Kinetic and mechanistic studies on the interaction of 2-aminopyrimidine with
dichloro[1-alkyl-2-(aryloazo)imidazole]palladium (II) complexes

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Nucleophilic substitution of Pd[RaaiR']Cl2 ([RaaiR' = 1-alkyl-2-(aryloazo)imidazole, p-R-C6H4-N=N-C6H4NN-1-R' where R = H(1)/Me(2)/Cl(3) and R' = Et(1)/Bz(2)], with 2-aminopyrimidine (2-NH2-Pym) in MeCN at 303 K, to form [Pd(N,N'-Pym)2Cl2], has been studied spectrophotometrically under pseudo-first-order conditions. The results obtained support a nucleophilic association path. The reaction follows the rate law, Rate = [k1 + k<P2-NH2-Pym>][Pd[RaaiR'Cl2], first order each in Pd[RaaiR'Cl2 and 2-NH2-Pym]. The rate increases as follows: Pd[RaaiEt]Cl2 < Pd[RaaiBz]Cl2 and Pd[Meaai]Cl2 < Pd[Haaai]Cl2 < Pd[Chaaai]Cl2. External addition of Cl- (LiCl) suppresses the rate inversely. The reactions have been studied at different temperatures (298-313 K) and activation parameters, ΔH° and ΔS° of the reactions have been calculated from the Eyring plot. The data support the proposed mechanism.

Heterocyclic compounds are very widely distributed in nature, and are essential to many biochemical processes. The most thoroughly studied ring system amongst these compounds is that of pyrimidine. They serve as building units of many valuable chemotherapeutic agents (Bleomycine), vitamins (Vitamin B1), drugs (hyproic, antibacterial, antimalarial), nucleic acids (cytosine and uracil). This has encouraged us to study the reactions of pyrimidine derivatives with different metal complexes1. We are interested in exploring the reactions of aryloazoheterocycles with platinum metals2. Palladium (II) forms several complexes of the Pd(N,N')Cl2 type with a cis-PdCl2 configuration3. Current research on palladium (II) and platinum (II) with N-donor ligands is targeted on synthesis of analogues of cisplatin. The antitumor activity of cisplatin has been explained on considering its reaction with DNA bases. It is, therefore, of interest to study the kinetics and mechanism of reactions of heterocyclic bases with Pd(N,N')Cl2 complexes. We have earlier reported the kinetics and mechanism of pyridine bases with Pd(N,N')Cl24. We report herein the reactions of 2-aminopyrimidine with dichloro[1-alkyl-2-(aryloazo)imidazole]palladium (II) and their reaction mechanism.

Materials and Methods

The complexes were prepared by an earlier reported procedure5. 2-Aminopyrimidine was obtained from Sigma-Aldrich. Spectrophotometric quality of MeCN was used, as obtained from SRL, India. For the kinetic measurements, stock solutions of the complexes (ca. 10−3 M) and of 2-aminopyrimidine (ca. 10−2 M) were prepared in MeCN. IR spectra (KBr disk) were recorded on a JASCO FT-IR (model 420) spectrophotometer and microanalyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer.

Kinetic measurements

All kinetic and spectral measurements were recorded on a Shimadzu UV-1700 spectrophotometer. The kinetics of the reactions between Pd[RaaiR'Cl2] and 2-NH2-Pym were studied under pseudo-first-order conditions with excess amount of 2-NH2-Pym in MeCN at 303 K. In all experiments, initial molar concentration of 2-NH2-Pym, [2-NH2-Pym]0, was at least ten times that of [complex]0 so as to maintain pseudo-first-order conditions. On addition of 2-NH2-Pym to the solution of Pd[RaaiR'Cl2] in MeCN, the orange solution slowly changes to yellow. The change proceeds through a single isobestic point at ca. 396 nm with a decrease in absorbance at ca. 460 nm and an increase at ca. 374 nm. Solutions of different
concentrations were prepared by accurate dilution of stock solutions. All experiments were performed at 303 K by mixing required volumes of the thermostated reactants with proper dilution to the required volume and transferred to the absorption cell (1 cm path length). The decrease in absorbance ($A_t$) of the reaction mixture was recorded at 460 nm at different time intervals. $A_t$ was measured after completion of reaction (~ after 24 hours of mixing) when the absorbance became constant. Pseudo-first-order rate constants ($k_{obs}$) and their standard deviations were calculated by linear regression using a PC-based programmed Microcal-Origin ver. 6.1. The $k_{obs}$ values were obtained from the plots of ($A_t$-$A_0$) versus time(s) (Fig. 1) for the reaction using Microcal-Origin ver. 6.1. The integrated rate equation used for the plots is: $$(A_t-A_0)=A_0 \exp(-k_{obs}t)$$ which is first order exponential decay equation.

The product isolated from the reaction mixture was characterized by micro analytical data and IR and $^1$H-NMR spectra. Micro analytical data: [Pd$_2$(2-NH$_2$-Pym)$_2$Cl$_4$]. Found: C, 17.8; H, 2.0; N, 15.3%. C$_8$H$_{10}$N$_2$Pd$_2$Cl$_4$. Calcd.: C, 17.8; H, 1.8; N, 15.4%. Major IR frequencies: $v$(NH$_2$), 3375 cm$^{-1}$; $v$(CH$_2$), 1664 cm$^{-1}$; $v$(Pd-Cl), 356 cm$^{-1}$. $^1$H-NMR data (CDCl$_3$) ($\delta$, ppm): C(2)-H, 7.88 (1H, doublet); C(3)-H, 7.41 (1H, triplet); C(4)-H, 7.94 (1H, doublet); N(6)-H, 4.49 (2H, broad).

### Results and Discussion

Two classes of aryloimidazole complexes of palladium (II) have been used in this study: 1-Ethyl-2-(aryloimidazole) (RaaiEt = 1) and 1-benzyl-2-(arylo) imidazole (RaaiBz = 2) (where R=Hra/ Met(b)/Cl(c)). The ligands belong to the unsymmetrical bidentate $N,N'$-donor type and form dichloro palladium (II) complexes. Hereinafter we have abbreviated the complex as Pd($N,N'$)Cl$_2$ (A). The kinetics of the reactions between Pd($N,N'$)Cl$_2$ and 2-aminopyrimidine (2-NH$_2$-Pym) were studied spectrophotometrically. The reactions are first order in complex as $k_{obs}$ values are almost constant when all other variables are constant except complex concentration. The $k_{obs}$ values (Table 1) and the linear plots with positive slope and a small positive intercept for the $k_{obs}$ versus [2-NH$_2$-Pym]$_0$ indicate the reaction is first order in 2-NH$_2$-Pym. The slope of the plot is second order rate constant ($k$) of the reaction ($r=0.9999(1a)$, $0.99999(1b)$, $0.99999(1c)$, $0.99994(2a)$, $0.99988(2b)$, $0.99966(2c)$). The presence of the small intercept of the plots of $k_{obs}$ versus [2-NH$_2$-Pym]$_0$ indicates a competing reaction of the complex with the solvent parallel to the same with 2-NH$_2$-Pym. MeCN is a coordinating solvent and may form an adduct (B)$^{6,7}$ (Eq. 1).

The rate increases with rise in temperature as expected from Eyring equation. Activation parameters, $\Delta H$ and $\Delta S$, were calculated using Eyring plots. The $\Delta H$ and $\Delta S$ values (Table 1) corroborate the experimental $k$ values. The order for $\Delta H$ and $\Delta S$ is: Pd(RaaiEt)Cl$_2$ > PdRaiBzCl$_2$ and Pd(MetaEt)Cl$_2$ > Pd(Hraa)Cl$_2$ > Pd(Claa)Cl$_2$ and corroborate with the order for $k$ which is just reverse of the order of $\Delta H$ and $\Delta S$ values. The linear iso-kinetic plot ($\Delta H$ versus $\Delta S$) supports the identical mechanism for the reactions of Pd($N,N'$)Cl$_2$ with 2-NH$_2$-Pym. Kinetic studies in presence of externally
added Cl (as LiCl) reveal that the rate as well as $k_{obs}$ decreases inversely with [Cl$^-$]. The products isolated from the reaction were characterized spectrophotometrically and by micro analytical data. They are identical and formulated as [Pd$_2$(2-NH$_2$-Pym)$_2$Cl$_4$] (D). Thus the nucleophilic substitution process involves direct displacement of N,N' by 2-aminopyrimidine (Scheme 1).
The observed rate is:

\[ \text{Rate} = \{k_0 + k [2\text{-NH}_2\text{-Pym}]_0\} [\text{Pd(N,N')Cl}_2] \]

When \([2\text{-NH}_2\text{-Pym}]_0 \gg [\text{Pd(N,N')Cl}_2]_0\), then

\[ \text{Rate} = k_0 [\text{Pd(N,N')Cl}_2] \]

where \(k_{obs} = k_0 + k [2\text{-NH}_2\text{-Pym}]_0\) and \(k_0\) and \(k\) are the intercept and slope respectively of the plot of \(k_{obs}\) versus \([2\text{-NH}_2\text{-Pym}]_0\). The values of \(k_0\) and \(k\) are constant when temperature and CT concentration are constant. The first step of the reaction is the formation of a five-coordinated species \(X\) from the complex with \(2\text{-NH}_2\text{-Pym}\). The lone pair of the nucleophile attacks the electrophilic Pd centre. It is highly probable that the lone pair of \(\text{NH}_2\) will coordinate first with the slightly positively charged metal centre due to \(\pi\)-acidity of \(N,N\) ligand. However, upon coordination the species undergoes a series of unidentified structural changes including de-chelation and finally forms an intermediate species \(C\) which on fast dimerisation produces final product \(D\).

The proposed mechanism is given in Scheme 2. Firstly, there are two competing paths: one is solvation path where co-ordinating solvent, MeCN forms a solvated species \(\text{Pd(N,N')Cl}_2(\text{MeCN})\) \((B)\) and the other is nucleophilic attack by \(2\text{-NH}_2\text{-Pym}\) to form
intermediate species X. Increase in the negative charge density at the metal center of adduct X elongates the M-L distances and may cause ring-opening and formation of Pd(amine). Intermediate. The first step of the reaction is the intermediate species X. Increase in the negative charge density at the metal center of adduct X using the conventional spectroscopic time scale. 2-NH₂-Pym coordination with metal increases the negative charge and steric crowding around the reaction center. This is relieved by elongation of the Pd-N/Pd-N/Pd-Cl bonds and leads to dechelation. Heterocyclic-N donors generally prefer to bind with palladium (II) and platinum (II) than with azo-N donor Variations). The X-ray structure determination reveals that the M-N (heterocycle) is shorter than the M-N (azo) (M = Pd, Pt) bond length. This helps us to conclude that the ring opening of Pd(N,N)(2-NH₂-Pym)Cl₂ chelate structure will take place via Pd-N (azo) bond dissociation. We were unable to isolate [Pd(amine)(N,N)(2-NH₂-Pym)Cl₂] type intermediates to establish confirmatory evidence in support of the mechanistic interpretation.

**Mechanism**

The kinetic data in Table 1 reveal that the magnitude of k increases firstly with the increase in π acidity of the arylazo backbone of arylazo-heterocycle and, secondly upon introducing an electron-withdrawing substituent in arylazo backbone of arylazoimidazoles. π-heterocycles are poor π-acceptors and better π-donors than six-membered N-heterocycles Variations). The presence of electron withdrawing substituents on the arylazo group and imidazole group influences the π-acidity of the ligand. The π-acidity order is: Cl(c) > H(a) > Me(b) and Bz(2) > Et(1). Increase of ligand’s π-acidity in a metal complex increases the hardness of the metal center and favours nucleophilic association. Hence, the observed change of reaction rate is in the order: Pd(RaaiEt)Cl₂ < Pd(RaaiBz)Cl₂ and Pd(MeaaR')Cl₂ < Pd(HaaR')Cl₂ < Pd(ClaaR')Cl₂. The plots of Hammett-σ values (for substituent R in Pd(RaaiEt/RaaiBz)Cl₂ complexes) versus log k values are linear. The slope of the Hammett correlation diagram is positive and is indicative of the transition state Variations) for the rate-limiting step of the overall reaction. This fact supports nucleophilic association.

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**References**


