Coordination and *peri*-Carbon Metalation of 1-Nitro-9-[(2-aminoethyl)amino]acridines toward Platinum(II). Evidences for Hydrogen Bonding between Endocyclic N(10)H and Chloride Ion

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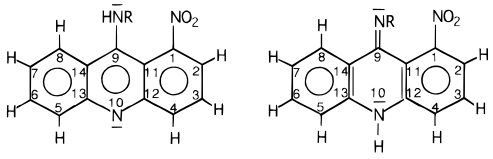
The antitumor drugs 1-nitro-9-[(2-(dialkylamino)ethyl)amino]acridines (alkyl = Me, A_1; Et, A_2) with platinum(II) give tridentate coordination compounds in which the two nitrogens of the ethylenediamine side chain and the C(8) carbon atom of the acridine ring system act as donor atoms. An excess of triphenylphosphine displaces the residual chloride coordinated to platinum but leaves unaltered the tridentate acridine ligand. The structures of [Pt(A_1-H)Cl], **1**, and [Pt(A_1-H)(PPh_3)]Cl, **3**, have been solved by single-crystal X-ray diffraction. **1**·$CHCl_3$ crystallizes in the orthorhombic system, space group $P2_12_12_1$ (no. 19), with $a = 8.715(1)$ Å, $b = 11.045(2)$ Å, $c = 22.609(4)$ Å, $Z = 4$, $R = 0.0559$, and $R_w = 0.0561$ for 1502 reflections with $F > 3\sigma(F)$. **3**·$^1/_2CH_2Cl_2$ crystallizes in the monoclinic system, space group $P2_1/c$ (no. 14), with $a = 13.418(3)$ Å, $b = 14.053(3)$ Å, $c = 18.918(4)$ Å, $\beta = 97.21(3)°$, $Z = 4$, $R = 0.0591$, and $R_w = 0.0611$ for 3608 reflections with $F > 4\sigma(F)$. In both complexes the acridine ligand adopts an imino-type configuration with the proton of the exocyclic 9-amino group shifted on N(10). Because of a severe steric interaction between the nitro group in the 1-position and the chelate diamine chain in the 9-position, the acridine moiety is folded about the C(9)−N(10) vector with an average angle between outer rings of 12°. Moreover, the acridine aromatic moiety and the platinum coordination planes are twisted, forming a dihedral angle of *ca.* 20°. The steric repulsion between the nitro and the diamine groups appears to provide the driving force to metalation. The H(10) proton has a great tendency to be engaged in H-bonding as shown by X-ray and solution studies. The formation of a H-bond with a rather poor acceptor such as the chloride ion can cause a downfield shift of the H-resonance as large as 6 ppm.

Introduction

The biological activity of acridines (essentially as antibacterial and antimalaric agents) has been known for many decades.[1] More recently, new interest has grown over these molecules since 1-nitro-9-(aminoalkyl)acridines possess anticancer properties,[2] and one of them, namely 1-nitro-9-[(3-(dimethylamino)-propyl)amino]acridine (commercial names: nitracrine and ledakrine), has also been used in clinical therapy.[2a,3] Nitracrine proved also to have potent hypoxia selective cytotoxicity *in vitro*,[4] and some substituted analogues showed hypoxia selective cytotoxicity also *in vivo*.[5]

When the nitro substituent shifts from the 1-position to another ring position (2, 3, or 4), the nitroaminoacridines lose their antitumor activity[6] (hypoxia selective cytotoxicity is retained by 4-nitro isomers).[7] Data, so far collected, strongly suggest that 1-nitro-9-(aminoalkyl)acridines undergo, *in vivo*, a metabolic activation which induces DNA cross-links and single-strand breaks while parent compounds themselves do not have such abilities.[7,8] There have been, though, several studies aimed to clarify the reasons for the unique behavior of 1-nitro-9-(aminoalkyl)acridines with respect to other isomers.

These molecules can exist in two tautomeric forms, amino and imino, depending upon the presence of a proton either on (C9)N or on N(10), and the composition of equilibrium changes with the position of the nitro substituent.



Amino Imino

The results of several X-ray studies[9] carried out on nitro-9-(aminoalkyl)acridines did show that the nitro group in the 1-position of the acridine ring system interacts strongly with the side chain in the 9-position, causing a folding of the acridine plane about the C(9)−N(10) vector (dihedral angle between outer rings of 13−22°) and preference for the imino-type

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configuration. In contrast, the nitro substituent in the positions 2 and 3 ensures planarity of the acridine moiety and amino-type configuration. In the imino tautomer the C(9)−N bond order increases with respect to that of the amino tautomer, and accordingly, the bond length becomes shorter.

Also in water solution, at physiological pH (7−8), 1-nitroacridines have the usual imino-type configuration while 2- and 3-nitroacridines are again present in the amino form.[10] The lower pK_a values observed for 1-nitroacridines as compared to those of 2-, 3-, and 4-nitro isomers go along with their preference for the imino tautomeric form.[7]

The presence of the imino tautomer appears to be relevant to the biological activity of these molecules. Hypoxia selective cytotoxicity is exhibited by 1- and 4-nitroacridines. In the latter case, in which an equilibrium between imino and amino tautomers is present, the cytotoxic activity appears to correlate with the percentage of imino tautomer.[11]

A greater anticancer activity has been found when the side chain in the 9-position bears a second amine functionality and two or three methylene spacers are placed in between the two nitrogens.[6] The diamine chain, with the two nitrogen atoms separated by two or three carbon spacers, is proposed to play a crucial role in the metabolic activation of such a drug.

These acridines are also amenable to coordination studies toward platinum. The diamine chain could act as a bidentate ligand toward platinum; in this way a powerful alkylating agent would be incorporated in the acridine molecule and a preliminary metabolic activation for its biological action could no longer be required.[12] Coordination to a metal atom is also likely to induce variations in the amino−imino tautomerism.

In this paper we report on the synthesis and structural characterization of some platinum(II) complexes with 1-nitro-9-[(2-(dialkylamino)ethyl)amino]acridines.

Experimental Section

Starting Materials. The complex [$PtCl_2(DMSO)_2$] was prepared according to ref 13. Dry chlorinated solvents were obtained by distillation from calcium hydride. 1-Nitro-9-[(2-(dimethylamino)ethyl)-amino]acridine, A_1, and 1-nitro-9-[(2-(diethylamino)ethyl)amino]acridine, A_2, were prepared according to ref 8b.

Preparation of Complexes. [PtCl(A_1-H)], 1. Compound **1** was prepared by reaction of [$PtCl_2(DMSO)_2$] with ligand A_1 in dry CH_2Cl_2 (in a typical experiment 1 mmol of both reagents and 10 mL of solvent were used). The mixture was refluxed for 4 h in an argon atmosphere to prevent contact with moist air. During the reaction time, the [$PtCl_2(DMSO)_2$] progressively dissolved and a deep red color developed. An excess of LiCl (2−3 mmol) was then added, and the mixture was kept stirring for an additional 2 h (the need for this step is commented on later in this section). The reaction solution was concentrated and then chromatographed over a silica gel column. The first yellow fraction, eluted with CH_2Cl_2, contained a few milligrams of the product of hydrolysis of A_1 to the corresponding 9-acridone. The main fraction was eluted with dichloromethane containing 3% (v/v) acetone. Evaporation to dryness under reduced pressure gave a dark red crystalline solid [PtCl(A_1-H)] which always contained some solvent of crystallization. Small amounts of other products could be eluted using higher contents of acetone (>10%, v/v), but they have not been identified at this stage of the work. The yield of desired product was 60% relative to platinum. Anal. Calcd for $C_{17}H_{17}ClN_4O_2Pt\cdot{}^1/_2CH_2Cl_2$: C, 36.1; H, 3.1; N, 9.6; Cl, 12.2. Found: C, 36.0; H, 3.2; N, 9.4; Cl, 12.0.

Table 1. Crystallographic Data for **1**·$CHCl_3$ and **3**·$^1/_2CH_2Cl_2$

	1·$CHCl_3$	**3**·$^1/_2CH_2Cl_2$
formula	$C_{18}H_{18}Cl_4N_4O_2Pt$	$C_{35.5}H_{33}Cl_2N_4O_2PPt$
a, Å	8.715(1)	13.418(3)
b, Å	11.045(2)	14.053(3)
c, Å	22.609(4)	18.918(4)
α, deg	90	90
β, deg	90	97.21(3)
γ, deg	90	90
V, Å^3	2176(1)	3539(2)
ρ_{calcd}, g·cm^{-3}	1.919	1.585
Z	4	4
fw	628.6	844.6
space group	$P2_12_12_1$ (no. 19)	$P2_1/c$ (no. 14)
T, °C	25	25
λ, Å	0.71073	0.71073
μ (Mo Kα), cm^{-1}	70.2	42.37
transm coeff	0.48, 0.93	0.54, 0.96
$R(F_o)^a$	0.0559	0.0591
$R_w(F_o)^b$	0.0561	0.0611

^{a} $R(F_o) = \sum||F_o| - |F_c||/\sum F_o$. ^{b} $R_w(F_o) = \sqrt{w}||F_o| - |F_c||/\sum\sqrt{w}$.

[PtCl(A_2-H)], 2. Compound **2** was prepared in a similar way as **1**. In this case, however, the acridine, A_2, was available as a dihydrochloride salt and the free base was formed *in situ* by addition of the stoichiometric amount of LiOH. In spite of the water formed in the neutralization reaction, the content of 9-acridone was almost as low as that in the previous case (probably the formed LiCl did act as a drying agent). Yield: 55%. Anal. Calcd for $C_{19}H_{21}ClN_4O_2Pt\cdot{}^1/_2CH_2Cl_2$: C, 38.4; H, 3.6 N, 9.2; Cl, 11.6. Found: C, 39.2; H, 3.9; N, 8.9; Cl, 11.2.

[Pt(A_1-H)(PPh_3)]Cl, 3. A 25 mg (0.04 mmol) sample of **1** was dissolved in 3 mL of dichloromethane and treated with a 3-fold excess of triphenylphosphine. The solution was kept stirring for 2 h at room temperature. Meanwhile, a color change from violet−red to orange−red took place. The solvent was evaporated under reduced pressure, and the solid residue was repeatedly washed with pentane to remove unreacted phosphine and then dried *in vacuo*. It proved to be the product of incorporation of one molecule of triphenylphosphine in **1**; the yield was quantitative. Anal. Calcd for $C_{35}H_{32}ClN_4O_2Pt$: C, 52.4; H, 4.0; N, 7.0; Cl, 4.4. Found: C, 52.6; H, 4.1; N, 6.8; Cl, 4.1.

Physical Measurements. Infrared spectra were recorded as KBr (in the range 4000−400 cm^{-1}) or polythene pellets (in the range 400−200 cm^{-1}) on a Perkin-Elmer 283 spectrophotometer. Proton NMR spectra were recorded on Varian XL 200 and Bruker AM 300 and AM 500 spectrometers.

X-ray Crystallography for 1. Crystals of **1** were grown from $CHCl_3$ solution. A well-formed red prism was selected for the X-ray analysis. Crystallographic data are listed in Table 1. Unit cell parameters were obtained by least-squares refinement of the values (in the range $2\theta = 10-25°$) of 28 carefully centered reflections chosen from different regions of the reciprocal space. On the basis of the systematic extinctions, the space group was selected as $P2_12_12_1$. This choice was in agreement with the analysis of the normalized structure factors which indicated a non-centrosymmetric space group ($|E^2 - 1| = 0.659, 0.736$ for non-centrosymmetric space groups, and 0.968 for

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Table 2. Fractional Atomic Coordinates ($\times 10^4$) for the Non-Hydrogen Atoms of **1**·$CHCl_3$

atom	*x*/*a*	*y*/*b*	*z*/*c*
Pt	3682(1)	4610(1)	2342(1)
Cl	4011(6)	3594(5)	1458(2)
O(1)	2123(19)	3888(14)	4141(7)
O(2)	3246(24)	4623(19)	4912(7)
N(1)	3307(20)	5329(15)	3128(6)
N(2)	5903(18)	4178(13)	2705(8)
N(3)	2470(20)	4711(17)	4473(8)
N(10)	−492(21)	7415(15)	3199(7)
H(10)	−1225(285)	8383(210)	3164(94)
C(1)	1673(23)	5874(17)	4356(8)
C(2)	1109(28)	6436(20)	4864(10)
C(3)	34(27)	7382(26)	4798(11)
C(4)	−422(25)	7710(20)	4234(9)
C(5)	−716(29)	7109(21)	2133(10)
C(6)	−261(28)	6539(22)	1619(11)
C(7)	972(26)	5696(18)	1636(10)
C(8)	1701(20)	5408(16)	2167(8)
C(9)	1985(20)	5834(15)	3225(8)
C(11)	1324(23)	6217(17)	3779(8)
C(12)	130(22)	7159(17)	3734(8)
C(13)	−43(23)	6821(20)	2686(10)
C(14)	1128(22)	5990(16)	2702(8)
C(15)	4681(22)	5205(20)	3557(9)
C(16)	6115(24)	5128(19)	3161(9)
C(17)	5952(27)	2980(19)	2958(11)
C(18)	7161(28)	4248(23)	2271(11)
Cl(1d)	4742(14)	1456(11)	4441(5)
Cl(2d)	2112(15)	21(10)	4708(9)
Cl(3d)	3462(15)	1534(13)	5572(4)
C(d)	3069(35)	1388(27)	4845(13)

centrosymmetric space groups). The structure amplitudes were obtained after the usual Lorentz-polarization reductions. The absorption correction was also performed, via the ψ-scan technique, by using four reflections: 1, 1, 6; 2, 6, 18; −1, −1, −4; and −2, −6, −16.

The structure was solved by Patterson and Fourier methods and refined by a full-matrix least-squares method on the basis of 1502 independent reflections with $F > 3\sigma(F)$. Since not all the H atoms could be located through the difference Fourier map, the AFIX instructions of SHELX-76[14] were employed to include in the refinement the remaining hydrogen atoms. The H atom linked to N(10) [H(10)] was located through the difference Fourier synthesis. The thermal parameters were refined to 0.1154, fixed at 0.06, Å^2, refined to 0.0920, and fixed at 0.08 Å^2 for aromatic, methylene, methyl, and chloroform (C)H's, respectively; the thermal parameter for H(10) was fixed at 0.06 Å^2. All these thermal parameters resulted to be higher than those of the C atoms to which the H atoms were connected.

The Pt, Cl, O, and N atoms were treated anisotropically, and all the C and H atoms were treated isotropically. The R and R_w agreement factors converged to 0.0559 and 0.0561, respectively. The weighted agreement factor R_w became 0.064 when a set of atomic coordinates, related to the previous one via the *-x*, *-y*, *-z* transformation, was used. As a consequence, the second set was rejected. The fractional atomic coordinates are reported in Table 2.

X-ray Crystallography for 3. Crystals of **3** were grown from CH_2Cl_2 solution. A very thin (*ca.* 0.15 × 0.20 × 0.03 mm) red plate was selected for the X-ray analysis and mounted on a glass fiber. Crystallographic data are listed in Table 1. Unit cell parameters were computed via least-squares refinement of the values (in the range $2\theta = 10-25°$) of 27 carefully centered reflections chosen from different regions of the reciprocal space. The space group $P2_1/c$ was selected on the basis of the systematic extinctions. This finding was in agreement with the analysis of the normalized structure factors which indicated a centrosymmetric space group ($|E^2 - 1| = 0.911$, 0.736 for non-centrosymmetric space groups, and 0.968 for centrosymmetric space groups). The structure amplitudes of 9793 reflections ($\pm h$, $\pm k$, l, 25 °C, $R_{int} = 0.035$ for 4850 equivalences) were obtained after the usual Lorentz-polarization reduction. The absorption correction was performed via the ψ-scan technique by using three reflections: 1, −4, 2; 3, −12, 8; and −1, 3, 2.

Table 3. Fractional Atomic Coordinates ($\times 10^4$) for the Non-Hydrogen Atoms of **3**·$^1/_2CH_2Cl_2$[a]

atom	*x*/*a*	*y*/*b*	*z*/*c*
Pt	2276(1)	2114(1)	1542(1)
Cl	9475(3)	1148(2)	1983(2)
P	3520(2)	1663(2)	2380(1)
O(1)	1415(9)	3714(7)	−556(6)
O(2)	−32(10)	4431(8)	727(6)
N(1)	1194(8)	2477(8)	733(5)
N(2)	1658(7)	3376(7)	2003(5)
N(3)	3479(12)	3715(9)	−676(6)
C(11P)	4759(8)	1555(7)	2088(5)
C(21P)	4859(10)	1623(9)	1363(7)
C(31P)	5814(10)	1524(9)	1134(8)
C(41P)	6657(9)	1354(10)	1639(8)
C(51P)	6537(9)	1334(9)	2344(8)
C(61P)	5602(9)	1433(9)	2581(8)
C(12P)	3206(8)	520(7)	2772(6)
C(22P)	2255(10)	381(8)	2866(7)
C(32P)	1961(12)	−455(11)	3180(8)
C(42P)	2697(12)	−1163(10)	3369(7)
C(52P)	3635(11)	−1033(9)	3258(7)
C(62P)	3931(10)	−204(9)	2973(7)
C(13P)	3811(8)	2421(8)	3172(6)
C(23P)	3473(10)	2194(8)	3812(6)
C(33P)	3610(13)	2870(11)	4377(7)
C(43P)	4072(12)	3724(11)	4297(8)
C(53P)	4434(11)	3935(11)	3665(8)
C(63P)	4291(9)	3274(9)	3090(8)
C(1)	−10(11)	2805(10)	−835(7)
C(2)	−763(13)	2768(12)	−1380(8)
C(3)	−1110(12)	1896(12)	−1645(8)
C(4)	−639(9)	1086(11)	−1421(7)
C(5)	2028(10)	−619(8)	−29(6)
C(6)	2768(9)	−634(9)	538(6)
C(7)	2931(9)	121(8)	1012(6)
C(8)	2406(8)	959(7)	911(5)
C(9)	1062(8)	1864(9)	189(6)
N(10)	661(7)	278(8)	−697(5)
H(10)	448(7)	−353(8)	−1005(5)
C(11)	430(10)	1953(9)	−484(7)
C(12)	140(9)	1086(9)	−865(6)
C(13)	1455(8)	209(9)	−145(6)
C(14)	1654(9)	997(7)	301(5)
C(15)	638(11)	3322(10)	826(7)
C(16)	624(10)	3432(10)	1616(7)
C(17)	2206(10)	4235(10)	1882(9)
C(18)	1509(12)	3315(12)	2773(6)
Cl(1d)[a]	7052(14)	1438(14)	4565(11)
Cl(2d)[a]	6043(10)	−458(9)	4414(7)
C(d)[a]	6747(27)	358(17)	5004(12)

[a] The occupancy factor of Cl and C atoms of the CH_2Cl_2 molecule was fixed at 0.5, whereas the C−Cl bond distances were fixed at 1.80 ± 0.03 Å via the AFIX instruction of SHELX-76.

The structure was solved through Patterson and Fourier methods and refined by a full-matrix least-squares method on the basis of 3608 independent reflections with $F > 4\sigma(F)$. Since only a few H atoms could be located via the difference Fourier map, the AFIX instructions of SHELX-76[14] were employed to include in the refinement the remaining H atoms of the acridine ligand.

The C−Cl distances of dichloromethane were fixed at 1.80 ± 0.03 Å, whereas the site occupation factors of the C and Cl atoms of dichloromethane were fixed at 0.5.

All the non-hydrogen atoms of the complex molecule and the Cl^- ion were refined anisotropically; the H atoms and the C and Cl atoms of CH_2Cl_2 were refined isotropically. The fractional atomic coordinates are reported in Table 3.

Results and Discussion

Coordination of the Acridine. 1-Nitro-9-[(2-(dialkylamino)-ethyl)amino]acridines (alkyl = Me, A_1; Et, A_2) react with

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Table 4. ^{1}H Chemical Shifts [δ, Downfield from $Si(CH_3)_4$; J(Pt−H) in Hz in Parentheses When Assignable] for Compounds **1**, **2**, and **3** and Ligands A_1 and A_2[a]

												R	
compound	solvent	H(2)	H(3)	H(4)	H(5)	H(6)	H(7)	H(8)	H(10)	$C(15)H_2$	$C(16)H_2$	CH_3	CH_2CH_3
A_1	$CDCl_3$	8.02	7.36	7.66	7.91[b]	7.50[c]	7.63[c]	7.81[b]		3.55	2.46	2.31	
1	$CDCl_3$	7.56	7.62	7.44	6.72	7.35	7.49[d]		8.02	3.75 (33)	3.03 (9)	2.86 (18)	
	$(CD_3)_2CO$	7.77[e]	7.80[e]	7.67[e]	6.83	7.27	7.32 (60)		10.80	3.77 (36)	3.13 (10)	2.79 (15)	
	CD_2Cl_2	7.60	7.66	7.51	6.78	7.35	7.32 (∼40)		8.16	3.75 (37)	3.03 (10)	2.82 (14)	
1 + Cl^-[f]	CD_2Cl_2	7.49	7.51	8.39	7.30	7.25	7.20 (40)		13.35	3.68 (37)	3.00 (9)	2.80 (12)	
3	CD_2Cl_2	7.67	7.69	8.65	7.55	6.76	6.12 (52)		14.50	3.66 (14)	3.01 (9)	2.22 (18)	
A_2·2HCl	$CDCl_3$	8.15	7.54	7.81	8.02[b]	7.43[c]	7.71[c]	8.06[b]		3.39	2.48		2.56 (CH_2)
													1.00 (CH_3)
2	$CDCl_3$	7.54	7.60	7.49	6.72	7.29	7.50		8.19	3.76 (32)	3.08		3.33 (CH_2)
													3.07 (CH_2)
													1.34 (CH_3)

[a] Numbering of atoms in the side chain: C(9)−N(1)−$C(15)H_2$−$C(16)H_2$−$N(2)R_2$ (R = CH_3, A_1 or CH_2CH_3, A_2). [b] The assignment for H(5) and H(8) can be reversed. [c] The assignment for H(6) and H(7) can be reversed. [d] Coupling with platinum obscured by overlapping signals. [e] Tentative assignment. [f] [**1**] = 1.8 mM, [Cl^-] = 4 mM.

$[PtCl_2(DMSO)_2]$ in anhydrous CH_2Cl_2 to give the compounds [Pt(A-H)Cl] (A = A_1, **1**; A_2, **2**) in good yield. The reaction cannot be performed in protic solvents since the alkaline conditions created by the acridine bases promote a ready hydrolysis at C(9) with conversion of the acridine into the corresponding acridone. The chemical formula, [Pt(A-H)Cl], indicates the presence of only one chloride ion per platinum atom and loss of a proton by the acridine moiety. ^{1}H NMR spectra (Table 4) gave clear indication of the coordination to the metal of both nitrogens of the side chain (numbering of atoms in the side chain: C(9)−N(1)−$C(15)H_2$−$C(16)H_2$−N(2)-R_2); the two methylene groups between the two nitrogens were both coupled with the metal ($^3J_{Pt,H} \approx 30$ and 10 Hz for C(15)-H_2 and $C(16)H_2$, respectively). The different coupling constants indicate that the two nitrogens are trans to ligands of different trans influence. One of them should be the chloride, and the other is presumably the carbon atom of a metalated acridine ring, most likely the C(8) atom which appeared to have lost its proton. In order to prove such a structure, complex **1** was reacted with excess triphenylphosphine which is known to displace coordinated amines but not covalently bound carbon atoms.[15] A new compound incorporating one molecule of PPh_3 was obtained (**3**), but contrary to our expectations, **3** appeared to keep the terdentate acridine ligand and substitute a phosphine ligand for the chloride ion. The lack of a coordinated chloride ligand was suggested by the absence, in the infrared spectrum, of any bands assignable to a Pt−Cl stretching vibration (ν_{Pt-Cl} = 310 cm^{-1} in **1**). Moreover, in the ^{1}H NMR spectrum of the new phosphine complex, the $C(15)H_2$ methylene group reduced its coupling with platinum to 14 Hz and showed, in addition, a $^4J_{P,H}$ of 4 Hz.

The Aromatic Moiety. The free ligands A_1 and A_2 exhibit, in deuteriochloroform, a ^{1}H NMR pattern for the aromatic protons which is in accord with the presence of the amino tautomer. It has already been reported that even 1-nitroacridines have a preference for amino-type configuration in organic solvents.[7]

In compound **1**, as a consequence of coordination, the aromatic protons shift upfield ($\Delta\delta \approx 0.5$ and 1.2 ppm for H(2) and H(5), respectively) in full agreement with the presence of the imino tautomer.[16] The lower multiplicity of the $C(15)H_2$ methylene resonance also indicates that the proton which in the free ligand was on N(1) is moved on N(10); this gives a singlet resonance at 8.16 ppm (CD_2Cl_2 solution).

In compound **2** the resonances of the aromatic protons fall in the same range as those of compound **1** with similar shifts with respect to those of the free ligand; moreover, a proton is localized on N(10) which gives a singlet resonance at 8.19 ppm ($CDCl_3$ solution). Therefore, also in this case the ligand has adopted the imino tautomeric form. At the working temperature (21 °C), the two ethyl substituents at N(2) are equivalent but the methylene protons exhibit a diastereotopic splitting indicating that the rotation about the N−ethyl bond is sufficiently slow for the methylene protons to experience different chemical environments.

In compound **3** ^{1}H NMR data (including a COSY experiment) also indicate that the acridine is in the imino form with a proton fixed on N(10). In this compound, however, there is a considerable spread in the resonance frequencies of the aromatic protons with respect to compound **1**. H(7) and H(6) are shifted upfield ($\Delta\delta \approx 1.2$ and 0.6 ppm, respectively) due to ring current effects of triphenylphosphine; a similar effect is suffered by the methyl groups on N(2) ($\Delta\delta \approx 0.6$ ppm). H(4) and H(5), on the contrary, have a considerable downfield shift ($\Delta\delta \approx 1.1$ and 0.8 ppm, respectively) with respect to their field position in **1**. The shift becomes dramatic for H(10) which resonates at 14.5 ppm as compared to the 8.16 ppm value of the corresponding proton in **1** (CD_2Cl_2 solution). The low-field shifts of H(4) and H(5) and particularly that of H(10) are far too big to be the consequence of the net positive charge of compound **3**. A better explanation can be found in a strong hydrogen bond involving N(10) and the chloride counterion;[17] this point will be discussed later on in this section.

X-ray Structure of 1. The metal atom is linked to the C(8) atom of the acridine moiety as well as to the N(1) and N(2) atoms of the exocyclic chain; a chloride ion completes the pseudo-square-planar coordination geometry (Figure 1 and Table 5). There are relatively high deviations from the mean plane defined by the donor atoms [Cl, −0.012(5); C(8), 0.18(2); N(1), −0.16(1); N(2), 0.12(1); Pt, 0.019(1) Å]. The Pt−N(1) [1.973-(15) Å] and Pt−N(2) [2.156(15) Å] bond distances differ from each other by more than 12 times the esd. This difference can be attributed to two main factors: (i) the different trans influence of the C(8) and Cl^- donors and (ii) the different hybridization of the nitrogen atoms [sp^2 for N(1) and sp^3 for N(2)]. The Pt−

(15) Onoue, H.; Mimami, K.; Naka Gawa, K. *Bull. Chem. Soc. Jpn*. **1970**, *43*, 3480. Maresca, L.; Natile, G.; Cattalini, L.; Gasparrini, F. *J. Chem. Soc., Dalton Trans.* **1975**, 1601.

(16) An overall upfield shift which is particularly significant for H(5) and for the proton ortho to the nitro group [H(2) in this case] is always observed on going from amino to imino tautomer.

(17) Bertolasi, V.; Gilli, P.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **1991**, *113*, 4917. Maresca, L.; Natile, G.; Fanizzi, F. P.; Stasi, F. *J. Am. Chem. Soc.* **1989**, *111*, 1492.

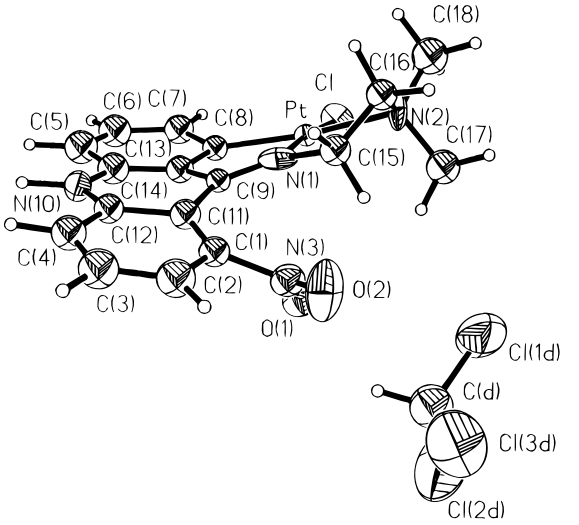

Figure 1. ORTEP drawing of complex **1** with the atom-labeling scheme. The ellipsoids enclose 50% probability.

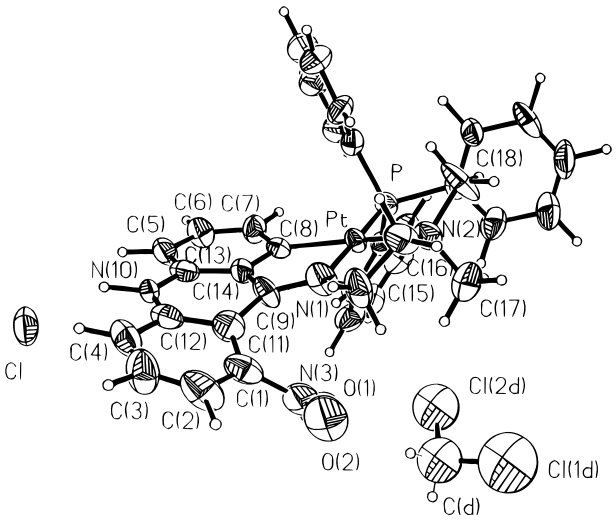

Figure 2. ORTEP drawing of complex **3** with the atom-labeling scheme. The ellipsoids enclose 50% probability. The labeling of the atoms of the PPh_3 ligand is omitted for clarity.

C(8) bond distance [1.978(17) Å] falls in the normal range.[18] As expected, one of the two five-membered chelates is nearly planar [torsion angles: Pt−C(8)−C(14)−C(9), −3(2); C(8)−C(14)−C(9)−N(1), 10(2), and C(14)−C(9)−N(1)−Pt, −12(2)°] while the second ring exhibits the usual puckering [torsion angles: Pt−N(1)−C(15)−C(16), 27(2); N(1)−C(15)−C(16)−N(2), −52(2), and C(15)−C(16)−N(2)−Pt, 50(2)°].

The aromatic moiety is folded along the C(9)−N(10) axis by 8.8(7)°. This value is, however, smaller than those found in uncomplexed molecules (range 13−22°).[9] The bond distances within the acridine system are mostly normal, but two bonds, C(8)−C(14) [1.46(3) Å] and C(11)−C(12) [1.48(3) Å], appear to be significantly longer. The imino configuration of the acridine ligand is confirmed by the presence of a proton on N(10) and by relatively high values of the N(10)−C(12) and N(10)−C(13) bond lengths [average 1.371(20) Å] and of the C(12)−N(10)−C(13) angle [122(2)°] (Singh rule).[19] Moreover the C(9)−N(1) bond distance [1.299(25) Å] is quite short, and the value is very close to the mean value reported for free acridines in the imino tautomeric configuration.

The steric repulsion between the nitro group and the side chain in *peri* positions [O(1)···C(15), 2.97(2); O(1)···H(15A), 2.31(4), O(1)···N(1), 2.97(2); N(3)···C(15), 2.88(2); N(3)···H-(15A), 2.37(4), and N(3)···N(1), 3.20(2) Å] appears to be responsible for the displacement of the two groups on opposite sides with respect to the acridine plane [torsion angles: O(1)−N(3)−C(1)−C(11), −35(3); N(3)−C(1)−C(11)−C(9), −21(3); C(1)−C(11)−C(9)−N(1), −20(3), and C(11)−C(9)−N(1)−C(15), −12(3)°]. As a consequence, the coordination plane (least-squares plane of the donor atoms) and the acridine plane (least-squares plane of the 14 atoms of the ring systems) make an angle of 22.7(3)° and the nitro group is twisted with respect to the acridine system by 42(1)° [this value is intermediate between those reported for the free base (60°) and for the protonated form (30°)].

The formation of a C(8)−N(1) chelate ring also causes a narrowing of the N(1)−C(9)−C(14) angle [112(2)°] and, consequently, an increasing of the complementary N(1)−C(9)−C(11) angle [129(2)°] which contributes to the release of steric hindrance between the substituents on C(1) and C(9).[20,21] The steric repulsion between the nitro group and the ethylenediamine side chain in *peri* positions appears to provide the driving force to the metalation reaction.

X-ray Structure of 3. The coordination geometry of complex **3** is very similar to that of **1** apart from a triphenylphosphine which has taken the place of the chloride ion (Figure 2 and Table 5). The phosphine ligand causes a lengthening of the trans Pt−N(1) bond [2.038(9) Å] which, however, remains significantly shorter than the Pt−N(2) bond [2.185(9) Å] trans to the carbon donor. The phosphine ligand also causes a slight lengthening of the two cis coordination bonds. In **3**, with respect to **1**, there is a slight contraction of bonds within the N(1)−N(2) chelating chain and a slight lengthening of bonds within the N(1)−C(8) chelating chain.

The acridine keeps the imino configuration with a proton on N(10). The imino configuration is also supported by the relatively large N(10)−C(12) and N(10)−C(13) bond distances [average value 1.374(15) Å] and the C(12)−N(10)−C(13) bond angle [123.9(10)°] (Singh rule).[19] The bond distances of the acridine system are mostly normal within the esd; significant differences, with respect to compound **1**, are a lengthening of the C(1)−C(11) bond and a slight contraction of the bonds within the C(1)−C(4) and C(5)−C(8) sequences.

The aromatic moiety is more bent in **3** than in **1**, the dihedral angle between outer rings being 16.1(5)° as compared to the value of 8.8(7)° found in compound **1**; in contrast the dihedral angle between the least-squares planes of the donor atoms and of the acridine system is slightly smaller in **3** [18.0(2)°] than in **1** [22.7(3)°]. Finally, the angle formed by the acridine system and the nitro group [43.7(9)°] is very similar to that found in the previous compound.

Intermolecular Interactions. Compounds **1** and **3** crystallize with one and one-half molecule of solvent per molecule of complex, respectively (chloroform in **1** and dichloromethane in **3**). The solvent of crystallization acts as a hydrogen bond donor with respect to the nitro group [O(1)···H(d) and O(1)···C-(d) distances are 2.33(5) and 3.29(3) Å in **1** and 2.33(5) and 3.29(3) Å in **3**, respectively]. The C···O contact distances in the range 3.31−3.57 Å have been reported for C−H···O (water) hydrogen bonding in 46 neutron diffraction crystal structures.[21]

(18) Orpen, A. G.; Brammer, L.; Allen, F. H.; Kennard, O.; Watson, D. G.; Taylor, R. *J. Chem. Soc., Dalton Trans.* **1989**, S1. Ceci, E.; Cini, R.; Karaulov, A.; Hursthouse, M. B.; Maresca, L.; Natile, G. *J. Chem. Soc., Dalton Trans.* **1993**, 2491.
(19) Singh, C. *Acta Crystallogr.* **1965**, *19*, 861.
(20) For uncoordinated 1-nitroacridines, the N−C(9)−C(11) angle has an average value of 116° in the free base and a value of 125° in N-protonated salts (see ref 9).
(21) Steiner, T.; Saenger, W. *J. Am. Chem. Soc.* **1993**, *115*, 4540.

Table 5. Bond Distances (Å) and Angles (deg) for the Atoms of **1**·$CHCl_3$ and **3**·$^1/_2CH_2Cl_2$[a]

	1·$CHCl_3$	**3**·$^1/_2CH_2Cl_2$		**1**·$CHCl_3$	**3**·$^1/_2CH_2Cl_2$
Pt-P		2.244(3)	Pt-C(8)-C(7)	132(1)	133.0(8)
Pt-Cl	2.311(5)		Pt-C(8)-C(14)	109(1)	109.7(7)
Pt-C(8)	1.978(17)	2.036(10)	C(8)-C(14)-C(9)	117(1)	117.7(9)
Pt-N(1)	1.973(15)	2.038(9)	N(1)-C(9)-C(14)	112(2)	114.1(9)
Pt-N(2)	2.156(15)	2.185(9)	N(1)-C(9)-C(11)	129(2)	129.0(11)
			Pt-N(1)-C(9)	118(1)	115.5(8)
C(8)-C(14)	1.458(26)	1.434(15)	Pt-N(1)-C(15)	114(1)	116.8(8)
C(14)-C(9)	1.408(26)	1.455(16)	C(9)-N(1)-C(15)	128(1)	127.7(10)
C(9)-N(1)	1.299(25)	1.337(15)	N(1)-C(15)-C(16)	106(1)	106.3(10)
N(1)-C(15)	1.548(26)	1.425(17)	C(15)-C(16)-N(2)	110(2)	110.9(10)
C(15)-C(16)	1.540(28)	1.505(17)	Pt-N(2)-C(16)	103(1)	102.9(7)
C(16)-N(2)	1.484(25)	1.487(16)	Pt-N(2)-C(18)	114(1)	116.5(8)
N(2)-C(17)	1.442(28)	1.447(17)	C(16)-N(2)-C(17)	112(2)	109.8(10)
N(2)-C(18)	1.473(29)	1.498(15)	C(16)-N(2)-C(18)	110(1)	104.6(10)
			Pt-N(2)-C(17)	112(1)	112.8(8)
C(1)-C(11)	1.392(27)	1.458(17)	C(17)-N(2)-C(18)	107(2)	109.5(12)
C(1)-C(2)	1.397(29)	1.352(21)			
C(2)-C(3)	1.410(34)	1.383(21)	C(11)-C(1)-C(2)	125(2)	122.6(14)
C(3)-C(4)	1.385(33)	1.344(20)	C(1)-C(2)-C(3)	118(2)	119.7(13)
C(4)-C(12)	1.371(28)	1.386(17)	C(2)-C(3)-C(4)	119(2)	120.8(13)
C(13)-C(5)	1.419(33)	1.397(16)	C(3)-C(4)-C(12)	123(2)	121.3(13)
C(5)-C(6)	1.379(32)	1.368(16)	C(13)-C(5)-C(6)	121(2)	117.8(11)
C(6)-C(7)	1.422(32)	1.388(16)	C(5)-C(6)-C(7)	120(2)	122.3(11)
C(7)-C(8)	1.395(28)	1.374(15)	C(6)-C(7)-C(8)	121(2)	121.9(11)
C(11)-C(9)	1.441(27)	1.442(17)	C(7)-C(8)-C(14)	117(1)	116.2(10)
C(12)-N(10)	1.355(26)	1.350(15)	C(11)-C(9)-C(14)	119(1)	116.8(10)
N(10)-C(13)	1.388(27)	1.398(15)	C(12)-N(10)-C(13)	122(2)	123.9(10)
C(11)-C(12)	1.475(28)	1.444(18)	C(12)-C(11)-C(9)	116(2)	117.4(11)
C(13)-C(14)	1.374(28)	1.398(15)	C(1)-C(11)-C(9)	130(2)	129.2(12)
			C(1)-C(11)-C(12)	114(2)	113.4(12)
C(1)-N(3)	1.484(26)	1.452(19)	C(4)-C(12)-N(10)	120(2)	119.9(12)
N(3)-O(1)	1.217(24)	1.247(15)	C(11)-C(12)-N(10)	119(2)	119.5(10)
N(3)-O(2)	1.205(24)	1.215(15)	C(11)-C(12)-C(4)	120(2)	120.6(12)
			C(5)-C(13)-C(14)	119(2)	120.4(10)
C(d)-Cl(1d)	1.722(31)	1.801(10)	N(10)-C(13)-C(14)	120(2)	117.8(10)
C(d)-Cl(2d)	1.753(32)	1.786(10)	N(10)-C(13)-C(5)	121(2)	121.8(11)
C(d)-Cl(3d)	1.687(30)		C(13)-C(14)-C(8)	122(2)	121.2(10)
			C(13)-C(14)-C(9)	120(2)	121.0(9)
Cl-Pt-C(8)	98.7(5)				
Cl-Pt-N(1)	174.3(4)		C(2)-C(1)-N(3)	114(2)	117.8(12)
Cl-Pt-N(2)	96.3(5)		C(11)-C(1)-N(3)	120(2)	118.9(12)
P-Pt-C(8)		94.5(3)	C(1)-N(3)-O(2)	119(2)	118.5(14)
P-Pt-N(1)		176.2(3)	C(1)-N(3)-O(1)	115(1)	117.1(11)
P-Pt-N(2)		103.5(3)	O(2)-N(3)-O(1)	126(2)	124.1(14)
C(8)-Pt-N(1)	81.7(7)	82.2(4)			
C(8)-Pt-N(2)	163.4(6)	161.1(4)			
N(1)-Pt-N(2)	84.0(7)	80.0(4)			

[a] Distances and angles for the PPh_3 ligand of **3** are reported in Table S4.

Stacking interactions are practically absent even though the acridine moieties are piled almost perpendicular and parallel to the [110] plane in **1** and almost parallel to the [101] plane in **3** (Figures 3 and 4 of the supporting information, respectively). The folding of the acridine ring system associated with displacements on opposite sides of the acridine plane of the substituents in 1- and 9-positions (the NO_2 group and the metal coordinated alkyl chain) appears to prevent such a stacking interaction.

If stacking interactions are absent, intermolecular hydrogen bonding interactions are extensive in both compounds. In **1** the chloro ligand is hydrogen bonded to N(10) and C(2) atoms of different molecules [N(10)···Cl, 3.421(15); C(2)···Cl, 3.61-(1) Å]. In **3**, in which the chloride is a free anion, the N(10)···Cl contact becomes very close [3.14(1) Å].

H-Bonding in Solution. The tendency of H(10) to be engaged in hydrogen bonding is supported not only by crystal packing studies but also by NMR data.

In compound **3** the H(10) resonance occurs 6 ppm downfield with respect to compound **1**; a persistence in solution of the strong N(10)H···Cl hydrogen bond, observed in the solid state, is a likely and attractive explanation.

To prove this hypothesis the ^1H NMR spectrum in CD_2Cl_2 solution of **1** was monitored in the presence of an equimolar amount of tetrabutylammonium chloride. The proton resonance of N(10), initially at 8 ppm, shifted to 12 ppm (downfield from TMS). The same resonance was shifted further downfield (to 13 ppm) when the amount of chloride in solution was doubled. Therefore the 6 ppm difference in H(10) chemical shift between **1** and **3** is only due to the availability, in the latter case, of a chloride counterion in solution which can act as a H-bonding acceptor. H-bonding with the solvent could also explain the 2.5 ppm downfield shift of H(10) resonance observed when the NMR spectrum of **1** was taken in acetone instead of chloroform. In recent years there has been a number of reports concerned with H-bonding association in different solvents between two neutral or a neutral and a charged species, some of them involving a chloride ion.[22] In connection with this it is worth

(22) Miura, K.; Tanaka, M.; Fukui, H.; Toyama, H. *J. Phys. Chem.* **1988**, *92*, 2390. Barcza, L.; Lenner, L. *J. Pharm. Sci.* **1988**, *77*, 622. Dieter, K. M.; Dymek, C. J., Jr.; Heimer, N. E.; Rovang, J. W.; Wilkes, J. S. *J. Am. Chem. Soc.* **1988**, *110*, 2722. Dymek, C. J., Jr.; Stewart, J. P. *Inorg. Chem.* **1989**, *28*, 1472. Avent, A. G.; Chaloner, P. A.; Day, M. P.; Seddon, K. R.; Weton, T. *J. Chem. Soc., Dalton Trans.* **1994**, 3505.

mentioning the stabilization effect by chloride ions in certain organic-protonated bases. For instance, the diprotonated tetrapyridylpyridazine assumes a distorted structure with Cl^- as counterions while substitution of tetraphenylborate for chloride ion causes collapsing to a quasi planar structure with intramolecular N−H···N hydrogen bonds.[23] Similarly, chloride counterions stabilize the diprotonated form of 5,10,15,20-tetraphenylporphirine *via* association into tight contact ion pairs.[24] The N−H···Cl hydrogen interaction is also thought to be crucial in stabilizing the bis(dithiooxamide)platinum(II) dication.[25]

Conclusions

The severe steric interactions between the 1-nitro and the 9-alkylamino groups in the *peri* positions of the acridine ring system, which are responsible for the imino-type configuration and folding about the C(9)−N(10) vector of the 1-nitro-9-[(2-aminoethyl)amino]acridines and possibly their antitumor activity, are also responsible for their unexpected reactivity toward platinum.

Coordination to platinum of the 9-(2-aminoethyl)amino chain is accompanied by a simultaneous metalation reaction which prevents the obtainment of the simple N-coordinated product. A metalation reaction in such bland conditions has not been observed with strictly related ligands which also can give tricoordinate (N,N,C) species.[26] The steric repulsion between the 1-nitro and the 9-(2-aminoethyl)amino groups, enhanced by the imino-type configuration of the acridine which forces the sp^2-hybridized N(1) moiety to be coplanar with the acridine ring system, brings the platinum atom very close to C(8)H, thus providing a driving force to metalation. Moreover in the metalated species, because of the constraints within the chelate ring, the N(1)−C(9)−C(14) angle is narrowed (112°), and consequently the complementary N(1)−C(9)−C(11) angle becomes larger (129°) and contributes to some release of steric hindrance between the substituents in C(1) and C(9). The steric interaction, however, remains rather large and promotes a 20° rotation of the coordination plane with respect to the acridine plane.

Coordination appears to stabilize the imino tautomer with a proton on N(10). It is to be noted that also the unsubstituted 9-aminoacridine, when coordinated to platinum through its exocyclic nitrogen atom, was found to adopt the imino tautomeric form.[27] If the imino tautomerism of 1-nitroacridines has some relevance to their antitumor activity, the coordination of a platinum atom to the 9-(2-aminoethyl)amino chain would be beneficial.

The H(10) proton has a great tendency to be engaged in hydrogen bonding as shown by X-ray and solution studies. The H-bond formation can cause a downfield shift of the H-resonance as large as 6 ppm.

Finally, the toxicity of these complexes in which the platinum moiety is not tethered but is incorporated in the intercalator moiety appears to be comparable to that of the free acridines.

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Supporting Information Available: Full table of crystallographic data (Table S1), full list of atomic coordinates [Tables S2 (**1**) and S3 (**3**)], bond distances and angles for the phosphine ligand in **3** (Table S4), listing of thermal parameters [Tables S5 (**1**) and S6 (**3**)], and crystal packing diagrams [Figures 3 (**1**) and 4 (**3**)] (10 pages). Ordering information is given on any current masthead page.

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