JCTC Journal of Chemical Theory and Computation

Computational Electrochemistry of Ruthenium Anticancer Agents. Unprecedented Benchmarking of Implicit Solvation Methods†

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Received September 24, 2007

Abstract: Two ruthenium(III) complexes {(HIm)[*trans*-$RuCl_4$(DMSO)(Im)] (NAMI-A) and (HInd)-[*trans*-$RuCl_4(Ind)_2$] (KP1019), DMSO = dimethyl sulfoxide, Im = imidazole, Ind = indazole} have been tested in phase I clinical trials as potential anticancer drugs. Ru(III) anticancer agents are likely activated in vivo upon reduction to their Ru(II) analogs. Aiming at benchmarking implicit solvation methods in DFT studies of ruthenium pharmaceuticals at the B3LYP level, we have calculated the standard redox potentials (SRPs) of Ru(III/II) pairs that were electrochemically characterized in the literature. 80 SRP values in four solvents were calculated using three implicit solvation methods and five solute cavities of molecular shape. Comparison with experimental data revealed substantial errors in some of the combinations of solvation method and solute cavity. For example, the overall mean unsigned error (MUE) with the PCM/UA0 combination, which is the popular default in Gaussian 03, amounts to 0.23 V (5.4 kcal/mol). The MUE with the CPCM/UAKS combination, which was employed by others for recent computational studies on the hydrolysis of NAMI-A and *trans*-$[RuCl_4(Im)_2]^-$, amounts to 0.30 V (7.0 kcal/mol) for all compounds and to 0.60 V (13.9 kcal/mol) for a subset of compounds of the medicinally relevant type, *trans*-$[RuCl_4(L)(L')]^-$. The SRPs calculated with the PCM or CPCM methods in Gaussian 03 can be significantly improved by a more compact solute cavity constructed with Bondi's set of atomic radii. Earlier findings that CPCM performs better than PCM cannot be confirmed, as the overall MUE amounts to 0.19 V (4.3−4.4 kcal/mol) for both methods in combination with Bondi's set of radii. The Poisson−Boltzmann finite element method (PBF) implemented in Jaguar 7 together with the default cavity performs slightly better, with the overall MUE being 0.16 V (3.7 kcal/mol). Because the redox pairs considered in this study bear molecular charges from +3/+2 to −1/−2 and the prediction of solvation free energies is most challenging for highly charged species, the present work can serve as a general benchmarking of the implicit solvation methods.

Introduction

Due to the success of cisplatin as an anticancer drug,[1] the search for new metallopharmaceuticals has continued and extended to non-platinum complexes,[2] most notably ruthenium[3] and rhodium.[4] Two Ru(III) complexes, NAMI-A[5] and KP1019,[6] with the common lead structure, *trans*-$[RuCl_4(L)(L')]^-$ (Figure 1), successfully completed phase I clinical trials.[7] Recent developments of organometallic Ru(II) anticancer complexes are promising as well.[8,9] Ru(III) complexes are believed to be activated in vivo upon reduction to their Ru(II) analogs.[10] A selective reduction in cancer cells occurs likely due to the reducing environment caused by deficiency of molecular oxygen in tumors (*hypoxia*),[11] as the blood flow to the rapidly growing tumor is insufficient. The standard redox potential (SRP) of a Ru(III) complex is believed to be crucial to its anticancer activity.[12] If it is too low, then

† Quantum Chemical Studies of Metals in Medicine, IX.

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10.1021/ct700247g CCC: $40.75
Published on Web 02/02/2008

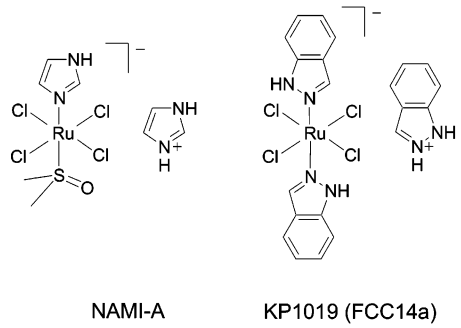

Figure 1. NAMI-A and KP1019 (FCC14a), two Ru(III) anticancer complexes in clinical trials.

the complex is not reduced and remains inactive. If it is too high, then the complex is reduced too easily and the selectivity to cancer cells is lost.

The prediction of SRPs can rationalize and accelerate the search for new drugs, because an in silico screening can be performed before relevant compounds are selected, synthesized, and tested in vitro and in vivo. So far, SRPs were often predicted using an empirical increment system[13] derived from experimentally measured SRPs. This empirical approach is particularly successful if strongly related complexes with the same stereochemical arrangement of ligands are compared to one other. Note that geometric isomers (e.g., *cis* vs *trans*; *mer* vs *fac*) require different parameter sets. A more general approach for the prediction of SRPs is based on modern quantum chemical calculations.[14] The accurate prediction of solvation free energies poses a true challenge in these calculations. The objective of the present work is benchmarking various implicit solvation methods[15] and molecule-shaped solute cavities employed for density functional theory (DFT) studies at the B3LYP[16,17] level.

Recent computational studies of other groups are highly complementary to the present work. *First*, benchmarking studies were carried out to assess the performance of different implicit solvation protocols for organic and main group element compounds.[18,19] *Second*, computation of SRPs of group 8 metal complexes mostly in organic solvents demonstrated that the approach is valid for a wide range of SRPs.[20] *Third*, the SRP of the aqueous $Ru^{3+}_{aq}/Ru^{2+}_{aq}$ pair was calculated using a variety of quantum chemical methods, effective core potentials (ECPs), and basis sets, implicit solvent models, and cavities.[21] The influence of the first and second solvation shells on the SRP of the $Ru^{3+}_{aq}/Ru^{2+}_{aq}$ pair was investigated as well.[21] DFT studies on Ru(III) anticancer agents were recently reported, but validation of the method by predicting their SRPs was not taken into account.[22,23] In the present work, we consider 80 SRPs of 61 ruthenium complexes in four solvents.[24,25] While various types of ruthenium complexes are included, an emphasis is placed on anticancer complexes in aqueous solution, the SRPs of which were measured recently[25−27] and fall into a fine biologically relevant window (from −0.4 to +0.8 V vs NHE).[28] We believe that the results of this benchmarking work will improve the accuracy and credibility of future computational studies of ruthenium pharmaceuticals and other metal complexes.

Methods

The geometries of the molecules were optimized at the gradient-corrected DFT level using the 3-parameter fit of exchange and correlation functionals of Becke[16] (B3LYP), which includes the correlation functional of Lee, Yang, and Parr (LYP),[17] as implemented in Gaussian 03.[29] The Stuttgart-Dresden scalar-relativistic energy-consistent small-core ECPs and the corresponding valence-basis sets were used for the Ru (MWB28 ECP together with an (8s7p6d)[6s5p3d] basis set)[30] and I atoms (MWB46 ECP together with a (4s5p)-[2s3p] basis set),[31] and the 6-31G(d,p) basis sets were used for the other atoms.[32] This basis-set combination is denoted M. Vibrational frequencies were also calculated at B3LYP/M; all structures reported herein are minima on the potential energy surfaces. Improved total energies were calculated at the B3LYP level using for Ru the MWB28 ECP[30] and the valence-basis set augmented with two sets of f functions and one set of g functions to obtain an (8s7p6d2f1g)[6s5p3d2f1g] basis set,[33] using for I the MWB46 ECP[31] together with an (14s10p3d1f)[3s3p2d1f] basis set,[33] with the 6-311+G(3d) on S, Cl, and Br atoms, and the 6-311+G(d,p) basis sets at the other atoms. Note that large basis sets are required for obtaining accurate energies of S[34] and I[35] compounds. This basis-set combination is denoted XL. Free energies in vacuo (G^1) were calculated by adding corrections from unscaled zero-point energy (ZPE), thermal energy, work, and entropy evaluated at the B3LYP/M level at 298.15 K, 1 atm to the energies calculated at the B3LYP/XL//M level.

Solvation free energies (ΔG_{solv}) of the structures optimized in vacuo at the B3LYP/M level were calculated using three implicit solvation methods:[15] The Polarizable Continuum model (PCM)[36] in its integral equation formalism (IEF)[37] as implemented in Gaussian 03 and the Conductor-like[38] Polarizable Continuum Model (CPCM)[39] in Gaussian 03[29] and the Poisson−Boltzmann finite element method (PBF)[40] in Jaguar 7.[41] These methods belong to the class of self-consistent reaction field (SCRF) methods. The solute is embedded in a continuum dielectric with a dielectric constant ϵ representing the solvent.[42] The solute charge distribution polarizes the continuum dielectric, and the potential arising from the solvent polarization in turn modifies the solute Hamiltonian. The calculation of the solute wave function is carried out iteratively until self-consistency. The PCM method describes the solvent reaction potential in terms of apparent surface charges localized on tesserae at the continuum boundary. The CPCM method uses apparent surface charges as well but describes the solvent first as a conductor ($\epsilon = \infty$) and then rescales the charges for a finite value of the dielectric constant. The PBF method uses finite elements for numerical solution of the Poisson−Boltzmann differential equation. The PCM and CPCM calculations were done at the B3LYP/M level, while the PBF calculations were done at the B3LYP/LACVP** level, which includes a scalar-relativistic energy-consistent small-core ECP[43] and basis set at the metal and the 6-31G(d,p) basis sets at the other atoms.

The three solvation methods were used together with solute cavities of molecular shape; the PCM and CPCM methods together with the cavities based on the UA0, UAHF, UAKS,

Table 1. Radii (Å) Used for Constructing the Solute Cavities Considered in This Work

	UA0	UAHF	UAKS	Bondi	PBF
H				1.200	1.150
C				1.700	1.900
C[e]	1.925	1.725	1.725		
CH[e]	2.125	1.905	1.905		
CH_2[e]	2.325	2.193	2.193		
CH_3[e]	2.525	1.950	1.950		
N				1.550	1.600
N[a]	1.830	1.551	1.461		
NH[a]	1.930	1.641	1.551		
NH_2[c]	2.030	1.680	1.680		
NH_3[b]	2.130	1.770	1.770		
O				1.520	1.600
O[a]	1.750	1.569	1.479		
OH[d]	1.780	1.590	1.590		
OH_2[b]	1.950	1.569	1.569		
S	2.017[a]	1.959[a]	1.959[a]	1.800	1.900
Cl	1.973[a]	1.959[a]	1.959[a]	1.750	1.974
Br	2.094[c]	2.080[c]	2.080[c]	1.850	2.095
Ru	1.482	1.482	1.482	1.482	1.481
I	2.250[f]	2.350[f]	2.350[f]	1.980	2.250

[a] In *trans*-$[RuCl_4(DMSO)(Im)]^-$. [b] In *cis*-$[Ru(NH_3)_4(OH_2)_2]^{3+}$. [c] In *trans*-$[Ru(NH_3)_4Br(isonicotinamide)]^{2+}$. [d] In $[Ru(NH_3)_5(OH)]^{2+}$. [e] In *mer,trans*-$[RuCl_3(Et_2S)(Ind)_2]$. [f] In *cis*-$[Ru(NH_3)_4I(py)]^{2+}$.

and Bondi radii and the PBF method in Jaguar 7 together with the default set of radii. In the United Atom (UA) topological models,[44] the cavity is obtained from spheres centered on non-hydrogen atoms. The radius of each sphere depends on the atom type, its connectivity, and the number of hydrogen atoms attached; typical values are listed in Table 1. The UA0 radii are based on the Universal Force Field (UFF).[45] Variants of these radii were optimized at the Hartree−Fock level (UAHF)[46] and the Perdew-Burke-Ernzerhof (PBE)[47] Kohn−Sham DFT level (UAKS).[29] In contrast, Bondi's[48] set of radii consider hydrogen atoms explicitly, and the values depend on atom identity rather than on its connectivity or hybridization. The radii are used in several ways for the construction of cavity in the calculation of the solvation free energy $\Delta G_{solv}^{\epsilon}$, which is decomposed into solute−cavity-formation[49] (ΔG_{cav}), electrostatic (ΔG_{elst}), and dispersion and repulsion ($\Delta G_{dis-rep}$) contributions ($\Delta G_{solv} = \Delta G_{elst} + \Delta G_{dis-rep} + \Delta G_{cav}$). In the PCM and CPCM implementations, the nonelectrostatic contributions $\Delta G_{dis-rep}$ and ΔG_{cav} are calculated using a solvent accessible surface (SAS),[50] whereas ΔG_{elst} is calculated using a similar surface constructed by the radii scaled by a factor[51] and additional spheres to smoothen the surface. In the PBF method, ΔG_{elst} is calculated using an SAS constructed by a set of standard radii including explicit hydrogen atoms (Table 1). An empirical formula depending linearly on the SAS area is employed for the remaining terms, $\Delta G_{dis-rep} + \Delta G_{cav}$. Our attempts to further refine this set of radii or change the basis sets indicated that the PBF protocol had been reasonably optimized.

Standard redox potentials (SRPs) were calculated on the basis of the thermodynamic cycle shown in Figure 2,[14,52] which is similar to that proposed for the prediction of acidity constants.[53] The SRP is related to the reaction free energy in solution (ΔG^{ϵ})

$$\mathrm{SRP} = -(\Delta G^{\epsilon}/zF) - \Delta \mathrm{SRP}_{\mathrm{NHE}}$$

with

$$\Delta G^{\epsilon} = -\Delta G_{solv}(\mathrm{Ox}) + \Delta G^{1} + \Delta G_{solv}(\mathrm{Red})$$

according to Figure 2. ΔG^1 is the reaction free energy in vacuo, ΔG_{solv}(Ox) and ΔG_{solv}(Red) are the solvation free energies in the oxidized and reduced form, $F = 96\,485$ C/mol $= 23.061$ kcal/(Vmol) is the Faraday constant, and $z = 1$ for one-electron reductions. The SRPs are shifted by $\Delta \mathrm{SRP}_{\mathrm{NHE}} = 4.28$ V to align the results to the scale of the Normal Hydrogen Electrode (NHE).[54]

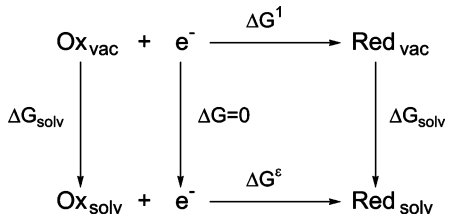

Figure 2. Thermodynamic cycle for calculating redox potentials.

Results and Discussion

We start with the *default* solvation protocol in Gaussian 03, which consists of the Polarizable Continuum Model (PCM)[28] together with the default definition of the solute cavity on the basis of the united atom topological model UA0.[32] This approach is denoted as Protocol I. Figure 3a shows the calculated (PCM/UA0) vs experimental SRPs. The results are displayed as follows: (i) The *solvent* (ACN, DMF, DMSO, water) is indicated by the color of symbol. (ii) The *molecular charge* of the redox pairs ranging from +3/+2 to −1/−2 is indicated by the shape of symbol. (iii) The *medicinal relevance* of the aqueous SRPs for the complexes of the type *trans*-$[RuCl_4(L)(L')]^-$ is indicated by filled symbols. The two drug candidates in the clinics, KP1019 and NAMI-A, belong to this category (Figure 1). To analyze the results in a quantitative manner, mean unsigned errors (MUE) are listed in Table 2, sorted by solvent, molecular charge, and medicinal relevance. The overall MUE of Protocol I for the complete set of data (all compounds in all solvents) is 0.23 V (5.4 kcal/mol). Similar MUE values are obtained for subsets of complexes in water and medicinally relevant complexes, 0.26 V (6.0 kcal/mol) and 0.29 V (6.8 kcal/mol), respectively.[55]

Protocol II combines the PCM method with the UAHF cavity, as implemented in Gaussian 03. This approach has been frequently used, as it is recommended for the prediction of solvation free energies by comparing solution- and gas-phase free energies.[29] Figure 3b displays the calc. vs exp. SRPs, and Table 2 includes the MUEs. The calculations reveal that this protocol performs worse than Protocol I: The MUE for the complete set of data (all compounds in all four solvents) is 0.32 V (7.4 kcal/mol). Considering the molecular

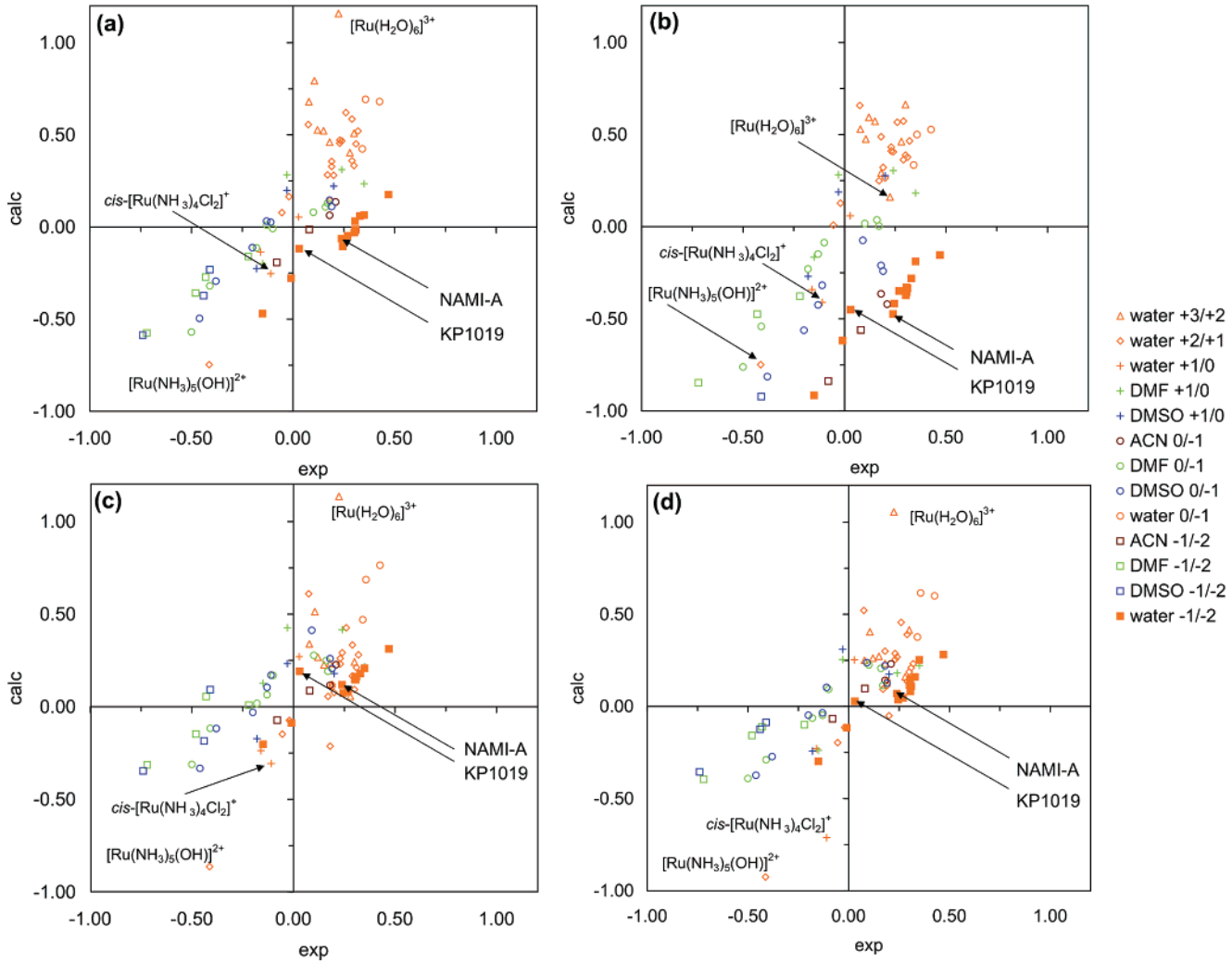

Figure 3. Calculated vs experimental SRPs. (a) Protocol I, PCM/UA0, (b) Protocol II, PCM/UAHF, (c) Protocol IV, PCM/Bondi, (d) Protocol VII, PB. The data are sorted by solvent (color of symbol) and charge (shape of symbol). Aqueous SRPs of the medicinally relevant complexes with the lead structure, *trans*-$[RuCl_4(L)(L')]^-$, are displayed as filled symbols.

Table 2. Mean Unsigned Errors (MUE) in the Calculation of SRPs Using Protocols I−VII[b]

compds	no.	I PCM UA0	II PCM UAHF	III PCM UAKS	IV PCM Bondi	V CPCM UAKS	VI CPCM Bondi	VII PBF
all	80	0.23	0.32	0.31	0.19	0.30	0.19	0.16
solvent								
ACN	4	0.10	0.64	0.65	0.02	0.64	0.03	0.02
DMF	16	0.10	0.16	0.16	0.25	0.15	0.26	0.16
DMSO	14	0.34	0.38	0.36	0.21	0.35	0.22	0.17
water	46	0.26	0.33	0.31	0.18	0.31	0.17	0.17
charge								
+3/+2	8	0.45	0.30	0.27	0.27	0.27	0.27	0.23
+2/+1	18	0.19	0.18	0.16	0.15	0.16	0.15	0.13
+1/0	10	0.10	0.15	0.13	0.19	0.13	0.19	0.19
0/−1	21	0.26	0.24	0.24	0.18	0.23	0.19	0.11
−1/−2	23	0.23	0.59	0.57	0.20	0.57	0.20	0.19
lead[a]	14	0.29	0.63	0.61	0.14	0.60	0.14	0.16

[a] Aqueous SRPs of the compounds with the lead structure *trans*-$[RuCl_4(L)(L')]^-$. [b] All values are in volt (V).

charges of the redox couples, the most unsatisfactory results are obtained for the highly charged complexes, as the +3/+2 pairs and −1/−2 redox pairs have MUEs of 0.30 V (7.0 kcal/mol) and 0.59 V (13.5 kcal/mol), respectively. An even higher MUE of 0.63 V (14.6 kcal/mol) is obtained for the medicinally relevant subset. Protocol III uses the same PCM method together with the UAKS radii, as implemented in Gaussian 03; this definition of the solute cavity is recommended for DFT calculations.[29] The calculations show only a very minor improvement in comparison with the UAHF approach, as the MUEs are similar to those of Protocol II (Table 2).

To analyze the performance of the methods further and to identify systematic errors, we have also calculated the mean signed errors (MSE, see Table 3). For protocols I−III, the MSEs are positive for *cationic* redox pairs charge (+3/+2), but they are negative for *anionic* redox pairs (−1/−2). The relatively large errors for these highly charged complexes remained undiscovered in the past, because typical benchmarking studies used pK_a values and SRPs involving only species that have a molecular charge between +1 and −1. Because SRPs are derived from the differential free energies of the reduced forms (Figure 2), the MSEs translate to an underestimation of solvation free energies that is strongest for the species bearing the highest (positive or negative)

Table 3. Mean Signed Errors (MSE) in the Calculation of SRPs Using Protocols I−VII[b]

compds	no.	I PCM UA0	II PCM UAHF	III PCM UAKS	IV PCM Bondi	V CPCM UAKS	VI CPCM Bondi	VII PBF
all solvent	80	0.01	−0.17	−0.17	0.08	−0.17	0.08	0.03
ACN	4	−0.10	−0.64	−0.65	−0.01	−0.64	0.00	0.00
DMF	16	0.06	−0.11	−0.11	0.23	−0.10	0.24	0.11
DMSO	14	−0.18	−0.33	−0.33	0.21	−0.33	0.22	0.15
water	46	0.06	−0.09	−0.10	−0.01	−0.10	−0.01	−0.03
charge								
+3/+2	8	0.45	0.29	0.25	0.20	0.25	0.20	0.20
+2/+1	18	0.14	0.14	0.12	−0.07	0.11	−0.07	−0.05
+1/0	10	0.03	−0.01	−0.02	0.10	−0.02	0.10	−0.02
0/−1	21	−0.11	−0.22	−0.20	0.18	−0.19	0.19	0.09
−1/−2	23	−0.15	−0.59	−0.57	0.04	−0.57	0.05	−0.01
lead[a]	14	−0.29	−0.63	−0.61	−0.12	−0.60	−0.11	−0.16

[a] Aqueous SRPs of the compounds with the lead structure *trans*-$[RuCl_4(L)(L')]^-$. [b] All values are in volt (V).

molecular charge q. Bearing the simple Born model[56] for ions in spherical cavities (ΔG_{solv} proportional $-q^2r^{-1}$) in mind, one would expect that a more compact molecular cavity improves the results, because of the reciprocal dependence of the solvation free energy ΔG_{solv} on the sphere radius r. While our attempts to manually adjust the cavity within the united atom approach did not improve the results, we have also considered the PCM model combined with a more compact cavity based on Bondi radii (Table 1); this combination is denoted as Protocol IV. SRPs are plotted in Figure 3c, and the MUE and MSE are listed in Tables 2 and 3. The calculations reveal that Protocol IV significantly improves the agreement with the experimental values. The overall MUE for the complete set of data (all compounds in all solvents) is 0.19 V (4.3 kcal/mol). Remarkably, the MUEs are now relatively similar for all charges of redox pairs from +3/+2 to −1/−2 (Table 2). The MSEs indicate that the systematic errors have been largely eliminated (Table 3). The performance of this protocol is convincing, as is indicated by MUEs of 0.18 V (4.0 kcal/mol) for the complexes in aqueous solution and 0.14 V (3.3 kcal/mol) for the medicinally relevant set (Table 2).

On the basis of pK_a predictions for neutral and monocationic organic molecules, it was convincingly shown[18] that the conductor-like screening approach (CPCM) performs better than the polarizable continuum model (PCM). Without further benchmarking calculations for metal complexes, the CPCM method together with the UAKS cavity was recently employed for a computational studies on the hydrolysis of NAMI-A and *trans*-$[RuCl_4(Im)_2]^-$.[23] Hence, we have included the CPCM/UAKS approach in our benchmarking (Protocol V). The calculations reveal that Protocol V performs as disappointingly as does Protocol II (PCM/UAKS). For example, the MUE for the set of medicinally relevant compounds of the *trans*-$[RuCl_4(L)(L')]^-$ type amounts to 0.60 V (13.9 kcal/mol). To compare the PCM and CPCM performance further, we have also considered the CPCM method and the Bondi radii (Protocol VI); these results are very similar to those of Protocol III (PCM/Bondi). In summary, there is a striking agreement between the PCM and CPCM approaches, which is consistent with a benchmarking study of the SRPs of nitrogen oxides.[19] An appropriate definition of the solute cavity appears to be at least as important as the choice of the solvent model.

We have also employed a finite element method for the numerical solution of the Poisson−Boltzmann equation (PBF) as implemented in Jaguar 7, together with the default set of radii for setting up the solute cavity (Protocol VII). This approach has been used in our series *Quantum chemical studies of metals in medicine*[57] and in other studies[58] of medicinally relevant metal complexes. Figure 3d visualizes the SRPs, and Tables 2 and 3 list the errors. The overall MUE for the complete set of data (all compounds in all solvents) is 0.16 V (3.7 kcal/mol), which is the best value among all solvation protocols considered in this work. The approach performs well for all four solvents and all molecular charges of redox pairs from +3/+2 to −1/−2. The MUE is 0.17 V (4.0 kcal/mol) for the complexes in water and 0.16 V (3.7 kcal/mol) for the medicinally relevant set. The performance of Protocol VII (PB) is very similar to the PCM and CPCM methods with the Bondi radii.

Despite the overall success of the PBF method, we have identified a few cases where this approach predicts unsatisfactory results, as compared to the experimental values. The aqueous SRP of the hydrated Ru ion redox couple, $[Ru(OH_2)_6]^{3+/2+}$, is computationally overestimated by +0.83 V (Figure 3d).[59] In contrast, the SRPs of $[Ru(NH_3)_5(OH)]^{2+/+}$ and *cis*-$[Ru(NH_3)_4Cl_2]^{+/0}$ are computationally underestimated by −0.52 V and −0.60 V, respectively (Figure 3d). The other protocols perform better for the latter compound (see Figure 3 and Table S-3), but all protocols using the Bondi and UA0 cavities overestimate the SRP of $[Ru(OH_2)_6]^{3+/2+}$ by +0.91−0.93 V. The fact that the aqueous Ru(III/II) redox couple poses a challenge to computational chemistry was also pointed out in a recent article that focuses entirely on this redox pair.[21] These authors made extensive use of their computationally efficient solvation model termed SM6[60] and predicted at B3LYP a SRP that is +0.77 V higher than the experimental value. As the $[Ru(OH_2)_6]^{3+}$ is highly charged and contains six aqua ligands, the predicted SRP depends strongly on the radius employed for the oxygen and hydrogen atoms. We find that shrinking the H atom radius or H and O atom radii in the PBF method to 1.02 Å or 1.02 and 1.52 Å, respectively, reduces the error in the calculated SRP to +0.46 V or +0.39 V but increases the errors for the other two problem cases. The surface charge density of $[Ru(OH_2)_6]^{3+}$ can be lowered by the second hydration shell, which was represented in the recent study[21] by a symmetric arrangement of 12 additional water molecules. Remarkably, this approach led at B3LYP to a SRP that is −0.23 V lower than the experimental value.

Finally, we would like to emphasize that there is some arbitrariness in the prediction of absolute SRPs because of the choice of ΔSRP_{NHE}. Several studies[19,20] used an electrochemical estimate of the absolute ΔSRP_{NHE} of 4.43 V.[61] Alternatively, ΔSRP_{NHE} may be calculated using a thermodynamic cycle for the reaction, $^1/_2H_2 \rightarrow H^+ + e^-$, analogue to that in Figure 2: ΔSRP_{NHE} is the sum of the gas-phase free energy ΔG^1_{NHE} of this reaction and the solvation free

energy of H^+, $\Delta G_{solv}(H^+)$. The authors of ref 54 chose $\Delta G^1_{NHE} = 362.59$ kcal/mol obtained from thermochemical data[62] and $\Delta G_{solv}(H^+) = -263.98$ kcal/mol extrapolated from cluster ion solvation data[63] to arrive at $\Delta SRP_{NHE} = 4.28$ V,[54] which is the value employed for the present work. Considering a former experimental $\Delta G_{solv}(H^+)$ value of -259.5 kcal/mol[64] determined electrochemically led to $\Delta SRP_{NHE} = 4.44$ V.[65,66] Because of this uncertainty, one may simply treat ΔSRP_{NHE} as a free parameter to be obtained in a fitting procedure. Given that the mean signed error (MSE) of the PBF method (Protocol VII) amounts to only 0.03 V (Table 3), however, we believe that $\Delta SRP_{NHE} = 4.28$ V suggested in ref 54 is an excellent choice.

In conclusion, we recommend the Poisson−Boltzmann finite element solver (PBF) implemented in Jaguar (Protocol VII) and the PCM or CPCM method together with the Bondi radii implemented in Gaussian (Protocols IV and VI) for future studies. However, caution is advised if the solute is highly charged and contains many hydrogen bond donors in the first shell. Our recommendation is not limited to ruthenium complexes, as the metal center in the compounds considered in this work is surrounded by an octahedral ligand environment and not directly exposed to solvent. In addition, the wide range of the molecular charges of the redox pairs from +3/+2 to −1/−2 has made the calculation of solvation free energies very challenging. Consideration of highly charged species has led to the identification of systematic errors in the solvation free energies that were difficult to find in previous benchmarking studies involving compounds with molecular charges from +1 to −1. Hence, the results of the present work may serve as an unprecedented benchmarking of implicit solvation methods for density functional studies of the reactions of metal complexes involved in catalysis, biology, and medicine.

Acknowledgment. We thank the Gaussian and Jaguar developers for helpful discussions, the Austrian Science Foundation (FWF) and the Swiss National Science Foundation (SNF) for financial support, and the Swiss National Computing Center and the Schroedinger Computing Center at the University of Vienna for computing time.

Supporting Information Available: Mean unsigned errors (MUE) and mean signed errors (MSE) of calculated SRPs, in kcal/mol, calc. vs exp. SRPs of individual compounds, and plot of calc. vs exp. SRPs for Protocols III, V, and VII. This material is available free of charge via http://pubs.acs.org.

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