Tuning the Reactivity and Bonding Properties of Metal Square-Planar Complexes by the Substitution(s) on the Trans-Coordinated Pyridine Ring

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ABSTRACT: The kinetics of the hydration reaction on trans-[Pt(NH₃)₂(pyrX)Cl]⁺ (pyr = pyridine) complexes (X = OH⁻, Cl⁻, F⁻, Br⁻, NO₂⁻, NH₂⁻, SH⁻, CH₃, C≡CH, and DMA) was studied by density functional theory calculations in the gas phase and in water solution described by the implicit polarizable continuum model method. All possible positions ortho, meta, and para of the substituent X in the pyridine ring were considered. The substitution of the pyr ligand by electron-donating X⁻ led to the strengthening of the Pt–N(pyrX) (Pt–NpyrX) bond and the weakening of the trans Pt–Cl or Pt–O⁻ bonds. The electron-withdrawing X's led to the strengthening of the NpyrX bonds. Substitution in the meta position led to the highest shifts of the substituent e⁻-back-donation abilities of the ligands 6 and 7. The changes of the strengths of these bonds can be predicted from the basicity of sigma electrons on the NpyrX atom determined on the isolated pyrX ligand. As the pyrX ring was oriented perpendicularly with respect to the plane of the complex, the nature of the X=C=O electrostatic interaction was the decisive factor for the transition-state (TS) stabilization which resulted in the highest selectivity of ortho-substituted systems with respect to the reaction rate. Because of a smaller size of X’s, the steric effects influenced less importantly the values of activation Gibbs energies ΔG‡ but caused geometry changes such as the elongation of the Pt–NpyrX bonds. Substitution in the meta position led to the highest ΔG‡ values for most of the X’s. The changes of ΔG‡ because of electronic effects were the same in the gas phase and the water solvent. However, as the water solvent dampened electrostatic interactions, 2200 and 150 times differences in the reaction rate were observed between the most and the least reactive mono-substituted complexes in the gas phase and the water solvent, respectively. An additional NO₂ substitution of the pyrNO₂ ligand further decelerated the rate of the hydration reaction, but on the other hand, the poly-NH₂ complexes were no more reactive than the fastest e-NH₂ system. In the gas phase, the poly-X complexes showed the additivity of the substituent effects with respect to the Pt–ligand bond strengths and the ligand charges.

INTRODUCTION

Platinum anticancer complexes are administered in their inactive neutral form as prodrugs, and at least one hydrolysis step is needed for their activation. The activated drug reacts rapidly with DNA or proteins, and the hydrolysis step is the rate-determining step of the whole process. Because platinum binding to proteins is probably responsible for the side effects of the drug,1 the activation should not be too fast to enable the drug to reach the nuclei of the malignant cells. Thus, the rate of hydrolysis is one of the important factors which should be considered for new drug development.

The reactivity of square-planar Pt(II)-complexes is driven by the trans effect; that is, the stability of the ligand is strongly influenced by the ligand in the trans position.2–4 It is a kinetic phenomenon whose origin lies in reactant destabilization and/or the transition state (TS) stabilization. The reactant destabilization is manifested itself by the Pt–trans ligand bond elongation, and it is sometimes called the trans influence.10 The trans effect can be explained by different σ-donation and π-back-donation abilities of the ligands9 and depends on the nature of the coordinating atom and its hardness.7 However, the chemistry of currently used drugs11 is rather limited because only slowly hydrolyzing compounds are needed, considering the length of the delivery route. Thus, the non-leaving groups are always bound to the central Pt(II) by a nitrogen atom and are either two amines or a diammine with an attached carbohydrate residue. The non-leaving group influence interactions with the proteins affecting cellular uptake of the drug and the repair of DNA-drug lesions.12 The influence of the leaving groups on the biotransformation kinetics of the drug is less clear but two chlorine atoms in the first-generation drug cisplatin were displaced by bidentate groups (e.g. cyclobutanedicarboxylate or oxalate group) bound by the oxygen atom to the platinum central atom in the second- and third-generation drugs. The mechanism of hydrolysis of bidentate groups is still not well understood.
and it is not clear in which form these drugs react with DNA.13–15

The substitution effects were explored on Pt(II)-complexes with different N,N,N-tridentate and N,N-bidentate ligands which mainly differ in Π-back-donation ability. Strong Π-acceptor ligands increase the electrophilicity of the Pt(II) center increasing the rate of the substitution.16–22

Complexes with aromatic monodentate ligands having anticancer properties were also reported including those based on pyridine and its derivatives.23–27 To minimize the inactivating interactions with thiols, a sterically hindered complex AMD 473 with 2-picoline (2-methylpyridine) ligand was synthesized.28 The reactivity of Pt(II) complexes with 2- and 3-picoline as ligands was experimentally compared by Sadler and co-workers. The complex with 2-picoline showed a 45 times slower hydration reaction of the Cl\(^-\) ligand in the trans position which was attributed to the steric effect of the methyl group on the pyridine ring.29 Hydrolysis of AMD 473 and its binding to guanine were studied also theoretically.30–32

The influence of the substitution in the para position of the pyridine ring on the spin densities and NMR spectra was studied for analogues of the Ru(III) complex NAMI.33

Monofunctional Pt complexes, which offer unique ways of transmembrane transport and DNA interactions, form another promising group of anticancer drugs. Pyrriplatin and phenanplatin contain three non-leaving ligands: two amines with pyridine and phenanthridine, respectively.23,34 Despite rather negligible DNA structure deformation, the inhibition of transcription was seen in vitro as well as in vivo.35,36 The antineoplastic effect of phenanplatin was discovered by Lippard and co-workers.37,38 Very recently, the importance of stacking interactions for the binding of phenanplatin to DNA was shown in studies of Veclani at al. and Almaqwashi et al.39,40

The replacement of chloride ligands by water ligands in cisplatin and its derivatives was a subject of many previous studies41–46 and was recently reviewed by Ahmad47 and by Kozelka.48

The substitution on the pyr ring affects the electron density on the coordinating atom through the inductive and resonance effects. In this study, we explored how the substitutions on the aromatic non-leaving group in the trans position influence the reactivity of the Pt(II)-complexes. We used \(\text{trans-[Pt-(NH}_3)_2(\text{pyrX})\text{Cl]}^+\) (pyrX = pyridine with the X substituent) complexes \((X = \text{OH}^-, \text{Cl}^-, \text{F}^-, \text{Br}^-, \text{NO}_2^-, \text{NH}_2^-, \text{SH}^-, \text{CH}_2, \text{C≡CH}, \text{DMA = dimethylamine})\) as the model compounds.

We studied how the stability of Pt–pyrX, Pt–Cl, and Pt–w \(\text{(w = water)}\) bonds and the kinetics of the hydration reaction are affected by the nature and the position of the X in the pyrX ligand (Scheme 1).

All possible positions ortho, meta, and para of the X in the pyr ring were considered. X was represented by electron-donating \((\text{NH}_2, \text{OH}, \text{and SH})\) and electron-withdrawing \((\text{C≡CH}, \text{and NO}_2)\) groups as well as by halides \((\text{F, Cl, and Br})\) with mixed (resonance) donating and (inductive) withdrawal effects.

Because of a large number of optimized reaction pathways, only results for \(X = \text{NH}_2\) and \(X = \text{NO}_2\) as the main representatives of electron-donating and electron-withdrawing groups, respectively, together with reference non-substituted \(X = \text{H}\) structures are shown in most tables in the text. Complete versions of the respective tables can be found in the Supporting Information.

Finally, the metal complexes with poly-substituted pyrX \((\text{poly-X})\) ligands were considered. The reasons were threefold: (1) to evaluate more generally the limits for \(\Delta G^\ddagger\) values due to substituent effects; (2) to test the additivity of substituent effects with respect to the bond strengths, bond lengths, NPA ligand charges, and \(\Delta G^\ddagger\) values; and (3) to provide an independent set of structures for the validity testing of the \(2\pi(N_{\text{pyrX}})\) natural atomic orbital (NAO) energy as the predictor of the Pt–ligand bond strengths and \(\Delta G^\ddagger\) activation free energies (see below). We used \(\text{NH}_2\) and \(\text{NO}_2\) ligands as the representatives of electron-donating and electron-withdrawing groups, respectively. Furthermore, we used fluorine as the ligand with a small size and high electronegativity. Its derivatives may have interesting properties and found many applications mainly as agrochemicals and pharmaceuticals.49

All poly-X ligands considered in this contribution are shown in Scheme 2.

**Scheme 2. Poly-X Ligands Considered in This Study and Their Designation \((X = \text{F, NH}_2, \text{NO}_2)\)**

![Scheme 2](image)

**RESULTS AND DISCUSSION**

**Structure Labeling.** The designation of the complexes with pyrX ligands reflects the position of the X on the pyr ring with respect to the \(N_{\text{pyrX}}\) atom: ortho \((o-)\), meta \((m-)\), and para \((p-\)). For corresponding transitions states and product structures, the letter ‘R’ is replaced by ‘TS’ and ‘P’, respectively. X-R and X-P structures represent isolated complexes without weakly bound \(\text{H}_2\text{O}\) and \(\text{Cl}^–\) ligands, respectively, and they were used for the evaluation of bonding properties and the electronic structure.

The same principle will be used for the complexes with the poly-X ligand for which \(o-(m-, p-)\)X will be replaced by the designation from Scheme 2.
The reaction energetics of the hydration reactions were determined by the supermolecular approach. Here, "w" and "Cl" suffixes in o-(m-, p-)X-R and o-(m-, p-)X-P_Cl products represent entering water and leaving chloride anion, respectively, being associated to Pt-complexes by H- bonding.

**Electronic Structure of the Isolated pyrX Ligands.** The influence of substitution effects on the reactivity of aromatic systems was studied in many previous studies. \(^{30-52}\) In the pyrX ring, the \(\pi\)-electrons are shifted in accordance with the mesomeretic effect. For electron-donating NH\(_2\) substituent, \(\pi\)-electron density is increased on atoms in the ortho and para positions with respect to NH\(_2\) while the opposite is true for the electron-withdrawing X such as NO\(_2\) (Figure S1). However, the \(\sigma\)-electrons are shifted independently and in fact contrarily with respect to \(\pi\)-electrons.\(^{30}\) For p-NH\(_2\), the density of \(\sigma\)-electrons is decreased on the N\(_{\text{pyrX}}\) atom while the opposite is true for p-NO\(_2\) (Figure S1).

-looking at atomic NPA charges, the shifts of the \(\sigma\)-electrons are masked by quantitatively larger shifts of the \(\pi\)-electrons. Values of NPA charge of the N\(_{\text{pyrX}}\) atom \((q(N_{\text{pyrX}}))\) in pyrX molecules are shown in Table 1. As expected, in the isolated pyrX molecule, \(q(N_{\text{pyrX}})\) is increased in electron-donating \(-\text{NH}_2\) while the opposite is true for p-NO\(_2\) (Figure S1).
Strength of the Pt–pyrX Bonds. The differences of $q(N_{pyrX})$ between the positional isomers in metallic X-R and X-P complexes were qualitatively similar to the isolated pyrX ligands (Table 1) and are discussed in more detail below. The Pt–pyrX bond was stabilized mainly by electrostatic energy $\Delta E_{elst}$ due to $+e$ and $+2e$ total charges of metal complex fragments in X-R and X-P (Table 2 and Table S1), respectively. The binding was accompanied by the charge transfer and polarization effects whose extent strongly depended on the charge of the complex. As expected, the amount of transferred negative charge from pyrX toward the metal was much higher in doubly charged X-P products compared to X-R reactants. For $X = H$, the respective pyrH charges were 0.424 and 0.241 (Table 2). The amounts of $\Delta E_{elst}$ energy are about one-half ($52 \pm 2\%$) and two-thirds ($69 \pm 3\%$) of the values of $\Delta E_{elst}$ energy in X-R and X-P, respectively (cf. below).

Pt–pyrX interaction energies were almost two ($1.77 \pm 0.03$) times higher for X-P than for X-R, and all stabilizing terms contributed to this difference (Table 2 and Table S1). The nature of the X on the pyrX ring influenced strongly the strength of the Pt–pyrX bond being weakened by electron-withdrawing X’s and made stronger by electron-donating ones. The binding energies were usually larger for para-X complexes than for ortho-X and meta-X ones (Figure 1). For X-R, the highest value of the binding energy was obtained for p-DMA-R ($-76.8$ kcal/mol) while the lowest for m-NO$_2$-R ($-55.6$ kcal/mol).

Electron-donating X’s promoted higher charge transfer from the pyrX ligand to the Pt atom by up to 10% (Table 2 and Table S1) being caused by stronger $\sigma$-donation. Five most important ETS-NOCV deformation density contributions describing the formation of the Pt–N$_{pyrX}$ bond in H-R, H-TS, and H-P structures are shown in Figure S2. The $\sigma$-donation energy $\Delta E_{\sigma\sigma}$ and $\pi$-donation energy $\Delta E_{\pi\pi}$ contributions were the most stabilizing terms for all structures. The $\sigma$-donation energy $\Delta E_{\sigma\sigma}$ contributions correlated well with total $\Delta E_{elst}$ energies for meta-X and para-X subsets (Figure 2B and Figure S3) accounting for 65.2 $\pm$ 0.8, 67.1 $\pm$ 0.9, and 61.7 $\pm$ 0.8% of their values for X-R, X-TS, and X-P structures, respectively.

For ortho-X’s, the correlation was worse (Figure 2B and Figure S3), and relative importance of $\Delta E_{elst}$ was slightly lower (by 2–3%) due to the existence of X···Pt and X···ligand nonbonding interactions in some structures (Figure S4). Similar information can be also seen from the dependence of Pt–pyrX bonding energy on the transferred $q(N_{pyrX})$ charge. The amount of the total transferred charge from the pyrX ligand to the metal complex correlated very well with the Pt–N$_{pyrX}$ bond lengths for o-X and p-X subsets (Figure S5). For the o-X subset, the correlation was worse with a less steep slope compared to m-X and p-X subsets and $R^2$ values 0.807, 0.690, and 0.799 for X-R, X-TS, and X-P structures, respectively (Figure S5). It reflected the existence of additional charge transfer channels (nonbonding interactions of X with Pt or NH$_3$ ligands) besides the Pt–N$_{pyrX}$ bond (cf. Figure S4).

The dependence of $\Delta E_{elst}^{\text{p-DMA-R}}$ on the Pt–N$_{pyrX}$ bond lengths was steeply linear for meta-X and para-X complexes (Figure 2A). The ortho-X complexes had clearly larger Pt–N$_{pyrX}$ bond lengths for given values of $\Delta E_{elst}^{\text{p-DMA-R}}$, and the correlation between the two variables was also linear for all o-X’s including those not involved in any nonbonding interactions ($o$-CH$_3$) but with exception of o-DMA as the bulkiest X. o-DMA complexes showed a substantial Pt–N$_{pyrX}$ bond elongation at a large value of $\Delta E_{elst}^{\text{p-DMA-R}}$ (Figure 2A and Figure S3). Thus, the steric hindrance should be responsible for the Pt–N$_{pyrX}$ bond elongation.

No clear trends were found for the $\pi$-bonding energy $\Delta E_{\pi\pi}$ and $\Delta E_{\sigma\sigma}$ contributions which involve $\pi$ and $\sigma$ orbitals of the pyrX ring, respectively, as the main source of the transferred contributions.
Figure 2. X-R structures: panel A: dependence of pyr-X ligand binding energies on the Pt−NpyrX bond lengths. The σ-DMA point was not included in the regression analysis for the ortho-X subset (blue line). Panel B: dependence of the σ-donation energy $\Delta E_{\sigma}^{\text{orb}}$ contributions on total $\Delta E_{\sigma}$ energies. One regression line was constructed for both meta-X and para-X subsets in the two graphs (black lines). The graphs for X-TS and X-P structures are shown in Figure S3.

Figure 3. Electron density difference isosurfaces of p-NH$_2$-R (A) and p-NO$_2$-R (B) structures with respect to the reference H-R structure which show electron accumulation (blue: 0.0004 a.u.) and depletion (red: −0.0004 a.u.) regions caused by p-NH$_2$ (A) and p-NO$_2$ (B) substitution of the pyr ring. Electron densities were calculated on the H-R geometry for all atoms of respective complexes except the atoms of the X substituent whose positions were optimized.

Electrons (Figure S2). $\Delta E_{\sigma}^{\text{orb}}$ was always the second most stabilizing contribution, and it was enhanced slightly for the CCH and NO$_2$ X's with conjugated multiple bonds with respect to the pyr ring. This term was much more important than $\Delta E_{\text{n-pi}}$, which could be mixed with the $\sigma$-back-donation or nonbonding interaction contributions in some ortho-X systems (Figure S4). Note that the $\pi$-back-donation was not apparent in the NOCV analysis possibly due to the positive charge of the Pt(II) fragment. For example, the $\pi$-back-donation transferred charges of 0.005, 0.001, and 0.009 e were calculated by the charge decomposition analysis, as provided by the Multiwfn program for the Pt−N$_{pyrX}$ bonds in H-R, p-NH$_2$-R, and p-NO$_2$-R structures, respectively.

Despite the positive charge of pyrX ligands, the negative NPA charge on the N$_{pyrX}$ atom ($q$(N$_{pyrX}$)) increased by about 10% (varying from 5.6% for o-NH$_2$-R up to 19.7% for o-NO$_2$-R, cf. Table 1) in X-R reagents and almost did not change in X-P products compared to the isolated pyrX ligand. It was caused by the polarization of the aromatic pyrX ligand upon binding with the positively charged metal complex. The transferred charge was drained from the CH and CX groups of the pyrX ligand roughly following the order para > meta > ortho (cf. ETS-NOCV deformation density contributions in Figure S2).

The changes of total electron densities with respect to the H-R structure caused by the H → X substitution are shown in Figure 3 for p-NH$_2$-R and p-NO$_2$-R structures. These differences reflected only pure electronic effects caused by the H → X substitution not considering accompanying changes of molecular structures. The shifts of electron density within the pyrX ligand were very similar to those in the isolated pyrX system (cf. Figure S1). With respect to the Pt(II) fragment, the substitution by the electron-donating NH$_2$ group led to exactly opposite changes of electron density compared to the electron-withdrawing NO$_2$ group (Figure 3). Thus, let us describe only the changes caused by the H → p-NH$_2$ substitution here: (1) the strengthening of the Pt−pyrX bond could be clearly documented by an increase of electron density roughly in the middle of this bond. (2) The electron density was increased in the $p_x$ orbital of the trans Cl$^-$ ligand (if the x axis is oriented along the Pt−Cl bond). It reflected the lower $\sigma$-donation and the weakening of the Pt−Cl bond (cf. below). (3) The changes of the total charge on the Pt atom ($q$(Pt)) were small for X-R structures (Table 2 and Table S1) due to compensating effects on the 5d NAOs: electron density was increased in 5d$_{xy}$, but decreased in 5d$_{3z^2-r^2}$ orbital (Figure 3). However, for the water trans ligand as a weaker electrophile, the changes of $q$(Pt) were larger and $q$(Pt) was decreased/increased for electron-donating/withdrawing X's (Table 2 and Table S1).

We used also the concept of the activation strain model and performed the fragment energy decomposition of the Pt−pyrX bond for the structures in Figure 3. For p-NH$_2$-R (p-NO$_2$-R), the Pauli, electrostatic, orbital, and dispersion energies were 130.5 (125.0), $-130.9$ ($-111.4$), 63.7 ($-61.3$), and $-7.2$ ($-7.3$) kcal/mol, respectively. A comparison of these values and also the ones for H-R (Table 2) confirmed the influence of X on the strength of the Pt−pyrX bond mainly through electrostatic energy which is in agreement with the analyses on fully optimized structures (cf. above).

Trans Influence: The Strength of the Pt−Cl and Pt−w Bonds. Trans influence is a thermodynamic phenomenon in which the binding of a more strongly bound ligand weakens the Pt−trans ligand bond which becomes elongated. Thus, the electron-withdrawing X’s strengthened the Pt−Cl ligand bond, and the opposite was true for electron-donating ones (Table 3 and Table S2). The influence of the X on the strengths of Pt−Cl and Pt−w bonds was roughly 8 and 14% of
Table 3. Interactions of Cl− and Water Ligands with the Rest of the Complex in the Gas Phase Optimized X-R and X-P Structures (X = H, NH2, NO2), Respectively: Pt−Cl, Pt−O bond lengths (in Å); the Total NPA Charges of the Cl− and Water Ligands (q(Cl), q(w)); and ETS-NOCV Energy Decomposition Terms ΔEbind, ΔEelst, ΔEorb, ΔEdisp, ΔEπ, and ΔEσ Obtained at the BLYP-D3BJ//TZ2P/B3LYP/BS1 Levela,b

| X-R | Pt−Cl | q(Cl) | ΔEbind | ΔEelst | ΔEorb | ΔEdisp | ΔEπ | ΔEσ | ΔEbind |
|-----|-------|-------|--------|--------|--------|--------|------|------|--------|
| H   | 2.315 | −0.477| 130.5  | −283.4 | −95.3  | −3.0   | −67.5| −9.8 | −248.7 |
| NH2 | 2.317 | −0.486| 131.8  | −278.3 | −95.8  | −3.0   | −68.5| −9.7 | −243.6 |
| NO2 | 2.320 | −0.492| 128.4  | −275.0 | −92.5  | −3.0   | −65.2| −10.1| −240.0 |

| X-P | Pt−O   | q(w)  | ΔEbind | ΔEelst | ΔEorb | ΔEdisp | ΔEπ | ΔEσ | ΔEbind |
|-----|--------|-------|--------|--------|--------|--------|------|------|--------|
| H   | 2.137  | 0.177 | 60.9   | −64.4  | −37.9  | −3.0   | −27.9| −5.9 | −46.8  |
| NH2 | 2.141  | 0.174 | 60.1   | −63.2  | −37.0  | −3.0   | −27.3| −5.7 | −45.6  |
| NO2 | 2.116  | 0.191 | 64.1   | −67.6  | −40.7  | −3.1   | −26.6| −5.5 | −44.4  |

All energy values are in kcal/mol. The data for all X’s are shown in Table S2. b ΔEbind energies were calculated at the B3LYP-D3BJ//BS2//B3LYP/BS1 level.

their relative value, respectively. These values were obtained from a comparison of binding energies of the strongest respective bond with the weakest one (Figure 1). Such low values reflected a rapid weakening of the electronic effects with increasing distance from the bound X because the relative change of the Pt−pyrX bond strength was more than 32%. This trend is visible in Figure 3 as the decrease of the local electrostatic potential at the NpyrX atom. The energy of the 2p orbitals on the isolated pyrX (Figure S7) probably due to a strong interference of o-X and one order of units of kcal/mol when systems with di-X substituents while the opposite was true for ortho-X substituents. Therefore, the 2p orbitals on isolated pyrX (Figure S7) can be still clearly seen as the result of smaller electron donation from Cl bond, the changes of the absolute values of its ΔEelst could be by up to one order of magnitude higher (see Table 2 and Table S1).

Prediction of the Pt−Ligand Bond Strengths. In previous studies, the strength of the Pt−ligand bonds was proportional to the properties such as the Pt−ligand bond lengths6,56 (cf. Figure 2A and Figure S3), the linear combinations of electron densities at bond critical bonds,56,57 or the populations in 5d orbitals of the Pt(II) atom.6,56 These properties were calculated for the optimized structures of whole metal complexes. However, our aim was to propose a predictor for the Pt−pyrX bond strength, which would be based just on the property of the isolated pyrX ligand as the putative reactant. First, we started with predictors typical for electrostatic energy such as the q(NpyrX) atomic NPA charge, the total dipole moment of pyrX, and the projection of the dipole moment into the C4−NpyrX bond direction. These predictors worked well for para-X subset but completely failed for meta-X and ortho-X ones (Figure S6).

The minimum surface electrostatic potential calculated on the surface of the N atom of the amino groups enabled accurate estimation of their basicities and pKb values.58 Here, these calculations were performed on the surface of the NpyrX atom, and a very good prediction of the Pt−pyrX bond strength was obtained for meta and para subsets but not for some ortho-X’s (o-DMA, o-NO2, o-NH2, o-OH, and o-F) (Figure S7) probably due to a strong interference of o-X and NpyrX local electrostatic fields.

The electron shifts caused by the H → X substitution in the isolated pyrX ring (see above and Figure S1) were accompanied by changes of the energies of NAO’s on the NpyrX atom. The energy of the 2p(NpyrX) NAO considering NpyrX and C4 atoms of the pyrX ring were oriented along the x axis (Figure 4I) reflected the origin of electrons which were involved in σ-donation as the decisive contributor to the formation of the Pt−pyrX dative bond (Figure 2B and Figure S3). Thus, the 2p(NpyrX) NAO energy quantified σ-electron basicity of the pyrX ligand, and it was increased for electron-donating X substituents while the opposite was true for electron-withdrawing X’s.

Differences in ΔEelst contributions to ΔEπ(NpyrX) were in the order of units of kcal/mol when systems with different X’s were compared while differences in ΔEorb could be by up to one order of magnitude higher (see Table 2 and Table S1). However, 2p(NpyrX) NAO energy is still a good predictor of the Pt−pyrX bond strength because prevailing ΔEelst is linearly correlated with ΔEorb (see below and Figure S8), as it was already shown in our previous studies on similar systems.6,59 Polarization and charge transfer effects as parts of ΔEelst, are strongly influenced by ΔEorb.

The steric effect was quantified from the relation between complex stability and ligand basicity.60 The graphs on panels A, B, E, F in Figure 4 have a similar meaning because 2p(NpyrX) NAO energies and Pt−NpyrX binding energies can be expected to be related to ligand basicities and complex stabilities, respectively. Ortho-X substituents had mostly a stabilizing effect showing higher Pt−NpyrX bond strengths at a given value of 2p(NpyrX) NAO energy compared to meta-X and para-X counterparts (see Figure 4A, B).

Because Pt−pyrX and Pt−trans ligand binding energies are dependent quantities due to the trans influence (see above), the 2p(NpyrX) NAO energies calculated on the isolated pyrX
Note that the energy of the lone pair on the Npyr \textsubscript{X} atom (LP(Npyr \textsubscript{X}) NBO) gave slightly worse correlation with Pt−ligand binding energies than 2p\textsubscript{X}(Npyr \textsubscript{X}) NAO energy (Figure S9) although both these parameters quantified a dative ability of the pyrX ligand. The reason may lie in the fact that LP(Npyr \textsubscript{X}) NBO is an sp\textsuperscript{2} hybrid NBO (Figure S91) with a variable contribution of 2s(Npyr \textsubscript{X}) NAO which depended on the nature and the position of X and ranged from 27.9% (α-Cl) to 29.9% (p-DMA).

Trans Effect: The Binding Properties of the Transition State X-TS Structures and Kinetics of the Substitution Reactions. Pt−pyr\textsubscript{X} bonds in the X-TS structures were shortened by about 0.02−0.03 Å as observed for cisplatin in our previous study,\textsuperscript{41} but contrary to our expectation, they were also weakened by about 4 ± 3% compared to X-R structures. It was caused by a large increase of \(\Delta E\textsubscript{Pauli}\) as the leaving Cl\textsuperscript{−} and entering water ligands lied in the plane of the pyr\textsubscript{X} ligand in most X-TS structures. This increase of \(\Delta E\textsubscript{Pauli}\) was not compensated by a rise of \(\Delta E\textsubscript{diss}\) and \(\Delta E_{solv}\) terms (Table 2 and Table S1).

The influence of X on binding energies of ligands in X-TS is similar to X-P and X-R structures: Pt−Npyr\textsubscript{X} bonds are stronger for electron-donating X’s, while Pt−Cl and Pt−H interactions are more stabilized for electron-withdrawing X’s (cf. above, Tables 4 and Sand Tables S3 and S4).

The substitution reaction proceeded by the associative interchange mechanism\textsuperscript{6} which assumed a comparable importance of the leaving ligand (Cl\textsuperscript{−}) destabilization in the reactant X-R structures and the X-TS transition state stabilization for the height of the activation barrier (\(\Delta G^{\ddagger}\)). Thus, \(\Delta G^{\ddagger}\) values resulted from a complex event of the X-TS formation which should not be predictable by a single variable. However, TS stabilization was important only for α-X-TS structures (see below), and thus, we obtained a reasonable correlation between the 2p\textsubscript{X}(Npyr \textsubscript{X}) NAO energy calculated on the isolated pyr\textsubscript{X} ligand (see above) and \(\Delta G^{\ddagger}\) values for m-X and p-X reaction pathways (Figure S5). Only the points which corresponded to the stabilized o-NH\textsubscript{2}-TS, o-OH-TS, and o-SH-TS structures (see below) were considerably outside the linear correlation.

Nucleophilicity of organic compounds was estimated by the Hirshfeld charges.\textsuperscript{61} However, here the Hirshfeld charge on the Pt(II) center offered a slightly worse correlation with the \(\Delta G^{\ddagger}\) energies for meta and para subsets (\(R^2 = 0.596\)) than 2p\textsubscript{X}(Npyr \textsubscript{X}) NAO energies (Figure S11).

In accordance with the influence of X on the stability of the Pt−Cl bond (see above), the electron-donating X’s tend to
lower the activation $\Delta G^\ddagger$ energy while the opposite was true for electron-withdrawing X's (Figure 6). It was caused by much higher relative importance of the Pt−Cl bond destabilization compared to Pt−water ligand stabilization in X-TS structures.

In the ortho position, the electronic effects were probably stronger than in para and meta positions (cf. NPA charges in Table 1) but were hardly distinguishable from the structural (de)stabilizations (see below), giving together the widest range of $\Delta G^\ddagger$ values of 3.8 kcal/mol between the analyzed reaction profiles (Figure 6). For para-X's, the structural effects were negligible, and the $\Delta G^\ddagger$ range of 1.8 kcal/mol could be attributed purely to electronic effects.

The meta-X substitution always decreased the electron density on the N$_{pyrx}$ atom (Table 1), which led to the formation of electron-deficient Pt(II) complexes compared to ortho and para analogues. It may be responsible for the highest $\Delta G^\ddagger$ values and the least reactivity of meta substituted systems. Thus, the dependence of $\Delta G^\ddagger$ on the position of X in the order ortho−meta−para has usually the shape of inverted “V”. The exceptions are DMA and CH$_3$ substituents, but they show very small $\Delta G^\ddagger$ differences of just tenths of kcal/mol between the three isomers’ reaction pathways (Figure 6).

Considering both the nature and the position of X on the pyrX ligand, we obtained the total difference of 4.6 kcal/mol in the height of the reaction free energy barrier between the slowest reaction for m-CCH and the fastest one for o-NH$_2$. It corresponds to ca. 2200-fold difference in the reaction rate at 298 K.

**TS Structure (de)stabilizations.** X-TS structures preserved all X−H/NH$_2$ and X−Pt nonbonding interactions (Figure 7) which were established already in X-R structures, and thus, these interactions did not contribute importantly to the decrease of $\Delta G^\ddagger$ (cf. below the case of o-DMA pathway). However, for most X-TS structures, the entering water and leaving Cl$^-$ ligands are roughly coplanar with the pyrX ligand which means that the nucleophilic attack of the water ligand occurred in the plane of the pyrX ligand. Depending on the nature of X, it may dictate the direction of the water attack and stabilize/(de)stabilize the TS structures through the electrostatic field of X. The most striking examples are o-NH$_2$, o-OH, and o-SH pathways, which showed the lowest activation energies (Figure 6) having the leaving Cl$^-$ ligand stabilized by internal HNH···Cl, OH···Cl, and SH···Cl contacts with distances 2.745 Å, 2.673 Å, and 2.560 Å in o-NH$_2$-TS, o-OH-TS, and o-SH-TS structures, respectively (Figure 7). NOCV analysis revealed neither any contribution of these contacts to the orbital energy nor any corresponding bond critical points were found by QTAIM analysis. Thus, these contacts had fully electrostatic nature (cf. $\Delta E_{elst}$ values in Table 5 and Table S4) but still led to the substantial lowering of the reaction free energy barrier of corresponding substitution reactions compared to meta- and

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**Table 5. Gas Phase Optimized X-TS Structures (X = H, NH$_2$, NO$_2$): ETS-NOCV Energy Decomposition Terms $\Delta E_{radial}$, $\Delta E_{static}$, $\Delta E_{disp}$, and $\Delta E_{orb}$ for the Interaction of the Joint (Cl + w) Fragment (Leaving and Entering Ligands) with the Rest of the Complex Were Obtained at the BLYP-D3BJ/TZ2P//B3LYP/BS1 Level$^a$**

| X            | $\Delta E_{radial}$ | $\Delta E_{static}$ | $\Delta E_{disp}$ | $\Delta E_{orb}$ | $\Delta E_{static} + \Delta E_{orb}$ | $\Delta G^\ddagger$ |
|--------------|---------------------|----------------------|-------------------|------------------|--------------------------------------|------------------|
| H            | −236.2              | −69.8                | −6.0              | −37.7            | −222.9                               | 33.2             |
| NH$_2$       | −243.6              | −69.6                | −6.8              | −36.7            | −225.3                               | 29.9             |
| NO$_2$       | −227.4              | −67.3                | −6.0              | −36.1            | −214.2                               | 32.6             |

$^a$All energy values are in kcal/mol. The data for all X's are shown in Table S4. $\Delta E_{bond}$ energies of the (Cl + w) fragment and activation Gibbs energies $\Delta G^\ddagger$ were calculated at the B3LYP-D3BJ/BS2//B3LYP/BS1 level.

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**Figure 5.** Dependence of the gas phase activation Gibbs free energies ($\Delta G^\ddagger$) on the energies of 2p$_x$(N$_{pyrx}$) NAO’s calculated on the isolated pyrX ligand (see Figure 4I). One regression line was constructed for m-X and p-X reaction paths while excluding all o-X and poly-X (see below) points.

**Figure 6.** Dependence of the relative values of the activation Gibbs free energy barriers ($\Delta (\Delta G^\ddagger)$) of the hydration reactions of the trans-[Pt(NH$_3$)$_2$(pyrX)Cl]$^-$ complexes on the nature of X and the position of X in the gas phase and water solvent. $\Delta (\Delta G^\ddagger)$ was calculated with respect to the reference values (33.2 and 25.7 kcal/mol in the gas and water solvent, respectively) determined for the X = H pathway. Absolute values of $\Delta G^\ddagger$ are shown in Table 5, Table S4 and Table 7, and Table S6 for the gas phase and the water solvent, respectively.

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**Figure 6.** Dependence of the relative values of the activation Gibbs free energy barriers ($\Delta (\Delta G^\ddagger)$) of the hydration reactions of the trans-[Pt(NH$_3$)$_2$(pyrX)Cl]$^-$ complexes on the nature of X and the position of X in the gas phase and water solvent. $\Delta (\Delta G^\ddagger)$ was calculated with respect to the reference values (33.2 and 25.7 kcal/mol in the gas and water solvent, respectively) determined for the X = H pathway. Absolute values of $\Delta G^\ddagger$ are shown in Table 5, Table S4 and Table 7, and Table S6 for the gas phase and the water solvent, respectively.
para-analogues (Figure 6). The conformation of the entering water ligand in the TS structure then clearly referred to the favored direction of the nucleophilic attack on the Pt(II) center being from the opposite semispace with respect to o-NH₂, o-OH, and o-SH substituents (Figure 7).

On the other hand, o-NO₂, o-F, o-Cl, and o-Br groups made a nucleophilic attack more difficult because their contact with the entering water ligand was destabilizing due to unsuitable orientation of the water ligand in o-NO₂-TS (see Figure 7), o-F-TS, o-Cl-TS, and o-Br-TS structures, respectively; nevertheless, it was more advantageous than the contact with the leaving Cl⁻ ligand (by 2.7, 1.9, 0.9, and 1.1 kcal/mol for o-NO₂, o-F, o-Cl, and o-Br reaction pathways, respectively). It is probably the main reason of their highest activation energies compared to other ortho-X’s (Figure 6).

The steric hindrance manifested itself by the elongation of the Pt−NpyrX bond (see above). It also changed the conformation of the o-DMA-R, o-DMA-TS, and o-DMA-P structures which had deformed geometries with the twist angles of 56.3, 54.4 (Figure 7), and 58.9°, respectively.

Table 6. Bonding Interactions in X-R and X-P Structures (X = H, NH₂, NO₂) Optimized in the Water Solvent and Calculated by the B3LYP-D3BJ-PCM/BS2//B3LYP-PCM/BS1 Method: Pt−NpyrX, Pt–Cl, and Pt–Ow Bond Lengths (in Å); the Total NPA Charges of the pyrX, Cl, and Water Ligands (q(pyrX), q(Cl) and q(w), Respectively) (in e); ΔEbind Energy Values are in kcal/mol

| X-R | Pt−NpyrX | q(pyrX) | ΔEbind | Pt−Cl | q(Cl) | ΔEbind |
|-----|----------|---------|--------|-------|-------|--------|
| H   | 2.052    | 0.284   | −43.9  | 2.370 | −0.597| −38.7  |
| NH₂ | o-       | 2.064   | 0.292  | −46.2 | 2.363 | −0.594| −38.2  |
|     | m-       | 2.051   | 0.289  | −45.3 | 2.363 | −0.599| −38.5  |
|     | p-       | 2.047   | 0.312  | −47.7 | 2.378 | −0.610| −37.0  |
| NO₂ | o-       | 2.084   | 0.231  | −35.4 | 2.341 | −0.560| −42.3  |
|     | m-       | 2.067   | 0.251  | −38.8 | 2.353 | −0.576| −41.2  |
|     | p-       | 2.046   | 0.247  | −39.7 | 2.360 | −0.580| −40.8  |

| X-P | Pt−NpyrX | q(pyrX) | ΔEbind | Pt−Ow | q(w) | ΔEbind |
|-----|----------|---------|--------|-------|-----|--------|
| H   | 2.011    | 0.356   | −54.3  | 2.118 | 0.195| −20.5  |
| NH₂ | o-       | 2.021   | 0.371  | −56.7 | 2.123| 0.195  | −19.7  |
|     | m-       | 2.008   | 0.364  | −55.9 | 2.120| 0.194  | −19.9  |
|     | p-       | 2.010   | 0.383  | −58.9 | 2.123| 0.189  | −19.7  |
| NO₂ | o-       | 2.034   | 0.306  | −44.2 | 2.098| 0.211  | −21.7  |
|     | m-       | 2.014   | 0.327  | −48.5 | 2.114| 0.202  | −21.0  |
|     | p-       | 2.011   | 0.322  | −49.1 | 2.108| 0.203  | −21.4  |

The data for all X’s are shown in Table S5.

The steric hindrance manifested itself by the elongation of the Pt−NpyrX bond (see above). It also changed the conformation of the o-DMA-R, o-DMA-TS, and o-DMA-P structures which had deformed geometries with the twist angles of 56.3, 54.4 (Figure 7), and 58.9°, respectively.
structures being ca. six times weaker in the solvent than in the water solvent and calculated by the B3LYP-D3BJ-PCM/BS2/B3LYP-PCM/BS1 method: Pt–N

The twist angle between the two planes is close to 90° (Figure 4E) but its influence on \( \Delta G^2 \) is unclear.

The steric hindrance should lead to an increase of \( \Delta G^2 \) of the DMA, ortho-CH₃, o-Br, o-Cl, and o-F pathways have elevated \( \Delta G^2 \) values which are within 0.1 kcal/mol compared to their meta counterparts. However, the differences in \( \Delta G^2 \) are too small to find a clear reason. For example, as the above described deformation is similar for all structures along the o-DMA pathway, it has little effect on \( \Delta G^2 \) as it can be manifested by the values of 7.2, 7.2, and 8.8 kcal/mol which represent the free energy destabilizations of o-DMA-R, o-DMA-TS, and o-DMA-P structures, respectively, with respect to their p-DMA isomeric counterparts. Note that \( \Delta G^2 \) is even by 0.1 kcal/mol lower for the o-DMA pathway than for the p-DMA one (Figure 6 and Table S4).

### Solvent Effects

Water environment dampened the electrostatic forces which were the most contributive to the stabilization of the Pt–ligand bonds of our charged complexes in the gas phase (see above). Thus, binding energies of all Pt–ligand bonds were lowered in the water environment (Tables 6 and 7 and Tables S5 and S6). Similarly as in the gas phase, the Pt–ligand binding energies could be estimated from 2p\(_x\)(N\(_{pyrX}\)) NAO energies calculated for the isolated pyrX ligand immersed in the polarizable continuum model (PCM) water solvent (Figure 4E–H). The linear correlations are even slightly better here than in the gas phase probably due to a smaller relative importance of electrostatic interactions. Note also that the changes of electron density induced by X’s are qualitatively the same as in the gas phase (cf. Figure 3 and Figure S10). Thus, the findings described above for the gas phase should be qualitatively valid also for the water phase.

The weakening of the Pt–ligand bonds did not automatically lead to their elongation because bond length changes were inversely related to the changes of the ligand → Pt transferred charge. The trend of the change (increase/decrease) of the charge transfer and polarization effects depended on the nature of the interaction and nature of the complex.

As expected, Pt–Cl was the most affected bond in the X-R structures being ca. six times weaker in the solvent than in the gas phase because the arising Cl\(^{-}\) anion was stabilized by hydration. The charge donation from the Cl\(^{-}\) ligand was by 22 ± 0.8% lower in the water solvent which resulted in 0.047 ± 0.006 Å Pt–Cl bond elongation. The ligand environment was crucial for the behavior of the pyrX ligand: the charge transfer from pyrX is higher/lower by 14.1 ± 1.7%/17.3 ± 1.3% in the solvent, and Pt–N\(_{pyrX}\) bond lengths were shortened/slightly elongated by 0.026 ± 0.003 Å/0.002 ± 0.002 Å in R-X/P-X structures. The Pt–N\(_{pyrX}\) bond was always weakened: by 54 ± 1.5% in P-X structures and by 34.4 ± 2.0% in R-X ones. The Pt–w bonds in the water solvent-optimized X-P structures were shortened by 0.019 ± 0.004 Å compared to the gas phase. The transferred charge from the water ligand increased by 11.7 ± 0.8%, and the Pt–O\(_w\) bond was weakened by 56 ± 0.7%. As the result, the NPA charge of the Pt center was by 10.2 ± 0.8 and 7.9 ± 0.8% more positive in the solvent than in the gas phase in R-X and P-X structures, respectively.

The activation Gibbs energies (\( \Delta G^2 \)) were substantially reduced: by 6.9 ± 0.5 kcal/mol compared to the gas phase (Table 7 and Table S6). 2p\(_x\)(N\(_{pyrX}\)) NAO energies worked substantially worse as the predictor of \( \Delta G^2 \) values giving the R² value of 0.483 for meta and para subsets (cf. Figure 5). It could be caused by higher complexity of the reaction in the water solvent and/or by a lower precision of our calculations.

Despite a general weakening of the Pt–ligand coordination bonds, the relative values of the activation barriers for different X’s were similar to the gas phase when driven by the electronic effects. Thus, the meta and para subsets gave almost the same maximum \( \Delta (\Delta G^2) \) differences of 1.5 and 1.8 kcal/mol (cf. with respective values of 1.8 and 1.8 kcal/mol for the gas phase, see Figure 6). However, the water environment caused substantial weakening of the electrostatic forces which lowered spatial preferences of the nucleophilic attack in the TS structures and the importance of the long-range X–Cl and X–w interactions therein (cf. \( \Delta (\Delta G^2) \) differences in Figure 7).

The weakening of HNH–Cl and HO–Cl stabilization interactions in o-NH₂-TS and o-OH-TS, respectively (cf. above), resulted in the decrease of \( \Delta (\Delta G^2) \) variance for the ortho subset to the value of 2.4 kcal/mol. Taken the results for all three subsets together, \( \Delta (\Delta G^2) \) between the fastest (o-NH₂) and the slowest (m-NO₂) reaction was 3.0 kcal/mol in the water solvent which corresponded to ca. 150 times change in the reaction rate at 298 K. It is by about one order of magnitude smaller value than for the gas phase.

### Complexes with the Poly-X Ligand

The 2p\(_x\)(N\(_{pyrX}\)) NAO energies and the Pt–ligand bond strengths for poly-substituted complexes were compatible with the results for the mono-substituted ligand complexes (cf. above). The mean deviations of 2.5 ± 1.3, 4.0 ± 2.8, 1.3 ± 0.9, and 0.7 ± 0.3

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| X-TS | Pt–N\(_{pyrX}\) | q(pyrX) | \( \Delta E_{bind}^{Pt} \) | Pt–Cl | q(Cl) | \( \Delta E_{bind}^{Pt} \) | Pt–O\(_w\) | q(w) | \( \Delta E_{bind}^{Pt} \) | \( \Delta G^2 \) |
|------|----------------|---------|------------------|------|-------|------------------|------|-------|------------------|------|
| H    | 2.034          | 0.318   | –42.9            | 2.837| –0.837| 2.476            | 0.050| –18.6| 25.9            |
| NH₂  | 2.042          | 0.333   | –45.0            | 2.806| –0.832| 2.482            | 0.053| –18.5| 24.3            |
| m-   | 2.032          | 0.327   | –44.3            | 2.843| –0.841| 2.469            | 0.050| –18.1| 26.0            |
| p-   | 2.029          | 0.350   | –47.0            | 2.846| –0.841| 2.495            | 0.044| –17.3| 25.4            |
| NO₂  | 2.074          | 0.252   | –33.0            | 2.783| –0.821| 2.431            | 0.067| –21.9| 26.5            |
| m-   | 2.042          | 0.281   | –37.2            | 2.822| –0.830| 2.447            | 0.059| –20.2| 27.3            |
| p-   | 2.035          | 0.272   | –38.1            | 2.816| –0.828| 2.448            | 0.059| –19.6| 27.2            |

**Note:** The data for all X’s are shown in Table S6.

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**Table 7.** Activation Free Energies (\( \Delta G^2 \)) and Bonding Interactions in X-TS Structures (X = H, NH₂, NO₂) Optimized in the Water Solvent and Calculated by the B3LYP-D3BJ-PCM/BS2/B3LYP-PCM/BS1 Method: Pt–N\(_{pyrX}\)–Pt, and Pt–O\(_w\) Bond Lengths (in Å); Total NPA Charges of the pyrX, Cl and Water Ligands (q(pyrX), q(Cl) and q(w), Respectively) (in e); and \( \Delta E_{bind} \) and \( \Delta G^2 \) Energy Values in kcal/mol

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kcal/mol from the linear functions derived for the mono-substituted complexes (Figure 4) were calculated for Pt−pyrX (in X-R), Pt−pyrX (in X-P), Pt−Cl, and Pt−w binding energies, respectively, in the gas phase. In the water solvent, the respective values were 1.4 ± 1.2, 1.9 ± 1.2, 0.4 ± 0.3, and 0.2 ± 0.2 kcal/mol. The highest deviation values of 6.3 and 11.2 kcal/mol were detected for Pt−pyrX bonds of the gas phase 2op-NH2-R and 2op-NH2-P structures, respectively (Figure 4). This underestimation of the binding energies was caused by the presence of two strong H2NH⋯NH3 H-bonds (Figure S12) whose energies were not compensated by the elongation of the Pt−NpyrX bond (by about 0.01 Å) (cf. above and values in the Tables S9 and S10).

The gas phase ΔG⧧ free energy values could be also estimated from the 2p_{i}(N_{pyrX}) NAO energies of the poly-substituted ligand complexes except for the om-NH2, op-NH2, and 2op-NH2 pathways which involved o-NH2⋯Cl electrostatic stabilization of the TS structures (cf. above). For the other poly-X pathways, the mean deviation of the ΔG⧧ values from the linear function in Figure 5 was 0.5 ± 0.3 kcal/mol.

The additivity of the substituent effects on the pyr ring was already shown for proton affinities and gas phase basicities of the substituted pyridines62 while electron shifts within the pyrX ring were non-additive.63 In this contribution, the values \( X_{\text{poly}} = X_{\text{H}} + \sum_{i} n_{i} \Delta x_{i} \) (1)

where the summation goes over all positions \((i = \text{o, m, p})\); \(X_{\text{H}}\) is the value for the non-substituted complex \((X = \text{H})\); \(\Delta x_{i}\) is the measured changes of the monosubstituted complexes with respect to the non-substituted complex \((X = \text{H})\); and \(n_{i}\) is the number of substituents in the position \(i\). The plots of calculated versus estimated values for the ligand binding energies are shown in Figure 8. Numerical values are shown in Tables S7–S12. In the gas phase, the absolute differences between calculated and estimated values were within the experimental error for the binding energies (≤2.5 kcal/mol), NPA charges (≤0.01 e), and bond lengths (≤0.01 Å). For poly-F and poly-NO2 complexes, the relative errors were below 20% (Tables S7, S8, S11, and S12). For the most sterically hindered complexes with the 2op-NH2 ligand, this error reached almost 50% for \(q(\text{Cl})\) and \(q(\text{w})\) NPA charges (Tables S9 and S10). However, for the poly-NH2 complexes, the additive approach failed to predict the subtle changes of Pt−ligand bond lengths. Note that the relative error of 30% was measured for the additivity of substituent effects on much simpler (de)protonation processes of substituted pyridines in the gas phase.62

In the water solvent, the additive approach worked less satisfactory especially for the weakest Pt−w interaction (Figure 8H and Tables S8, S10, and S12). Partly, it might be caused by a lower precision of PCM calculations.

For ΔG⧧ activation energies, the additive approach did not offer useable results due to high relative errors (Tables S7, S9, and S11). The largest errors were for poly-NH2 pathways (Figure S13). While any single NH2 substitution of the non-substituted pyrH system led to the decrease of ΔG⧧ activation free energy (except m-NH2 in the water solvent), any additional NH2 substitution of o-NH2 led to the ΔG⧧ value increase (Table S9). The electron-withdrawing poly-F and poly-NO2 systems worked more predictably and offered an increase of the ΔG⧧ values (with exception of the op-F system and in the water solvent of the om-F one, too) compared to mono-substituted systems. The 2m-NO2 and op-NO2 pathways showed the highest ΔG⧧ values of 35.1 and 27.7 kcal/mol (Table S11), which are by 0.6 and 0.5 kcal/mol larger than the ones for the slowest hydration reactions of complexes with mono-functional pyrX ligands (Tables S4 and S6) in the gas phase and the water solvent, respectively. Thus, the ΔG⧧ value ranges (cf. above) increased up to 5.2 and 3.4 kcal/mol for the
gas phase and the water solvent, respectively, which corresponded to ca. 6400 and 320 times differences in the reaction rate at 298 K.

Reliability of Our Results. To obtain accurate absolute values of observables, one has to choose the appropriate combination of the density functional theory (DFT) functional, the solvation method, and the basis set. In this contribution, we rely on the relative values which should be much less sensitive in this respect.

To check the influence of the B3LYP functional on the height of the activation barriers and Pt–ligand bond lengths, the X-R \_w distances and X-TS structures were also optimized and energy of optimized structures was evaluated by M06-2X, PBE0 functionals \(^{67}\) using BS1 and BS2 basis sets, respectively, in the gas phase (M062X/BS2//M062X/BS1, and PBE0-D3BJ/BS2//PBE0/BS1 calculations). In the solvent, these calculations were performed only with the M06-2X functional.

All M062X and PBE0 gas phase optimized Pt–ligand bond lengths correlated very well linearly with the B3LYP counterparts (\(R^2 > 0.94\)) and were systematically shorter with the exception of Pt–O distances in M06-2X optimized X-TS structures (Figures S14 and S15). Reasonable correlation was found also for activation Gibbs free energies which were systematically lower by 2.8 ± 0.5 kcal/mol and higher by 0.9 ± 0.4 kcal/mol for the M06-2X and PBE0-D3BJ functionals, respectively. Thus, for the gas phase, the relative changes of the variables studied in this paper should be not sensitive on the chosen functional.

For the M06-2X/PCM optimizations, the correlation was generally worse and not very satisfactory for Pt–Cl distances in X-TS structures (\(R^2 = 0.430\)) (Figure S16). No correlation was found for solvent phase activation energies. In agreement with the B3LYP results, the fastest reaction was detected for the o-NH2 substitution (Figure S17), but for the other X’s, the \(\Delta (\Delta G^\ddagger)\) differences are probably too small compared to the precision of our calculations. Thus, except of the \(\Delta G^\ddagger\) values and the properties of the Pt–Cl bond in X-TS structures, the relative changes of variables studied in this contribution and calculated in the water solvent should be described in our opinion satisfactorily and should be little dependent on the chosen functional.

Comparison with Experimental Data. We have not found experimental data about any of the complexes studied in this contribution. 2-Picoline and 3-picoline complexes are related compounds to \(\sigma\)-CH\_3-R and \(\eta\)-CH\_3-R, respectively, but one of the ammine NH\_3 groups is replaced by the chlorine Cl\^- ligand. We obtained slightly longer Pt–N\_pyrx (by 0.070 and 0.071 Å) and Pt–Cl bond lengths (by 0.019 and 0.007 Å) compared to the crystal structures of the 2- and 3-picoline complexes \(^{29}\) (cf. Tables S1 and S2). In the crystal structure, the 3-picoline ligand is tilted by 48.9° while 2-picoline ligand is almost perpendicular (102.7°). \(^{29,66}\) In o-CH\_3-R and m-CH\_3-R, both \(\sigma\)-CH\_3 and \(\eta\)-CH\_3 ligands were perpendicular to the plane of the complex (90.0 and 87.7°). The difference for the 3-picoline complex has to be attributed to the Cl\^- ligand in the cis position because the gas phase mPW1PW1 DFT-optimized geometries of 2-picoline and 3-picoline complexes were in very good agreement with the crystal structures. \(^{69}\)

According to our calculations, the rates of hydrolysis were the same for two related complexes: the experimental trans-[Pt(NH\_3)(H\_2O)(2-picoline)Cl\^-] complex \(^{29}\) and m-CH\_3-R which differed only by the nature of the group in the cis position (H\_2O vs NH\_3). However, in the water solvent, we did not observe any steric hindrance of the \(\sigma\)-CH\_3 ligand (unlike the gas phase) and the kinetic constant for the \(\sigma\)-CH\_3 pathway was by two orders of magnitude higher compared to the trans-[Pt(NH\_3)(H\_2O)(2-picoline)Cl\^-] experimental analogue.\(^{29}\)

The meta-X substitution of the pyrx ligand led to the slowest reaction for most X’s in both the gas phase and the water solvent, which is in agreement with experimental evidence.\(^{68,70}\)

CONCLUSIONS

Substitution of the pyridine ligand by electron-donating groups in the trans-[Pt(NH\_3)\_2(pyrX)Cl\^-] complexes led to the strengthening of the Pt–N\_pyrx bond and the weakening of the bonds in the trans direction (Pt–Cl and Pt–O\_w in X-R and X-P structures, respectively). The electron-withdrawing groups had exactly the opposite effect. In both the gas phase and the water solvent, the strengths of Pt–N\_pyrx, Pt–Cl, and Pt–O\_w bonds in the X-R and X-P complexes were dependent on σ-electron basicity of the N\_pyrx atom which correlated linearly best with the energy of the 2p(N\_pyrx) NAO oriented in the C4–N\_pyrx direction and calculated on the isolated pyrx ligand. These correlations were successfully validated on the complexes with the poly-substituted ligand.

The electron-donating/withdrawing groups tend to decrease/increase \(\Delta G^\ddagger\) free activation energies. In the gas phase, the 2p(N\_pyrx) NAO energy can be used also as a predictor for the estimation of \(\Delta G^\ddagger\) of the meta-X and para-X reaction pathways with dominating influence of electronic effects.

Because of the perpendicular orientation of the pyrx ligand with respect to the metal complex plane, the substitution reactions occurred in the pyrx plane. The attractive X–Cl electrostatic interaction was established for o-X’s with the H-bond donor ability (\(\sigma\)-NH\_3, \(\sigma\)-OH, \(\sigma\)-SH) which led to the X-TS structure stabilization and a substantial decrease of the \(\Delta G^\ddagger\) values. The fastest reaction rate was observed for the o-NH2 pathway. On the other hand, steric hindrance in o-X-TS structures led only to a moderate increase of \(\Delta G^\ddagger\) probably due to a small size of X’s considered in this study. Anyway, taken together the activation free \(\Delta G^\ddagger\) energy of the hydration reactions can be most easily modified by the substitution of the pyridine ring in the ortho position giving the \(\Delta G^\ddagger\) values range of 3.8 kcal/mol between the fastest \(\sigma\)-NH\_3 and slowest \(\sigma\)-Br pathways (Table S4). Substitutions in the meta position led usually to the highest activation energies.

In the gas phase, the X’s on the pyridine ring can be ordered according to their ability to promote the hydration reaction as follows: NH\_2 > OH ≥ SH ≈ CH\_3 > DMA > H > F ≥ Cl ≈ CCH > Br > NO\_2.

Water solvent weakens all coordination Pt–ligand bonds and lowers the activation free energies compared to the gas phase. Both shortening and elongations of the bond lengths are possible being inversely related to the changes of the ligand → Pt transferred charge. The dampening of electrostatic interactions lowered the range of the \(\Delta G^\ddagger\) values for the ortho subset to 2.4 kcal/mol. The ranges of \(\Delta G^\ddagger\) for meta and para subsets being driven mainly by electronic effects remained almost unchanged with respect to the gas phase (ca. 1.8 kcal/mol).

Considering all three ortho, meta, and para positions (all mono-substituted systems), the range of \(\Delta G^\ddagger\) values for all X’s were 4.6 and 3.0 kcal/mol, which corresponded to ca. 2200
and 150 times differences in the reaction rate at 298 K in the gas phase and the water solvent, respectively.

The acceleration of the hydration reaction by an additional NH$_2$ substitution of the o-NH$_2$ ligand was not observed. On the other hand, a further slowdown of the Pt(II) complex reactivity with respect to the complexes with mono-substituted ligands was possible. The 2m-NO$_2$ and op-NO$_2$ pathways increased the maximum value of $\Delta G^\circ$ by 0.6 and 0.5 kcal/mol in the gas phase and the water solvent, respectively. As the result, if poly-X complexes were considered, the ranges of possible $\Delta G^\circ$ values were increased up to 5.2 and 3.4 kcal/mol which corresponded to ca. 6400 and 320 times differences in the reaction rate at 298 K for the gas phase and the water solvent, respectively.

The additivity of substituent effects on poly-X complexes was shown with respect to the Pt–ligand bond strengths and the ligand NPA charges in the gas phase which had the relative errors below 30%.

## COMPUTATIONAL METHODS

All geometries of the structures were optimized at the DFT level with the hybrid B3LYP functional$^{74}$ and 6-31+G(d) basis set for the first and second row elements. Heavier atoms were treated by Dresden–Stuttgart quasirelativistic energy-averaged effective pseudopotentials$^{75,76}$ with a pseudo-orbital basis set augmented by the set of diffuse (for Pt with exponents $\alpha_e = 0.0075$, $\alpha_s = 0.013$, $\alpha_p = 0.025$; for Cl: $\alpha_e = 0.09$, $\alpha_s = 0.0075$) and polarization ($\alpha_{e(Pt)} = 0.98$; $\alpha_{e(Cl)} = 0.618$) functions.$^{77}$ These calculations are labeled as B3LYP/BS1 in further text.

The nature of the obtained stationary points was always checked by the Hessian matrix evaluation. Thermal contributions to the energetic properties were calculated using the canonical ensemble at standard gas phase conditions ($T = 298$ K, $p = 101.325$ kPa).

The energy profiles and wave function properties were determined at the B3LYP-D3BJ/MWB-60(2fg)/6-311++G(2d,2p) single point calculations which combined the B3LYP functional with Grimme’s DFT-D3 dispersion correction and Becke–Johnson damping$^{75}$ (labeled as D3BJ). The Pt atom was augmented by the set of diffuse functions in analogy to BS1 and by the set of polarization functions ($\alpha_{e(Pt)} = 1.419$; $\alpha_s = 0.466$, $\alpha_p = 1.208$)$^7$ (B3LYP-D3BJ/BS2 calculations). All possible rotamers were considered for the reactant and product structures, and the energy of the given minimum structure was obtained by Boltzmann averaging over all optimized rotamers at $T = 298$ K. For calculation of activation free energies ($\Delta G^\circ$), the lowest lying TS structure was considered. In calculations of binding energies $\Delta E_{\text{bind}}$, the basis set superposition error (BSSE) was included by the counterpoise correction.$^{78}$

Deformation energies were not included.

Additional single-point calculations on selected optimized structures were conducted using the Amsterdam Density Functional 2014.05 package (ADF)$^{79}$ to calculate fragment energy decompositions according to the extended transition state theory$^{80}$ combined with natural orbitals for chemical valence (ETS-NOCCV)$^{79,80}$.

Gas phase interaction energies $\Delta E_{\text{INT}}$ were decomposed to Pauli ($\Delta E_{\text{Pauli}}$), electrostatic ($\Delta E_{\text{elstat}}$), orbital ($\Delta E_{\text{orb}}$), and dispersion ($\Delta E_{\text{disp}}$) energy contributions

$$\Delta E_{\text{INT}} = \Delta E_{\text{Pauli}} + \Delta E_{\text{elstat}} + \Delta E_{\text{orb}} + \Delta E_{\text{disp}}$$

In these calculations, scalar relativistic effects were treated within the zeroth order regular approximation (ZORA).$^{81}$ The BLYP-D3BJ functional was used with the all-electron TZ2P (ZORA) basis set for all atoms.

To include solvent effects, the above described B3LYP/BS1 optimizations and B3LYP-D3BJ/BS2 single point calculations were performed also in the water environment for all structures using IEFPCM (PCM) implicit solvent approach. BSSE corrections with the PCM regime were calculated with ghost atomic orbital functions localized inside the cavity having the same size as the whole complex.$^{82}$

All optimizations and single point calculations were carried out by the Gaussian 09, revision D.01 (G09) program package.$^{83}$ Atoms in molecules (AIM) topological analysis of the electron density in bond critical points was performed on selected structures by the AIMAll program.$^{84}$ NBO analysis was carried out, and atomic charges based on NAO’s (natural population analysis (NPA) charges) were determined by the NBO 3.1 program.$^{85}$ Wave function properties were analyzed by the Multiwfn 3.7 program.$^{54}$

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01161.

Complete versions of Tables 2–7 with the data for all X’s; electron density difference isosurfaces of p-NH$_2$ and p-NO$_2$ structures with respect to the reference pyrH structure; five most important ETS-NOCCV deformation density contributions describing the formation of the Pt−N$_{pyrX}$ bond in H−R, H−TS, and H−P structures; dependence of pyr-X ligand bond energies on the Pt−N$_{pyrX}$ bond lengths and the dependence of the σ-donation energy $\Delta E_{\text{orb}}$ contributions on total $\Delta E_{\text{orb}}$ energies for X−TS and X−P structures; ETS-NOCCV deformation density contributions for the formation of the Pt−N$_{pyrX}$ bond in X−R structures which involve contribution from Pt−H (o-NH$_2$−R, o-NO$_2$−R), Pt−S (o-SH−R) nonbonding interactions or NH$_2$−N (o-DMA−R), NH$_2$−O (o-NO$_2$−R) H-bond interactions; dependence of the Pt−pyrX binding energy on the transferred q(pyrX) charge for X−R, X−TS, and X−P structures; dependence of the gas phase Pt−pyrX binding energy on the NBO charge of the N$_{pyrX}$ atom ($q(N_{pyrX})$), the total dipole moment of pyrX ($p(pyrX)$), and the projection of the dipole moment into C4−N$_{pyrX}$ direction ($p_C(pyrX)$) for X−R, X−TS, and X−P structures; dependence of the gas phase Pt−pyrX binding energies for X−R, X−TS, and X−P structures on the minimum surface electrostatic potential calculated on the surface of the N$_{pyrX}$ atom in the isolated pyrX ligand; correlation between $\Delta E_{\text{elstat}}$ and $\Delta E_{\text{orb}}$ terms for the Pt−pyrX interaction in X−R, X−TS, and X−P structures; dependence of Pt−ligand binding energies on the LP(N$_{pyrX}$) NBO energy in the gas phase and the water solvent; electron density difference isosurfaces of p-NH$_2$−R and p-NO$_2$−R structures with respect to the reference H−R structure calculated in the water solvent; dependence of the gas-phase activation Gibbs free energies ($\Delta G^\circ$) on the Hirschfeld charges calculated on the Pt(II) atom; bonding energies, bond lengths, and ligand NPA charges in poly-X−R and poly-X−P structures (X = F, NH$_2$, NO$_2$) optimized in the gas phase.
phase and water solvent, $\Delta G^\ddagger$ activation free energies, and estimated values of all these variables (eq 1) with absolute and relative errors; stabilizing $H$-bonds in the 2op-NH$_2$-R and 2op-NH$_2$-P structures; plots of calculated versus estimated (eq 1) values of $\Delta G^\ddagger$ activation free energies for complexes with poly-substituted ligands in the gas phase and the water solvent; correlations between B3LYP/BS1 and M06-2X/BS1 bond lengths for the X-R$_w$ and X-TS structures and the correlations between B3LYP-D3BJ//BS2//B3LYP/BS1 and M06-2X/BS2//M06-2X/BS1 activation free energies in the gas phase and the water solvent; correlations between B3LYP/BS1 and PBE0/BS1 bond lengths for the X-R$_w$ and X-TS structures and the correlations between B3LYP-D3BJ//BS2//B3LYP/BS1 and PBE0-D3BJ//BS2//PBE0/BS1 activation free energies in the gas phase; and dependence of the relative values M06-2X/BS2//M06-2X/BS1 calculated activation free energy barriers ($\Delta (\Delta G^\ddagger)$) of the hydration reactions of the trans-[Pt(NH)$_2$]$_2$(ppyX) Cl$^-$ complexes on the nature and the position of the X in the gas phase and in the water solvent (PDF)

Optimized Cartesian coordinates of all TS and the most stable minimum structures (XYZ)

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**Notes**

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