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Study of the different behaviour of thiazolin and thiazin indazole derivatives with palladium(II) acetate

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ABSTRACT

The study of the reactivity of the ligands 2-(indazol-1-yl)-2-thiazoline (**1**) and 2-(indazol-1-yl)-1,3-thiazine (**2**) with palladium(II) acetate has allowed the isolation of different compounds. For the thiazolin indazole derivative (**1**) a cyclopalladated compound: $(\mu\text{-OAc})_2[Pd(k^2\text{-}C,N\text{-TnInA})]_2$ (**1a**) with a bidentate $[C(sp^2,phenyl),N]^-$ ligand and a central "$Pd(\mu\text{-OAc})_2Pd$" unit was obtained. Treatment of the dimeric compound **1a** with sodium acetylacetonate produced the mononuclear compound $[Pd(k^2\text{-}O,O'\text{-acac})(k^2\text{-}C,N\text{-TnInA})]$ (**1c**). The reaction of **1a** with LiCl followed by the addition of PPh_3 gave the compound $[PdCl(PPh_3)(k^2\text{-}C,N\text{-TnInA})]$ (**1e**) where the acetate groups were replaced by Cl^- and PPh_3 ligands, and with the PPh_3 in a *cis*-arrangement to the metallated carbon atom. The solid-state structure of **1e** was determined by single-crystal X-ray diffraction methods. The reaction of **2** with palladium(II) acetate produced, in contrast to ligand **1**, the complex *cis*-$[Pd(OAc)_2(k^2\text{-}N,N'\text{-TzIn})]$ (**2a**) with a bidentate $[N,N']$ ligand. Compound **2a** reacted with LiCl giving *cis*-$[PdCl_2(k^2\text{-}N,N'\text{-TzIn})]$ (**2b**), where the acetate groups were exchanged by chloride ligands. DFT calculations suggest that the most favoured compound obtained from the reaction between **1** and palladium(II) acetate should be the cyclopalladated one, while for **2** the formation of the $[N,N']$ coordinated complex is less unfavoured.

1. Introduction

Heterocyclic compounds represent a very important class of molecules that find a number of applications as pharmaceuticals, agrochemicals, fine and bulk chemicals as well as ligands for catalysis [1]. Among the different heterocycles thiazoline, thiazine and indazole have attracted a great deal of attention from synthetic and medicinal chemists over the last 20 years.

The thiazoline ring is present in many biologically active products, including natural [2] and synthetic products. Some thiazoline-containing compounds exhibit anti HIV-1, antimitotic, and bioluminescent activities, and have recently found applications as building blocks in pharmaceutical drug discovery [3]. On the other hand, thiazines derivatives present antitumoral, antihistaminic, anti-inflammatory, analgesic and antibiotic properties [4]. Besides, the range of pharmacological effects of indazole derivatives includes among others DNA intercalating, activation of the nitric oxide receptor, HIV protease inhibition, anticancer and anti-inflammatory activities [5].

In some cases, the structural and/or biological properties of these ligands can be modified when they coordinate a metal ion [6a].

Indazole and its derivatives may exhibit different binding modes towards a metal ion. Their coordination chemistry has been the subject of several investigations in the last years [6]. In particular, Co(II), Zn(II) and Cd(II) complexes with the ligands 2-(indazol-1-yl)-2-thiazoline (TnInA) (**1**) and 2-(indazol-1-yl)-1,3-thiazine (TzIn) (**2**) (Fig. 1) have been synthesized [7]. In these compounds, the ligands are bonded to the metal ions through the indazole and thiazoline or thiazine (for **1** and **2**, respectively) nitrogen atoms, acting as bidentate groups. In addition to the N donors, these ligands can coordinate also via the S atoms and may undergo the activation of the σ(C–H) bond of the phenyl ring generating cyclometallated compounds.

The most common palladacycles are derived from tertiary amines and imines and are usually five- or less commonly six-membered rings. The factors that govern metallation appear to depend on many parameters, including the hybridization of the palladated carbon atom, the type and structural characteristics of

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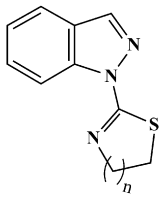


Fig. 1. Structural formulae of the ligands 2-(indazol-1-yl)-2-thiazoline (TnInA) (1) ($n = 1$) and 2-(indazol-1-yl)-1,3-thiazine (TzIn) (**2**) ($n = 2$).

the ligand, and the palladium source, which ultimately determines kinetic and thermodynamic preferences for palladation [8]. In the present paper, we report on the study of the reaction of $Pd(OAc)_2$ with **1** and **2** (which only differ in a CH_2 unit) that has lead to Pd^{II} complexes in which L adopts different binding modes, under identical experimental conditions.

2. Results and discussion

2.1. Synthesis and characterization of the complexes

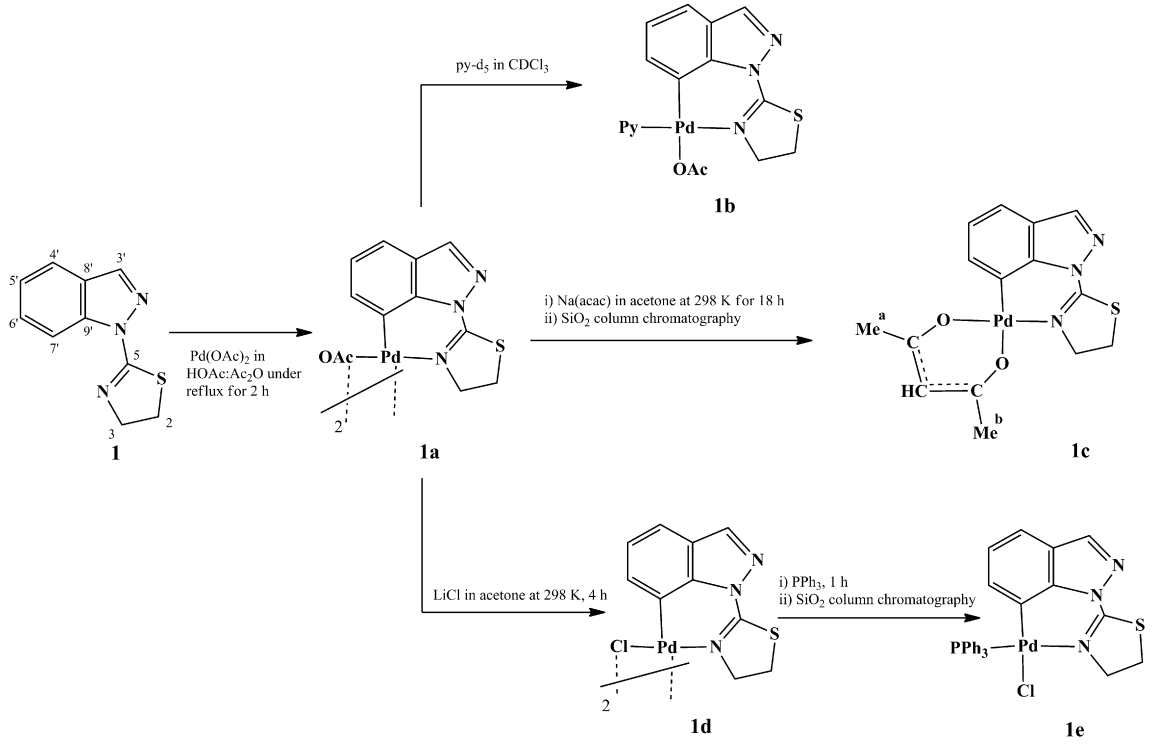
Treatment of ligands 2-(indazol-1-yl)-2-thiazoline (**1**) and 2-(indazol-1-yl)-1,3-thiazine (**2**) with an equimolar amount of $Pd(OAc)_2$ in a mixture of glacial acetic acid and acetic anhydride (9:1) under reflux for 2 h gave different compounds for ligands **1** and **2**, respectively.

The reaction of **1** with $Pd(OAc)_2$ produced a yellow compound (**1a**) (Scheme 1). Characterization data of **1a** (Section 4) were consistent with those expected for a cyclopalladated complex: $(\mu\text{-}OAc)_2[Pd(k^2\text{-}C,N\text{-}TnInA)]_2$ that arises from the metallation of the indazole phenyl ring. The infrared spectrum of **1a** showed two bands due to the symmetric and asymmetric stretchings of the carboxylato groups at 1580 and 1447 cm^{-1}, respectively. Their significant separation (142 cm^{-1}) suggested, according to the bibliography [9], that the AcO^- behaved as a [O,O′] bridging ligand.

It is well known that dimeric cyclopalladated complexes with acetate groups as bridging ligands may exhibit different isomeric forms [10]. In these isomers, the two halves of the molecule may be in a *cis*- or *trans*-arrangement. It has been reported that for the *trans*-isomers, the resonance of the methyl groups of the bridging ligands, in the ^1H NMR spectra, appears as one singlet; However, this signal splits into two singlets for the *cis*-isomer. In spite of the low solubility of compound **1a** in most usual solvents, its ^1H NMR spectrum could be recorded in DMSO-d_6. It showed only one singlet (at 2.08 ppm), suggesting that in **1a** the two halves are in a *trans* arrangement.

Acetato-bridged cyclopalladated dimers present a folded structure (commonly known as *open-book* structure), in solution as well as in the solid-state [11]. On this basis we assumed that in **1a** the relative orientation of the acetato ligands corresponds to the *open-book* type, with a C_2 symmetry. The absence in the spectrum of the signal ascribed to the proton $H^{7'}$ and the high-field shift of the resonances arising from the aromatic protons of the indazole ring when compared with the free ligand **1** are consistent with the metallation of the phenyl ring on position 7′. It was not possible to record the due to the low solubility of the complex.

When this cyclopalladated complex reacted with py-d_5 (in an NMR scale), Na(acac) or LiCl followed by the addition of PPh_3 (Scheme 1), more soluble products were obtained that allow a better characterization of the starting complex. The addition of an excess of deuterated pyridine to a $CDCl_3$ suspension of **1a** produced a colourless solution indicating the formation of the corresponding mononuclear cyclopalladated compound (**1b**). The deuterated pyridine was located in a *cis* position relative to the palladated carbon [12], which is inferred by the high-field shift of the aromatic proton in the adjacent position to the palladated carbon, this effect being caused by the pyridine ring.



Scheme 1. Synthesis of palladium compounds of the ligand 2-(indazol-1-yl)-2-thiazoline (TnInA) (**1**).

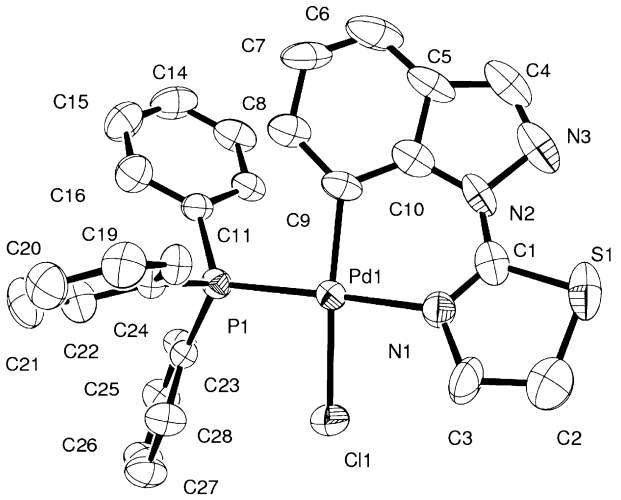


Fig. 2. ORTEP plot of the crystal structure of the compound [PdCl(PPh3)(k^2-*C*,*N*-TnInA)] (**1e**). Selected bond lengths (in Å) and angles (in °): Pd1–C10, 2.027(6); Pd1–N1, 2.103(5); Pd1–Cl1, 2.381(2); Pd1–P1, 2.267(2); C1–N1, 1.279(9); C1–N2, 1.34(1); C1–S1, 1.755(7); C2–S1, 1.773(9); C3–N1, 1.472(9); C4–N3, 1.30(1); C10–N2, 1.37(1); C9–Pd1–N1, 88.7(2); C9–Pd1–P1, 92.5(2); N1–Pd1–Cl1, 88.4(2); P1–Pd1–Cl1, 90.82(6), C3–N1–Pd1, 122.9(4); C1–N1–C3, 111.3(6); C1–N1–Pd1, 125.6(5); C1–N2–N3, 119.1(6); C10–N2–N3, 112.0(6); C11–P1–Pd1, 117.8(2); C23–P1–Pd1, 117.2(2).

The action of sodium acetylacetonate to an acetone suspension of **1a** produced a yellow solution which gave, after concentration followed by SiO_2 column chromatography [Pd(k^2-*O*,*O*′-acac)(k^2-*C*,*N*-TnInA)] (**1c**) (Scheme 1). Characterization data (Section 4) agreed with the proposed formula. The resonances of the methyl protons of the acac ligand (Me^a and Me^b) appeared as two singlets at about 2 ppm, and the analysis of the 1D NOESY spectrum allowed the assignation of the peaks (2.13 and 2.03 ppm, respectively).

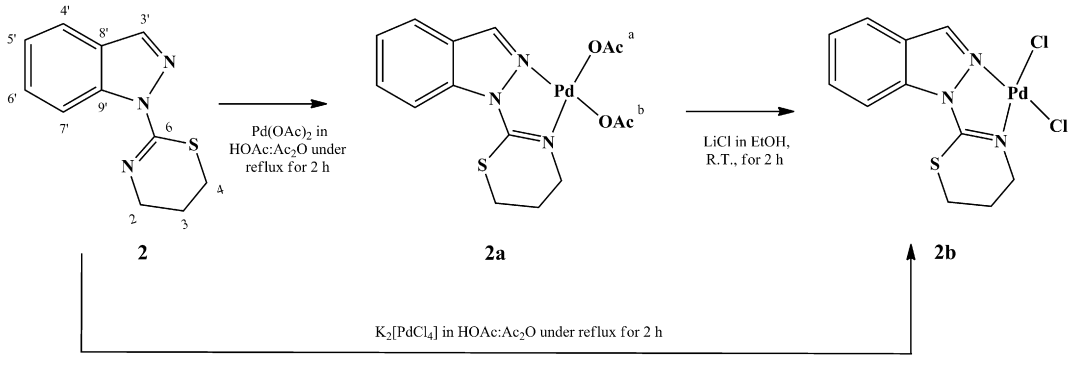
A metathesis reaction between **1a** and LiCl yielded the expected chloro-bridged cyclopalladated dimer (μ-Cl)$_2$[Pd(k^2-*C*,*N*-TnInA)]$_2$ (**1d**). Compound **1d** was characterized directly by ^{1}H and ^{13}C NMR in DMSO-d_6 solution that contained an excess of LiCl and compound **1a**. The most relevant features were a low-field shift of the resonance of the $H^{6'}$ proton of the ligand, the absence of the signal of coordinated acetate (2.08 ppm) and the presence of the signal corresponding to free acetate (1.69 ppm). Bridge-splitting reaction of the cyclopalladated dimer **1d** with PPh_3 produced a yellow precipitate of mononuclear derivative [PdCl(PPh_3)(k^2-*C*,*N*-TnInA)] (**1e**) (Scheme 1). This compound was obtained on a preparative scale and isolated. Compound **1e** was characterized by elemental analyses, IR and ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} and two-dimensional NMR studies. Elemental analyses were consistent with the proposed formulae. The IR spectrum showed the typical bands due to the coordinated PPh_3 ligand [9,13] which was observed as a singlet at 31.05 ppm in the ^{31}P{^{1}H} NMR spectrum. Besides, in the ^{13}C{^{1}H} NMR spectrum the signal ascribed to the metallated carbon ($C^{7'}$) appeared as a doublet due to the phosphorus coupling. These results are indicative of a *cis*-arrangement of the phosphorus and the metallated carbon.

The structure of compound **1e** was established by single-crystal X-ray diffraction study. Yellow crystals were obtained by slow evaporation of the solvent of a CH_2Cl_2 solution of **1e**. The structure of this compound agrees with the palladation of the 7′ position of the indazole ring. Thus, the palladium atom is bound to a chloride atom, the phosphorus of a PPh_3 ligand, the N1 of the thiazoline and the C10 of the indazole ring, confirming a [Csp^2, N]$^-$ binding mode of the ligand (Fig. 2). The palladium is in a slightly distorted square-planar environment (torsion angle C9–N1–Cl1–P1 = 6.9°).

The Pd–N1 bond length [2.103(5) Å] is longer than the single bond predicted value of 2.011 Å, and reflects the *trans* effect of the phosphorous atom [14]. The Pd–C9, Pd–P and Pd–Cl bond distances [2.027(6), 2.267(2) and 2.381(2) Å, respectively] fall in the range reported for related palladacycles containing bidentate [Csp^2, N]$^-$ ligands [15]. The value of the C9–Pd–P1 angle [92.5(2)°] confirms a *cis*-arrangement between the metallated carbon and the phosphine ligand. The angles between adjacent atoms in the coordination sphere of palladium(II) lie in the range 88.4(2)°–92.5(2)°, the largest corresponding to the C9–Pd1–P1 angle.

The six-membered palladacycle adopts a pseudo-boat conformation with the palladium and the N2 atoms deviating by 0.665 and 0.160 Å, respectively, from the plane formed by N1, C1, C10 and C9.

In contrast with the results obtained with **1**, when the ligand **2** was reacted with $Pd(OAc)_2$ the coordination complex *cis*-[$Pd(OAc)_2$(k^2-*N*,*N*′-TzIn)] (**2a**) (Scheme 2) is obtained exclusively. In this product, ligand **2** acts as a [*N*,*N*′] bidentate group. Elemental analyses were consistent with the proposed formula. The infrared spectrum of **2a** showed the typical two bands ascribed to the symmetric and asymmetric stretchings of the carboxylato groups at 1586 and 1408 cm^{-1}, respectively. The separation between these two absorption bands (178 cm^{-1}) suggested, according to the bibliography [9], that the acetate behaved as a monodentate ligand. The ^{1}H NMR spectrum of **2a** showed a doublet at 8.06 ppm due to the $H^{7'}$ proton, thus indicating that metallation was not occurring. The resonances of the methyl protons of the acetate ligand (Me^a and Me^b) appeared as a two singlets at about 2 ppm, and the analysis of the 1D NOESY spectrum allowed their assignment (2.12 and 2.06 ppm, respectively).



Scheme 2. Synthesis of palladium compounds of the ligand 2-(indazol-1-yl)-1,3-thiazine (TzIn) (**2**).

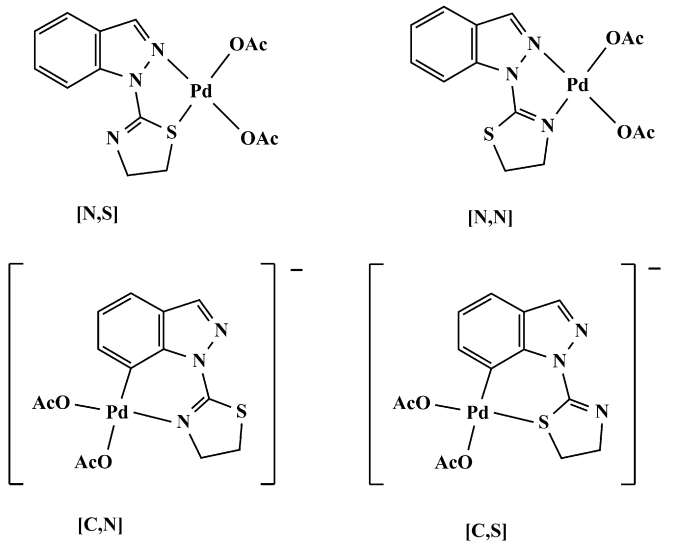


Fig. 3. Possible compounds that may obtained by reaction of palladium acetate with TnInA, this ligand acting as a bidentate one.

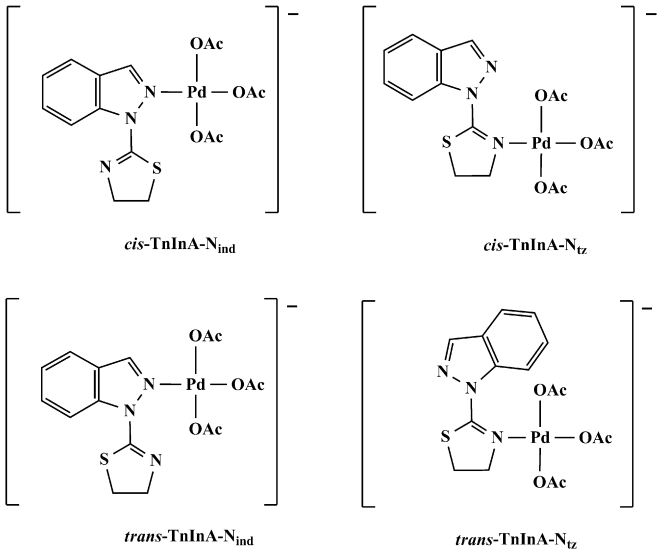


Fig. 4. Hypothetical compounds where the $[Pd(AcO)_3]^-$ moiety is bonded to the indazole (N_{ind}) or to the dihydrothiazole nitrogen (N_{tz}) in TnInA.

Compound **2a** reacted with LiCl to give *cis*-$[PdCl_2(k^2\text{-}N,N'\text{-TzIn})_2]$ (**2b**), with exchange of the acetate groups by chloride ligands, which has been fully characterized (see Section 4). This complex can also be obtained with higher yield by direct reaction of ligand **2** with $K_2[PdCl_4]$. The characterization data confirmed that the two compounds were identical; in both cases, the ligand cyclometallation is not observed.

2.2. Theoretical calculations

In order to study the regioselectivity of these reactions, we have performed a theoretical study using density functional theory. The reaction of the ligands (TnInA or TzIn) with palladium acetate may, in principle, yield four different complexes forming a chelate; as an example, the TnInA derivatives are shown in Fig. 3. Two of them {[N,N] and [S,N]} are neutral; while the other two, that arise from a cyclometallation reaction {[C,N] and [C,S]} are anionic. We have calculated the relative energies corresponding to the formation of the four TnInA and the four TzIn derivatives, both in vacuum and in acetic acid. For each series, the energy of the [N,N] system has been taken as the reference; the results are shown in Table 1. It must be noted that the formation of the cyclometallated complexes [C,N] and [C,S] implies also the protonation of an acetate anion to give acetic acid. In both TnInA and TzIn, the [C,N] cyclopalladated complex is the most energetically favoured, and the relative order of energies is [C,N] < [C,S] < [N,N] < [N,S]. The inclusion of solvent effects results in a destabilization of the cyclopalladated complexes, mainly [C,S], with respect to [N,N], as well as a small destabilization of the [N,S] isomer. Thus, while [C,N] is again the most stable isomer, the energy difference with [N,N] decreases from 36 to 16 kcal/mol for TnInA, and from 32 to 11 kcal/mol for TzIn.

The accepted cyclopalladation mechanism involves the coordination of palladium to the nitrogen atom and subsequently the activation of the C–H bond [8]. Moreover, the greater stability of the N-bonded complexes compared to the S bonded isomers (Table 1) suggests that the first step should be the coordination of the palladium to one of the nitrogen atoms. In order to discern which nitrogen is more prone to bind to the palladium we have calculated the relative energies of the complexes TnInA-N_{ind}, TnInA-N_{tz}, TzIn-N_{ind} and TzIn-N_{tz}, where the $[Pd(OAc)_3]^-$ moiety is bonded to the indazole (N_{ind}) or dihydrothiazole (in TnInA)/dihydrothiazine (in TzIn) nitrogen (N_{tz}) (Fig. 4). The results of the calculations, both in vacuum and in acetic acid, are shown in Table 2.

In the case of TnInA, the most stable isomer is the one with the palladium coordinated to the dihydrothiazole nitrogen, with the indazole coordinated isomer is 6.62 kcal/mol higher in energy; the addition of solvent effects lowers the energy difference to 4.44 kcal/mol. The nitrogen atoms in both rings are in a *trans* arrangement; for this reason, the molecule is oriented in such a way that the palladium atom is directed to the C–H bond that should be activated in order to yield the cyclopalladated complex, which is the most stable.

On the other hand, the situation with TzIn is less straightforward. Thus, according to Table 2, although the isomer with the palladium coordinated to the dihydrothiazine ring is again the most stable, the complex with the metal bound to the indazole nitrogen is only 0.30 kcal/mol higher in energy (0.22 kcal/mol in solution),

Table 1
Relative energies corresponding to the formation of the four TnInA and the four TzIn derivatives discussed in the text, in vacuum and in acetic acid (kcal/mol).

	TnInA		TzIn	
Coordination mode	Vacuum	Solution	Vacuum	Solution
[N,N]	0.0[a]	0.0[a]	0.0[a]	0.0[a]
[N,S]	5.99	7.45	3.56	6.19
[C,S]	−25.76	−3.79	−22.99	−0.58
[C,N]	−35.95	−16.07	−31.71	−10.93

[a] Values taken as reference.

Table 2
Relative energies (in kcal/mol) of the different modes of coordination (indazole nitrogen vs. dihydrothiazole/dihydrothiazine nitrogen) for the $[PdL(AcO)_3]^-$ complexes, where L = TnInA or TzIn. Values in solution are shown in parentheses.

	TnInA		TzIn	
[N,N] arrangement	N_{ind} coordinated	N_{tz} coordinated	N_{ind} coordinated	N_{tz} coordinated
cis	7.20 (4.71)	2.23 (1.69)	3.20 (1.49)	6.34 (5.27)
trans	6.62 (4.44)	0.00[a] (0.00[a])	0.30 (0.22)	0.00[a] (0.00[a])

[a] Values taken as reference.

Table 3
Crystal data details of the refinement of the crystal structure of compound [PdCl(PPh_3)(k^2-*C*,*N*-TnInA)] (**1e**).

Crystal size (mm^3)	$0.36 \times 0.24 \times 0.16$
Empirical formula	$C_{28}H_{23}ClN_3PPdS$
Formula weight	606.37
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	*P* 21/*c*
Unit cell dimensions	
a (Å)	10.5020(19)
b (Å)	16.235(2)
c (Å)	14.859(4)
β (°)	90.35(2)
V ($Å^3$)	2533.4(9)
Z	4
D_{calc} ($mg \times m^{-3}$)	1.590
μ (mm^{-1})	1.007
F(000)	1224
Θ range for data collection (°)	1.86–25.98
Index ranges	$-12 \leq h \leq 12$, $0 \leq k \leq 20$, $0 \leq l \leq 18$
Reflections collected	5436
Independent reflections	5436
Completeness to Θ	100.0%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4960/0/316
Goodness-of-fit on F^2	0.965
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0559$, $wR2 = 0.0963$
R indices (all data)	$R1 = 0.1395$, $wR2 = 0.1117$
Largest diff. peak and hole (e $Å^{-3}$)	0.500 and −0.636

well inside the error of the calculations. Moreover, the isomer with the indazole ring coordinated and the nitrogen atoms with *cis* orientation, that would yield the [N,N] isomer, is only 1.49 kcal/mol higher in energy in solution. Therefore, our calculations do not show a clear trend in the stability of the TzIn derivatives, although the formation of the TzIn-N_{ind} isomer is less disfavoured than in the case of TnInA. The coordination of the palladium to the indazole nitrogen prevents the formation of the cyclometallated ligand because the carbon that should undergo the metallation is in the same indazole moiety as the nitrogen coordinated to the metal. Thus, upon a rotation of the dihydrothiazine ring, the [N,N] isomer could be formed.

3. Conclusions

The reaction of 2-(indazol-1-yl)-2-thiazoline (**1**) with palladium(II) acetate has allowed the isolation of a new cyclopalladated compound: (μ-OAc)$_2$[Pd(k^2-*C*,*N*-TnInA)]$_2$ (**1a**). This compound is easily transformed into the dimeric derivative (μ-Cl)$_2$[Pd(k^2-*C*,*N*-TnInA)]$_2$ (**1d**) or the mononuclear complexes [Pd(k^2-*O*,*O*′-acac)(k^2-*C*,*N*-TnInA)] (**1c**) and [PdCl(PPh_3)(k^2-*C*,*N*-TnInA)] (**1e**).

On the other hand when the reaction was carried out under the same conditions but with the ligand TzIn, which only differs in that the heterocyclic ring [N,S] contains one additional methylene group, the dinuclear cyclometallated compound was not obtained but instead a mononuclear complex *cis*-[Pd(OAc)$_2$(k^2-*N*,*N*′-TzIn)] (**2a**) was produced, in which the acetate groups do not act as bridging ligands to the palladium atoms. The calculations for ligand TzIn are not conclusive but show that this ligand has a greater tendency to coordinate through the nitrogen atom of the indazole ring than in the case of ligand TnInA, and therefore more likely to act as a bidentate ligand [N,N′].

Finally, due to the applications in pharmaceutical research of this family of heterocycles ligands, the new compounds presented in this work appear to be excellent candidates for further studies in this field.

4. Experimental

4.1. Materials and methods

Triphenylphosphine, Pd(OAc)$_2$, LiCl and sodium acetylacetonate were used as purchased from commercial sources. Solvents were distilled and dried before use [16].

The ligands 2-(indazol-1-yl)-2-thiazoline (TnInA) (**1**) and 2-(indazol-1-yl)-1,3-thiazine (TzIn) (**2**) were synthesized according to a method described previously [7b and 7c respectively].

Elemental analyses were carried out at the Serveis Científico Tècnics (*Universitat de Barcelona*). Infrared spectra were obtained with a Nicolet 400FTIR using KBr pellets. ^1H, $^{13}C\{^1H\}$, ^1H NOESY and two-dimensional $\{^1H-^{13}C\}$ HSQC, HMBC and $\{^1H-^1H\}$ NOESY NMR spectra were recorded with a Mercury-400 MHz spectrometer at room temperature. The chemical shift values (δ) are given in ppm. The solvents for the NMR experiments were DMSO-d_6 or $CDCl_3$ (99.9%) and $SiMe_4$ was used as reference and they are indicated in each case.

4.2. Synthesis of the TnInA (*1*) compounds

4.2.1. (μ-OAc)$_2$[Pd(k^2-*C*,*N*-TnInA)]$_2$ (*1a*)

Pd(OAc)$_2$ (0.110 g, 0.49 mmol) and a stoichiometric amount of **1** (0.100 g) were added to 20 mL of a mixture of glacial acetic and acetic anhydride (9:1). The mixture was heated under reflux for 2 h. After this period the resulting hot solution was filtered through celite to remove the black palladium formed. The brown solution was concentrated under reduced pressure to about 5 mL. The yellow precipitate formed was filtered off, washed with methanol and air dried. Yield: 32%. Characterization data: Anal. Calc. for $C_{24}H_{22}O_4N_6S_2Pd_2$: C, 39.20; H, 3.02; N, 11.43; S, 8.72. Found: C, 39.2; H, 3.0; N, 11.3; S, 8.6. IR data (KBr, cm^{-1}): 1580 (ν_{as} COO^-) and 1447 (ν_{sym} COO^-). ^1H NMR (DMSO-d_6): δ = 8.38 (s, 1H, $H^{3'}$), 7.53 (d, 1H, J = 7.6, $H^{4'}$), 7.21 (d, 1H, J = 7.2, $H^{6'}$), 7.16 (t, 1H, J = 7.6, $H^{5'}$), 4.38 (br m, 2H, H^3), 3.75 (br m, 2H, H^2) and 2.08 [s, 3H, Me (OAc)].

4.2.2. [Pd(OAc)(py-d_5)(k^2-*C*,*N*-TnInA)] (*1b*)

This product was prepared in an NMR scale and characterized in solution by ^1H NMR. 10 mg of the dimeric compound **1a** were introduced in an NMR tube, and then 0.7 mL of $CDCl_3$ were added. The resulting suspension was then treated with one drop of deuterated pyridine (py-d_5) and shaked for a few seconds. This produced a colourless solution that contained the desired complex. Characterization data: ^1H NMR: δ = 8.15 (s, 1H, $H^{3'}$), 7.40 (d, 1H, J = 7.6, $H^{4'}$), 6.15 (d, 1H, J = 7,2, $H^{6'}$), 6.88 (t, 1H, J = 7.6, $H^{5'}$), 4.61 (t, 2H, J = 8.0, H^3), 3.56 (t, 2H, J = 8.0, H^2) and 1.88 [s, 3H, Me (OAc)]. $^{13}C\{^1H\}$ NMR δ = 176.2 [$-CO_2$ (OAc)], 159.1 (C^5), 142.5 ($C^{3'}$), 138.8 ($C^{9'}$), 135.9 ($C^{6'}$), 124.0 ($C^{5'}$), 122.0 ($C^{8'}$), 117.7 ($C^{4'}$), 117.1 ($C^{7'}$), 60.3 (C^3), 31.9 (C^2) and 24.3 [Me (OAc)].

4.2.3. [Pd(k^2-*O*,*O*′-acac)(k^2-*C*,*N*-TnInA)] (*1c*)

A suspension formed by the complex **1a** [42 mg (0.057 mmol)], 16 mg of Na(acac) (0.11 mmol) and 15 mL of acetone was stirred for 18 h at room temperature. The resulting solution was concentrated under vacuum and the residue was passed through a silica gel column. Elution with CH_2Cl_2 produced the release of a yellow band which was collected and concentrated to dryness on a rotary evaporator. The solid formed was dried in vacuum. Yield: 77%. Characterization data: Anal. Calc. for $C_{15}H_{15}O_2N_3SPd$: C, 44.18; H, 3.70; N, 10.30; S, 7.86. Found: C, 44.5; H, 3.6; N, 10.2; S, 7.6. IR data (KBr, cm^{-1}): 1588 (ν_{as} COO^-) and 1447 (ν_{sym} COO^-). ^1H NMR ($CDCl_3$): δ = 8.16 (s, 1H, $H^{3'}$), 7.93 (d, 1H, J = 7.6, $H^{6'}$), 7.44 (d, 1H, J = 7.6, $H^{4'}$), 7,25 (t, 1H, J = 7.6, $H^{5'}$), 5.43 [s, 1H, >CH(acac)], 4.72 (t, 2H, J = 8.0, H^3), 3.61 (t, 2H, J = 8.0, H^2), 2.13 (s, 3H, Me[a]) and 2.03 (s,

3H, Me^b). $^{13}C\{^1H\}$ NMR δ = 187.9 and 186.7 [>CO (acac)], 158.8 (C^5), 142.6 ($C^{3'}$), 139.0 ($C^{9'}$), 132.5 ($C^{6'}$), 123.6 ($C^{5'}$), 121.8 ($C^{8'}$), 117.7 ($C^{4'}$), 116.2 ($C^{7'}$), 59.1 (C^3), 32.2 (C^2), 28.0 (Me^b) and 27.8 (Me^a).

4.2.4. $(\mu\text{-}Cl)_2[Pd(k^2\text{-}C,N\text{-}TnInA)]_2$ (**1d**)

This product was prepared in an NMR scale and characterized in solution by ^1H and $^{13}C\{^1H\}$ NMR. 2 mg of LiCl were added to a suspension of 10 mg of the dimeric compound **1a** in 0.7 mL of DMSO-d_6 in an NMR tube and shaked for a few seconds. Characterization data: ^1H NMR: δ = 8.39 (s, 1H, $H^{3'}$), 8.03 (d, 1H, J = 7.2, $H^{6'}$), 7.40 (d, 1H, J = 7.6, $H^{4'}$), 7.00 (t, 1H, J = 7.6, $H^{5'}$), 4.70 (br m, 2H, H^3), 3.52 (br m, 2H, H^2) and 1.69 [s, 3H, Me (free OAc)]. $^{13}C\{^1H\}$ NMR δ = 176.4 [$-CO_2$ (free OAc)], 158.4 (C^5), 143.8 ($C^{3'}$), 143.7 ($C^{9'}$), 139.7 ($C^{6'}$), 139.0 ($C^{7'}$), 124.2 ($C^{5'}$), 122.5 ($C^{8'}$), 118.0 ($C^{4'}$), 63.5 (C^3), 32.5 (C^2) and 25.9 [Me (free OAc)].

4.2.5. $[PdCl(PPh_3)(k^2\text{-}C,N\text{-}TnInA)]$ (**1e**)

44 mg (0.06 mol) of **1a** and LiCl (13 mg, 0.3 mmol) were suspended in 20 mL of acetone. The resulting suspension was stirred for 2 h at room temperature, and after this time triphenylphosphine (32 mg, 0.2 mmol) was added. The mixture was left to react again for 1 h at 298 K. The resulting suspension was concentrated under vacuum and the residue was eluted through a silica gel column chromatography. Elution with CH_2Cl_2 produced the release of a yellow band which was collected and concentrated to dryness on a rotary evaporator. The solid formed was dried in vacuum. Yield: 48%. Characterization data: Anal. Calc. for $C_{28}H_{23}ClN_3PPdS$: C, 55.46; H, 3.82; N, 6.93; S, 5.29. Found: C, 55.5; H, 4.1; N, 7.0; S, 5.5. IR data (KBr, cm^{-1}): 1090 (PPh_3 coordinated ligand). ^1H NMR ($CDCl_3$): δ = 8.09 (s, 1H, $H^{3'}$), 7.30–7.48 (m, 15H, aromatic protons of the PPH_3 ligand), 7.14 (d, 1H, J = 8.0, $H^{4'}$), 6.81 (d, 1H, J = 8.0, $H^{6'}$), 6.39 (t, 1H, J = 8.0, $H^{5'}$), 5.00 (t, 2H, J = 8.0, H^3) and 3.50 (t, 2H, J = 8.0, H^2). $^{13}C\{^1H\}$ NMR δ = 160.3 (C^5), 142.5 ($C^{3'}$), 141.0 ($C^{6'}$), 140.3 ($C^{9'}$), 124.7 ($C^{8'}$), 123.6 ($C^{5'}$), 122.9 ($C^{7'}$), 117.1 ($C^{4'}$), 61.9 (C^3), and 32.7 (C^2). $^{31}P\{^1H\}$ NMR data: δ = 31.05.

4.3. Synthesis of the TzIn (**2**) compounds

4.3.1. Cis-$[Pd(OAc)_2(k^2\text{-}N,N'\text{-}TzIn)]$ (**2a**)

$Pd(OAc)_2$ (0.103 g, 0.46 mmol) and a stoichiometric amount of **2** (0.100 g) were added to 20 mL of a mixture of glacial acetic and acetic anhydride (9:1). The mixture was heated under reflux for 2 h. After this period the resulting hot solution was filtered through celite to remove the black palladium formed. The brown solution was then concentrated to dryness on a rotary evaporator giving a brownish solid, that was collected and dried in vacuum. Yield: 56%. Characterization data: Anal. Calc. for $C_{15}H_{17}O_4N_3SPd$: C, 40.78; H, 3.88; N, 9.51; S, 7.26. Found: C, 40.7; H, 4.3; N, 9.4; S, 7.2. IR data (KBr, cm^{-1}): 1586 (ν_{as} COO^-) and 1408 (ν_{sym} COO^-). ^1H NMR ($CDCl_3$): δ = 8.32 (s, 1H, $H^{3'}$), 8.06 (d, 1H, J = 8.5, $H^{7'}$), 7.83 (d, 1H, J = 8.4, $H^{4'}$), 7.68 (t, 1H, J = 7.4, $H^{6'}$), 7.44 (t, 1H, J = 7.6, $H^{5'}$), 3.78 (t, 2H, J = 6.0, H^4), 3.41 (t, 2H, J = 6.0, H^2), 2.21 (br m, 2H, H^3), 2.12 [s, 3H, Me^a $(OAc)^a$] and 2.06 [s, 3H, Me^b $(OAc)^b$]. $^{13}C\{^1H\}$ NMR δ = 179.2 and 178.8 [$-CO_2$ (OAc)], 156.0 (C^6), 143.0 ($C^{3'}$), 138.0 ($C^{9'}$), 132.4 ($C^{6'}$), 125.8 ($C^{5'}$), 124.5 ($C^{8'}$), 123.4 ($C^{4'}$), 112.5 ($C^{7'}$), 47.5 (C^3), 26.9 (C^2), 23.1 [$Me^{a,b}$ $(OAc)^{a,b}$] and 20.6 (C^3).

4.3.2. Cis-$[PdCl_2(k^2\text{-}N,N\text{-}TzIn)_2]$ (**2b**)

This product can be obtained by two different procedures using either the ligand **2** or the coordination compound **2a**.

4.3.2.1. Method (a). $K_2[PdCl_4]$ (0.100 g, 0.31 mmol) and a stoichiometric amount of **2** (0.067 g) were added to 20 mL of a mixture of glacial acetic and acetic anhydride (9:1). The mixture was heated under reflux for 2 h. After this period the orange solid formed was filtered out, washed with ethanol and air dried. Yield: 75%.

4.3.2.2. Method (b). To a solution containing 50 mg (0.011 mmol) of **2a** and 20 mL of ethanol, 90 mg (0.022 mmol) of LiCl were added. The resulting mixture was stirred at 298 K for 2 h. After this period the orange solid formed was filtered out, washed with ethanol and air dried. Yield: 57%.

4.3.2.3. Characterization data. Anal. Calc. for $C_{11}H_{11}Cl_2N_3SPd\cdot 0.25H_2O$: C, 33.10; H, 2.90; N, 10.50; S, 8.0. Found: C, 33.5; H, 2.6; N, 10.5; S, 7.8. ^1H NMR (DMSO-d_6): δ = 8.90 (s, 1H, $H^{3'}$), 8.25 (d, 1H, J = 8.8, $H^{7'}$), 8.10 (d, 1H, J = 8.8, $H^{4'}$), 7.85 (t, 1H, J = 7.6, $H^{6'}$), 7.55 (t, 1H, J = 7.6, $H^{5'}$), 3.91 (t, 2H, J = 5.6, H^4), 3.50 (t, 2H, J = 5.6, H^2) and 2.11 (br m, 2H, H^3). $^{13}C\{^1H\}$ NMR δ = 156.0 (C^6), 142.2 ($C^{3'}$), 137.9 ($C^{9'}$), 133.2 ($C^{6'}$), 126.2 ($C^{5'}$), 125.0 ($C^{4'}$), 124.2 ($C^{8'}$), 112.5 ($C^{7'}$), 49.6 (C^4), 27.6 (C^2) and 21.3 (C^3).

4.4. X-ray structural characterization

A selected transparent colourless crystal of **1e** was glued at the end of a glass fibre and mounted on an Enraf–Nonius CAD4 diffractometer, where the X-ray diffraction experiment was carried out. Unit-cell parameters were determinated from automatic centring of 25 reflections and refined by least-squares method. A summary of the crystal data obtained is shown in Table 3.

The structural resolution procedure was made using the WinGX [17] package. Solving for structure factor phases was performed by the SIR2004 program [18], and the full-matrix refinement by SHELXL97 [19]. Non-H-atoms were refined anisotropically and H-atoms were introduced in calculated positions and refined riding on their parent atoms. A summary of the refinement parameters is also shown in Table 3.

4.5. Calculation details

All DFT calculations were carried out with the Gaussian 03 [20] package of programs using the B3LYP hybrid functional [21]. The basis set was chosen as follows: for Pd LANL2DZ was used [22], where an effective core potential was utilized to replace the 36 innermost. For carbon, hydrogen, oxygen, sulphur and nitrogen the 6-31G(d) basis including polarization functions for non-hydrogen atoms [23] was used. Geometry optimizations and frequency calculations were performed with no imposed symmetry restrictions. Solvent effects were calculated on the preoptimized geometries using the C-PCM model [24].

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Appendix A. Supplementary material

CCDC 846925 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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