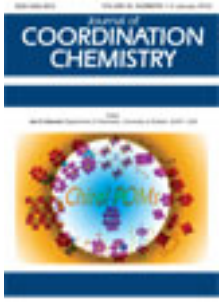


Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

Synthesis and solution structures of some platinum(II) complexes containing chelating safrole and amine

Tran Thi Da [a], Le Xuan Chien [a], Nguyen Thi Thanh Chi [a], Le Thi Hong Hai [a] & Nguyen Huu Dinh [a]

[a] Department of Chemistry, Hanoi National University of Education, 136 Xuanthuy Street, Caugiay, Hanoi, Vietnam

Published online: 14 Dec 2011.

To cite this article: Tran Thi Da, Le Xuan Chien, Nguyen Thi Thanh Chi, Le Thi Hong Hai & Nguyen Huu Dinh (2012) Synthesis and solution structures of some platinum(II) complexes containing chelating safrole and amine, Journal of Coordination Chemistry, 65:1, 131-142, DOI: 10.1080/00958972.2011.643789

To link to this article: http://dx.doi.org/10.1080/00958972.2011.643789

Journal of Coordination Chemistry
Vol. 65, No. 1, 10 January 2012, 131–142

Taylor & Francis
Taylor & Francis Group

Synthesis and solution structures of some platinum(II) complexes containing chelating safrole and amine

TRAN THI DA*, LE XUAN CHIEN, NGUYEN THI THANH CHI, LE THI HONG HAI and NGUYEN HUU DINH

Department of Chemistry, Hanoi National University of Education, 136 Xuanthuy Street, Caugiay, Hanoi, Vietnam

(*Received 25 August 2011; in final form 24 October 2011*)

Reaction of the dinuclear chelate ring complex $[Pt_2Cl_2(Saf\text{-}1H)_2]$, Saf-1H: deprotonated safrole, with various amines afforded *cis*-[Pt(Saf-1H)(Am)Cl], Am: NH_3 (**1**), Me_2NH (**2**), Et_2NH (**3**), morpholine (**4**), cyclohexylamine (**5**), benzylamine (**6**), aniline (**7**), *o*-toluidine (**8**), *m*-toluidine (**9**), *p*-toluidine (**10**), pyridine (**11**), 2-aminopyridine (**12**), and quinoline (**13**). The ^{1}H NMR and nuclear overhauser effect spectroscopy (NOESY) spectra of the reported complexes were accurately analyzed. NOESY spectra show that the complexes have a *cis*-configuration, in which the alkyl and aryl groups of coordinated amines are in proximity to the allyl group of chelating safrole. Complexes **11**, **12**, and **13** exhibit inhibitory activities on human cancer cells HepG2 and Lu with $IC_{50} = 2.5\text{–}5.0\ \mu g\,mL^{-1}$.

Keywords: Platinum(II) complex; Safrole; *trans* Effect; ^{1}H NMR

1. Introduction

Safrole (4-allyl-1,2-methylendioxybenzene) from sassafras oil (*Ocotea pretiosa* Mer., *Lauraceae*) has interesting functionality and chemical reactivity suggesting its use as an efficient and versatile natural synthon [1, 2]. Safrole has been chemically transformed into numerous biologically active compounds [3–5]. One important example is its isomerization into isosafrole followed by oxidation, which produces piperonal (3,4-methylenedioxybenzaldehyde). Piperonal is a compound commonly used in flavor, fragrance industry, and an intermediate to L-Dopa (L-3,4-dihydroxyphenylalanine) [6], used in the treatment of Parkinson disease, and to methyldopa (α-methyl-3,4-dihydroxyphenylalanine), used as an anti-hypertensive agent [7].

Platinum-based drugs, notably cisplatin, carboplatin, and oxaliplatin, have dominated the treatment of various cancers. However, since these drugs cause serious side effects, chemists are looking into other platinum complexes as potential anticancer agents. Studies over the past two decades have shown a range of platinum complexes with useful cytotoxicity and anti-tumor activity not strictly limited to structural analogs of cisplatin. Most of the well-known platinum anticancer complexes have

*Corresponding author. Email: datransp@yahoo.com

ISSN 0095-8972 print/ISSN 1029-0389 online © 2012 Taylor & Francis
http://dx.doi.org/10.1080/00958972.2011.643789

amines as ligands. Platinum coordination compounds comprising of at least one amine and the use of such compounds in the treatment of cancer have been previously described [8–11].

Considering these findings, we have decided to synthesize some platinum(II) complexes containing safrole (a natural arylolefin) and an amine, and to investigate whether the resulting compounds have useful cytotoxicity.

2. Experimental

2.1. *General and instrumental*

Elemental analysis: Pt was analyzed according to the weight method [12] and C and H were analyzed on a LECO CHNS model 932 elemental analyzer. Infrared (IR) spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs from 400 to 4000 cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE 500 MHz, at 298–300 K, with TMS as the internal standard in a suitable solvent (tables 1 and 2). The anticancer activities were tested at the Experimental Biological Laboratory – Institute of Chemistry of Natural Compounds (in Hanoi), according to the described method [13]; IC_{50} values were calculated based on OD values taken on an Elisa instrument at 515–540 nm.

2.2. *Preparation*

2.2.1. [Pt(Saf-1H)(NH_3)Cl] (1). 0.1 mL (1.3 mmol) concentrated ammonia was added to a mixture of 392 mg (0.5 mmol) [Pt_2(Saf-1H)$_2Cl_2$] (previously prepared [14]) and 10 mL ethanol. The mixture was stirred at room temperature for an hour and then the resulting solution was cooled to 0°C. The crystalline compound obtained was isolated by filtration and washed with a solution of water and cold acetone. The crude product was recrystallized from acetone to afford the product as light yellow crystals (212 mg, 52%). Anal. Calcd for [$PtC_{10}H_{12}NO_2Cl$]: Pt, 47.73; C, 29.37; H, 2.94. Found: Pt, 47.48; C, 29.03; H, 3.16. IR (cm^{-1}): 3327, 3214, 3151 (ν_{NH}); 3020, 2960, 2891 (ν_{CH}); 1627 (δ_{NH}); 1590, 1497 (aromat. $\nu_{C=C}$). ^{1}H NMR: see tables 1 and 2.

2.2.2. [Pt(Saf-1H)(Me_2NH)Cl] (2). This complex was prepared starting from 392 mg (0.5 mmol) [Pt_2(Saf-1H)$_2Cl_2$] and 1.1 mmol dimethylamine according to the procedure for preparation of **1**. Recrystallization from ethanol/acetone 2 : 1 by volume gave light yellow crystals (262 mg, 60%). Anal. Calcd for [$PtC_{12}H_{16}NO_2Cl$]: Pt, 44.67; C, 32.99; H, 3.66. Found: Pt, 44.29; C, 33.24; H, 3.85. IR (cm^{-1}): 3275 (ν_{NH}); 3060, 3010, 2981, 2852 (ν_{CH}); 1597, 1496 (aromat. $\nu_{C=C}$). ^{1}H NMR: see tables 1 and 2.

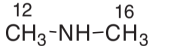
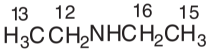
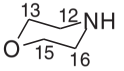
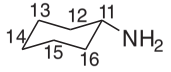
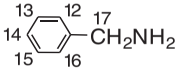
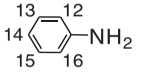
2.2.3. [Pt(Saf-1H)(Et_2NH)Cl] (3). This complex was prepared starting from 392 mg (0.5 mmol) [Pt_2(Saf-1H)$_2Cl_2$] and 1.1 mmol diethylamine according to the procedure for preparation of **1**. Recrystallization from ethanol/acetone 2 : 1 by volume gave light yellow crystals (302 mg, 65%). Anal. Calcd for [$PtC_{14}H_{20}NO_2Cl$]: Pt, 41.98; C, 36.17;

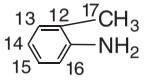
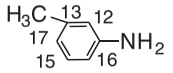
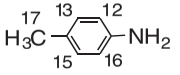
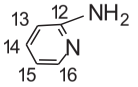
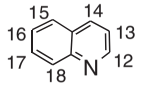
Table 1. The resonances of safrole protons in **1**–**13**, δ (ppm), J (Hz).

Complex*	H3	H6	H7a; H7b	H8a	H8b	H9	*trans*-H10	*cis*-H10
1[a]	6.56 s	6.79 s; $^3J_{PtH}$ 40	5.77 s; 5.78 s	2.56 d; ^2J 17; $^3J_{PtH}$ 110	3.51 dd; ^2J 17; ^3J 5.5	4.80 m; $^2J_{Pt\ H}$ 75	3.48 d; ^3J 13.5	3.96 d; ^3J 7.5; $^2J_{PtH}$ 75
2[a]	6.51 s	6.95 s; $^3J_{PtH}$ 40	5.76 d; ^2J 1.5; 5.77 d; ^2J 1.5	2.58 d; ^2J 17; $^3J_{PtH}$ 105	3.60 dd; ^2J 17; ^3J 5.0	4.74 m; $^2J_{PtH}$ 75	3.61 dd; ^2J 13; ^3J 5.0; $^2J_{PtH}$ 72	3.86 d; ^3J 7.5; $^2J_{PtH}$ 75
3[a]	6.51 s	6.98 s; $^3J_{PtH}$ 40	5.76 d; ^2J 1.5; 5.77 d; ^2J 1.5	2.58 d; ^2J 17; $^3J_{PtH}$ 110	3.60 dd; ^2J 17; ^3J 5.5	4.63 m; $^2J_{PtH}$ 75	3.64 dd; ^3J 13; ^4J 1; $^2J_{PtH}$ 75	3.79 d; ^3J 8; $^2J_{PtH}$ 75
4[a]	6.49 s	6.92 s; $^3J_{PtH}$ 40	5.76 d; ^2J 1.0; 5.77 d; ^2J 1.0	2.58 d; ^2J 17; $^3J_{PtH}$ 110	3.59 dd; ^2J 17; ^3J 5.5	4.77 m; $^2J_{PtH}$ 75	3.62 dd; ^3J 13; ^4J 1; $^2J_{PtH}$ 75	3.94 d; ^3J 7.5; $^2J_{PtH}$ 75
5[a]	6.50 s	6.97 s; $^3J_{PtH}$ 40	5.75 d; ^2J 1.5; 5.77 d; ^2J 1.5	2.58 d; ^2J 17; $^3J_{PtH}$ 105	3.59 dd; ^2J 17; ^3J 5.5	4.73 m; $^2J_{PtH}$ 75	3.58 d; ^3J 12; $^2J_{PtH}$ 75	3.93 d; ^{3}J 7.5; $^2J_{PtH}$ 75
6[a]	6.54 s	6.83 s; $^3J_{PtH}$ 40	5.78 s; 5.79 s	2.48 d; ^2J 17	3.40 dd; ^2J 17; ^3J 5.5	4.47 m; $^2J_{PtH}$ 70	3.42 d; ^3J 13; $^2J_{PtH}$ 70	3.89 d; ^3J 8; $^2J_{PtH}$ 70
7[a]	6.46 s	6.92 s; $^3J_{PtH}$ 40	5.75 d; ^2J 1.5; 5.77 d; ^2J 1.5	2.48 d; ^2J 17; $^3J_{PtH}$ 105	3.45 dd; ^2J 17; ^3J 5.5	4.36 m; $^2J_{PtH}$ 75	3.52 d; ^3J 13; $^2J_{PtH}$ 75	3.72 d; ^3J 8; $^2J_{PtH}$ 75
8[a]	6.45 s	6.93 s; $^3J_{PtH}$ 40	5.75 d; ^2J 1; 5.77 d; ^2J 1	2.44 d; ^2J 17; $^3J_{PtH}$ 110	3.43 dd; ^2J 17; ^3J 5.5	3.96 m; $^2J_{PtH}$ 75	3.47 d; ^3J 13; $^2J_{PtH}$ 70	3.38 d; ^3J 8; $^2J_{PtH}$ 70
9[b]	6.46 s	7.01 s; $^3J_{PtH}$ 40	5.78 d; ^2J 1; 5.81 d; ^2J 1	2.41 d; ^2J 17; $^3J_{PtH}$ 110	3.55 dd; ^2J 17; ^3J 5.5	4.14 m; $^2J_{PtH}$ 75	3.67 d; ^3J 13; $^2J_{PtH}$ 70	3.41 d; ^3J 8; $^2J_{PtH}$ 70
10[b]	6.45 s	7.00 s; $^3J_{PtH}$ 40	5.79 d; ^2J 1; 5.81 d; ^2J 1	2.41 d; ^2J 17; $^3J_{PtH}$ 110	3.54 dd; ^2J 17; ^3J 5.5	4.14 m; $^2J_{PtH}$ 75	3.66 d; ^3J 13; $^2J_{PtH}$ 70	3.41 d; ^3J 8; $^2J_{PtH}$ 70
11[b]	6.54 s	7.10 s; $^3J_{PtH}$ 40	5.80 d; ^2J 1; 5.83 d; ^2J 1	2.65 d; ^2J 17; $^3J_{PtH}$ 110	3.81 dd; ^2J 17; ^3J 5.5	4.65 m; $^2J_{PtH}$ 75	3.98 d; ^3J 13; $^2J_{PtH}$ 75	3.66 d; ^3J 8; $^2J_{PtH}$ 75
12[a]	6.54 s	7.01 s; $^3J_{PtH}$ 42	5.78 d; ^2J 1; 5.80 d; ^2J 1	2.71 d; ^2J 17; $^3J_{PtH}$ 110	3.77 dd; ^2J 17; ^3J 5.5	4.75 m; $^2J_{PtH}$ 75	3.83 d; ^3J 13; $^2J_{PtH}$ 75	3.73 d; ^3J 8; $^2J_{PtH}$ 75
13[a]	6.58 s	7.00 s; $^3J_{PtH}$ 41	5.81 d; ^2J 1; 5.83 d; ^2J 1	2.70 d; ^2J 17; $^3J_{PtH}$ 105	3.84 dd; ^2J 17; ^3J 5.5	4.76 m; $^2J_{PtH}$ 75	3.93 d; ^3J 11; $^2J_{PtH}$ 75	3.69; m; [br.] –

*Solvent, [a]CD_3COCD_3; [b]$CDCl_3$; br.: broadened.

Table 2. The coordinated amines and their NMR signals in **1–12**, δ (ppm), J (Hz).

Complex	Am	NH	H12	H13	H15	H16	Other
1[a,*]	NH_3	4.88 s; 1H; 3.07 s; 2H	–	–	–	–	–
2[a]		2.86 br. s	2.57 d; ^3J 6	–	–	2.60 d; ^3J 6	–
3[a]		3.35 br. s	2.95 m	1.36 t; ^3J 7	1.96 t; ^3J 7	3.08 m	–
4[a]		3.73 br. s	H12a: 3.26 qd; ^2J 13; $^3J_{aa}$ 12; $^3J_{ae}$ 2; H12e: 2.91 d; ^2J 12	H13a: 3.63 td; ^2J 13; $^3J_{aa}$ 12; $^3J_{ae}$ 2; H13e: 3.79 dd; ^2J 12; $^3J_{ae}$ 3	H15a: as H13a, H15e: as H13e	H16a: as H12a H16e: 2.94 d; ^2J 12	–
5[a]		3.22 br. s; 3.26 br. s	H12a: 1.30 m; H12e: 2.18 m	H13a: 1.25 m; H13e: 1.76 m	H15a: as H13a, H15e: as H13e	H16a: as H12a H16e: as H12e	H11: 2.99 m; H14a: 1.13 m; H14e: 1.63 m
6[a]		4.09 m; 4.11 m	7.45 d; ^3J 7.5	7.36 t; ^3J 7.5	7.36 t; ^3J 7.5	7.45 d; ^3J 7.5	H14: 7.30 t; ^3J 7.5; H17: 3.87 t; ^3J 7
7[a]		5.72 br. s; 5.78 br. s	7.25 d; ^3J 7.5	7.36 t; ^3J 7.5	7.46 t; ^3J 7.5	7.35 d; ^3J 7.5	H14: 7.13 t; ^3J 7.5

8[a]		5.53 d; ^{2}J 11; 5.58 d; ^{2}J 11	–	7.27 d; ^{3}J 7	7.19 m	7.20 m	H14: 7.07 m; H17: 2.54 s
9[b]		4.55 d; ^{2}J 11; 5.83 d; ^{2}J 11	6.83 s	–	7.21 t; ^{3}J 8	6.81 d; ^{3}J 8	H14: 6.95 d; ^{3}J 8; H17: 2.34 s
10[b]		4.53 d; ^{2}J 11; 5.81 d; ^{2}J 11	6.91 d; ^{3}J 8.0	7.13 d; ^{3}J 8	7.13 d; ^{3}J 8	6.91 d; ^{3}J 8	H17: 2.34 s
11[b]		–	8.70 dd; ^{3}J 6.5; ^{2}J 1.5	7.46 dd; ^{3}J 8; ^{3}J 6.5	7.46 dd; ^{3}J 8; ^{3}J 6.5	8.70 dd; ^{3}J 6.5; ^{2}J 1.5	H14: 7.83 tt; ^{3}J 8; ^{4}J 1.5
12[a]		6.42 s; 2H	–	6.85 dd; ^{3}J 8.5; ^{4}J 1.5	7.46 td; ^{3}J 6.0; ^{4}J 1.5	8.07 dd; ^{3}J 6; ^{4}J 1.5	H14: 7.56 td; ^{3}J 8.5; ^{4}J 1.5
13[a]		H14: 8.65 d; ^{3}J 8.5	9.20 s; br.	7.77 dd; ^{3}J 8.5; ^{3}J 5	7.16 d; ^{3}J 8	7.79 td; ^{3}J 8; ^{4}J 1.5	H17: 8.02 td; ^{3}J 8; H18: 9.14 br. s

*Solvent, [a]CD_3COCD_3; [b]$CDCl_3$; br.: broadened.

H, 4.30. Found: Pt, 42.21; C, 35.89; H, 4.11. IR (cm^{-1}): 3211 (ν_{NH}); 3061, 3012, 2968, 2883 (ν_{CH}); 1610, 1500 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.4. [Pt(Saf-1H)(Morpholine)Cl] (4). This complex was prepared starting from 392 mg (0.5 mmol) $[Pt_2(Saf\text{-}1H)_2Cl_2]$ and 1.1 mmol morpholine according to the procedure for preparation of **1**. Recrystallization from ethanol/acetone 3 : 1 by volume resulted in light yellow crystals (263 mg, 55%). Anal. Calcd for $[PtC_{14}H_{18}NO_3Cl]$: Pt, 40.75; C, 35.11; H, 3.76. Found: Pt, 40.41; C, 35.39; H, 4.01. IR (cm^{-1}): 3232 (ν_{NH}); 3053, 2967, 2888, 2852 (ν_{CH}); 1597, 1493 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.5. [Pt(Saf-1H)(Cyclohexylamine)Cl] (5). This complex was prepared starting from 392 mg (0.5 mmol) $[Pt_2(Saf\text{-}1H)_2Cl_2]$ and 1.1 mmol morpholine according to the procedure for preparation of **1**. Recrystallizing from ethanol/acetone 3 : 1 by volume produced light yellow crystals (285 mg, 58%). Anal. Calcd for $[PtC_{16}H_{22}NO_2Cl]$: Pt, 39.75; C, 39.14; H, 4.48. Found: Pt, 40.10; C, 39.49; H, 4.19. IR (cm^{-1}): 3284, 3227 (ν_{NH}); 2998, 2927, 2890, 2862 (ν_{CH}); 1607, 1576, 1496 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.6. [Pt(Saf-1H)(Benzylamine)Cl] (6). This complex was prepared starting from 392 mg (0.5 mmol) $[Pt_2(Saf\text{-}1H)_2Cl_2]$ and 1.1 mmol benzylamine according to the procedure for preparation of **1**. Recrystallization from ethanol/acetone 3 : 1 by volume gave light yellow crystals (304 mg, 61%). Anal. Calcd for $[PtC_{17}H_{18}NO_2Cl]$: Pt, 39.12; C, 40.92; H, 3.61. Found: Pt, 39.45; C, 40.61; H, 3.29. IR (cm^{-1}): 3311, 3254 (ν_{NH}); 3039, 2895, 2840 (ν_{CH}); 1577, 1497 ($\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.7. [Pt(Saf-1H)(Aniline)Cl] (7). 0.10 mL (1.0 mmol) aniline was added to a mixture of 392 mg (0.5 mmol) $[Pt_2(Saf\text{-}1H)_2Cl_2]$ and 15 mL ethanol. The mixture was shaken for 15 min, kept at room temperature for 12 h, and then evaporated to 7 mL. The solid compound obtained was isolated by filtration and washed with ethanol and cold acetone, and recrystallized from acetone. The crude product was recrystallized from ethanol/acetone 2 : 1 by volume to afford the product as light yellow crystals (270 mg, 55%). Anal. Calcd for $[PtC_{16}H_{16}NO_2Cl]$: Pt, 40.24; C, 39.62; H, 3.33. Found: Pt, 39.95; C, 39.89; H, 3.55. IR (cm^{-1}): 3297, 3246 (ν_{NH}); 3053, 3017, 2895, 2837 (ν_{CH}); 1600, 1492 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.8. [Pt(Saf-1H)(*o*-Toluidine)Cl] (8). This complex was prepared starting from 392 mg (0.5 mmol) $[Pt_2(Saf\text{-}1H)_2Cl_2]$ and 1.0 mmol *o*-toluidine according to the procedure for preparation of **7**. The product is light yellow crystals (354 mg, 71%). Anal. Calcd for $[PtC_{17}H_{18}NO_2Cl]$: Pt, 39.12; C, 40.92; H, 3.61. Found: Pt, 39.45; C, 40.61; H, 3.39. Found: Pt, 38.78; C, 41.22; H, 3.36. IR (cm^{-1}): 3275, 3246 (ν_{NH}); 3053, 2988, 2888 (ν_{CH}); 1600, 1492 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.9. [Pt(Saf-1H)(*m*-Toluidine)Cl] (9). 107 mg (1.0 mmol) *m*-toluidine was added to a mixture of 392 mg (0.5 mmol) $[Pt_2(Saf\text{-}1H)_2Cl_2]$, 15 mL ethanol, and 5 mL chloroform.

The mixture was shaken for 15 min. The resulting solution was kept at room temperature for 12 h and then evaporated to 10 mL. The solid compound obtained was isolated by filtration and washed with chloroform. The crude product was recrystallized from chloroform to afford the product as light yellow crystals (374 mg, 75%). Anal. Calcd for [$PtC_{17}H_{18}NO_2Cl$]: Pt, 39.12; C, 40.92; H, 3.61. Found: Pt, 39.45; C, 40.64; H, 3.41. IR (cm^{-1}): 3270, 3214 (ν_{NH}); 3029, 2894, 2840 (ν_{CH}); 1600, 1586, 1495 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.10. [Pt(Saf-1H)(*p*-Toluidine)Cl] (10). This complex was prepared starting from 392 mg (0.5 mmol) [Pt_2(Saf-1H)$_2Cl_2$] and 1.0 mmol *p*-toluidine according to the procedure for preparation of **9**. The product is light yellow crystals (389 mg, 78%). Anal. Calcd for [$PtC_{17}H_{18}NO_2Cl$]: Pt, 39.12; C, 40.92; H, 3.61. Found: Pt, 38.85; C, 41.22; H, 3.32. IR (cm^{-1}): 3304, 3239 (ν_{NH}); 3010, 2895, 2850 (ν_{CH}); 1596, 1513 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.11. [Pt(Saf-1H)(Pyridine)Cl] (11). This complex was prepared starting from 392 mg (0.5 mmol) [Pt_2(Saf-1H)$_2Cl_2$] and 1.0 mmol pyridine according to the procedure for preparation of **7**. The yield was 268 mg (57%). Anal. Calcd for [$PtC_{15}H_{14}NO_2Cl$]: Pt, 41.44; C, 38.25; H, 2.98. Found: Pt, 41.70; C, 38.51; H, 3.25. IR (cm^{-1}): 3067, 3002, 2881, 2830 (ν_{CH}); 1602, 1500 ($\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.12. [Pt(Saf-1H)(2-H_2NPyridine)Cl] (12). This complex was prepared starting from 392 mg (0.5 mmol) [Pt_2(Saf-1H)$_2Cl_2$] and 1.0 mmol pyridine according to the procedure for preparation of **7**. The yield was 281 mg (58%). Anal. Calcd for [$PtC_{15}H_{15}N_2O_2Cl$]: Pt, 40.16; C, 37.07; H, 3.09. Found: Pt, 40.67; C, 36.81; H, 3.28. IR (cm^{-1}): 3449, 3357 (ν_{NH}); 3067, 3003, 2881, 2830 (ν_{CH}); 1602, 1500 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

2.2.13. [Pt(Saf-1H)(Quinoline)Cl] (13). This complex was prepared starting from 392 mg (0.5 mmol) [Pt_2(Saf-1H)$_2Cl_2$], 1.0 mmol quinoline according to the procedure for preparation of **7**. The yield was 328 mg (63%). Anal. Calcd for [$PtC_{19}H_{16}NO_2Cl$]: Pt, 37.46; C, 43.80; H, 3.07. Found: Pt, 37.71; C, 43.57; H, 2.89. IR (cm^{-1}): 3060, 3012, 2980, 2850 (ν_{CH}); 1602, 1500 (aromat. $\nu_{C=C}$). ^1H NMR: see tables 1 and 2.

3. Results and discussion

The reported complexes were prepared by the reaction of dinuclear chelate ring complex [Pt_2(Saf-1H)$_2Cl_2$] (in which (Saf-1H) is chelating safrole) [14] and various amines (Am, see table 2) as described in figure 1 (the numeration on these structures is specifically used for NMR analysis only).

For the product formed, the dominant isomer is *cis*-[Pt(Saf-1H)(Am)Cl], in which the amine is *cis* with respect to ethylenic double bond of the allyl group.

Interaction of [$Pt_2(C_2H_4)_2Cl_4$] and amines gives *trans*-[$Pt(C_2H_4)$(Am)Cl_2], as ethylene has a large *trans* effect. Surprisingly, in the reaction of [Pt_2(Saf-1H)$_2Cl_2$] and amines, the

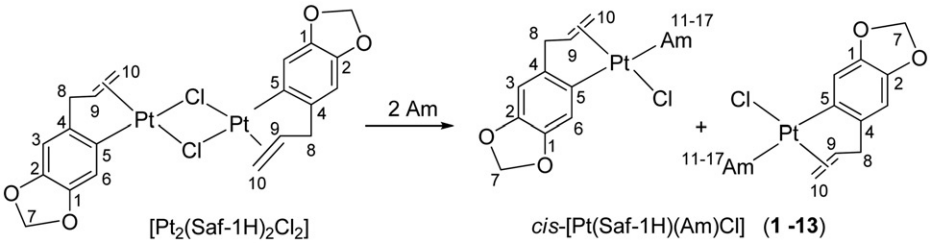


Figure 1. The formation of complexes containing chelating safrole and an amine.

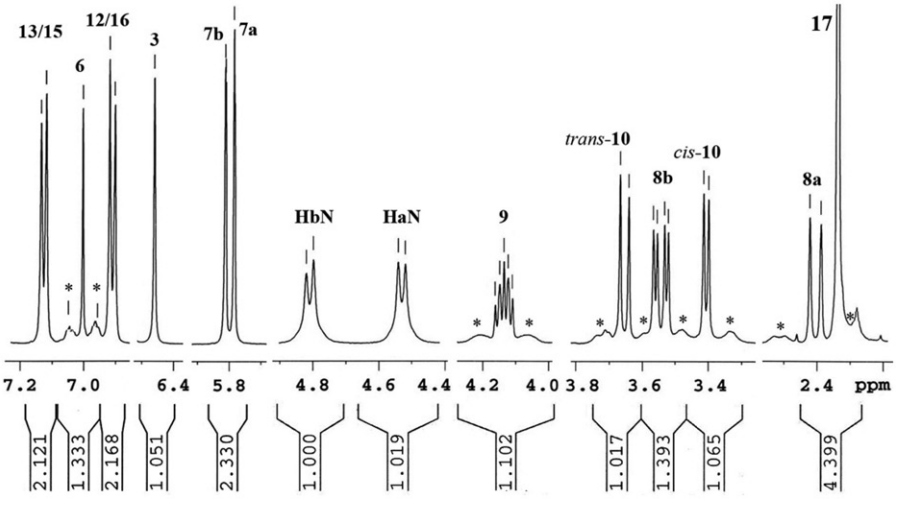


Figure 2. The expanded ^{1}H NMR signals of **10**.

amine was not introduced *trans* to the ethylenic double bond of the allyl but was *trans* to C5 of the phenyl group (figure 1); that is, not obeying the *trans* effect. We suggest that this selectivity is controlled by steric effects rather than the *trans* effect.

The IR spectra of *cis*-[Pt(Saf-1H)(Am)Cl] show bands for coordinated safrole and amines. In addition, the absence of a band at 1640 cm^{-1} from the C=C double bond of allyl group in non-coordinated safrole indicates the allyl group coordinates in an η^2 manner.

NMR data of the examined compounds were most informative with regard to their solution structures. All resonance signals in ^{1}H NMR spectra of the compounds were accurately assigned based on analyzing the spin–spin splitting patterns and nuclear overhauser effect spectroscopy (NOESY) spectra (e.g., in figures 2 and 3); the results are listed in tables 1 and 2.

Upon coordination to Pt(II), the resonances of ethylenic protons (H9, *cis*-H10, *trans*-H10, table 1) shift upfield in comparison to those of non-coordinated safrole (5.90, 5.02, 5.00 ppm, respectively). The ^{195}Pt satellites from H9, *cis*-H10, and *trans*-H10 are clear (indicated with * in figure 2) with the distance between them, $^{2}J_{PtH}$, 70–75 Hz (table 1), showing that the allyl of safrole is an η^2-coordinated olefin.

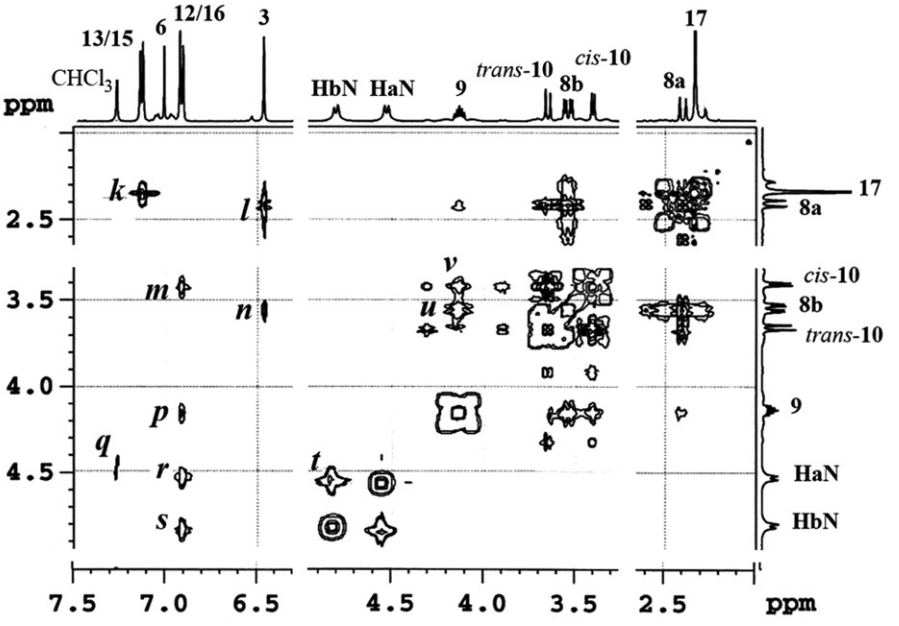


Figure 3. Partial NOESY spectrum of **10**.

For non-coordinated safrole, two protons H8 give a doublet at 3.26 ppm with $^3J = 6.5$ Hz, but in spectra of **1**–**13**, we usually observed a doublet of doublets centered at 2.44–2.70 ppm for H8a and another doublet of doublets centered at 3.40–3.84 ppm for H8b (table 1, figure 2). This is expected, as on coordination to Pt(II), C9 becomes a chiral center and H8a and H8b become diastereotopic. For chelating safrole, the H6-singlet is distinguished from the H3-singlet by ^{195}Pt satellites with a $^3J_{PtH}$ value of 40–42 Hz (table 1, figure 2). This value is comparable to $^3J_{PtH}$ in analogous platinum(II) complexes [15]. The presence of these ^{195}Pt satellites indicates that the coordinated safrole is bound with Pt(II) by a σ-bond (C5)-Pt as shown in figure 1.

For **1**–**13**, there are some anomalies: first, two methylene protons of the 1,3-dioxole ring become nonequivalent (denoted with H7a and H7b), whereas for non-chelating safrole, such as K[Pt(Saf)Cl$_3$], *trans*-[Pt(Saf)(Amine)Cl], they are equivalent [14, 16]. Second, the distance between two ^{195}Pt satellites of H8a, $^3J_{PtH8a}$, is quite large (105–110 Hz), larger than those of $^2J_{PtH9}$, $^2J_{PtH10}$. Third, in complexes *cis*-[Pt(morpholine)(amine)Cl$_2$] [17] and *cis*-[Pt(piperidine)(amine)Cl$_2$] [18], in the case of $(CH_3)_2NH$ and $(CH_3CH_2)_2NH$, two methyl groups are equivalent, and two methylene groups are also equivalent; for primary amines such as methylamine, ethylamine, and substituted phenylamines, two amino protons are equivalent giving a broadened singlet. However, in **2** and **3**, two methyl groups are nonequivalent and two methylene groups are also nonequivalent. In **5**–**10**, two amino protons are nonequivalent giving two broadened singlets (in **5**, **6**, and **7**) or two broadened doublets (in **8**, **9**, and **10**, table 2).

To determine the configuration of the complexes and to explain the anomalies, NOESY spectra were studied. For example, in the spectrum of **10** (figure 3), there are cross peaks *m*, *p* between H12/H16 of *p*-toluidine (H12 and H16 are equivalent) and

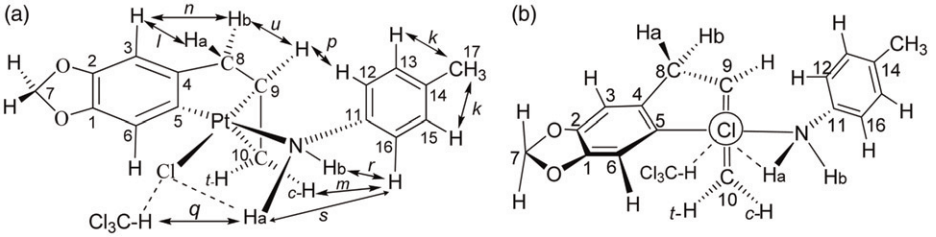


Figure 4. (a) NOESY-interaction (↔) and structure of **10** and (b) complex **10** viewed along the Cl–Pt bond from Cl.

cis-H10, H9 of the allyl group, but there are no cross peaks between H12/H16 or HN of *p*-toluidine and neither H3 nor H6 of the phenyl group of chelating safrole. These show that *p*-toluidine is *cis* to the ethylenic double bond, i.e. in the *trans*-position in comparison to C5 of the safrole-phenyl group, as shown in figures 1 and 4. In addition, two cross peaks *l*, *n* of H8a, H8b confirm the assignment for H3; cross peak *k* of H17 (methyl group of *p*-toluidine) confirms the assignment for H13/H15 (H13 and H15 are equivalent) and cross peaks *u* and *v* indicate that H9 is in proximity to H8b and *cis*-H10.

It is interesting to note that two protons of the amino group in **10** give two separate doublets (HaN at 4.53 and HbN at 4.81 ppm with the roof effect and $^{2}J_{\mathrm{HaHb}} = 11$ Hz). HaN and HbN give two cross peaks *r*, *s* with H12/H16, and they also give rise to cross peak *t* with one another. HaN and HbN do not give any cross peaks with neither H9 nor H10, that is, HaN and HbN are removed from the allyl group, whereas H12/H16 give cross peaks *m* and *p* with *cis*-H10 and H9, that is, H12/H16 are adjacent to the allyl group. All NOESY-data of **10** allow us to suggest its structure as in figure 4.

In figure 4(a), each double-headed arrow shows the spatial closeness between two protons and each letter accompanied by the double-headed arrow associates with one cross peak in the NOESY spectrum in figure 3. In figure 4(b), **10** is viewed along the Cl–Pt bond from Cl to the middle of the C9–C10 bond; atoms N, Cl, C5, and the middle of the C9–C10 bond form the coordination plane of Pt(II). The benzene ring of chelating safrole and the coordination plane of Pt(II) are neither coplanar nor perpendicular to one another, but the benzene ring of chelating safrole is canted with C3, C4, and C8 above the coordination plane, whereas C1 and C6 are under it. Since C9 is above the coordination plane (figure 4b), the benzene ring and the 1,3-dioxole ring of chelating safrole are obliged to deform. These features bring about the differences between H7a and H7b on the 1,3-dioxole ring as well as between H8a and H8b on the allyl group (H8a is just above the square plane of Pt but H8b is not). The spatial difference between H8a and H8b, H9, and H10 in the coordination entity of Pt possibly causes the large difference in the value of $^{3}J_{\mathrm{PtH8a}}$ in comparison to $^{2}J_{\mathrm{PtH9}}$ and $^{2}J_{\mathrm{PtH10}}$.

The NOESY spectra of **2**, **5**–**7**, **9**, **11**–**13** were also analyzed. The distinguishing features in these spectra are similar to those of **10**, in particular, proton H12 or H16 usually have cross peaks with proton H9 or *cis*-H10 but do not have any cross peak with H6. These show that the examined complexes have *cis*-configuration, in which the alkyl and aryl of coordinated amines are adjacent to the allyl group of chelating safrole; therefore, rotation around the Pt–N bond does not occur on the NMR time scale at the

Table 3. The cell *in vitro* cytotoxicity of examined compounds, IC_{50}, $\mu g\,mL^{-1}$.

Compound	KB	HepG2	Lu	MCF7
cis-[Pt(Saf-1H)(pyridine)Cl]	15.3	5.0	4.6	18.7
cis-[Pt(Saf-1H)(2-aminopyridine)Cl]	6.7	4.5	3.2	10.5
cis-[Pt(Saf-1H)(quinoline)Cl]	5.6	2.5	2.7	4.8

recorded temperature. This brings up the following question of why the alkyl and aryl groups of coordinated amines are usually in proximity to the allyl of chelating safrole. To our knowledge, in solution the amino protons prefer to form hydrogen-bonds with solvent, for instance, in the case of d_6-acetone, $N–H\cdots O{=}C(CD_3)_2$. Since $N–H\cdots O{=}C(CD_3)_2$ is a large moiety, it cannot form beside the allyl group; thus, a rotation about the Pt–N bond places the alkyl, aryl groups in proximity to the allyl group. In the case of **10**, it is most likely that an intramolecular $NH\cdots Cl–Pt$ interaction keeps the amino-proton HaN in proximity to Cl (marked by dashed line in figure 4a); in consequence, the alkyl and aryl groups are in proximity to the allyl group. Similarly, for **1**, NH_3 gives two broadened singlets (table 2). HaN of **10** gives a weak cross peak *q* with $CHCl_3$ (figure 3), i.e. HaN is in proximity to the proton of $CHCl_3$, suggesting an intermolecular hydrogen-bond $Cl_3C–H\cdots Cl–Pt$ (figure 4), which has attracted the interest of many researchers [19].

Three complexes were tested for cell *in vitro* cytotoxicity on human cancer cells KB, HepG2, Lu, and MCF7. The IC_{50} values are listed in table 3. *cis*-[Pt(Saf-1H)(pyridine)Cl], *cis*-[Pt(Saf-1H)(2-aminopyridine)Cl], and *cis*-[Pt(Saf-1H)(quinoline)Cl] exhibit strong activities on human cancer cells HepG2 and Lu ($IC_{50} = 2.5–5.0\,\mu g\,mL^{-1}$).

4. Conclusion

Thirteen new complexes *cis*-[Pt(Saf-1H)(Am)Cl] were synthesized and characterized by elemental analyses, IR, ^1H NMR, and NOESY spectra. Their NOESY spectra indicate that the complexes have *cis*-configuration, in which the alkyl and aryl groups of coordinated amines are in proximity to the allyl group of chelating safrole. Some compounds exhibit inhibitory activities on human cancer cells HepG2, and Lu with $IC_{50} = 2.5–5.0\,\mu g\,mL^{-1}$.

Acknowledgments

This work was supported by Vietnam National Foundation for Science and Technology Development (NAFOSTED).

References

[1] A.S. Lages, K.C.M. Silva, A.L.P. Miranda, C.A.M. Fraga, E.J. Barreiro. *Bioorg. Med. Chem. Lett.*, **8**, 183 (1998).

[2] M. Cox, G. Klass, S. Morey, P. Pigou. *Forensic Sci. Int*., **179**, 44 (2008).
[3] A. Archellas, R. Furstoss. *Annu. Rev. Microbiol*., **51**, 491 (1997).
[4] S. Freeman, J.F. Alder. *Eur. J. Med. Chem*., **37**, 527 (2002).
[5] A.C. Lima Leite, K.P. da Silva, I.A. de Souza, J.M. de Araújo, D.J. Brondani. *Eur. J. Med. Chem*., **39**, 1059 (2004).
[6] A.S. Santos, N. Pereira Jr, I.M. da Silva, M.I.M. Sarquis, O.A.C. Antunes. *Process Biochem*., **39**, 2269 (2004).
[7] L.B. Chiavetto, G. Guglielmetti, C. Querci, M. Ricci. *Tetrahedron Lett*., **37**, 1091 (1996).
[8] N. Farrell. *Cancer Invest*., **11**, 578 (1993).
[9] T. Okada, I.M. El-Mehasseb, M. Kodaka, T. Tomohiro, K. Okamato, H. Okuno. *J. Med. Chem*., **44**, 4661 (2001).
[10] N.J. Wheate, J.G. Collins. *Coord. Chem. Rev*., **241**, 133 (2003).
[11] I. Lakomska, E. Szlyk, J. Sitkowski, L. Kozerski, J. Wietrzyk, M. Pełczyńska, A. Nasulewicz, A. Opolski. *J. Inorg. Biochem*., **98**, 167 (2004).
[12] A.D. Ghelman, E.F. Karandasova, L.N. Essen. *Izv. Sectora Platinum, Inst. Obsch. Nheorg. Khim. AN SSSR*, **24**, 68 (1949).
[13] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J.T. Warren, H. Bokesch, S. Kenney, M.R. Boyd. *J. National Cancer Institute*, **82**, 1107 (1990).
[14] T.T. Da, Y.M. Kim, N.T.T. Chi, L.X. Chien, N.H. Dinh. *Organometallics*, **27**, 3611 (2008).
[15] T.T. Da, Y. Kim, T.T.C. Mai, N.C. Cuong, N.H. Dinh. *J. Coord. Chem*., **63**, 473 (2010).
[16] N.T.T. Chi, T.T. Da, V.Q. Nhu, N.H. Dinh. *J. Chem*., **42**, 142 (2007).
[17] T.T. Da, D.B. Vu, N.H. Dinh. *J. Coord. Chem*., **57**, 485 (2004).
[18] N.H. Dinh, T.T. Da. *J. Coord. Chem*., **56**, 683 (2003).
[19] P.V. Gushchin, G.L. Starova, M. Haukka, M.L. Kuznetsov, I.L. Eremenko, V. Yu. Kukushkin. *Cryst. Growth Des*., **10**, 4839 (2010).