2.6\,H_2O$) were chemicals of LACHEMA, Brno. Solvents (dichloromethane, dimethyl sulfoxide(d_5), methanol) were used without purification, or were dried by standard methods (ethanol, benzene).

Analytical procedures. Carbon, hydrogen and nitrogen in the solid samples were determined by elemental microanalysis on a Carlo Erba instrument. Chloride was determined by argentometric titration with potentiometric end point detection.

Instruments. Infrared spectra were measured on a Perkin–Elmer M-180 spectrophotometer in KBr disks (3 mg of sample in 300 mg of KBr) over the region of 4 000—600 cm^{-1}. Electronic spectra were measured on a Specord M 40 spectrophotometer (Carl Zeiss, Jena) in Nujol mulls (30 000—11 000 cm^{-1}) and in DMF solutions (37 000—11 000 cm^{-1}). ^1H NMR spectra were recorded on a Bruker 82 instrument in DMSO(d_5) (δ(DMSO) = 2·5), ^{13}C NMR spectra were scanned on a JEOL FX-100 spectrometer (δ(DMSO) = 39·5). The free bases in dichloromethane solutions were analyzed gas chromatographically using an 18 m column packed with 0·4% CW 20M.

Separation of DACH *isomers.* The following modification of the separation procedure[7] was used. Solution of $NiCl_2.6\,H_2O$ (26·0 g, 0·11 mol) in 440 cm^3 of methanol was added to a solution of freshly distilled DACH (25·0 g, 0·22 mol) in 160 cm^3 of methanol, and the mixture was stirred for 2 h. The yellow Ni(*cis*-DACH)Cl_2 complex was filtered out, washed with methanol, and dried in a vacuum. The filtrate was made acidic with dilute (1 : 1 v/v) HCl to pH < 4. Methanol was then removed on a rotary evaporator, and the aqueous solution obtained was used for precipitation of the light violet Ni(*trans*-DACH)$Cl_2.2\,H_2O$ complex, which was accomplished by dropwise addition of 15% NaOH until the appearance of the first portion of green $Ni(OH)_2$ precipitate. The Ni(*trans*-DACH)$Cl_2.2\,H_2O$ complex was filtered out, washed with water and dried in a vacuum.

Preparations of DACH *dihydrochlorides.* Ni(*cis*-DACH)Cl_2 (35·8 g, 0·1 mol) was added to 80 cm^3 of dilute (1 : 1 v/v) HCl, and the mixture was stirred until the complex was completely dissolved. The system was concentrated on a rotary evaporator at approximately 35°C to obtain a syrupy matter. After addition of a double amount of dry ethanol the mixture was allowed to crystallize, the crystals were filtered out, rinsed with a small volume of cold dry ethanol, and dried in a vacuum. Yield about 50% (m.t. 304—309°C, decomposition). For $C_6H_{16}Cl_2N_2$ (187·1) calculated: 37·90% Cl, 14·97% N; found: 37·74% Cl, 15·11% N.

Ni(*trans*-DACH)$Cl_2.2\,H_2O$ (39·4 g, 0·1 mol) was aded to 80 cm^3 of dilute (1 : 1 v/v) HCl and stirred at approximately 35°C for the complex to dissolve, and the resulting solution was allowed to crystallize. The crystals were collected, rinsed with a small volume of cold dry ethanol, and dried in a vacuum. Yield about 60% (m.t. 321—326°C, decomposition). Found: 38·24% Cl, 14·96% N.

Note: in both cases, additional amounts of the products could be reclaimed from the mother liquors after removing water by vacuum distillation of the azeotropic water–benzene–ethanol mixture, thereby replacing the solvent with ethanol.

Syntheses of the platinum complexes. DACH.2 HCl (1·6711 g) dissolved in 17·8 cm^3 of 1M-KOH was added to a solution of $K_2[PtCl_4]$ (2·1803 g) in 20 cm^3 of water. The mixture was adjusted to pH 10 and stirred in dark for 3—4 h to obtain a colourless solution over a precipitate. The product was filtered out, rinsed triply with water and triply with methanol, and dried in a dessicator over a molecular sieve.

[Pt(*cis*-DACH)Cl_2], light yellow, yield about 92%; ([Pt(*trans*-DACH)Cl_2], dark yellow, yield about 96%. For $C_6H_{14}Cl_2N_2Pt$ (380·2) calculated: 18·95% C, 3·71% H, 18·65% Cl, 7·37% N; found: [Pt(*cis*-DACH)Cl_2]: 18·75% C, 3·79% H, 18·45% Cl, 7·39% N; [Pt(*trans*-DACH)Cl_2]: 18·70% C, 3·75% H, 18·34% Cl, 7·34% N.

RESULTS AND DISCUSSION

The [Pt(*cis*-DACH)Cl_2] and [Pt(*trans*-DACH)Cl_2] complexes were studied with the aim to find the optimum conditions for reproducible synthesis of good-quality products from commercially available chemicals. This task includes the isolation of the *cis*- and *trans*-DACH isomers from their mixture and preparation of their platinum(II) complexes.

The direct synthesis of the complexes can be described by the equation[5]

$$K_2[PtCl_4] + DACH \rightarrow [Pt(DACH)Cl_2] + 2\,KCl \qquad (A)$$

The majority of drawbacks of this procedure is due to the sensitivity of the free ligand to air humidity, carbon dioxide, etc. Exposed to air, the colourless or slightly yellowish liquid turns rapidly brown, particularly in the presence of light or on slight heating. Various preparation procedures were tested for preventing the final products from becoming contaminated with the brown impurities. The best results (higher quality as checked by elemental analysis, higher yields, etc.) were obtained when liquid DACH was replaced with its hydrochloride. The procedure can be expressed by the equation

$$K_2[PtCl_4] + DACH.2\,HCl + 2\,KOH \rightarrow$$
$$\rightarrow [Pt(DACH)Cl_2] + 4\,KCl + 2\,H_2O \qquad (B)$$

The effects of the platinum(II)-to-DACH molar ratio, pH and other factors on the synthesis were studied. The optimum conditions established are as given in the Experimental.

Two methods, nearly equally efficient, are conventional for the separation of *cis*- and *trans*-DACH from their mixtures[7,8]. The simpler method[8] is based on the lower solubility of *trans*-DACH adipate as compared to *cis*-DACH adipate. The other method[7] relies on the selective formation of insoluble nickel(II) complex with *cis*-DACH. Although somewhat more tedious than the former, a modification of the latter approach was given preference in view of the possibility of preparing DACH.2 HCl directly from the nickel(II) complexes.

The spectral properties of [Pt(*cis*-DACH)Cl_2] and [Pt(*trans*-DACH)Cl_2] are presented in Table I. Bands 1 and 2 can be attributed[4,9-12] to the singlet–triplet spin-forbidden transitions ($^1A_1 \rightarrow {}^3A_2$ and $^1A_1 \rightarrow {}^3E$), whereas the other two bands can belong to spin-allowed transitions ($^1A_1 \rightarrow {}^1A_2$ and $^1A_1 \rightarrow {}^1E$). Data for [Pt.(*trans*-DACH)Cl_2] are in a good agreement with the results and conclusions presented in ref.[11]. The slightly lower intensities and small shifts of all bands to higher energies for [Pt(*cis*-DACH)Cl_2] can be explained[11] as a consequence of both equatorial and axial amino groups being present in this complex, as against the two equatorial amino groups in the [Pt(*trans*-DACH)Cl_2] complex.

The relatively narrow range of δ values of methine protons in the ^{1}H NMR spectrum of [Pt(*trans*-DACH)Cl_3] (Table II) is apparently due to the equivalence of those protons (both in axial orientation); in [Pt(*cis*-DACH)Cl_2] the methine protons are nonequivalent (axial and equatorial orientation). The separation of the signals of the methylene protons into two relatively well-resolved multiplets (6 + 2) is presumably due to the mutual spatial orientation of the cyclohexane and metallocycle rings. For DACH.2 HCl, on the other hand, the methylene proton signals are split into two well separated multiplets, each of them being due to four protons: 1·30–1·75 and 1·75–2·20 ppm for *cis*-DACH.2 HCl, and 1·20–2·00 and 2·00 to 2·40 ppm for *trans*-DACH.2 HCl. The ^{13}C NMR spectral data of the two complexes are given in Table III. Except for the unexplained occurrence of the majority of signals in doublets, the data – chemical shifts and $^3J_{Pt-C}$ interaction constants – are in a good agreement with those of the [Pt(DACH)$(NO_3)_2$] complexes[13]. As has been demonstrated[14], the $^3J_{Pt-C}$ values can be of assistance in establishing the mutual position of the β carbon and the five-membered metallocycle. For carbon

TABLE I

Electronic spectra of the [Pt(*cis*-DACH)Cl_2] and [Pt(*trans*-DACH)Cl_2] complexes in DMF solution and in Nujol mull

Band	[Pt(*cis*-DACH)Cl_2]			[Pt(*trans*-DACH)Cl_2]		
	DMF		Nujol	DMF		Nujol
	ν, cm^{-1}	log ε	ν, cm^{-1}	ν, cm^{-1}	log ε	ν, cm^{-1}
1	19 000	[a]	18 000	17 000	[a]	16 000
2	27 100	1·51	27 100	27 000	1·54	25 300
3	32 250	2·42	[b]	32 200	2·43	[b]
4	36 100	2·07	[b]	35 900	2·17	[b]

[a] Band is too weak. [b] Not measured.

atoms in the axial position the $^3J_{Pt-C}$ values should approach zero. The data found for [Pt(*cis*-DACH)Cl_2] in solutions suggest that the "average" values can be due to a dynamic exchange of carbon atoms in the equatorial and axial positions. In this relation it is noteworthy that the difference in the positions of spectral bands of the forbidden *d–d* transitions is significantly higher for Nujol mulls than for solutions (Table I).

The infrared spectra of the [Pt(*cis*-DACH)Cl_2] and [Pt(*trans*-DACH)Cl_2] complexes exhibit some differences in all spectral regions; most interesting is the 1 050 to 1 100 cm^{-1} range because the frequency of the ν(C—N) vibration depends appreciably on the position of the amino group with respect to the cyclohexane ring. The [Pt(*cis*-DACH)Cl_2] complex exhibits a strong band at 1 093 cm^{-1} and a very

TABLE II

^{1}H NMR spectra (ppm) of the [Pt(*cis*-DACH)Cl_2] and [Pt(*trans*-DACH)Cl_2] complexes in DMSO(d_5) solution

[Pt(*cis*-DACH)Cl_2]		[Pt(*trans*-DACH)Cl_2]		Assignment, character
δ	intensity	δ	intensity	
0·8—1·4	2 H	0·6—1·6	6 H	CH_2, m
1·4—2·0	6 H	1·6—2·0	2 H	CH_2, m
2·2—3·0	[a]	2·0—2·4	2 H	CH, m
4·2—6·5	4 H	4·2—6·5	4 H	NH_2, m

[a] Overlapped by the DMSO(d_5) signal.

TABLE III

^{13}C NMR spectra (ppm) of the [Pt(*cis*-DACH)Cl_2] and [Pt(*trans*-DACH)Cl_2] complexes in DMSO(d_5) solution at 40°C

[Pt(*cis*-DACH)Cl_2]		[Pt(*trans*-DACH)Cl_2]		Assignment
δ	$^3J_{Pt-C}$, Hz	δ	$^3J_{Pt-C}$, Hz	
57·58		61·15		C(α)
57·99		61·44		
25·34	32·5	31·37	61·4	C(β)
25·52	34·0	31·48	61·4	
19·49		23·76		C(γ)
20·95		—		

weak band at 1 065 cm^{-1}, whereas the [Pt(*trans*-DACH)Cl_2] complex displays a strong band at 1 061 cm^{-1} and a very weak band at 1 090 cm^{-1}. Thus, the bands at 1 061 and 1 093 cm^{-1} can be attributed to the stretching vibration of the equatorial and axial C—N bonds, respectively. Moreover, [Pt(*cis*-DACH)Cl_2] exhibits two strong bands at 784 and 727 cm^{-1} and a medium-intensity band at 882 cm^{-1}, which are absent from the spectrum of [Pt(*trans*-DACH)Cl_2]; they probably belong to bending vibrations of the NH_2 group and of the cyclohexane ring which, due to the steric conditions of the [Pt(*cis*-DACH)Cl_2] molecule in the crystal structure, should be more distorted.

With respect to the separation method employed it should be mentioned that none of the techniques used provided information on isomeric impurities in the complexes prepared. The purity of the free bases isolated from their hydrochloride salts was checked gas chromatographically. The contents found, viz. approximately 1% of the other isomer in the product, are to be considered as crude data only, because the method of isolation of the free bases from the salts (including, e.g., heating during distillation) can induce some isomerization reactions.

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