Using potential energy surface scans to examine the bond dissociation energies of *trans*-ReOS₂N₂ and [ReOS₃N]¹⁻ model complexes

Yawen Li, Jacob A. Kreuer, Dustin Wayne. Demoin, Silvia S. Jurisson, and Carol A. Deakyne*

Abstract

Developing Re(V)-based therapeutic agents, where the ReO³⁺ core is coordinated to a multidentate ligand, is of interest in the radiopharmaceutical sciences because of the desirable nuclear properties of ¹⁸⁶Re/¹⁸⁸Re. A reliable yet cost-effective computational method for evaluating the strength of each coordination bond while preserving the integrity of the metal-ligand complex would provide quantitative input for ligand design. A relaxed potential energy surface (PES) scan approach is assessed for *trans*-ReO(SH)₂(NH₂)(NH₃), [ReO(SH)₃(NH₂)]¹⁻, and [ReO(SH)₃(N(H)CHO)]¹⁻ model complexes to calculate bond dissociation energies (BDEs) for Re–NH₃, Re–NH₂, Re–N(H)CHO and Re–SH bonds, common components of Re(V) coordination environments. The PES scans were performed using various combinations of DFT/coupled-cluster methods and basis sets, and the effect of bulk solvent was examined by using the integral equation formalism of the polarizable continuum model (IEF-PCM). BDEs obtained from the PES scans are compared to those obtained for infinite separation. In the gas phase, the BDE curves reach about 90% of the total BDE at 2 Å and plateau by 3.0 to 3.5 Å beyond the equilibrium bond length; in the presence of implicit solvent, the BDE_{water} curves plateau at a shorter distance and more than 90% of the total BDE is recovered at 2 Å. The gas-phase PES scans follow the desired reaction coordinate for NH₃, [N(H)CHO]¹⁻ and SH¹⁻, but not for the poor leaving group NH₂¹⁻. The desired heterolytic cleavage of the Re–NH₂ bond is achieved when the PES scans are performed in the presence of solvent. Elongating the Re–S/N bonds in a rigid, multidentate *trans*-ReO–N₂S₂ complex yields BDE trends similar to those found for the model complexes (Re–NH₂ > Re–N(H)CHO > Re–SH > Re–NH₃).

Keywords: Complex stability, correlation consistent basis sets, PBE0, Pople basis sets, thermochemistry

1. Introduction

Relaxed potential energy surface (PES) scans have been widely used for understanding reaction mechanisms, locating transition structures, studying bond stability and evaluating conformational flexibility [1-8]. This method does not require thorough exploration of the PES of both the reactant and product, so it is advantageous in terms of computational cost for treating large systems. It is especially advantageous for metal-multidentate ligand systems, which have extensive applications in the radiopharmaceutical sciences [9-13]. By evaluating each bond individually, the relative strength of each coordination bond in the context of the ligand system can be compared. This information provides a rationale for improving the ligand systems. In vivo chemical stability is critical for radiopharmaceuticals; if the radiometal dissociates from its targeting vehicle in vivo, it will not reach its target site and may result in radiation to normal tissues. For example, Tc(V)-cyclized Tyr³-octreotate [DPhe-c(Cys-Tyr-DTrp-Lys-Thr-Cys)-Thr-(OH)] has been shown to be unstable in mice [14]. The radiometal dissociates from the ligand, accumulates in the stomach and is excreted through the kidneys.

Computational chemistry may aid in the design of chelate systems for rhenium(V), which is of interest due to the attractive nuclear properties of ¹⁸⁶Re and ¹⁸⁸Re. Rhenium-186 has a 90-hour half-life and emits beta particles of 1.07 MeV maximum energy, along with 137 keV (9%) gamma rays; rhenium-188 has a 17-hour half-life and emits beta particles of 2.1 MeV maximum energy, along with 155 keV (15%) gamma rays. The emitted beta particles would be useful for the treatment of tumors and the emitted gamma rays would allow for internal dosimetry monitoring. Since the late 1980s, ¹⁸⁶Re/¹⁸⁸Re-1,1-hydroxyethylidene-diphosphonate (HEDP) has been recognized as an effective agent for the treatment of bone metastases in patients with primary breast, prostate or lung cancer [15].

The design of suitable Re(V)-cyclized octreotide analogues for targeting neuroendocrine tumors [14, 16, 17]

would be facilitated by a combined computational/experimental approach. Previous experimental studies showed Re(V)-cyclized Tyr³-octreotate had the best somatostatin receptor binding affinity among many analogues evaluated [16], but its Tc-99m counterpart showed poor chemical stability in phosphate buffered saline [14]. The metal is bound to the thiolates of Cys² and Cys⁷, the amide of Tyr³ and the amine of Phe¹ in Re(V)-cyclized Tyr³-octreotate. It was proposed that the Re/Tc-amine bond is the weak link (due to the 8-membered chelate ring formed) that leads to the breakdown of the metal-peptide complex in vivo. Several analogues in which the metal binds to three cysteine thiolates and one backbone nitrogen were synthesized to overcome the instability, and they showed good in vitro chemical stability but poor receptor binding affinity [17]. The ultimate goal is to use computational methods to evaluate relative ligand bond strengths for a variety of coordination systems and to use the computational results to guide further modifications to the peptide sequence. Identifying the weakest metal-ligand bond is of particular interest with respect to preventing the in vitro/in vivo breakdown of a monooxorhenium(V) complex via attack by a sixth ligand *trans* to the Re=O bond.

In earlier work, we assessed a range of computational methods and basis sets with respect to the equilibrium structures and bond dissociation energies (BDEs) of the Re(V) model complexes, ReOX₃ and [ReOX₄]¹⁻, where X = Cl¹⁻, NH₂¹⁻, PH₂¹⁻, OH¹⁻, SH¹⁻ and SeH¹⁻ [18]. On the basis of this assessment, we recommended the PBE0/6-31G(d,p):LANL2TZ computational level for predicting geometries, whereas the PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ level was recommended for predicting bond dissociation energies. In the current study, Re-amine, Re-amide and Re-thiolate bonds are studied using the 5-coordinate *trans*-ReO(SH)₂(NH₂)(NH₃), [ReO(SH)₃(NH₂)]¹⁻ and [ReO(SH)₃(N(H)CHO)]¹⁻ model complexes because they better represent the mixed ligand coordination environment of the Re(V)-cyclized octreotide analogues investigated experimentally. The approach is also applied to an experimentally observed monoamine-monoamide dithiol complex [ReO(S(CH₂)₂NC(O)CH₂NH(CH₂)₂S)] (ReO-222-MAMA [19]). N₂S₂ and NS₃ mixed ligand environments are common

for Re(V) complexes because the thiols help to prevent oxidation of Re(V) to Re(VII), thus improving the stability of the complex, whereas the amides/amines help to counteract the lipophilicity of the thiol moieties.

The three main questions addressed in this work with respect to obtaining BDEs for Re(V) complexes via relaxed PES scans are the following: 1) Are the methods recommended in our earlier work [18] also reliable for the non-equilibrium structures encountered along a scan pathway? 2) Do the BDE curves plateau at a distance that is accessible for complexes with multidentate ligands? 3) Do the PES scans predict the same relative bond energies as the dissociation reactions do?

2. Computational details

For metal complexes with multidentate ligands, it is challenging to study the bond dissociation energy of a specific bond or the overall binding energy of all the metal-donor bonds using dissociation reactions, such as Equations 1-3, without disturbing the integrity of the systems. Selecting the “best” product for a reaction analogous to Equation 3 for a metal-multidentate ligand complex reactant is not always straightforward, and more than one reaction may need to be evaluated. Thus, one advantage of PES scans is that they allow evaluation of an individual bond as opposed to the multidentate ligand as a unit. By leaving the ligand in situ, the effects of changing the coordinating atom, ring size and ring substituents on individual BDEs, all important aspects of ligand design, can be assessed.

Here, X = NH₃; Y = NH₂¹⁻ or [N(H)CHO]¹⁻; Z = SH¹⁻; n + m + k = 4.

In the past, PES scans have been used mainly for studying homolytic bond dissociations with DFT and/or multi-reference ab initio methods [3, 4, 6]. Gas-phase PES scan calculations alone may not be sufficient to reveal reaction mechanisms or locate transition structures for heterolytic bond dissociations, and solvent effects, zero-point energy corrections, basis set superposition errors and entropy effects may need to be taken into account to develop realistic computational models [20, 21]. However, carefully calibrated calculations in which implicit solvent effects are taken into account are reliable and cost effective for obtaining qualitative results. In this work, BDEs for Re–N and Re–S bonds obtained with Equation 1 or 2 and with the PES scan method are compared for a variety of method and basis set combinations. The protocol developed from this investigation will be applied to larger, more representative models of Re(V)-cyclized octreotide analogues.

All geometry optimization, vibrational frequency and single-point energy (SPE) calculations were carried out with the Gaussian 03/09 software packages [22-24]. For *trans*-ReO(SH)₂(NH₂)(NH₃), fully optimized structures for all possible arrangements of the hydrogen atoms were obtained using the B3LYP method and the cc-pVDZ-(pp) basis set. The geometries of the global minimum and selected local minima located at this level of theory were reoptimized at the CCSD/cc-pVDZ-(pp), PBE0/cc-pVDZ-(pp), PBE0/6-31G(d,p):LANL2TZ and PBE0/6-31G(d):LANL2DZ levels of theory. The selected local minima included only those used as starting equilibrium structures in the scans. On the basis of the scan results for *trans*-ReO(SH)₂(NH₂)(NH₃), the conformers of [ReO(SH)₃(NH₂)]¹⁻ were screened at the PBE0/cc-pVDZ-(pp) level of theory. The structures of the relevant minima were reoptimized at the three remaining levels. Vibrational frequencies were computed at each optimization level to verify that the stationary points found correspond to minima.

Re-ammine, Re-amide and Re-thiolate bond dissociation energies were calculated by Equations 1 and 2 at the PBE0/6-311+G(d):LANL2TZ level of theory on geometries optimized at the PBE0/6-31G(d,p):LANL2TZ level, the protocol recommended from our earlier calibration study [18]. PESs of the 4-coordinate subunits of *trans*-ReO(SH)₂(NH₂)(NH₃) and [ReO(SH)₃(NH₂)]¹⁻, specifically ReO(SH)₂(NH₂), ReO(SH)₃, and NH₃, NH₂¹⁻ and SH¹⁻, were explored to locate the global minima. All possible tetrahedral and square planar arrangements of the ligands around the metal center were examined, as well as all possible orientations of the hydrogen atoms.

For the PES scans, the chemical bond being evaluated was elongated by either 3.5 or 6.5 Å starting from the equilibrium bond length, in increments of 0.2, 0.5 or 1.0 Å. At each step, the relevant bond length was fixed, while the remaining geometric parameters were optimized. Initially, the Re–NH₃ bond in *trans*-ReO(SH)₂(NH₂)(NH₃) was scanned with a C_s symmetry restriction (the symmetry of the global minimum), which allowed CCSD(T)/aug-cc-pVTZ-(pp) SPEs to be evaluated. B3LYP/cc-pVDZ-(pp), PBE0/cc-pVDZ-(pp), CCSD/cc-pVDZ-(pp), PBE0/6-31G(d):LANL2DZ, and PBE0/6-31G(d,p):LANL2TZ PES scans were performed and CCSD(T)/aug-cc-pVTZ-(pp)//PBE0/cc-pVDZ-(pp), CCSD/cc-pVDZ-(pp)//PBE0/6-31G(d):LANL2DZ, PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ, PBE0/6-311+G(d,p):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ and PBE0/aug-cc-pVTZ-(pp)//PBE0/cc-pVDZ-(pp) SPEs were calculated at selected points along the energy curve.

Dissociations of Re–NH₃, Re–SH and Re–NH₂ bonds without symmetry restrictions (C₁ point group) were studied with *trans*-ReO(SH)₂(NH₂)(NH₃) and [ReO(SH)₃(NH₂)]¹⁻. The protocol followed for the Re–NH₃ and Re–SH bond dissociations was similar to that described above; however, scans were repeated only for those methods that reproduced the CCSD(T)/aug-cc-pVTZ-(pp)//PBE0/cc-pVDZ-(pp) Re–NH₃ bond dissociation energy within 3 kcal/mol. That is, no B3LYP/cc-pVDZ-(pp) scans were performed and SPEs were obtained only at the

CCSD/cc-pVDZ-(pp)//PBE0/6-31G(d):LANL2DZ and PBE0/6-311+G(d)/LANL2TZ//PBE0/6-31G(d,p):LANL2TZ levels of calculation. In addition, the effect on the dissociation energy curve of inclusion of tight d-functions on the sulfur was assessed by carrying out a PBE0/cc-pV(D+d)Z-(pp) scan. The dissociation of NH_2^{1-} from $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$ was scanned at only the PBE0/6-31G(d,p):LANL2TZ level of theory as a result of the large discrepancy between the dissociation energies obtained from Equation 2 and the scan. PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ SPEs were also computed. Local minima were used as the initial structures for both the Re-NH₂ and Re-SH bond dissociations to prevent non-physical hydrogen abstractions.

To further understand the discrepancy observed in the Re-NH₂ results, the formamide complex $[\text{ReO}(\text{SH})_3(\text{N}(\text{H})\text{CHO})]^{1-}$ was studied. The complex and deprotonated formamide were fully optimized at the PBE0/6-31G(d,p):LANL2TZ level and PBE0/6-311+G(d)/LANL2TZ//PBE0/6-31G(d,p):LANL2TZ SPEs were computed. Various trigonal bipyramidal and pentagonal planar starting geometries were examined to identify the lowest-energy structure of the complex. The PES scan was carried out following the protocol used for Re-NH₂ in $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$.

For the experimentally observed ReO-222-MAMA complex [19], PES scans were also performed at the PBE0/6-31G(d,p):LANL2TZ and PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ levels of theory. The Re-S/N bonds were elongated up to 2 Å (1.4 Å and 1.5 Å for the Re-NHR₂ bond and Re-S₂ bond, respectively) beyond the equilibrium bond length, in increments of 0.1 Å.

T1 diagnostic tests were performed for all coupled-cluster calculations to ascertain whether a single reference method is appropriate for these systems. In all cases the diagnostic met the criterion (≤ 0.05) suggested by Wilson and coworkers [25]. The T1 values average 0.0229 ± 0.0004 for all of the coupled-cluster calculations performed to scan the Re-NH₃ bond, suggesting an acceptable recovery of the dynamic electron correlation energy using a single reference

method for this system. For the dissociation of SH^{1-} from $\text{ReO}(\text{SH})_3(\text{NH}_2)$, the value rises from 0.02152 to 0.03597 as the equilibrium bond length is increased from 0 to 3 Å, resulting in an average of 0.029 ± 0.007 . The keyword “int=ultrafine” was used for all DFT calculations. Natural charges were calculated with Natural Bond Orbital (NBO) theory [26, 27], as implemented in the Gaussian programs. AIMAll (Version 11.12.19)[28] was used to perform AIM analyses.

Because radiopharmaceuticals are often injected into the bloodstream, the interaction of the drug with solvent molecules is an important factor in its pharmacokinetics and pharmacodynamics. In the current work, the effect of water as a polar medium on the BDEs of the Re-N/S bonds was studied using implicit solvent calculations. In particular, the integral equation formalism of the polarizable continuum model (IEF-PCM)[29] was used, with the default dielectric constant of 78.3553 for the water solvent. SPEs were obtained at the PCM-PBE0/6-311+G(d):LANL2TZ level on the gas-phase PBE0/6-31G(d,p):LANL2TZ geometries of the reactants and products in Equations 1 and 2 for the Re-NH₃, Re-SH, and Re-N(H)CHO bond dissociations, as well as on selected geometries along the gas-phase PES scan energy curves for these dissociations. Additionally, the reactants and products yielding the Re-NH₂ and Re-SH implicit water BDE ($\text{BDE}_{\text{water}}$) values via Equation 2 were reoptimized at the PCM-PBE0/6-31G(d,p):LANL2TZ level before obtaining the PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ SPEs. Relaxed PES scans were performed for the Re-NH₂ and Re-SH bonds of $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$ at the PCM-PBE0/6-31G(d):LANL2DZ and PCM-PBE0/6-31G(d,p):LANL2TZ levels of theory and SPEs were obtained at the PCM-CCSD/cc-pVDZ-(pp)//PCM-PBE0/6-31G(d):LANL2DZ, PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ, and PCM-CCSD/aug-cc-pVDZ-(pp)//PCM-PBE0/6-31G(d):LANL2DZ (Re-NH₂ only) levels of theory. For ReO-222-MAMA, PES scans were performed at the PCM-PBE0/6-31G(d,p):LANL2TZ level and SPEs were evaluated at the PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ level for all the Re-N/S bonds.

3. Results and Discussion

3.1. Optimized geometries

All minima identified for *trans*-ReO(SH)₂(NH₂)(NH₃), [ReO(SH)₃(NH₂)]¹⁻ and [ReO(SH)₃(N(H)CHO)]¹⁻ have a square pyramidal arrangement of the ligands around the ReO³⁺ core, and the four atoms bonded to Re lie in essentially the same plane. (The dihedral angles are: < NH₂-S-NH₃-S = 21° and < NHR-S-S-S = 4°.) The ReO³⁺ core lies above that plane. Despite starting with both tetrahedral and square planar coordination environments around the ReO³⁺ core in the product complexes of Equations 1 and 2, only tetrahedral coordination environments were found for the equilibrium structures. The NH₂¹⁻ adopts a trigonal planar rather than pyramidal geometry in all of the minima, which agrees with crystal structure data for ReO[N₂S₂]/ReO[NS₃] complexes [30-32]. Examination of the molecular orbitals (MOs) for [ReO(SH)₃(NH₂)]¹⁻ shows that the N lone pair MO has sp-character and the Re-NH₂ bonding MOs have primarily p-character on the N atom (Fig. S1). The PBE0/6-31G(d,p):LANL2TZ lowest-energy structures for *trans*-ReO(SH)₂(NH₂)(NH₃) and [ReO(SH)₃(NH₂)]¹⁻ and two local minima for [ReO(SH)₃(NH₂)]¹⁻ are shown in Fig. 1. The two local minima depicted (Fig. 1c and 1d) were used as starting geometries for the Re-SH (Fig. 1c) and Re-NH₂ (Fig. 1d) PES scans to have the hydrogen atoms oriented away from the dissociating ligand, making proton abstraction less likely. The Cartesian coordinates of the relevant PBE0/6-31G(d,p):LANL2TZ optimized geometries are available in the supplementary data.

Fig. 1. PBE0/6-31G(d,p):LANL2TZ minima for the model systems. a. Lowest-energy structure of *trans*-ReO(SH)₂NH₂NH₃. b. Lowest-energy structure of [ReO(SH)₃(NH₂)]¹⁻. c. The local minimum of [ReO(SH)₃NH₂]¹⁻ used for performing the PES scan along Re–SH bond. d. The local minimum of [ReO(SH)₃(NH₂)]¹⁻ used for performing the PES scan along Re–NH₂ bond. Color code: Re-cyan, O-red, N-blue, S-yellow, and H-white.

In our earlier work[18], we focused on the basis sets of Pople and coworkers [33-35], but in this work the correlation consistent basis sets of Dunning and coworkers [36, 37] were also examined. As shown in Table 1, there is little difference between the Re–X bond lengths and O=Re–X bond angles of *trans*-ReO(SH)₂(NH₂)(NH₃) optimized at the PBE0/6-31G(d,p):LANL2TZ and PBE0/cc-pVDZ-(pp) levels of calculation. Also, the Re–X bond lengths and O=Re–X bond angles in the calculated equilibrium structures generally lie within the ranges observed from crystallographic studies of typical ReO–N₂S₂ and –NS₃ complexes [30-32]. Similar results were observed for [ReO(SH)₃(NH₂)]¹⁻. Thus, the benchmark CCSD(T)/aug-cc-pVTZ-(pp) SPEs for *trans*-ReO(SH)₂(NH₂)(NH₃) were computed for only the PBE0/cc-pVDZ-(pp) geometries.

Table 1Selected bond lengths and bond angles for *trans*-ReO(SH)₂(NH₂)(NH₃) obtained with different basis sets.^a

Method	Re=O	Re–NH ₃	Re–NH ₂	Re–SH	O=Re–NH ₃	O=Re–NH ₂	O=Re–SH
PBE0/6-31G(d,p):LANL2TZ	1.682	2.244	1.911	2.313	95.3	106.5	113.4
PBE0/cc-pVDZ-(pp)	1.677	2.239	1.904	2.312	94.8	107.0	113.7
Experimental data ^b	1.7±0.1	2.21±0.03	2.00±0.06	2.31±0.04	100±5	115±4	107±5

^aBond lengths are in Å and bond angles are in degrees. ^bAverage values from multiple crystal structures [30-32].

3.2. Re–NH₃

The lowest-energy structure of *trans*-ReO(SH)₂(NH₂)(NH₃) was used to perform relaxed PES scans along the Re–NH₃ bond that were restricted to C_s symmetry, and the BDE curves obtained at the various levels of theory are given in Fig. 2. The benchmark calculation, CCSD(T)/aug-cc-pVTZ-(pp)//PBE0/cc-pVDZ-(pp), predicts the BDE to be 39.7 kcal/mol. All but three of the calculational levels reproduce the benchmark BDE within 3 kcal/mol. Among the three levels that have the larger errors, PBE0/6-311+G(d,p):LANL2TZ, with polarization functions included for the hydrogen atoms, does not perform better than PBE0/6-311+G(d):LANL2TZ. Also, increasing the size of the basis set from valence double-zeta to valence triple-zeta and by adding diffuse functions fails to improve the accuracy of the calculated BDE, as shown for example by the PBE0/aug-cc-pVTZ-(pp)//PBE0/cc-pVDZ-(pp) vs. PBE0/cc-pVDZ-(pp) energy curves. Finally, B3LYP/cc-pVDZ-(pp) underestimates the BDE by about 5 kcal/mol. That these three levels of calculation do not perform as well as the remaining levels agrees with our previous findings [18].

Fig. 2. Re–NH₃ relaxed PES scan BDE curves with C₅ symmetry for *trans*-ReO(SH)₂(NH₂)(NH₃).

Our earlier work, in which combinations of the two well-known DFT functionals B3LYP and PBE0 and a series of increasingly more complete basis sets were evaluated against the benchmark CCSD(T)/aug-cc-pVTZ-(pp)//MP2/aug-cc-pVTZ-(pp), focused on identifying equilibrium structures for ReOX₃ and [ReOX₄]¹⁻ systems, where X = Cl¹⁻, NH₂¹⁻, PH₂¹⁻, OH¹⁻, SH¹⁻ and SeH¹⁻. Overall, PBE0/6-31G(d,p):LANL2TZ and PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ outperformed the other levels of calculation for predicting geometries and BDEs, respectively[18]. In the current work, the recommended levels are also shown to be reliable for treating non-equilibrium structures, such as those along the scan pathways (Fig. 2). Even the level of theory recommended for predicting geometries reproduces the CCSD(T)/aug-cc-pVTZ-(pp)//PBE0/cc-pVDZ-(pp) energetic results for the nitrogen and sulfur mixed ligand systems investigated here. As shown in Fig. 2, the PBE0/6-31G(d,p):LANL2TZ energy curve levels off at 39.7 kcal/mol and the PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ curve levels off at 38.0 kcal/mol. Both are within 1 kcal/mol of the CCSD(T)/aug-cc-pVTZ-(pp)//PBE0/cc-pVDZ-(pp) BDE. The results also suggest that reliable geometries, at least, are obtained with the more cost-effective PBE0/6-31G(d):LANL2DZ

combination of method and basis set, which will be important for investigating larger Re(V)-containing radiopharmaceuticals.

Since our ultimate goal is to apply the relaxed PES scan method to multidentate systems, it is important that essentially all of the BDE is recovered at a dissociation distance that can be reached without significantly distorting the multidentate system. As shown in Fig. 2, all of the BDE curves begin to level off after the bond has been elongated 2 Å beyond the equilibrium bond length, and approximately 90% of the BDE obtained at 6.5 Å beyond the equilibrium bond length is recovered. The energy curves each plateau from 3 to 3.5 Å beyond the equilibrium bond length, recovering about 98% of the BDE. Although lengthening the bond by 3 to 3.5 Å is more desirable, in multidentate systems bond elongation may be limited to 2 Å, a distance at which the relaxed PES scans still provide a good estimate of the bond strength. All of the subsequent gas-phase PES scans reported herein begin to level off and plateau at the same distances; consequently, the BDE curves for these scans have been truncated at 3.5 Å beyond the equilibrium bond length. The distance found in this study for the BDE curves to plateau agrees with results from analogous studies on biochemical systems [3, 4, 6].

Relaxed PES scans without symmetry restrictions were also performed along the Re-NH₃ bond of *trans*-ReO(SH)₂(NH₂)(NH₃). The energy curves are shown in Fig. 3. Again, the BDEs calculated at the selected calculational levels differ by less than 3 kcal/mol. As shown in Table 2, the BDEs obtained from the PES scans are essentially identical to those obtained from Equation 1. As expected, when the BDEs evaluated with and without the symmetry restriction are compared, the former is about 4 kcal/mol too high. In the C₁ scan the ReO(SH)₂(NH₂) rearranges to an asymmetric local minimum as the Re-NH₃ bond is elongated, whereas in the C_s scan, the ReO(SH)₂(NH₂) rearranges to a transition structure. To ensure a meaningful comparison, the corresponding transition structure and local minimum of ReO(SH)₂NH₂ were used for the calculation of the Re-NH₃ BDEs using Equation 1.

Fig. 3. Re-NH₃ BDE curves for *trans*-ReO(SH)₂(NH₂)(NH₃) without symmetry constraint.

Table 2

Comparison of BDEs from infinite separation (Equations 1 and 2) and PES scans.^a

<i>trans</i> -ReO(SH) ₂ (NH ₂)(NH ₃)	ΔE (kcal/mol)		[ReO(SH) ₃ (NH ₂)] ¹⁻	ΔE (kcal/mol)	
	Equation 1	PES scan		Equation 2	PES scan
Re-NH ₃ (C ₁)	34.6	34.4 ^b	Re-NH ₂ (C ₁)	128.3	99.8 ^b
Re-NH ₃ (C _s)	38.0	38.0 ^c	Re-SH (C ₁)	73.9	68.4 ^b

^aPBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ data. The point group is given in parentheses after the bond. ^bBDE at 3.5 Å from the equilibrium bond length. ^cBDE at 6.0 Å from the equilibrium bond length, the corresponding value at 3.5 Å is 37.5 kcal/mol.

3.3. Re-SH

The BDE curves obtained at the various levels of theory for the dissociation of the SH¹⁻ ligand from the [ReO(SH)₃(NH₂)]¹⁻ complex are shown in Fig. 4. The BDE is predicted to be about 69 kcal/mol at the PBE0/6-31G(d,p):LANL2TZ, PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ and PBE0/6-31G(d):LANL2DZ levels of theory, with good consistency among the different levels. However, the agreement

among all the calculational levels is not as good as was found for the dissociation of NH_3 from *trans*- $\text{ReO}(\text{SH})_2(\text{NH}_2)(\text{NH}_3)$. The BDE predicted at the PBE0/cc-pVDZ-(pp) level (73.0 kcal/mol) is about 4 kcal/mol higher than that of the above levels, and the BDE predicted at the CCSD/cc-pVDZ-(pp) level (83.9 kcal/mol) is another 11 kcal/mol higher. The tight-d correlation consistent basis set cc-pV(D+d)Z-(pp) behaves essentially identically to the cc-pVDZ-(pp) basis set for this bond dissociation, although use of the tight-d basis sets has been shown previously to improve the energetic results for third-row elements [38]. The larger BDE obtained with the CCSD method primarily arises from a proton abstraction, allowed by the reorientation of the hydrogen atoms, which is complete at 3.5 Å and is not observed at the other levels of calculation.

Fig. 4. Re-SH and Re-NH₂ BDE curves for $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$.

NBO and AIM analyses were performed at the PBE0/6-31G(d,p):LANL2TZ calculational level to verify that the PES scan for the dissociation of the Re-SH bond is producing $\text{ReO}(\text{SH})_2(\text{NH}_2)$ and SH^{1-} (the products of Equation 2). The AIM analysis shows that a bond critical point remains between the Re and S at 3.5 Å, but the electron density at the bond critical point decreases by more than two orders of magnitude compared to the value at the equilibrium distance (i.e., from

9.2×10^{-2} to 5.6×10^{-4}). The net NBO charges on SH at these two Re–S distances change from -0.15 to -0.71 as the bond is elongated. A similar result is observed for the Mlliken charges; the net charge on SH changes from -0.18 to -0.69 as the Re–S bond is elongated by 3.5 . These results demonstrate that the interaction between the Re and S is extremely weak at 3.5 , consistent with the BDE recovery at that distance, and that the desired products ($\text{ReO}(\text{SH})_2(\text{NH}_2)$ and SH^{1-}) are observed. In fact, the Re–SH BDEs obtained from the PES scans at the PBE0/6-31G(d,p):LANL2TZ, PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ and PBE0/6-31G(d):LANL2DZ levels of theory (Fig. 4) show reasonable agreement with the BDE obtained from Equation 2. The BDE values differ by 5.5 kcal/mol (Table 2), on the order of the error of the method [18].

3.4. *Re–NH₂ and Re–N(H)CHO*

As shown in Table 2, the Re–NH₂ BDE from the PES scan for $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$ is 28.5 kcal/mol lower than that obtained from Equation 2; that is, the dissociation pathway followed by the PES scan does not yield the desired products ($\text{ReO}(\text{SH})_3$ and NH_2^{1-}). In Fig. 4, even the PBE0/6-31G(d,p):LANL2TZ BDE of the Re–NH₂ bond (105.9 kcal/mol) differs much more (6 kcal/mol) from the PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ BDE (99.8 kcal/mol) than is observed in the PES scans for the other bonds (≤ 1 kcal/mol). $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$ was initially chosen to study the BDE of the Re–NH₂ bond because the negative charge on the reactant complex could facilitate formation of $\text{ReO}(\text{SH})_3$ and NH_2^{1-} in the PES scan. However, the Mlliken charge of the NH₂ moiety changes only slightly from -0.33 to -0.39 as the equilibrium bond length is increased by 6.5 . Apparently, the NH_2^{1-} is a sufficiently poor leaving group in the gas phase that a different pathway is followed in the PES scans. However, in the ligands used for potential Re(V) radiopharmaceuticals, the negative charge on the leaving group is often distributed over an amide or a primary/secondary amine group. To test the effect of changing the leaving group, a PES scan for the Re–N(H)CHO bond

of $[\text{ReO}(\text{SH})_3(\text{N}(\text{H})\text{CHO})]^{1-}$ was performed. The PBE0/6-31G(d,p):LANL2TZ BDE of the Re–N(H)CHO bond predicted by the scan is 87.7 kcal/mol, which is 6.4 kcal/mol higher than the BDE calculated at the PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ level (Fig. 5). Thus, the discrepancy between these two calculational levels again is observed. However, the net Müliken charge for the $[\text{N}(\text{H})\text{CHO}]^{1-}$ group is -0.69 after the bond is elongated by 3.5 Å. Also, the BDE predicted by Equation 2 (84.1 kcal/mol) differs by less than 3 kcal/mol from that obtained from the PES scan (81.3 kcal/mol). The improved consistency in BDE between the two different approaches is encouraging with respect to applying the PES scan method to larger systems that allow better delocalization of the negative charge. In cases for which the Re–NH₂ bond is more representative for the system of interest, implicit solvent effects may be included to facilitate the desired heterolytic cleavage, which is discussed in more detail, vide infra.

Fig. 5. Re–N(H)CHO BDE curves for $[\text{ReO}(\text{SH})_3(\text{N}(\text{H})\text{CHO})]^{1-}$.

3.5. Effect of solvent

A common way in which solvent effects are taken into account is to calculate SPEs with an implicit solvent model on gas-phase geometries [39, 40]. For the Re–NH₃ bond in *trans*-ReO(SH)₂(NH₂)(NH₃), the Re–SH bond in

$[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$ and the $\text{Re}-\text{N}(\text{H})\text{CHO}$ bond in $[\text{ReO}(\text{SH})_3(\text{N}(\text{H})\text{CHO})]^{1-}$, the IEF-PCM BDE curves obtained at the PCM-PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ level of theory were compared to the BDEs generated in the gas phase at the corresponding calculational level, as shown in Fig. 6. As expected, for the neutral species, the solvent has little effect on the BDE. In fact, the implicit water BDE ($\text{BDE}_{\text{water}}$) of the $\text{Re}-\text{NH}_3$ bond is only 1.6 kcal/mol lower than its gas-phase counterpart. On the contrary, the presence of solvent decreases the gas-phase BDEs by 26.5 kcal/mol and 23.5 kcal/mol for the $\text{Re}-\text{SH}$ and $\text{Re}-\text{N}(\text{H})\text{CHO}$ bonds, respectively. For the charged species, we observe a smaller solvent effect when the charge is better delocalized, as expected. That is, the solvent stabilizes SH^{1-} and $[\text{N}(\text{H})\text{CHO}]^{1-}$, for which the charge is more localized, by 67.9 kcal/mol and 64.4 kcal/mol, respectively, whereas the solvent stabilizes $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$, $\text{ReO}(\text{SH})_2(\text{NH}_2)$, $[\text{ReO}(\text{SH})_3(\text{N}(\text{H})\text{CHO})]^{1-}$ and $\text{ReO}(\text{SH})_3$ are 52.4 kcal/mol, 14.5 kcal/mol, 47.4 kcal/mol and 8.3 kcal/mol, respectively. In addition, the PCM-PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ $\text{BDE}_{\text{water}}$ obtained from the PES scans and those obtained from Equations 1 and 2 have better agreement (within 2 kcal/mol) than do the corresponding gas-phase BDEs (Table 3). Overall, the trend in relative bond strength is not changed when implicit solvent is included in the calculations, but the solvent affects the BDEs of the $\text{Re}-\text{NH}_3$, $\text{Re}-\text{SH}$ and $\text{Re}-\text{N}(\text{H})\text{CHO}$ bonds differently. As a result, the strength of the $\text{Re}-\text{NH}_3$ bond becomes more competitive with respect to that of the other bonds in the presence of solvent, and the differences in the BDEs among the $\text{Re}-\text{NH}_3$, $\text{Re}-\text{SH}$ and $\text{Re}-\text{N}(\text{H})\text{CHO}$ bonds become much smaller.

Fig. 6. BDE curves for the Re–N(H)CHO, Re–SH and Re–NH₃ bonds in the presence of implicit solvent.

Table 3

Comparison of BDEs from infinite separation (Equations 1 and 2) and PES scans in the presence of implicit solvent.^a

Model	Bond	BDE _{water} from PES scan ^b (kcal/mol)	BDE _{water} from infinite separation (kcal/mol)
<i>trans</i> -ReO(SH) ₂ (NH ₂)(NH ₃)	Re–NH ₃ (C ₁)	32.8	32.7 ^c
[ReO(SH) ₃ (NH ₂)] ^{1–}	Re–SH	41.9	43.9 ^d
	Re–NH ₂	86.6	88.0 ^d
[ReO(SH) ₃ (N(H)CHO)] ^{1–}	Re–N(H)CHO	57.8	58.7 ^d

^aPCM-PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ data. The point group is given in parentheses after the bond. ^bBDE_{water} at 3.5 Å from the equilibrium bond length. ^cBDE_{water} calculated using Equation 1. ^dBDE_{water} calculated using Equation 2.

To verify that the use of the above approach is reasonable, relaxed PES scans were performed for the Re–SH bond of [ReO(SH)₃(NH₂)]^{1–} in the presence of implicit water. In Fig. 7, at the PCM-PBE0/6-311+G(d)/LANL2TZ/(PCM-)PBE0/6-31G(d,p):LANL2TZ level, the Re–SH BDE_{water} values calculated with and without reoptimization are 39.6 kcal/mol and 41.9 kcal/mol, differing by only 2.3 kcal/mol after the Re–SH bond is elongated by 3.5 Å. Also, the Re–SH BDE_{water} curves agree well among the different calculational levels. Although the difference in the Re–SH BDE_{water} values among the various levels of theory is as large as 15 kcal/mol in the gas phase, the

PCM-CCSD/cc-pVDZ-(pp)//PCM-PBE0/6-31G(d):LANL2DZ BDE_{water} differs from those at the other levels of theory by 5.7 to 7.8 kcal/mol. The difference among the PCM-PBE0/6-31G(d):LANL2DZ, PCM-PBE0/6-31G(d,p):LANL2TZ and PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ Re-SH BDE_{water} values is smaller than 3 kcal/mol at 3.5 Å. When the reactants and products in Equation 2 were reoptimized in the presence of implicit solvent, the Re-SH BDE_{water} is found to be 39.8 kcal/mol, only 0.2 kcal/mol higher than that calculated from the PCM-PES scan.

Relaxed PES scans were also performed for the Re-NH₂ bond of [ReO(SH)₃(NH₂)]¹⁻ in the presence of implicit solvent to determine whether inclusion of solvent leads to the desired heterolytic cleavage. As shown in Fig. 7, the PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ PES scan results in a BDE_{water} of the Re-NH₂ bond about 24 kcal/mol lower than that of the PCM-CCSD/cc-pVDZ-(pp)//PCM-PBE0/6-31G(d):LANL2DZ level and about 18 kcal/mol lower than that of the other two DFT levels. Furthermore, at the PCM-PBE0/6-31G(d):LANL2DZ and PCM-PBE0/6-31G(d,p):LANL2TZ levels, the BDE_{water} values from the PCM-PES scans are about 9 kcal/mol lower than those from Equation 2, whereas at the PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ and PCM-CCSD/cc-pVDZ-(pp)//PCM-PBE0/6-31G(d):LANL2DZ levels, the deviations in the two BDE_{water} values are 0.5 kcal/mol and 3.9 kcal/mol, respectively. Even in the presence of implicit solvent, heterolytic dissociation of the Re-NH₂ bond is not achieved in the PES scans at the PCM-PBE0/6-31G(d):LANL2DZ and PCM-PBE0/6-31G(d,p):LANL2TZ levels. Diffuse functions may be critical for the desired cleavage because at the PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ level, the net M $\ddot{u}$ lliken charge of the NH₂ moiety changes from -0.39 to -0.97 as the equilibrium bond length is increased by 3.5 Å, whereas at the PCM-PBE0/6-31G(d):LANL2DZ and the PCM-PBE0/6-31G(d,p):LANL2TZ levels, the net M $\ddot{u}$ lliken charge of the NH₂ moiety changes from -0.3 to -0.6. In our earlier work[18], diffuse functions were also found to be particularly important for the Re-NH₂ (and Re-PH₂) bond with respect to reproducing the benchmark thermochemical data. Their importance is

further demonstrated here by the 25 kcal/mol decrease in BDE when the cc-pVDZ-(pp) basis set is replaced by the aug-cc-pVDZ-(pp) basis set (Fig. 7). That is, the PCM-CCSD/aug-cc-pVDZ-(pp)//PCM-PBE0/6-31G(d):LANL2DZ BDE_{water} is 81.8 kcal/mol from the PES scan (3.5 Å) compared to the PCM-CCSD/cc-pVDZ-(pp)//PCM-PBE0/6-31G(d):LANL2DZ BDE_{water} of 107.1 kcal/mol. The former value is essentially identical to the corresponding value of 81.9 kcal/mol from Equation 2, and both of these values are in much better agreement with the corresponding PCM-PBE0/6-311+G(d)/LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ values (Table 3 and Fig. 7).

Fig. 7. Re-SH and Re-NH₂ BDE curves for $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$ in the presence of implicit solvent.

Finally, in the presence of implicit solvent, with or without reoptimization, the PES scans recover 90 to 98% of the BDE_{water} values at 2 Å beyond the equilibrium bond length (except for Re-NH₂ at some of the levels). This result is particularly advantageous with respect to elongating the bonds of the chelate rings in multidentate systems.

3.6. ReO-222-MAMA

A number of monoamine-monoamide dithiol (MAMA) ligands have been synthesized because they are easily derivatized with various functional groups and form neutral, stable and relatively hydrophilic Re(V)/Tc(V) complexes that are potentially useful for targeted radiotherapy or SPECT imaging [19, 41]. To test whether the Re–S/N bonds in such rigid, multidentate systems can be elongated sufficiently to provide reliable information with respect to relative bond strengths, the Re–S/N bonds in ReO-222-MAMA (Fig. 8) were studied using the relaxed PES scan method. The PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ BDEs are found to be 94.8 kcal/mol, 92.9 kcal/mol, 73.2 kcal/mol and 49.5 kcal/mol for the Re–S₁, Re–NC(O), Re–S₂ and Re–NHR₂ bonds, respectively. All four BDEs are higher than those of the corresponding bonds in *trans*-ReO(SH)₂(NH₂)(NH₃), [ReO(SH)₃(NH₂)]¹⁻ and [ReO(SH)₃(N(H)CHO)]¹⁻, which is not surprising because the five-membered chelate rings of ReO-222-MAMA are expected to improve the stability of the original 5-coordinate complex but to decrease the stability of the resultant 4-coordinate subunit by increasing the steric constraints. Due to the constraints of the chelate rings, the Re–NHR₂ bond was elongated to only 1.4 Å beyond the equilibrium bond distance, as opposed to the 2 Å elongation for the Re–S₁ and Re–NC(O) bonds. According to the results of the PES scans for the Re–NH₃ bond of the *trans*-ReO(SH)₂(NH₂)(NH₃) complex, about 80% of the total BDE is usually recovered at this elongation distance. Likewise, the Re–S₂ bond was elongated by only 1.5 Å due to the formation of a non-physical S₂...H–N(amine) hydrogen bond beyond this distance. According to the PES scan for the Re–SH bond of the [ReO(SH)₃(NH₂)]¹⁻ complex, 75 to 80% of the total BDE is usually recovered at the 1.5 Å elongation distance, so the Re–S₂ BDE is likely to be higher than 90 kcal/mol at 2 Å.

Fig. 8. The ReO-222-MAMA complex investigated via relaxed PES scans along the Re–N/S bonds.

The effect of implicit solvent on the BDEs of the Re–N/S bonds in the ReO-222-MAMA complex was also examined, and the PCM-PBE0/6-311+G(d):LANL2TZ//PCM-PBE0/6-31G(d,p):LANL2TZ BDE_{water} values of the Re–S₁, Re–NC(O), Re–S₂ and Re–NHR₂ bonds were found to be 68.8 kcal/mol, 84.3 kcal/mol, 56.3 kcal/mol and 51.6 kcal/mol, respectively. Compared with the gas-phase BDEs, the Re–S₁ BDE_{water} decreases by about 26 kcal/mol in the presence of solvent. For the Re–S₂ bond, the higher percentage of the total BDE_{water} recovered at 1.5 Å in the presence of solvent counteracts the solvent effect, to some extent, so that the decrease is about 17 kcal/mol. The Re–NC(O) BDE_{water} is about 9 kcal/mol lower than the gas-phase BDE. That the solvent has a smaller influence on the Re–NC(O) bond is likely because the built-up negative charge on the amide can be better delocalized throughout the ReO-222-MAMA complex as the bond is elongated. As expected, the BDE_{water} of the Re–NHR₂ bond is essentially the same as its gas-phase BDE, and this bond appears to be more competitive in the presence of solvent compared to the other bonds. The slight increase (2.1 kcal/mol) in the BDE_{water} is also due to the higher percentage of the total BDE_{water} recovered at 1.4 Å in the presence of solvent. In general, the drops in BDE_{water} values for the Re–S₁/S₂ and Re–NC(O) bonds of ReO-222-MAMA are smaller than those for the corresponding bonds in $[\text{ReO}(\text{SH})_3(\text{NH}_2)]^{1-}$ and $[\text{ReO}(\text{SH})_3(\text{N}(\text{H})\text{CHO})]^{1-}$. This result can again be rationalized by the greater capacity for delocalization of the negative charge in the leaving groups of ReO-222-MAMA.

Overall, bond elongations for ReO-222-MAMA in the presence of solvent reproduce the relative thermodynamic stabilities of the Re–S/N bonds in *trans*-ReO(SH)₂(NH₂)(NH₃), [ReO(SH)₃(NH₂)]¹⁻ and [ReO(SH)₃(N(H)CHO)]¹⁻.

Conclusions

The application of the relaxed PES scan method to study BDEs of Re(V) nitrogen and sulfur bonds is reported in this work using *trans*-ReO(SH)₂(NH₂)(NH₃), [ReO(SH)₃(NH₂)]¹⁻ and [ReO(SH)₃(N(H)CHO)]¹⁻ as model complexes. The results show that in the gas phase the BDE curves begin to level off at 2 Å and plateau at 3.0 to 3.5 Å beyond the equilibrium bond length, regardless of the choice of method/basis set combination. The inclusion of implicit solvent enhances the agreement in BDE_{water} values among the various calculational levels and between the PES scan and infinite separation approaches, and shortens the distance at which the BDE_{water} curves plateau. Also, elongating the Re-donor atom bonds by 1.4 to 2 Å in the rigid, multidentate system ReO-222-MAMA is sufficient to yield reliable bond strength trends. Moreover, PBE0/6-311+G(d):LANL2TZ//PBE0/6-31G(d,p):LANL2TZ, the calculational level recommended in our earlier work, is suitable for the non-equilibrium structures encountered along the PES scan pathway. For the model complexes investigated in this work, the relative BDEs at infinite separation (Equations 1 and 2) are Re–NH₂ > Re–N(H)CHO > Re–SH > Re–NH₃ [42]. This trend coincides with the results for the PES scans that lead to the appropriate (heterolytically-cleaved) products.

Acknowledgements

Research was supported by DOE grant DE-SC0007348 (YL). We acknowledge the University of Missouri Bioinformatics Consortium (UMBC) for their High Performance Computing (HPC) resources.

References and Notes

[1] D.J. Brust, T.M. Gilbert, Density Functional Theory Study of the d¹⁰ Series (H₃P)₃M(η^1 -SO₂) and (Me_nPh_{3-n}P)₃M(η^1 -SO₂) (M = Ni, Pd, Pt; *n* = 0–3): SO₂ Pyramidal and M–S Bond Dissociation Energies, *Inorg. Chem.*, 43 (2004) 1116-1121.

- [2] P. Banáš, L.r. Rulišek, V. Hánošová, D. Svozil, N.G. Walter, J.i. Šponer, M. Otyepka, General Base Catalysis for Cleavage by the Active-Site Cytosine of the Hepatitis Delta Virus Ribozyme: QM/MM Calculations Establish Chemical Feasibility, *J. Phys. Chem. B*, 112 (2008) 11177-11187.
- [3] P.M. Kozłowski, M. Kumar, P. Piecuch, W. Li, N.P. Bauman, J.A. Hansen, P. Lodowski, M. Jaworska, The Cobalt–Methyl Bond Dissociation in Methylcobalamin: New Benchmark Analysis Based on Density Functional Theory and Completely Renormalized Coupled-Cluster Calculations, *J. Chem. Theory Comput.*, 8 (2012) 1870-1894.
- [4] X. Li, L.W. Chung, P. Paneth, K. Morokuma, DFT and ONIOM(DFT:MM) studies on Co-C bond cleavage and hydrogen transfer in B12-dependent methylmalonyl-CoA mutase. Stepwise or concerted mechanism?, *J. Am. Chem. Soc.*, 131 (2009) 5115-5125.
- [5] J.A. Carrazana-Garcia, J. Rodriguez-Otero, E.M. Cabaleiro-Lago, A computational study of anion-modulated cation- π interactions, *J. Phys. Chem. B*, 116 (2012) 5860-5871.
- [6] R.A. Kwiecien, I.V. Khavrutskii, D.G. Musaev, K. Morokuma, R. Banerjee, P. Paneth, Computational Insights into the Mechanism of Radical Generation in B12-Dependent Methylmalonyl-CoA Mutase, *J. Am. Chem. Soc.*, 128 (2006) 1287-1292.
- [7] R.A. Wells, J.L. Kellie, S.D. Wetmore, Significant strength of charged DNA-protein π - π interactions: a preliminary study of cytosine, *J. Phys. Chem. B*, 117 (2013) 10462-10474.
- [8] T. Wolfle, A. Gorling, W. Hieringer, Conformational flexibility of metalloporphyrins studied by density-functional calculations, *Phys. Chem. Chem. Phys.*, 10 (2008) 5739-5742.
- [9] S.L. Barnholtz, J.D. Lydon, G. Huang, M. Venkatesh, C.L. Barnes, A.R. Ketring, S.S. Jurisson, Syntheses and Characterization of Gold(III) Tetradentate Schiff Base Complexes. X-ray Crystal Structures of [Au(sal₂pn)]Cl·2.5H₂O and [Au(sal₂en)]PF₆, *Inorg. Chem.*, 40 (2001) 972-976.
- [10] P.D. Benny, C.L. Barnes, P.M. Piekarski, J.D. Lydon, S.S. Jurisson, Synthesis and Characterization of Novel Rhenium(V) Tetradentate N₂O₂ Schiff Base Monomer and Dimer Complexes, *Inorg. Chem.*, 42 (2003) 6519-6527.
- [11] A. Cagnolini, B. Ballard, H.P. Engelbrecht, T.L. Rold, C. Barnes, C. Cutler, T.J. Hoffman, R. Kannan, K. Katti, S.S. Jurisson, Tetradentate bis-phosphine ligands (P₂N₂ and P₂S₂) and their Rh(III), Ni(II) and ¹⁰⁵Rh complexes: X-ray crystal structures of trans-[RhCl₂(L₂)]PF₆, [Ni(L₂)](PF₆)₂ and μ -O₂SO₂-[Ni(L₅)]₂(PF₆)₂, *Nucl. Med. and Biol.*, 38 (2011) 63-76.
- [12] C.S. Cutler, H.M. Hennkens, N. Sisay, S. Huclier-Markai, S.S. Jurisson, Radiometals for combined imaging and therapy, *Chem. Rev.*, 113 (2013) 858-883.
- [13] J. Chen, Z. Cheng, T.J. Hoffman, S.S. Jurisson, T.P. Quinn, Melanoma-targeting properties of (99m)technetium-labeled cyclic alpha-melanocyte-stimulating hormone peptide analogues, *Cancer Res.*, 60 (2000) 5649-5658.
- [14] H.M. Bigott-Hennkens, S.F. Dannoon, S.M. Noll, V.C. Ruthengael, S.S. Jurisson, M.R. Lewis, Labeling, stability and biodistribution studies of ^{99m}Tc-cyclized Tyr³-octreotate derivatives, *Nucl. Med. Biol.*, 38 (2011) 549-555.
- [15] G. Rubini, A. Nicoletti, D. Rubini, A.N. Asabella, Radiometabolic treatment of bone-metastasizing cancer: from ¹⁸⁶Rhenium to ²²³Radium, *Cancer Biother. Radiopharm.*, 29 (2014) 1-11.
- [16] H.M. Bigott-Hennkens, S. Junnotula, L. Ma, F. Gallazzi, M.R. Lewis, S.S. Jurisson, Synthesis and in vitro evaluation of a Rhenium-cyclized somatostatin derivative series, *J. of Med. Chem.*, 51 (2008) 1223-1230.
- [17] S.F. Dannoon, H.M. Bigott-Hennkens, L. Ma, F. Gallazzi, M.R. Lewis, S.S. Jurisson, In vitro structure-activity relationship of Re-cyclized octreotide analogues, *Nucl. Med. Biol.*, 37 (2010) 527-537.
- [18] D.W. Demoin, Y. Li, S.S. Jurisson, C.A. Deakyne, Method and Basis Set Analysis of Oxorhenium(V) Complexes for Theoretical Calculations, *Comp. Theor. Chem.*, 997 (2012) 34-41.

- [19] R.W. Riddoch, P. Schaffer, J.F. Valliant, A Solid-Phase Labeling Strategy for the Preparation of Technetium and Rhenium Bifunctional Chelate Complexes and Associated Peptide Conjugates, *Bioconjugate Chem.*, 17 (2005) 226-235.
- [20] J.L. Przybylski, S.D. Wetmore, Designing an appropriate computational model for DNA nucleoside hydrolysis: a case study of 2'-deoxyuridine, *J. Phys. Chem. B*, 113 (2009) 6533-6542.
- [21] M.H. Baik, R.A. Friesner, S.J. Lippard, Theoretical study on the stability of N-glycosyl bonds: why does N7-platination not promote depurination?, *J. Am. Chem. Soc.*, 124 (2002) 4495-4503.
- [22] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, A. Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision C.02, 2003.
- [23] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision B.01, Wallingford CT, 2009.
- [24] R. Dennington, T. Keith, J. Millam, GaussView, Semichem Inc, Shawnee Mission, KS, 2009.
- [25] W. Jiang, N.J. DeYonker, A.K. Wilson, Multireference Character for 3d Transition-Metal-Containing Molecules, *J. Chem. Theory Comput.*, 8 (2011) 460-468.
- [26] A.E. Reed, L.A. Curtiss, F. Weinhold, Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint, *Chem. Rev.*, 88 (1988) 899-926.
- [27] E.D. Glendening, A.E. Reed, J.E. Carpenter, F. Weinhold, NBO, 1993.
- [28] T.A. Keith, AIMAll, TK Gristmill Software, Overland Park KS, 2011.
- [29] J. Tomasi, B. Mennucci, R. Cammi, Quantum Mechanical Continuum Solvation Models, *Chem. Rev.*, 105 (2005) 2999-3094.
- [30] I.R. Baird, R. Mosi, M. Olsen, B.R. Cameron, S.P. Fricker, R.T. Skerlj, '3+1' mixed-ligand oxorhenium(V) complexes and their inhibition of the cysteine proteases cathepsin B and cathepsin K, *Inorg. Chim. Acta*, 359 (2006) 2736-2750.
- [31] A. Rey, I. Pirmettis, M. Pelecanou, M. Papadopoulos, C.P. Raptopoulou, L. Mallo, C.I. Stassinopoulou, A. Terzis, E. Chiotellis, A. Leon, Synthesis and characterization of mixed-ligand oxorhenium complexes with the SNN type of ligand. Isolation of a novel $\text{ReO}[\text{SN}][\text{S}][\text{S}]$ complex, *Inorg. Chem.*, 39 (2000) 4211-4218.

- [32] C. M. Archer, J. R. Dilworth, D. Vaughan Griffiths, M. J. Al-Jeboori, J. Duncan Kelly, C. Lu, M. J. Rosser, Y. Zheng, Technetium and Rhenium oxo-complexes of new tetradentate ligands with N₂S₂ and NS₃ donor sets, *J. Chem. Soc., Dalton Trans.*, 8 (1997) 1403-1410.
- [33] L.A. Curtiss, P.C. Redfern, V. Rassolov, G. Kedziora, J.A. Pople, Extension of Gaussian-3 theory to molecules containing third-row atoms K, Ca, Ga–Kr, *J. Chem. Phys.*, 114 (2001) 9287-9295.
- [34] R.C. Binning, L.A. Curtiss, Compact contracted basis sets for third-row atoms: Ga–Kr, *J. Comput. Chem.*, 11 (1990) 1206-1216.
- [35] M.M. Francel, W.J. Pietro, W.J. Hehre, J.S. Binkley, M.S. Gordon, D.J. DeFrees, J.A. Pople, Self-consistent molecular orbital methods. XXIII. A polarization-type basis set for second-row elements, *J. Chem. Phys.*, 77 (1982) 3654-3665.
- [36] T.H. Dunning, Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen, *J. Chem. Phys.*, 90 (1989) 1007-1023.
- [37] D.E. Woon, T.H. Dunning, Gaussian basis sets for use in correlated molecular calculations. III. The atoms aluminum through argon, *J. Chem. Phys.*, 98 (1993) 1358-1371.
- [38] A.K. Wilson, T.H. Dunning, SO₂ revisited: Impact of tight d augmented correlation consistent basis sets on structure and energetics, *J. Chem. Phys.*, 119 (2003) 11712.
- [39] N. Scherbak, Å. Strid, L.A. Eriksson, Non-enzymatic oxidation of NADH by quinones, *Chem. Phys. Lett.*, 414 (2005) 243-247.
- [40] J. Raber, C. Zhu, L.A. Eriksson, Theoretical Study of Cisplatin Binding to DNA: The Importance of Initial Complex Stabilization, *J. Phys. Chem. B*, 109 (2005) 11006-11015.
- [41] J.P. O'Neil, S.R. Wilson, J.A. Katzenellenbogen, Preparation and structural characterization of monoamine-monoamide bis(thiol) oxo complexes of Technetium(V) and Rhenium(V), *Inorg. Chem.*, 33 (1994) 319-323.
- [42] We recognize that the observed BDE trend is affected by the trans influence, among other factors and is unlikely to be general. .