Research article

Interaction of 2-aminopyrimidine with dichloro-[1-alkyl-2-(naphthylazo) imidazole]palladium(II) complexes: Kinetic and mechanistic studies

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Abstract

Background: The anticancer properties of cisplatin and palladium(II) complexes stem from the ability of the cis-MCl₂ fragment to bind to DNA bases. However, cisplatin also interacts with non-cancer cells, mainly through bonding molecules containing -SH groups, resulting in nephrotoxicity. This has aroused interest in the design of palladium(II) complexes of improved activity and lower toxicity. The reaction of DNA bases with palladium(II) complexes with chelating N,N donors of the cis-MCl₂ configuration constitutes a model system that may help explore the mechanism of cisplatin’s anticancer activity. Heterocyclic compounds are found widely in nature and are essential to many biochemical processes. Amongst these naturally occurring compounds, the most thoroughly studied is that of pyrimidine. This was one of the factors that encouraged this study into the kinetics and mechanism of the interaction of 2-aminopyrimidine (2-NH₂-Pym) with dichloro-[1-alkyl-2-(α-naphthylazo)imidazole]palladium(II) [Pd(α-NaiR)Cl₂, 1] and dichloro-[1-alkyl-2-(β-naphthylazo)imidazole]palladium(II) [Pd(β-NaiR)Cl₂, 2] complexes where the alkyl R = Me (a), Et (b), or Bz (c).

Results: 2-NH₂-Pym reacts with 1a, 1b, and 1c to yield [[1-alkyl-2-(α-naphthylazo)imidazole]bis(2-aminopyrimidine)]palladium(II) (3a, 3b, 3c) dichloride and with 2a, 2b, and 2c to yield [[1-alkyl-2-(β-naphthylazo)imidazole]bis(2-aminopyrimidine)]palladium(II) (4a, 4b, 4c) dichloride in an acetonitrile (MeCN) medium. The products were characterized using spectroscopic techniques (FT-iR, UV-Vis, NMR). The ligand substitution reactions follow second order kinetics – first order dependence on the concentration of the Pd(II) complex and 2-NH₂-Pym. Addition of LiCl to the reaction does not influence its rate. The thermodynamic parameters (standard enthalpy of activation, \( \Delta H^* \) and standard entropy of activation, \( \Delta S^* \)) were determined from variable temperature kinetic studies. The magnitude of the second order rate constant, \( k_2 \), at 298 K, was shown to increase thus: \( b < a < c \) as well as \( 1 < 2 \).

Conclusion: The kinetics of the reaction between Pd(II) complexes (1 and 2) and 2-NH₂-Pym were examined spectrophotometrically at 530 nm in MeCN under pseudo-first-order conditions. The reaction rate is largely influenced by the \( \pi \)-acidity of the chelating ligand, with substitution in the naphthyl azoimidazole backbone influencing the rate of the substitution process. The activation parameters, \( \Delta H^* \) and \( \Delta S^* \), were determined and support the kinetic rate data.
Background

The anticancer properties of cis-Pt(NH₃)₂Cl₂ or cisplatin [1-9] have given impetus to research in the field of platinum chemistry. This anticancer activity stems from the binding of the cis-PtCl₂ fragment with DNA bases. However, cisplatin also interacts with non-cancer cells, through bond formation with -SH groups, resulting in nephrotoxicity. The anticancer properties of biologically important palladium(II) complexes [10-14] have aroused interest in the design of platinum(II) and palladium(II) [4] and palladium(II) complexes [10-14] have aroused interest in the design of platinum(II) and palladium(II) complexes of better activity and lower toxicity.

Mono-dentate ligands can bind in both cis- and trans-arrangements around a metal center, with the stability of the isomers dependent upon several factors. Bidentate ligands, however, are more reliable for the preparation of cis-complexes, in particular those of palladium(II) and platinum(II) [15-22]. The reaction of DNA bases with Pt(II) complexes with chelating N,N/donors of the cis-MCl₂ configuration constitutes a model system that may permit the exploration of the mechanism of cisplatin's anticancer activity. The kinetics and mechanism of reactions involving Pd(II) complexes [23-27] prompted us to study palladium(II) cisplatin analogues. The kinetics and mechanism of the substitution reactions involving Pd(II) complexes of 1-alkyl-2-(aryazo)imidazoles (i) (Figure 1) with adenine [28], cytosine [29], 2-mercapto-pyridine [30], 2-amino-pyrimidine [31], picolinic acid [32,33], and 8-hydroxy quinoline [34,35] have been reported.

In order to introduce greater steric crowding around the target metal center, we aim to use different ligands containing the azoimine chelating mode (-N=N-C=N-). This will allow the mechanism of nucleophilic interaction with the metal centre under different local environments to be elucidated. Naphthyl azoimidazoles ((ii) in Figure 1) are chemical analogues to phenyl azoimidazoles ((i) in Figure 1) but with a greater degree of steric crowding and electron donating ability.

Heterocyclic compounds are found widely in nature, being essential to many biochemical processes, with the most thoroughly studied that of pyrimidine. Such ring systems form the building units of many valuable chemotherapeutic agents (Bleomycine), vitamins (Vitamin B₁), drugs (hypotonic, antibacterial, antimalarial), nucleic acids (cytosine and uracil). This fact has encouraged us to study the reactions of pyrimidine derivatives with different metal complexes [36,37]. In this study we present the kinetic and mechanistic studies of the reaction of 2-NH₂-Pym with 1 and 2.

Results and Discussion

The two classes of naphthyl azoimidazole palladium(II) complexes, 1 and 2, have been used in this work, that is, Pd(α-NaiR)Cl₂ (1) and Pd(β-NaiR)Cl₂ (2) where α-NaiR = 1-alkyl-2-(α-naphthylazo)imidazole, β-NaiR = 1-alkyl-2-(β-naphthylazo)imidazole, and R = Me (a), Et (b) or Bz (c). The ligands belong to the asymmetric bidentate N,N/ donors type and form dichloropalladium(II) complexes. Hereafter we shall use the abbreviation, Pd(N,N')Cl₂ (see Scheme 1), when referring to the complex.

![Scheme 1](https://example.com/scheme1.png)

The reaction kinetics between Pd(N,N')Cl₂ and 2-NH₂-Pym were examined spectrophotometrically. The reaction is first order with respect to the Pd(II) complex because \( k_{obs} \)-values are almost steady when all variants are constant, other than that of the complex concentration. The \( k_{obs} \)-values (Table 1) and the linear plots for the \( k_{obs} \) versus initial molar concentration of 2-NH₂-Pym, [2-NH₂-Pym]₀ (Figures 2 and 3) indicate the reaction is first order with respect to 2-NH₂-Pym. The slope of the plot gives the second order rate constant (k₂). The small intercept (k₀) value indicates the minor existence of a solvent assisted pathway to the overall reaction products, because MeCN is a coordinating solvent.

The reaction rate increases with temperature as expected from the Eyring equation. Activation parameters, standard enthalpy of activation (ΔH*) and standard entropy of

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**Figure 1**

Phenylazoimidazole (i) and Naphthylazoimidazole (ii).
activation (Δ‡S°) was calculated using Eyring plots (Figures 4 and 5), which are recorded in Table 2. The activation parameter values support the experimental k2-values. The order for the Δ‡H° and Δ‡S° values is: b > a > c and 1 > 2. The iso-kinetic plot (Figure 6) suggests an identical mechanism as that for the reaction of Pd(N,N)/Cl2 with 2-NH2-Pym. Kinetic studies in the presence of externally added Cl- ions (LiCl) reveal that the rate as well as kobs almost remain unchanged with variation of [Cl-]0 when all other variants are constant, thus supporting the mechanism outline (see Scheme 2). The dissociation of the first Pd-Cl bond is the rate-determining step, and is therefore not affected by externally Cl- ion as LiCl. The reaction product was isolated and characterized as [Pd(N,N/) (2-NH2-Pym)2](ClO4)2.

The overall nucleophilic substitution process involves direct displacement of 2 Cl- ions by 2-NH2-Pym (see Scheme 3), with the observed rate expressed as:

\[
\text{Rate} = \{k_0 + k_2 [2-NH_2-Pym]_0 \} [Pd(N,N/)Cl2] = k_{obs} [Pd(N,N/)Cl2], \text{ with } k_{obs} = k_0 + k_2 [2-NH_2-Pym]_0
\]

where \(k_0\) and \(k_2\) are the intercept and the slope of the plot of \(k_{obs}\) versus \([2-NH_2-Pym]_0\) respectively. The values of \(k_0\) and \(k_2\) are constant when the temperature is constant. The nucleophile is an N donor ligand. It is probable that the basic N coordinates quickly with the positively charged metal centre. The first step of the reaction is the formation of a five-coordinated square pyramidal species (X) from

| Table 1: |                  |
|----------|------------------|
|          | 10^3 [2-NH2-Pym]_0 (mol dm⁻³) | 10^3 kobs (s⁻¹) | \(k_2\) (dm³ mol⁻¹ s⁻¹) | \(k_0\) (s⁻¹) |
| 1a       | 1.00             | 3.28            | 2.53                      | 0.67          |
|          | 3.00             | 8.12            |                          |
|          | 5.00             | 13.45           |                          |
|          | 7.00             | 18.17           |                          |
|          | 10.00            | 26.03           |                          |
| 1b       | 1.00             | 3.06            | 2.24                      | 0.69          |
|          | 3.00             | 7.32            |                          |
|          | 5.00             | 11.70           |                          |
|          | 7.00             | 16.43           |                          |
|          | 10.00            | 23.11           |                          |
| 1c       | 1.00             | 3.35            | 2.68                      | 0.61          |
|          | 3.00             | 8.95            |                          |
|          | 5.00             | 14.25           |                          |
|          | 7.00             | 20.05           |                          |
|          | 10.00            | 28.15           |                          |
|          | 1.00             | 4.20            |                          |
| 2a       | 3.00             | 11.95           | 3.85                      | 0.33          |
|          | 5.00             | 19.33           |                          |
|          | 7.00             | 27.35           |                          |
|          | 10.00            | 38.80           |                          |
|          | 1.00             | 3.76            |                          |
| 2b       | 3.00             | 10.52           | 3.65                      | 0.11          |
|          | 5.00             | 18.46           |                          |
|          | 7.00             | 26.79           |                          |
|          | 10.00            | 35.97           |                          |
| 2c       | 1.00             | 4.47            | 4.13                      | 0.19          |
|          | 3.00             | 13.06           |                          |
|          | 5.00             | 19.65           |                          |
|          | 7.00             | 29.52           |                          |
|          | 10.00            | 41.63           |                          |

Observed pseudo-first-order rate constants (kobs) for the reactions of 2-aminopyrimidine with dichloro-{1-alkyl-2-(α-naphthylazo)imidazole}palladium(II) (1) and dichloro-{1-alkyl-2-[(β-naphthylazo)imidazole]palladium(II) (2) complexes where the alkyl R = Me(a), Et(b), or Bz(c) in MeCN: [Pd(NN)Cl2]0 = 1.0 × 10⁻⁴ mol dm⁻³, Temperature = 298 K.
the complex (1 or 2) with 2-NH₂-Pym. This species quickly converts into a more stable four coordinated square planar species (Y) by dissociation of first Pd-Cl bond. The second nucleophile coordinates rapidly with the mono positive species (Y) forming the final product (3 or 4) by simultaneous dissociation of second Pd-Cl bond. Because the first Pd-Cl bond cleavage is possibly slow, the step is therefore rate determining. This is supported by there being no effect on reaction rate from externally added Cl⁻ as LiCl. A plausible mechanism, outlined in Scheme 2, initially involves two competing steps: the first, a solvation step where coordinating solvent, MeCN, forms a solvated species Pd(N,N\textsuperscript{1}Cl\textsubscript{2}MeCN (Z); and the second, a nucleophilic attack by 2-NH₂-Pym (Scheme 2). Though the steric crowding of the α-/β-naphthyl group in N,N/chelating ligand is significant its strong electron withdrawing ability resulting from conjugation, stabilizes the chelated Pd(N,N\textsuperscript{1}) species, rather than resulting in dechelation.

The kinetic data in Table 1 reveal that the magnitude of $k_2$ increases thus: $b < a < c$. This is because of the electron withdrawing tendency of Bz group is greater than that of Me whilst that of the Me group it is slightly greater than for Et.

**Conclusion**

The kinetics of the interaction between Pd(N,N\textsuperscript{1})Cl\textsubscript{2} and 2-NH₂-Pym were examined spectrophotometrically at 530 nm in MeCN under pseudo-first-order reaction conditions. The reactions are first order with respect to the Pd(II) complex and 2-NH₂-Pym. The rate of reaction is largely influenced by the $\pi$-acidity of the chelating ligand; substitution in the naphthyl azoimidazole backbone influences greatly the rate of the substitution. The reaction activation parameters, $\Delta^H°$ and $\Delta^S°$, were calculated and correlate well with the kinetic rate data. The products isolated from the reaction between Pd(N,N\textsuperscript{1})Cl\textsubscript{2}and 2-NH₂-Pym in MeCN were characterized by spectroscopically, and the composition being confirmed as [Pd(N,N\textsuperscript{1})(2-NH₂-Pym)\textsubscript{2}][ClO\textsubscript{4}]\textsubscript{2}.

**Experimental**

The Pd(II) complexes were prepared according to a reported procedure [38,18]. 2-aminopyrimidinone was obtained from Sigma-Aldrich. Acetonitrile (MeCN) was purified using a known procedure [39,40]. All kinetic and spectroscopic measurements were recorded on an Agilent 8453E UV-visible Spectroscopy System. Quartz cells (1.0 cm path length) from Hellma were used. IR spectra (KBr pellet) were recorded on a FT-IR Spectrophotometer Spectrums RX1, Perkin-Elmer. H\textsuperscript{1} NMR spectra were carried out on a 300 MHz Bruker NMR instrument in CD\textsubscript{3}CN using TMS as the internal standard. Microanalyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. The specific conductance was measured on a JENCONS 4010 Conductivity Meter. Rate constants and standard deviations were calculated by linear regression using a PC-based programme, Microcal-origin version Origin-6.1.

For the kinetic measurements, stock solutions of the Pd(II) complexes (ca. 10\textsuperscript{-3} mol dm\textsuperscript{-3}) and of 2-amino-pyrimidinone (2-NH₂-Pym) (ca. 10\textsuperscript{-2} mol dm\textsuperscript{-3}) were prepared in dry MeCN. Solutions of different concentrations were
prepared by quantitatively diluting stock solutions using dry MeCN. All experiments were performed at 298 K (unless otherwise stated) by mixing the required volumes of the thermostated reactants, before being transferred into the absorption cells (1.0 cm length). On addition of 2-amino-pyrimidine (2-NH₂-Pym) to the solution of Pd(N,N')Cl₂ (1 or 2) in MeCN the orange solution changes to yellow-orange. The influence of the addition of 2-amino-pyrimidine (2-NH₂-Pym) on the spectra of Pd(N,N')Cl₂ (1b) is shown in the Figure 7. The change proceeds through a single isosbestic point at ca. 412 nm. The decrease in absorbance of the reaction mixture was recorded automatically at ca. 530 nm as a function of time. At was measured after ~24 h of mixing, when the absorbance became constant. In all experiments, the initial molar concentration of 2-NH₂-Pym, [2-NH₂-Pym]₀, was kept at least ten times higher than Pd(II) complex concentration so as to maintain pseudo-first-order kinetic conditions. Pseudo-first-order rate constants, kₜₐₙ, were obtained from the slopes of the plots of (Aₐ-Aₐₙ) versus time (Figure 8) where Aₐ = absorbance of the reaction mixture at time, t(s) after mixing of 2-NH₂-Pym solution, and Aₐₙ = absorbance of same after completion of the reaction.

**Synthesis of [Pd(α-NaiEt)(2-NH₂-Pym)₂](ClO₄)₂ (3b-diperchlorate)**

To the MeCN solution of the complex Pd(α-NaiEt)Cl₂ (25 mg, 5.85 × 10⁻² mmol), 2-NH₂-Pym (5.6 mg, 5.89 × 10⁻² mmol) was added and the resulting orange-colored solution stirred for about 24 h. Next, the solution was filtered and allowed to evaporate to dryness at room temperature. The resulting mass was then dissolved in methanol, before the addition of an aqueous solution of 1 g of NaClO₄. The resulting brown precipitate was filtered and washed with water. The dried product was then chromatographed over silica gel, with MeCN eluting an orange band. A yield of 29 mg (65.91%) was obtained.

All other complexes were prepared using the same procedure with yields varying from 58–70%.

Microanalytical data of the products are as follows: For [Pd(α-NaiMe)(2-NH₂-Pym)₂](ClO₄)₂ (3a-diperchlorate): Anal. Found: C, 36.02; H, 3.04; N, 19.59%. Calc. for C₂₂H₂₂O₈N₁₀PdCl₂: C, 36.07; H, 3.07; N, 19.62%. For [Pd(α-NaiBu)(2-NH₂-Pym)₂](ClO₄)₂ (3b-diperchlorate) Anal. Found: C, 37.10; H, 3.30; N, 18.69%. Calc. for C₂₃H₂₄O₈N₁₀PdCl₂: C, 37.03; H, 3.22; N, 18.78%. For [Pd(β-NaiBu)(2-NH₂-Pym)₂](ClO₄)₂ (3c-diperchlorate) Anal. Found: C, 41.72; H, 3.21; N, 17.11%. Calc. for C₂₃H₂₄O₈N₁₀PdCl₂: C, 41.62; H, 3.22; N, 17.34%. For [Pd(β-NaiMe)(2-NH₂-Pym)₂](ClO₄)₂ (3d-diperchlorate) Anal. Found: C, 36.18; H, 3.02; N, 19.36%. Calc. for C₂₂H₂₂O₈N₁₀PdCl₂: C, 36.10; H, 3.01; N, 19.14%. For [Pd(β-NaiEt)(2-NH₂-Pym)₂](ClO₄)₂ (3b-diperchlorate) Anal. Found: C, 37.08; H, 3.25; N, 18.75%. Calc. for C₂₃H₂₄O₈N₁₀PdCl₂: C, 37.03; H, 3.22; N, 18.78%. For [Pd(β-NaiBz)(2-NH₂-Pym)₂](ClO₄)₂ (3e-diperchlorate) Anal. Found: C, 41.60; H, 3.23; N, 17.30%. Calc. for C₂₈H₂₆O₈N₁₀PdCl₂: C, 41.62; H, 3.22; N, 17.34%.

**Product characterization**

To the MeCN solution of the complex, Pd(N,N')Cl₂, 2-NH₂-Pym was added and the orange-colored solution was stirred for about 24 h. Next the solution was filtered and allowed to evaporate to dryness at near to room temperature. The resulting solid was dissolved in methanol, before the addition of aqueous NaClO₄. The brown precipitate was filtered, washed with water and cold MeCN. The dried product was chromatographed over silica gel with MeCN eluting an orange-red band. Finally the micro-analytical data in addition to U.V.-Vis, IR, NMR (Table 3) spectral data were obtained for the dried product. The molar conductivity data for the compound in a MeCN solution (ΛM = 120–155 S cm² mol⁻¹) showed the 1:2 electrolytic nature of the complexes. The IR spectra of the complexes display stretches at 1350–1370 cm⁻¹ which corresponds to υ(N=N), suggesting lack of a significant interaction in the solid state [42].
nated 2-NH$_2$-Pym shows $\nu$(NH$_2$) as a doublet at ca. 3135 and 3200 cm$^{-1}$.

The electronic spectra of the complexes were recorded in the range of 900 – 200 nm in MeCN. The absorptions below 400 nm are due to intramolecular charge transfer and therefore do not need to be considered further. The absorption band in the range 500 – 530 nm for all the complexes is absent in free ligands, and may represent charge transfer transitions localized on the metallated fragment [43].

The H NMR spectra of the complexes were recorded in CD$_3$CN (Table 3). The proton-numbering is outlined in Scheme 1. The data reveal that the signals in the complexes are shifted downfield relative to the free ligand values [34] supporting the coordination of ligand to Pd(II). An important feature of the spectra is the general shifting observed for the imidazole protons 4-H and 5-H to lower $\delta$-values relative to naphthyl protons (6-H – 13-H); the imidazole protons are shifted by 0.1–0.2 ppm compared to the free ligand position.

This supports the strong preference of the binding of imidazole-N to Pd(II). The Naphthyl protons appear as multiplets except for the broad singlet for 6-H and doublet for 8-H (in [Pd(α-/β-NaiR)](2-NH$_2$-Pym)$_2$)(ClO$_4$)$_2$) and a doublet for 15-H in the case of all the complexes. The 1-alkyl group appears as a singlet to –N(1)-CH$_3$ of Me group in [Pd(α-/β-NaiMe)](2-NH$_2$-Pym)$_2$)(ClO$_4$)$_2$, quartet to –N(1)-CH$_2$-, triplet to –CH$_3$ of Et group in [Pd(α-/β-NaiEt)](2-NH$_2$-Pym)$_2$)(ClO$_4$)$_2$, and also singlet to –N(1)-

### Table 2:

| Pd(N,N/Cl$_2$ | Temperature (K) | $k_2$ (dm$^3$ mol$^{-1}$ s$^{-1}$) | $\Delta\tilde{H}^\circ$ (kJ mol$^{-1}$) | $\Delta\tilde{S}^\circ$ (J K$^{-1}$mol$^{-1}$) |
|----------------|-----------------|-------------------------------|--------------------------------------|--------------------------------------|
| 1a             | 293             | 2.03                          | 29.12                                | -139.51                              |
|                | 298             | 2.53                          |                                      |                                      |
|                | 303             | 3.12                          |                                      |                                      |
|                | 308             | 3.82                          |                                      |                                      |
|                | 313             | 4.66                          |                                      |                                      |
| 1b             | 293             | 1.80                          | 33.84                                | -124.46                              |
|                | 298             | 2.24                          |                                      |                                      |
|                | 303             | 2.93                          |                                      |                                      |
|                | 308             | 3.69                          |                                      |                                      |
|                | 313             | 4.62                          |                                      |                                      |
| 1c             | 293             | 2.31                          | 23.30                                | -158.38                              |
|                | 298             | 2.68                          |                                      |                                      |
|                | 303             | 3.26                          |                                      |                                      |
|                | 308             | 3.84                          |                                      |                                      |
|                | 313             | 4.62                          |                                      |                                      |
| 2a             | 293             | 3.38                          | 14.44                                | -185.32                              |
|                | 298             | 3.85                          |                                      |                                      |
|                | 303             | 4.26                          |                                      |                                      |
|                | 308             | 4.76                          |                                      |                                      |
|                | 313             | 5.30                          |                                      |                                      |
| 2b             | 293             | 3.18                          | 21.16                                | -162.87                              |
|                | 298             | 3.85                          |                                      |                                      |
|                | 303             | 4.41                          |                                      |                                      |
|                | 308             | 5.14                          |                                      |                                      |
|                | 313             | 5.98                          |                                      |                                      |
| 2c             | 293             | 3.82                          | 9.52                                 | -201.16                              |
|                | 298             | 4.13                          |                                      |                                      |
|                | 303             | 4.49                          |                                      |                                      |
|                | 308             | 4.85                          |                                      |                                      |
|                | 313             | 5.23                          |                                      |                                      |

Second order rate constants ($k_2$) at different temperatures and activation parameters for the reactions of 2-aminopyrimidine with dichloro-{1-alkyl-2-(α-naphthylazo)imidazole}palladium(II) (1) and dichloro-{1-alkyl-2-(β-naphthylazo)imidazole}palladium(II) (2) complexes where the alkyl R = Me(a), Et(b), or Bz(c) in MeCN: [Pd(N,N/Cl$_2$)$_2$]$_0 = 1.0 \times 10^{-4}$ mol dm$^{-3}$, [2-NH$_2$- Pym]$_0 = 1.0 \times 10^{-2}$ mol dm$^{-3}$. 
CH$_2$ of Bz group in [Pd(α-/β-NaiBz)(2-NH$_2$-Pym)$_2$](ClO$_4$)$_2$ complexes. The $\delta$(NH$_2$) appears as a broad band at ca. 4.30 ppm which is shifted to higher chemical shift with respect to $\delta$(NH$_2$) when the -NH$_2$ group is non coordinated. This also supports coordination of -NH$_2$ to Pd(II). Pyrimidine protons (a-H to c-H,) appear between 8.5 to 9.0 ppm, which confirms the coordination of 2-NH$_2$-Pym compared with the free amine [44].

**Authors’ contributions**

This work was prepared by AM’s research group: PKG helped design and carry out the experiments in addition to drafting the manuscript. SS carried out the IR and $^1$H NMR spectra analysis and product characterization and participated in the discussion of the manuscript. This

**Figure 4**

Plots of $\ln(k/T)$ versus $(1/T)$ for the reactions: Pd(α-NaiR)Cl$_2$ + 2-NH$_2$-Pym in MeCN.

**Figure 5**

Plots of $\ln(k/T)$ versus $(1/T)$ for the reactions: Pd(β-NaiR)Cl$_2$ + 2-NH$_2$-Pym in MeCN.

**Figure 6**

Plot of $\Delta$$^\ddagger$H$_0$ versus $\Delta$$^\ddagger$S$_0$, i.e., iso-kinetic plot for the reactions: Pd(R/aiR)Cl$_2$ + 2-NH$_2$-Pym in MeCN.

**Authors’ contributions**

This work was prepared by AM’s research group: PKG helped design and carry out the experiments in addition to drafting the manuscript. SS carried out the IR and $^1$H NMR spectra analysis and product characterization and participated in the discussion of the manuscript. This

**Figure 7**

Spectra of Pd(α-NaiEt)Cl$_2$ in MeCN and the reaction mixture of Pd(α-NaiEt)Cl$_2$ and 2-NH$_2$-Pym in MeCN solution at 298 K. The arrows indicate decrease and increase of band intensities over the course of the reaction.
project was based on the ideas of AM and carried out with his guidance and consultation.

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**Table 3: H NMR spectral data of 3a-, 3b-, 3c-, 4a-, 4b-, and 4c-perchlorates in CD$_3$CN**

| Compound | δ (ppm ± J, Hz) |
|----------|----------------|
| 3a-diperchlorate | 7.01 (6.83) | 7.88 (7.0)$^d$ | 7.59$^c$ | 7.60 | 4.12 | 9.03 (7.0) | 8.54 (7.0) |
| 3b-diperchlorate | 7.03 (6.86) | 7.90 (7.0)$^d$ | 7.62$^c$ | 7.62 | 4.30 (9.0)$^e$ | 1.65 (7.0)$^e$ | 9.05 (7.0) | 8.55 (7.0) |
| 3c-diperchlorate | 7.05 (6.90) | 7.92 (7.0)$^d$ | 7.72$^c$ | 7.63 | 5.71$^h$ | 0.1117 ± 0.0025 | 4.36 (9.0)$^e$ | 1.61 (7.0)$^e$ | 9.08 (7.0) | 8.57 (7.0) |
| 4a-diperchlorate | 7.02 (6.81) | 8.01 | 7.81 (7.0)$^d$ | 7.81 | 4.15 | 9.05 (7.0) | 8.58 (7.0) |
| 4b-diperchlorate | 7.03 (6.87) | 8.05 | 7.83 (7.0)$^d$ | 7.83 | 4.32 (9.0)$^e$ | 1.61 (7.0)$^e$ | 9.08 (7.0) | 8.59 (7.0) |
| 4c-diperchlorate | 7.07 (6.92) | 8.10 | 7.88 (7.0)$^d$ | 7.88 | 5.75$^h$ | 0.1117 ± 0.0025 | 4.36 (9.0)$^e$ | 1.61 (7.0)$^e$ | 9.10 (7.0) | 8.61 (7.0) |

$^a$ Broad singlet; $^b$ Singlet; $^c$ Multiplet; $^d$ Doublet; $^e$ Triplet; $^f$ Ph-H : 7.45 – 7.55 ppm; $^g$ Quartet; $^h$ δ(NH$_2$): 4.26–4.32 (broad) ppm

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**Figure 8**

Plot of (At-A$^\infty$) versus time(s) for reaction, where, [Pd(α-NaiEt)Cl$_2$]$^0$ = 1.0 × 10$^{-4}$ mol dm$^{-3}$, [2-NH$_2$-Pym]$^0$ = 1.0 × 10$^{-3}$ mol dm$^{-3}$, and temperature = 298 K.

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Data: Data1_I

Model: ExpDec1

Equation: $y = A_1*exp(-x/t_1) + y_0$

Chi$^2$/DoF = 1.0213E-6

$R^2 = 0.99929$

$y_0$ 0.1117 ± 0.00052

$A_1$ 0.1189 ± 0.00054

$t_1$ 326.30056 ± 4.90303
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