Comparison of hydration reactions for "piano-stool" RAPTA-B and [Ru(η^6– arene)(en)Cl]$^+$ complexes: Density functional theory computational study

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The hydration process for two Ru(II) representative half-sandwich complexes: Ru(arene)(pta)Cl_2 (from the RAPTA family) and [Ru(arene)(en)Cl]$^+$ (further labeled as Ru_en) were compared with analogous reaction of cisplatin. In the study, quantum chemical methods were employed. All the complexes were optimized at the B3LYP/6-31G(d) level using Conductor Polarizable Continuum Model (CPCM) solvent continuum model and single-point (SP) energy calculations and determination of electronic properties were performed at the B3LYP/6-311++G(2df,2pd)/CPCM level. It was found that the hydration model works fairly well for the replacement of the first chloride by water where an acceptable agreement for both Gibbs free energies and rate constants was obtained. However, in the second hydration step worse agreement of the experimental and calculated values was achieved. In agreement with experimental values, the rate constants for the first step can be ordered as RAPTA-B > Ru_en > cisplatin. The rate constants correlate well with binding energies (BEs) of the Pt/Ru–Cl bond in the reactant complexes. Substitution reactions on Ru_en and cisplatin complexes proceed only via pseudoassociative (associative interchange) mechanism. On the other hand in the case of RAPTA there is also possible a competitive dissociation mechanism with metastable pentacoordinated intermediate. The first hydration step is slightly endothermic for all three complexes by 3–5 kcal/mol. Estimated BEs confirm that the benzene ligand is relatively weakly bonded assuming the fact that it occupies three coordination positions of the Ru(II) cation. © *2011 American Institute of Physics*. [doi:10.1063/1.3515534]

I. INTRODUCTION

Despite cisplatin is a very effective anticancer metallodrug, an intensive research of some other metallocomplexes is carried out. The reason is based on the fact that cisplatin is very toxic with many side effects.[1] Another problem consists in low or even no activity for some kinds of carcinomas.[2] Therefore many studies appeared on complexes, which are active against cancer cells. Various biophysical and biochemical properties of rhodium,[3–7] titanium,[8–10] ruthenium,[11–24] and many other metal complexes[25,26] were explored.

Computational studies usually concentrate on coordination and structural effects. Description of the reaction mechanisms and electronic properties of cisplatin and its analogs were examined in several papers.[27–31] Some studies concerned the aquation process of platinum complexes, which is crucial in the activation step,[32–39] interactions with nucleobases,[40–51] or other competitive reactions with cellular components, such as side chains of amino acids.[52–56]

Ruthenium compounds also attract a lot of attention as can be noticed in recent computational chemistry literature.[19,57–64] A lot of interesting features, hypotheses and conclusions, which would be worth of computational confirmations or deserve a more detailed insight based on molecular modeling can be found in many experimental works.[18,21,24,25,65–72] An interesting paper on stacking interaction of Ru(II) complexes with guanine and adenine using density functional theory (DFT) study was presented by Platts.[73]

There are two basic families of half-sandwich ruthenium(II) complexes. First class (further labeled as Ru_en) is represented by [Ru(η^6−arene)(en)Cl]$^+$ complexes[67,74] (en = ethylenediamine, arene = benzene), which can coordinate to DNA helix in the form of monofunctional adducts (at least in the first step). This is one of the basic differences compared to Pt-complexes where bifunctional adducts are believed to be the key structure coordinated to the genomic sequence. The role of the size of the arene ligand was examined, too.[17] It was found that larger arene ligands like anthracene or biphenyl increase the drug efficiency due to possible intercalation into DNA helix via $\pi-\pi$ stacking interaction. This interaction is reduced in the case of smaller aromatic ligands with a single benzene ring. Also, a pronounced selectivity (higher affinity) of these Ru(II) complexes to guanine was discussed in Refs. 17 and 19. The explanation was searched in a formation of an additional H-bond between O6 and the amine group of the ethylenediamine ligand. Such a strong binding can be created neither with N7-adenine nor with N3-cytosine adduct. However, in our previous paper it was shown[75] that this is only

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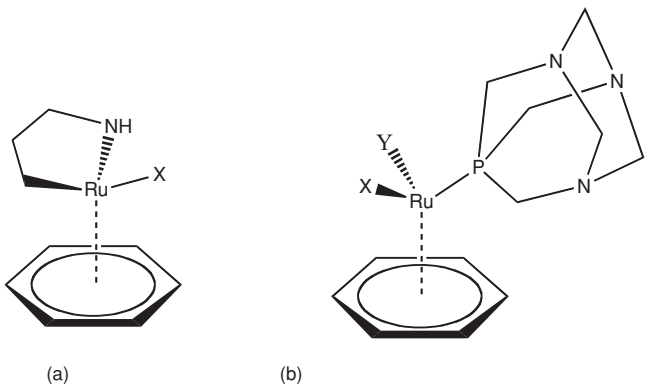

SCHEME 1. Structural formulas of (a) Ru_en and (b) RAPTA-B complexes.

partially true since some (weaker) H-bond can be formed also in the case of adenine. We confirmed that the size of arene ring does not play any role in the activation reaction so that the extent of aromatic system does not substantially change the coordination strength of the Ru-arene part of the complex.[75] Also, the H-bonding between ethylenediamine and exocyclic N6 amino group of adenine is markedly weaker than analogous interaction in the guanine complex (at least according to N6…H/O6…H distance which is 2.07 and 1.83 Å, respectively) or according to electron density of the bond critical points obtained from Bader's Atoms-in-Molecules (AIM) analysis.[76]

The second class of the Ru(II) "piano-stool" compounds examined in this study is the so-called RAPTA family. We used a model complex RAPTA-B (further called just RAPTA), which contain monofunctional pta ligand (1.3.5-triaza-7-phosphatricyclo[3.3.1.1]decane),[77,78] benzene, and two chloride anions. In this way, some similarities with cisplatin can be expected concerning the mechanism of the drug activity in the cancer cells.

The general structures of both Ru(II) classes are drawn in Scheme 1.

In the present study we compare activation process, e.g., hydration reactions of basic representatives of both classes of half-sandwich ruthenium complexes together with the frequently studied cisplatin complex. The DFT computational level and the CPCM continuum solvent model were employed for determination of all explored structures in reactants, products and transition states. Besides energy profiles, also some physicochemical and electronic characteristics were determined for the deeper insight into the reaction mechanism.

II. COMPUTATIONAL DETAILS

In the present study, the compounds of $[Ru(\eta^6-arene)(en)X]^{+/2+}$ and $[Ru(\eta^6-arene)(pta)XY]^{0/1+/2+}$ (X, Y = Cl^-, OH, H_2O) were examined. The general structures of both classes of Ru(II) complexes contain the pseudo-octahedral arrangement of the Ru atom. For the comparison cisplatin hydration is also included.

All the explored systems were optimized both in the gas phase and in water environment using the Klamt's COSMO (CPCM) implicit solvent approach[79,80] with dielectric constant $\varepsilon = 78$. In chosen model, default Klamt's cavities were used.

In the reaction course of the pseudoassociative mechanism (PAM), the Cl^- ligand(s) was/were replaced by water. In order to describe the reaction kinetics of the hydration reactions, the supermolecular approach was considered. In the reactant state, the Ru-complexes and water are associated by H-bonding. The transition states for the replacement of chloro ligand by water were found where formation of a seven-coordinated structure was revealed. In the Ru_en complexes, only one step is possible while activation of the RAPTA and cisplatin complexes can occur in two subsequent steps replacing both chloride ligands. Moreover in the RAPTA complex also a dissociative mechanism was explored where two reaction steps in each dechloration were determined. The first TS structure is linked with Ru–Cl bond breaking. Then the five-coordinated intermediate is formed with both chloride and water particles detached from the RAPTA complex. Finally, the second TS complex follows where oxygen of water is approaching and forming a new coordination bond.

All the geometries were optimized at the DFT level with the hybrid B3LYP functional and 6-31G(d) basis set (further labeled as BS1) with the description of heavy elements Pt, Ru, P, and Cl atoms by Stuttgart energy averaged pseudopotentials.[81,82] The original pseudo-orbital basis set was extended by polarization functions (with exponents $\boldsymbol{\alpha}_f$(Pt) = 0.98, $\boldsymbol{\alpha}_f$(Ru) = 1.29, $\boldsymbol{\alpha}_d$(P) = 0.51, and $\boldsymbol{\alpha}_d$(Cl) = 0.62) in the optimization part. The same level was used for the determination of the ΔG contributions (thermal and entropy terms) and also for confirmation of the proper character of the optimized geometries of TS structures as well as reactant and product supermolecules in both gas phase and CPCM approach. The energy profiles were determined at the B3LYP/6–311++G(2df,2pd)/CPCM level (BS2) expression where original pseudo-orbitals of metals were consistently augmented by a set of diffuse and polarization (2fg) functions optimized for neutral atoms at CCSD level, as mentioned elsewhere.[75,83]

As it can be noticed from Scheme 1 the complexes are composed from three/four ligands and the metal cation. The total stabilization energy (ΔE^{Stab}) of the complex is defined as

$$\Delta E^{\mathrm{Stab}} = -\left(E_{\mathrm{compl}} - \sum_{\mathrm{i}}^{\mathrm{Ligands}} E_{\mathrm{i}} - E_{\mathrm{Me}} + \Delta E^{\mathrm{deform}}\right). \quad (1)$$

Here E_{compl} is total energy of the whole complex, E_i and E_{Me} are BSSE corrected energies of a given ligand i and Me—the metal cation. In this case, the ligand deformation energies were included

$$\Delta E^{\mathrm{deform}} = \sum_{\mathrm{i}}^{\mathrm{Ligands}} \left(E_{\mathrm{i}}^{\mathrm{compl}} - E_{\mathrm{i}}^{\mathrm{opt}}\right). \quad (2)$$

In the equation the superscripts compl and opt denote calculations for the frozen ligand structure (taken from geometry of the complex) and for the optimized (isolated) ligand, respectively. The ligand binding and/or association energies (ΔE^{BE}) were evaluated according to equation

$$\Delta E^{\mathrm{BE}}(L) = (E_{\mathrm{compl}} - E_{\mathrm{L}} - E_{\mathrm{rest}}). \quad (3)$$

TABLE I. Metal-ligand coordination distances (in Å) within the hydration reactions for $[Ru(arene)(en)Cl]^+$, $[Ru(arene)(pta)Cl_2]$, and $[Pt(NH_3)_2Cl_2]$ complexes. The optimized bond lengths were obtained at the B3LYP/BS1/CPCM and T = 298 K level.

		Ru–Cl	Ru–Ben	Ru–N1	Ru–N2	Ru–O
Ru_en_Cl+w		2.479	1.713	2.146	2.151	4.218
TS_en		3.238	1.700	2.137	2.142	2.883
Ru_en_w+Cl		4.288	1.714	2.143	2.143	2.166
	Ru–Cl	Ru–Cl	Ru–Ben	Ru–P	Ru–O	Ru–O
Ru_pta_Cl2+w	2.473	2.477	1.740	2.343	3.810	
TS_pta1a	2.447	3.305	1.716	2.359	2.918	
TS_pta1d1	2.397	3.698	1.714	2.362	4.391	
Int1	2.380	5.244	1.717	2.365	4.794	
TS_pta1d2	2.358	4.960	1.711	2.382	3.584	
Ru_pta_Cl_w+Cl	2.448	4.375	1.741	2.348	2.159	
Ru_pta_Cl_w+w	2.458		1.743	2.347	2.175	4.070
TS_pta2a	3.206		1.715	2.367	2.199	2.724
TS_pta2d1	3.598		1.714	2.376	2.153	3.862
Int2	6.970		1.738	2.375	1.945	4.468
TS_pta2d2	5.137		1.703	2.398	2.16	3.461
Ru_pta_w2+Cl	4.207		1.740	2.362	2.176	2.148
Ru_pta_Cl_OH+w	2.496		1.763	2.335	2.087	
TS_pta2d1+OH	6.970		1.738	2.375	1.945	4.468
Int2_OH	4.397		1.711	2.387	1.957	3.090
TS_pta2d2_OH	4.477		1.734	2.352	2.064	2.18
Ru_pta_OH_w+Cl	2.496		1.763	2.335	2.087	
	Pt–Cl	Pt–Cl	Pt–N	Pt–N	Pt–O	Pt–O
Pt_a2_Cl2+w	2.361	2.363	2.066	2.065	3.862	
TS_cis1	2.354	2.798	2.058	2.045	2.467	
Pt_a2_Cl_w+Cl	2.349	4.083	2.070	2.034	2.082	
Pt_a2_Cl_w+w	2.360		2.068	2.074	2.021	3.738
TS_cis2	2.908		2.043	2.031	2.119	2.653
Pt_a2_2w+Cl	4.016		2.045	2.045	2.107	2.107
Pt_a2_Cl_OH+w	2.357		2.083	2.039	2.102	3.768
TS_cis2_OH	3.009		2.057	2.094	2.004	2.405
Pt_a2_OH_w+Cl	4.103		2.087	2.026	2.005	2.086

Similarly, the E_L and E_{rest} energies mean the BSSE corrected values of the given ligand and the remaining part of the complex, respectively. In these energies, deformation corrections were not considered.

The ground state of all the explored complexes is a closed-shell singlet. In the calculations of BSSE corrections within the CPCM regime, the ghost atomic orbital functions are localized inside the cavity, which has the same size as the whole complex. This is the simplest approach and discussion on other possibilities for determination of BSSE corrections within the PCM model can be found in Ref. 55.

The kinetic parameters of the studied reactions were determined according to Eyring's transition state theory. Because vibration modes, energies, and geometries are available from the above-described calculations, the rate constants can be estimated from the formula

$$k(T) = (k_B T/h)\exp(-\Delta G^{\neq}/RT). \quad (4)$$

The calculations of electronic properties [Natural Bond Orbital (NBO) and AIM analyses, and dipole moments] were performed at the same computational level as SP calculations (B3LYP/BS2). AIM analysis was performed by AIMALL program of T. Keith[84] and natural population analysis (NPA) partial charges were determined by NBO v.5 program from University of Wisconsin.[85]

A. Structures

All structures of the stationary points on the reaction profiles of the hydration reactions were optimized in both gas phase and CPCM levels. The obtained metal-ligand distances in water environment are collected in Table I. Longer distances between the metal and the arene ring can be noticed in the case of the RAPTA complexes compared to the Ru_en complexes due to higher steric crowding. The Ru–P bond of the pta ligand is about 2.34 Å in neutral reactant and it slightly increases with total charge of the complex up to 2.36 Å in the diaqua product. It means that origin of this bond is basically nonelectrostatic. In the product states of the both classes of Ru complexes, Ru–O distance (≈2.17 Å) is visibly longer than analogous Pt–O coordination bonds in cisplatin. The same is also true for the Ru–N bonds in Ru–en complexes and Ru–Cl bonds in Ru–pta reactants. All these distances are about 0.1 Å shorter in the Pt(II) complexes. The simplest possible explanation follows from a general study on covalent radii published recently[86] where the difference of covalent radii of Pt and Ru atoms is about

0.1 Å. The binding energy unambiguously correlates with electron density of the bond critical point, as it will be discussed below.

Transition states of Ru(II) piano-stool complexes in the 'pseudoassociative mechanism' are represented by the hepta-coordinated structures where one can easily expect relatively large sterical repulsion. However the exchanging ligands are practically nonbonded (see the part on binding energies below) in TSs so that lower binding competition occurs and visibly shorter Ru–arene distances can be noticed (in comparison with both reactant and product states). This effect is a little bit more pronounced in PCM geometries than in gas phase. Similar shortening is observed for the Ru–N coordination distances of the ethylenediamine ligand in TS of the Ru–en complex (TS_en) and for the equatorial amino ligands in the trigonal-bipyramidal TSs structures of cisplatin. On the contrary, in the case of the RAPTA TS structures, the Ru–P bond of the pta ligand is elongated. Similarly the Ru–O distance of the aqua ligand in second reaction step elongates in TS geometry (TS_pta2a) where the Ru–O bond is about 2.199 Å (despite of H-bonding between both water molecules and chloride) and in second hydration step (TS_cis2) where the axial Pt–N bond is also elongated (2.094 Å). The shortening can be explained by a lower competition to Pt–N bond in equatorial plane of trigonal-bipyramid due to very weakly bounded exchanging ligands. On the contrary, the coordination of the axial ligands is generally known to be always a little bit longer (and weaker).

Another reaction mechanism was revealed in the case of RAPTA complexes. The competitive dissociation mechanism is linked with two TS structures and one metastable penta-coordinated intermediate in each dechloration reaction. This intermediate has the two pta and Cl/aqua/hydroxo ligands oriented in a plane perpendicular to the arene ring. Such an arrangement minimizes the interligand repulsion. In this way it is obvious why this direct dissociative mechanism (dDM) could not occur in the Ru_en complex. The ethylenediamine bidentate ligand cannot form similar kind of structure (where en ligand would be perpendicular to arene ring) due to high-energy penalty caused by deviation of the donating electron lone-pairs of nitrogens from the ideal sp^3 orientation and by increased arene…H(en) steric repulsion. Basically all the structural trends from the discussion on TS of pseudoassociative mechanism are also valid for geometries of the intermediates and TS's of the dissociative pathway.

TABLE II. Gibbs energy reaction surface (in kcal/mol) and rate constants (in s^{-1} in gray) at the B3LYP/BS2/CPCM level.

	Calc.	Expt.
Ru_en_Cl+w	0.00	
TS_en	20.01	
Ru_en_w+Cl	2.79	
	1.32E-02	(1.98 ± 0.02) E-03[a]
Ru_pta_Cl2+w	0.00	
TS_pta1_a	18.95	
Ru_pta_Cl_w+Cl	3.31	
	7.98E-02	(3.33 ± 0.02) E-03[b]
Ru_pta_Cl2+w	0.00	
TS_pta1_d1	18.72	
Int_1	18.46	
TS_pta1_d2	20.59	
Ru_pta_Cl_w+Cl	4.12	
	4.72E-03[d]	
Ru_pta_Cl_w+w	0.00	
TS_pta2a	26.49	
Ru_pta_w2+Cl	10.83	
	2.37E-07	(5.5 ± 0.2) E-02[b]
Ru_pta_Cl_w+w	0.00	
TS_pta2_d1_w	19.90	
Int2_w	17.90	
TS_pta2_d2_w	27.98	
Ru_pta_2w+Cl	6.23	
	1.87E-08[d]	
Ru_pta_Cl_OH+w	0.00	
TS_pta2_d1_OH	11.88	
Int2_OH	6.96	
TS_pta2_d2_OH	12.56	
Ru_pta_OH_w+Cl	4.58	
	2.90E+03[d]	
Pt_a2_Cl2+w	0.00	
TS_cis1	23.86	
Pt_a2_Cl_w+Cl	5.24	
	1.99E-05	(1.9 ± 0.2)E-04[c]
Pt_a2_Cl_w+w	0.00	
TS_cis2	28.95	
Pt_a2_2w+Cl	10.99	
	3.73E-09	
Pt_a2_Cl_OH+w	0.00	
TS_cis2	25.90	
Pt_a2_OH_w+Cl	10.51	
	6.94E-07	(2.3 ± 0.3)E-04[c]

[a]Reference 19.
[b]Reference 88.
[c]Reference 89.
[d]$k_1k_2(k_1 + k_2)$ for subsequent reversible reactions.

B. Energy profile of hydration reactions

All the energy characteristics of the explored complexes are summarized in Table II and corresponding reaction energy profiles are drawn in Fig. 1 for PAM and in Fig. 2 for dDM. In the first reaction step of PAM, all the explored reactions are endoergic with $\Delta G_r \approx 3$–6 kcal/mol and have comparable activation barrier of about 20 kcal/mol for the replacement of the first chloride.

In the second reaction step of the RAPTA and cisplatin complexes, much higher activation energy (over 25 kcal/mol) was determined for pseudoassociative mechanism together with more pronounced endoergic reaction course of about 8–11 kcal/mol. This feature can be explained by the fact that in the monoaqua reactant the remaining chloro ligand is more strongly bond as follows from higher binding energy of the Ru–Cl in Table III (compare BE of 52 kcal/mol for monochloro reactant in the second hydration step with BE of 42 kcal/mol for dichloro-reactant in the first step). The same conclusion also follows from Table IV where the AIM critical points are displayed [corresponding Bond Critical Point (BCP) values of Ru–Cl are 0.065 versus 0.062 e/a.u.[3] (Ref. 3)].

The higher extent of similarity between the RAPTA complex and cisplatin follows not only from a structural factor but

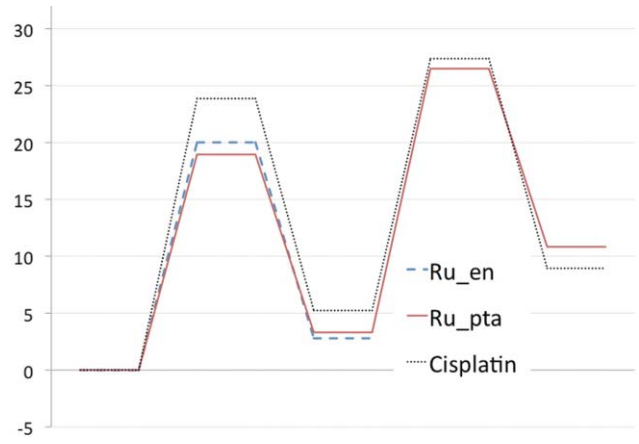

FIG. 1. Energy profile of pseudoassociative hydration reactions of $[Ru(arene)(en)Cl]^+$, $[Ru(arene)(pta)Cl_2]$, and $[Pt(NH_3)_2Cl_2]$ complexes at the B3LYP/6–31++G(2dp,2pd)/CPCM(UA0) level.

also from the shape of the reaction energy profile. In the case of cisplatin, the activation barrier of the first step is a little higher than in RAPTA (23 vs 19 kcal/mol) but otherwise the shape is more or less the same (energy of all the other stationary points on the reaction coordinate differs at most by 2 kcal/mol). However, one should keep in mind that the similarity deals only with the hydration reaction and (probably) does not concern the subsequent reactions since the role of arene ligand is believed to be important in stacking interactions with nucleobases in genomic code. This aspect was not considered in the study and it is not fully enlightened even *in vitro* and *in vivo* experiments at present. Our previous calculations[75] on this topic as well as results from other groups[57,87] seem to confirm this assumption.

In the neutral or basic solutions the hydroxo ligand should be considered instead of the aqua ligand (for cisplatin the experimental pK_a is 5.5; calculated value ≈6.2 (Ref. 54) and analogous calculations for Ru_pta_wCl complex lead to estimation of ca 7.7 (Ref. 19). This leads to lower activation barrier (by about 3 kcal/mol) due to higher competition of negatively charged OH group in comparison with neutral aqua ligand. Moreover, in the case of RAPTA_OH complex the second dechloration step cannot occur within the PAM mechanism. Instead, the direct dissociation mechanism was found with two lower reaction barriers (≈12 and 6 kcal/mol). The

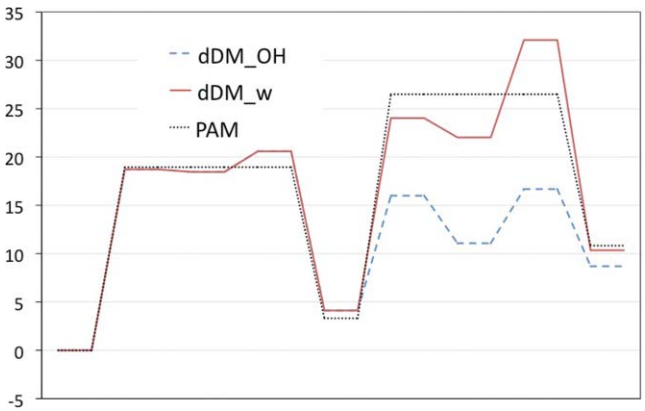

FIG. 2. Reaction coordinate for the dissociative mechanism of RAPTA dechlorination at the B3LYP/6-31++G(2dp,2pd)/CPCM level.

same dissociation mechanism was also determined for hydrated RAPTA complex in presence of aqua ligand. Here, the activation barriers were found 19 and 10 kcal/mol. It means that lower reaction barrier was also confirmed for dissociation mechanism in acidic and neutral solutions. The dDM pathway has practically the same activation energy for the first dechloration reaction as PAM ($\Delta G_a^1 \approx 19$ kcal/mol). No dDM was found in cisplatin hydration.

C. Binding energies

Table III summarizes the stabilization and binding energies evaluated according to Eqs. (1) and (3), respectively. Two different kinds of stabilization energies are present. Besides standard definition (ΔE^{Stab}) based on Eq. (1) the other energy (ΔE^{Stex}) represents total coordination energy of the metal cation with the ligands fixed in their optimal positions in the given complex. The ΔE^{Stex} energy is determined according to Eq. (3) supposing E_L is energy of the metal cation and E_{rest} represents the frozen structure of all the ligands. In this way, mutual repulsion of the ligands is not included from the obtained value and this repulsion basically forms the main difference between both ΔE^{Stab} and ΔE^{Stex} values (besides deformation correction involved in ΔE^{Stab} value). As to deformation energies, it can be seen that the smallest values were obtained in the case of cisplatin where smallest number of ligands (small molecules—water and ammonia) is present. The largest deformations are in the Ru_en complexes mainly due to deformation of the en-ligand (about 5 kcal/mol). The deformation of the benzene ligand is ≈3 kcal/mol in the both Ru complexes. The repulsion energy of the ligands (as a $E^{Stab} - E^{Stex}$ difference) clearly shows the highest values in cisplatin complexes where values up to 30 kcal/mol can be seen. Substantially smaller values were gained in the RAPTA complexes and the smallest repulsion was determined in the Ru_en complexes since only one negatively charged ligand is present there.

Comparing the metal-am(m)ino binding energies, it can be noticed that the en ligand is slightly less coordinated in the Ru_en complex than ammines in cisplatin. Confirmation of this fact can be observed from a comparison of BCP in Table IV where all the densities in BCP of Pt-N(H_3) are higher than 0.1 e a.u.$^{-3}$ while the Ru-N(en) densities are always lower than this value. The BE of benzene is slightly higher in the Ru_en complex than in RAPTA which is in accord with the larger number of BCP's of the Ru–C bonds in the Ru_en complexes. In this case also smaller partial charge of Ru(II) cation of the RAPTA complexes (cf. Table V) can be responsible for the lower electrostatic cation—π system contribution. In these complexes it can be noticed that the pta ligand is coordinated with similar BE as both chloride ligands. Electrostatic enhancement of Ru–Cl bond is compensated by a larger coordination character of the Ru–P bond as follows from BCP analysis. The Ru–P bond has by about 50% higher electron density in the BCP (0.097 vs 0.063 in the Ru–Cl BCP).

D. Rate of hydration process

Activation barriers can give an estimation of the rate constants using Eyring's transition state theory [Eq. (4)].

TABLE III. Stabilization and binding energies of the ligands (in kcal/mol), a = NH_3, w = H_2O, ben = benzene, en and pta ligands are defined in the text. The calculations were done at the B3LYP/BS2/CPCM level.

	Stab	Stex	Repulsion	Deformation		
Ru_en_Cl+w	409.4	435.1	18.2	7.6		
TS_en	394.3	417.6	14.3	9.0		
Ru_en_w+Cl	403.3	426.7	15.0	8.4		
Ru_pta_Cl2+w	417.8	444.5	21.7	5.0		
TS_pta1a	397.4	422.9	19.2	6.3		
TS_pta1d1	387.1	414.9	17.4	6.1		
Int1	392.7	416.2	15.7	5.9		
TS_pta1d2	394.5	422.4	16.9	7.4		
Ru_pta_Cl_w+Cl	404.9	435.0	23.3	6.8		
Ru_pta_Cl_w+w	398.8	423.7	19.6	5.3		
TS_pta2a	378.3	403.4	18.4	6.6		
TS_pta2d1	369.6	408.8	11.1	6.4		
Int2	375.5	411.5	16.5	6.6		
TS_pta2d2	381.1	409.2	16.9	7.1		
Ru_pta_w2+Cl	385.7	414.6	21.4	7.5		
Ru_pta_Cl_OH+w	426.8	449.5	19.7	5.8		
TS_pta2d1+OH	418.3	433.4	18.3	6.5		
Int2_OH	414.7	428.3	13.1	6.9		
TS_pta2d2_OH	415.2	431.2	16.3	7.4		
Ru_pta_OH_w+Cl	422.1	445.8	22.9	7.8		
Pt_a2_Cl2+w	407.1	440.5	32.6	0.8		
TS_cis1	391.8	423.2	30.6	0.8		
Pt_a2_Cl_w+Cl	399.1	423.1	21.3	2.6		
Pt_a2_Cl_w+w	395.6	415.1	19.5	1.0		
TS_cis2	371.2	390.8	19.6	1.0		
Pt_a2_2w+Cl	385.7	398.9	13.3	2.7		
Pt_a2_Cl_OH+w	435.1	454.3	17.7	1.6		
TS_cis2_OH	413.5	443.0	28.3	1.2		
Pt_a2_OH_w+Cl	422.1	449.8	25.2	2.5		
	Cl		ben	en	w	
Ru_en_Cl+w	46.7		72.7	99.3	4.4	
TS_en	21.3		87.4	104.8	7.0	
Ru_en_w+Cl	19.2		81.5	110.0	34.1	
	Cl	Cl	ben	pta	w/h	w
Ru_pta_Cl2+w	42.0	42.0	59.1	42.0	5.2	
TS_pta1a	47.6	16.8	71.6	46.9	4.9	
TS_pta1d1	49.1	12.5	78.4	48.2	5.9	
Int1	51.2	5.6	92.7	53.6	5.6	
TS_pta1d2	48.1	5.8	90.9	50.1	4.6	
Ru_pta_Cl_w+Cl	46.6	16.7	65.7	45.8	31.4	
Ru_pta_Cl_w+w	51.7		67.1	45.8	30.0	10.4
TS_pta2a	22.7		81.8	47.9	21.0	13.5
TS_pta2d1	*39*		67.7	49.0	20.7	1.5
Int2	13.1		86.6	55.3	37.8	14.1
TS_pta2d2	8.4		93.8	52.4	26.4	12.4
Ru_pta_w2+Cl	20.1		76.2	51.4	24.0	38.8
Ru_pta_Cl_OH+w	12.0		73.6	52.9	24.1	17.1
TS_pta2d1+OH	26.6		57.1	37.8	67.5[a]	9.0
Int2_OH	5.6		77.7	43.2	83.1[a]	7.5
TS_pta2d2_OH	4.1		85.5	46.6	91.9[a]	7.5
Ru_pta_OH_w+Cl	5.1		86.6	41.7	85.8[a]	5.1
	Cl	Cl	NH3	NH3	w/h	w
Pt_a2_Cl2+w	48.7	48.7	54.8	54.8	7.7	
TS_cis1	15.0	53.8	54.1	51.1	3.4	
Pt_a2_Cl_w+Cl	19.7	57.8	59.4	66.8	42.9	

TABLE III. (Continued).

	Cl	Cl	NH3	NH3	w/h	w
Pt_a2_Cl_w+w		60.7	59.8	69.1	41.7	13.7
TS_cis2		27.7	62.3	72.6	37.0	7.8
Pt_a2_2w+Cl		28.8	73.2	73.2	45.9	45.9
Pt_a2_Cl_OH+w		50.6	54.8	51.8	89.4[a]	10.4
TS_cis2_OH		12.1	53.1	50.1	86.8[a]	10.1
Pt_a2_OH_w+Cl		18.2	54.4	62.6	84.5[a]	40.1

[a]Hydroxo ligand.

Based on this equation, rate constants for pseudo-first order hydration process were evaluated and collected in the gray lines of Table II. According to these constants the fastest hydration in the first reaction step occurs in the case of RAPTA complex; hydration of the Ru_en complex is about one order of magnitude slower. Hydration of cisplatin is, according to our calculations, the slowest process.

Rate constants can be easily compared with experimental values. Recently published rate constants for hydration of RAPTA-C ($k_1=3.33\pm0.02\times10^{-3}$ and $k_2=5.5\pm0.2\times10^{-2}$ s^{-1}) can give a good estimation of hydration of structurally similar complexes of RAPTA-B.[88] Slightly lower rate constant ($k_{e1}=1.98\pm0.02\times10^{-2}$ s^{-1}) was obtained for hydration of Ru(arene)(en)Cl_2 complexes was obtained in Sadler's group.[19] As to cisplatin hydration, several measurements were performed,[89–93] estimating the k_{1c} constant between 5.2×10^{-5} and $1.9\pm0.2\times10^{-4}$ s^{-1}. Measurements of the second hydration step lead to the k_{2c}

TABLE IV. Critical points of all the M–L bonds (in *e*/a.u.^{3}). The analyses were done at the B3LYP/B2/CPCM level.

	Ru–N1[a]	Ru–N2	Ru–Cl	Ru–C[b]	Ru–O	
Ru_en_Cl+w	0.090	0.088	0.061	0.082		
TS_en	0.092	0.093	0.016	0.086	0.018	
Ru_en_w+Cl	0.091	0.092		0.082	0.068	
	Ru–P	Ru–Cl	Ru–Cl	Ru–C[d]	Ru–O	Ru–O
Ru_pta_Cl2+w	0.098	0.062	0.062	0.082		
TS_pta1a	0.097	0.067	0.014	0.090	0.017	
TS_pta1d1	0.096	0.075	0.007	0.089		
Int1	0.096	0.078		0.088		
TS_pta1d2	0.093	0.082		0.090		
Ru_pta_Cl_w+Cl	0.098	0.066		0.082	0.071	
Ru_pta_Cl_w+w	0.098	0.065		0.082	0.067	
TS_pta2a	0.096	0.017		0.089	0.064	0.023
TS_pta2d1	0.095	0.008		0.089	0.074	
Int2	0.093			0.089	0.086	
TS_pta2d2	0.091			0.089	0.072	
Ru_pta_w2+Cl	0.096			0.083	0.066	0.074
Ru_pta_Cl_OH+w	0.100	0.059		0.083	0.092	
TS_pta2d1+OH	0.093	0.010		0.089	0.119	
Int2_OH	0.093			0.089	0.132	
TS_pta2d2_OH	0.092			0.090	0.129	
Ru_pta_OH_w+Cl	0.097			0.082	0.099	0.068
	Pt–N[c]	Pt–N[d]	Pt–Cl	Pt–Cl	Pt–O	Pt–O[e]
Pt_a2_Cl2+w	0.117	0.117	0.086	0.085		
TS_cis1	0.124	0.118	0.086	0.038	0.043	
Pt_a2_Cl_w+Cl	0.126	0.116	0.088		0.093	
Pt_a2_Cl_w+w	0.113	0.125	0.087			0.088
TS_cis2	0.126	0.127	0.031		0.030	0.085
Pt_a2_2w+Cl	0.124	0.124			0.088	0.088
Pt_a2_Cl_OH+w	0.116	0.112	0.085			0.115
TS_cis2_OH	0.121	0.107	0.025		0.048	0.122
Pt_a2_OH_w+Cl	0.127	0.109			0.092	0.122

[a]*N* atom involved in H-bond interactions.
[b]Averaged value of BCPs.
[c]*N* atom in equatorial plane of TS or in H-bond interactions.
[d]*N* atom in axial position of TS.
[e]O from hydroxo ligand.

TABLE V. Natural population analysis of the key atoms (in *e*). The analyses were done at the B3LYP/B2/CPCM level.

	Ru	Cl		N1	N2	O	Benzene[a]
Ru_en_Cl+w	0.394	−0.590		−0.802	−0.790	−1.027	0.493
TS_en	0.553	−0.838		−0.812	−0.808	−1.030	0.577
Ru_en_w+Cl	0.493	−0.869		−0.803	−0.787	−0.942	0.531
	Ru	Cl	Cl	P	O	O	Benzene[a]
Ru_pta_Cl2+w	0.095	−0.568	−0.561	1.153		−1.046	0.483
TS_pta1a	0.260	−0.544	−0.831	1.101		−1.032	0.568
TS_pta1d1	0.242	−0.512	−0.907	1.035		−1.014	0.625
Int1	0.233	−0.494	−0.951	1.013		−1.012	0.646
TS_pta1d2	0.234	−0.481	−0.948	1.010		−0.994	0.634
Ru_pta_Cl_w+Cl	0.200	−0.548	−0.880	1.131		−0.929	0.513
Ru_pta_Cl_w+w	0.204		−0.546	1.122	−0.935	−1.010	0.536
TS_pta2a	0.354		−0.796	1.065	−0.924	−1.030	0.639
TS_pta2d1	0.372		−0.855	1.006	−0.990	−0.896	0.674
Int2	0.390		−0.918	0.968	−0.992	−0.889	0.713
TS_pta2d2	0.398		−0.942	0.967	−0.998	−0.882	0.746
Ru_pta_w2+Cl	0.311		−0.858	1.094	−0.940	−0.907	0.593
Ru_pta_Cl_OH+w	0.206		−0.601	1.173	−1.034	−1.002	0.392
TS_pta2d1+OH	0.377		−0.912	1.031	−1.029	−0.966	0.519
Int2_OH	0.352		−0.968	0.995	−1.030	−0.926	0.554
TS_pta2d2_OH	0.359		−0.957	1.015	−0.995	−0.935	0.533
Ru_pta_OH_w+Cl	0.294		−0.916	1.118	−0.892	−1.014	0.440
	Pt	Cl	Cl	N	N	O	O[b]
Pt_a2_Cl2+w	0.542	−0.615	−0.613	−1.027	−1.030	−1.035	
TS_cis1	0.710	−0.607	−0.839	−1.026	−1.007	−1.016	
Pt_a2_Cl_w+Cl	0.659	−0.602	−0.833	−1.049	−0.999	−0.961	
Pt_a2_Cl_w+w	0.669		−0.600	−0.946	−0.894	−0.976	−0.891
TS_cis2	0.812		−0.818	−0.897	−0.889	−0.975	−0.892
Pt_a2_2w+Cl	0.782		−0.801	−0.903	−0.903	−0.911	−0.911
Pt_a2_Cl_OH+w	0.645		−0.627	−1.039	−1.034	−1.072	−1.106
TS_cis2_OH	0.795		−0.881	−1.056	−1.004	−1.000	−1.105
Pt_a2_OH_w+Cl	0.735		−0.848	−1.062	−0.999	−0.964	−1.113

[a]Sum of partial charges of all C and H atoms.
[b]O of hydroxo group.

value of $1.1 \pm 0.1 \times 10^{-4}$.[89,92,94] It is probably not necessary to mention that the differences can be made by various experimental settings. While computational estimations of the rate constants for the first reaction steps are in acceptable agreement with measured data, calculated values for the second steps are substantially worse for cisplatin. In the RAPTA case, fairly good agreement was obtained for dissociation mechanism in neutral and acidic condition where aqua ligand is present. However, a different complex is considered as a reactant under the experimental conditions where authors[88] expect a hydration of the neutral complex with the negatively charged hydroxo group instead of the aqua ligand. Calculations with the neutral RAPTA complex lead to very fast reaction cause with rate constant $k_2 \approx 3 \times 10^3$ s^{-1}. The explanation can be searched in stronger Ru–OH coordination which represents a higher competition to the Ru–Cl interaction and facilitates a release of chloride particle and its replacement by second aqua ligand.

E. Properties of electron density

To complete the comparison of the hydration reactions of the chosen metal complexes several analyses were performed for all the stationary points on the reaction coordinates. Electron densities of the most important BCPs are collected in Table IV and charges obtained in the framework of natural population analysis are summarized in Table V.

Correlation between BEs and BCPs was already discussed above. Nevertheless, it is worth to note that in the RAPTA complexes, only three BCPs of the Ru–C bonds were found (with exception of the reaction product of the second step where already two relatively weaker aqua ligands are coordinated so that a stronger benzene coordination can occur). On the other hand in all the Ru_en complexes four BCPs were found.

It can be also mentioned that in accord with higher coordination, lower BCP densities for metal coordination of replacing ligands were obtained in TSs of Ru(II) complexes (both Ru–O and Ru–Cl bonds have ≈0.02 *e*/a.u.^{3}) in comparison with Pt(II) complexes (where values of 0.04 were acquired). Basically all BCP densities are visibly higher in cisplatin complexes in comparison with Ru(II) complexes due to lower ligand competition. The same conclusion can be also drawn from the BE decomposition.

Results of the NPA analysis for individual metal complexes are summarized in Table V. From partial charges of

metal cations it follows that while the charge of the Pt atom varies between 0.55 and 0.8 *e* in dependence on donation strength of coordinated ligands, the Ru charges of the Ru_en complexes lie in the range of 0.4–0.55 *e*. The lowest metal charges were found in the RAPTA complexes with values from 0.1 to 0.35 *e*. (In analogous analysis at the MP2/6-31++G(d,p) computational level even negative values were obtained for most of the RAPTA complexes.)

From Table V an estimation of electrostatic strengthening of the coordination-covalent bonds can be judged based on the Coulomb law. Since the covalent character of the bond basically follows from a BCP value, at least, an approximate estimation of the prevailing contributions to the given coordination can be ensued from Tables IV and V.

III. CONCLUSIONS

In this study hydration reactions and electronic properties of three different organometallic complexes were subject to quantum chemical calculations.

All the complexes were optimized at the B3LYP/6-31G(d)/CPCM level where metal atoms were treated with Stuttgart effective core potentials (ECPs). The SP energy calculations and determination of electronic properties were performed at the B3LYP/6-311++G(2df,2pd)/CPCM level.

It was found that our hydration model works fairly well for the replacement of the first chloride by water molecule—acceptable agreement for both Gibbs free energies and rate constants was obtained. In the second hydration step a visibly underestimated value of cisplatin rate constant can be noticed. On the contrary in direct dissociation mechanism in basic environment too fast dechlorination is predicted due to more strongly coordinated hydroxo ligand.

For the comparison of the hydration reaction of all three complexes, stabilization and binding energies together with BCP electron densities and NPA partial charges were evaluated in all stationary points of the reaction coordinates. Estimated BEs confirm that the benzene ligand is relatively weakly bonded assuming the fact that arene ligand occupies three and four coordination positions of the Ru(II) cation in the RAPTA and Ru_en complexes, respectively. In this way, this coordination has similar strength like coordination of the aqua ligand. The strongest coordination of the chloride ligand occurs in cisplatin complex in accord with the lowest rate constants (the highest activation barrier). The BE of the Ru–Cl bond in the Ru_en complex is by about 2 kcal/mol lower, which correlates well with faster hydration course in this complex and the fastest activation reaction in the RAPTA case is connected with the most "loosely" interacting chloride. From the point of BEs of chloride ligands, the higher barriers in the second reaction step are not surprising.

Basically all the relations in binding energies correlate with NPA partial charges and AIM analysis of BCPs as follows from the discussion above.

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