Relative Stability of Mixed [3 + 1] Tc and Re Complexes: a Computational and Conceptual DFT Study

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A computational and conceptual density-functional study has been performed on various [3 + 1] complexes of both Re(V) and Tc(V). The fully optimized complexes chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V) and chloro(3-thiapentane-1,5-dithiolato)oxotechnetium(V) show geometries that compare favorably with the X-ray data. These structures were used as a starting point to investigate the relative stability of Tc(V) and Re(V) complexes with various ligands containing combinations of N, O, and S as chelating atoms and to evaluate the stabilizing/destabilizing influence of these N, O, and S combinations. For both Tc and Re complexes, the S content (number and position of S atoms) together with the presence of an oxygen as the central chelating atom turns out to be decisive in the stability of the tridentate complexes, the latter factor being strongly destabilizing and the former stabilizing. The stabilization sequences for both Tc and Re are shown to be identical in the gas phase and in aqueous solutions treated in a polarizable continuum model. The Re(V) complexes are found to be more stable than their Tc(V) analogues. All of the results are successfully interpreted in terms of the hard and soft acids and bases principle, applied at the local level. For this purpose, a softness value for Tc is obtained by interpolating softness trends in neighboring elements of rows 5 and 6 in the periodic table.

I. Introduction

Radiopharmaceuticals are compounds used for diagnosis or systemic therapy.[1−3] For diagnosis, the compounds are not supposed to show any pharmacological effect. ^{99m}Tc can be obtained daily as ^{99}Tc pertechnetate by elution from a ^{99m}Mo generator. ^{99m}Tc has “the” radionuclidic properties, promoting it as ideal for daily, routine kit preparations for diagnosis in nuclear medicine.[4] In a kit formulation, ^{99}Tc pertechnetate is reduced in situ to the appropriate oxidation state (V, III, or I) for complex formation, allowing the obtainment of the required radiopharmaceutical compound.

Moreover, ^{99m}Tc has a half-life of about 6 h with the emission of a single photon with an energy of 141 keV, which makes it suitable for imaging with crystal-based tomographic devices [SPECT (single-photon computed tomography)] and also makes it “patient friendly” because burden doses are low. Recently, it was shown that two radioisotopes of Re, ^{186}Re and ^{188}Re, can be used as therapeutic isotopes because of their convenient β energies and their half-lives. The latter of these isotopes, ^{188}Re, can be obtained from ^{188}W/^{188}Re generators commercially available since 1989.[5−7] Some S-, N-, O-, and P-containing molecules that incorporate this isotope by complex formation were investigated for the radiolabeling of antibodies and peptides such as somatostatine, bombesin, and neurotensin analogues.[8,9]

The application of Tc and Re as radionuclides in a clinical environment is one of the reasons for the intense search for designing Tc(V) and Re(V) complexes of sufficient in vivo stability. $^{99m}TcO_4^-$ or $^{188/182}ReO_4^-$ has to be reduced to the appropriate oxidation state, which can be V, III, or I. Reduction is generally performed with Sn^{2+} in the presence of an auxiliary ligand such as gentisic acid and an appropriate supporting chelator. Kinetics are of great importance because complex formation in the appropriate oxidation state (V or III) must occur very quickly. Of capital importance is the in vivo stability of the respective Tc and Re complexes with the chelator attached to the bioactive molecule of interest.

The dominant feature of Tc(V) and Re(V) complexes is the presence of a metal-oxo $[MO]^{3+}$ core (M = central metal atom) forming square-pyramidal configurations with tetradentate ligands of the type $XH-CH_2-CH_2-E-CH_2-CH_2-XH$ [E = O, $N(CH_3)$, S; X = S, O]. These complexes are stable in water and versatile in combinations with ligands.

Many studies refer to mixed-ligand complexes, where the equatorial coordination plane is formed by a tridentate and monodentate ligand.[10] This class of complexes claims special attention because it enables the coupling of biologically relevant groups to a relatively small-sized chelate[11] and has, therefore, been widely used in the search for new radiotracers. Because all of the complexes are neutral, they mostly found application in the design of neuroreceptor-affined Tc- and Re-chelating biomolecules of the peptide type.[12]

The majority of the complexes in this group contain the thiadithiolate $HS-CH_2CH_2-S-CH_2CH_2-SH$ (SSS) ligand, but aza and oxa ligands (SNS and SOS, respectively) have also been obtained.[13] Among them are species where the aza group bears a diethylaminoethyl group ($E = N-CH_2CH_2-NEt_2$). The “3 + 1” mixed-ligand Tc(V) and Re(V) complexes can be prepared

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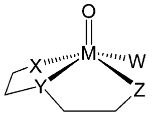

X, Y, Z = S, O, N and W = Cl

Figure 1. Schematic representation of Tc and Re [3 + 1] complexes.

in a one-pot procedure by common action of the monodentate and tridentate ligands with the appropriate M(V) precursor molecules, but they require purification after their synthesis, which is not the aim when producing ^{99m}Tc radiopharmaceuticals. A further drawback is their instability in physiological media, as recently described.[14] The structures of many of these complexes have been elucidated by the group of Spies and coworkers.[15]

To the best of our knowledge, systematic studies analyzing the relative stabilities of S, N, and O combinations in Re(V) and Tc(V) complexes are scarce, as are investigations on the relative stabilities of Re(V) and Tc(V) with the same ligands. An important exception exists concerning the studies by Liu et al.,[16−18] where the thermal-decomposition rates of a series of $[TcO]^{3+}$complexes with monodentate S, N, and O ligands were reported. It was found that compounds are more stable when they contain more S atoms as donors. Although the complexes studied are not of the [3 + 1] type but are monodentate, which, from the point of view of the stability of the structure, might not make a large difference, this study indicates that stability is governed by S content and that oxygen seems to have a larger destabilizing effect than nitrogen. The stability results correlate with solid angle factor sum (SAS) calculations based on the average X-ray crystallographic data for various backbone types of Tc complexes, showing the order $S_4 > S_3N > S_2N_2 > N_3S > N_4 > N_2O_2 > O_4$. Experimentally, the Re complexes are, in general, more stable than the Tc complexes,[18] in the sense that the off-rate of the ligands is slower in Re complexes. Therefore, less transmetalation results in less free ^{99}Tc pertechnetate or $^{186/188}$Re perrhenate taken up in the thyroid gland and stomach or bound to albumin, avoiding the important radiation burden in the case of $^{186/188}$Re radionuclidic therapy. From the theoretical side, Köstlmeier et al.[19] studied the Lewis acidity of CH_3TcO_3 and CH_3ReO_3. They found that the polarizability increases from CH_3ReO_3 to CH_3TcO_3 passing through OsO_4 and that [in the hard and soft acids and bases (HSAB) sense] the interaction with a hard Lewis base such as NH_3 will be favored by the harder Re center in comparison to one of Tc.

Nowadays, quantum chemistry permits inorganic chemists to predict and explain the properties of transition-metal complexes at the ab initio level. Recent developments in this area include the field of density-functional theory (DFT),[20] which meets the requirements of being accurate, easy to use, and fast enough to allow the study of relatively large molecules, such as the ones envisaged in this study.[21] Moreover, DFT provides the chemist with a variety of concepts describing reactivity such as electronegativity, hardness, softness, and Fukui functions, which have been successfully correlated with molecular properties and the reactivity of molecules. This branch has been termed conceptual DFT.[22] (For reviews, see ref 23.)

This prompted us to perform a theoretical study on the stabilities of various [3 + 1] complexes of Re(V) and Tc(V) (Figure 1) and to interpret, first, the relative stability of Re complexes versus that of Tc complexes and, second, the relative stabilities of complexes of a given metal (Re or Tc) with varying ligands using a combined computational and conceptual DFT approach. We will investigate whether a common pattern emerges from our computed results, which can be compared with experimental results, whether the stability sequences are identical in the gas phase and in aqueous solutions, and how these sequences can be interpreted in terms of the HSAB principle.[23d,24] Note that, in the past, only a relatively small number of nonempirical theoretical studies on the chemistries of Tc and Re[25] have been published, none of which treat, however, in the same vein the stability of the complexes as a function of the ligand.

II. Computational Method

The DFT results were obtained using the B3LYP functional.[26,27] The 6-31++G**[28] basis set has been chosen for the C, H, O, S, Cl, and N atoms; for Re and Tc, we have used the LANL2DZ basis set.[29] These two options are known to be compatible.[30] To study the stability of the complexes of Re and Tc, all of the complexes, ReOL and TcOL (L = ligand), were optimized. The energies of the isolated atoms Re and Tc have been calculated at the same level of theory, looking for the lowest energy corresponding to a sextet multiplicity. Atomic charges were calculated with the natural population analysis (NPA) method.[31] Solvation effects were taken into account by single-point calculations on the gas-phase optimized structures in an aqueous medium using the polarizable continuum model (PCM).[32,33] All of the calculations were performed with the GAUSSIAN 98 suite of programs.[34]

III. Results and Discussions

III.1. Geometries. The computational approach was tested by optimizing the two complexes of Re and Tc, chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V) and chloro(3-thiapentane-1,5-dithiolato)oxotechnetium(V), respectively, shown in Figures 1 and 2, hereafter referred to as complexes **1** and **2**, respectively, and comparing our calculated geometries with those of the experimental X-ray results. Table 1 gives a comparison of the B3LYP/LANL2DZ bond lengths, with the X-ray results, for the Tc(V) and Re(V) complexes given in Figure 2 for a selected number of bonds. For both the Tc and Re complexes, the B3LYP/LANL2DZ calculations give bond distances comparable to those of the X-ray results[15] and yield a Re−O bond that is larger than the Tc−O one, as it should be, according to the X-ray results. This also is in agreement with the theoretical study of the geometries of $[TcO_4]^-$ and $[ReO_4]^-$ given in ref 25e. Trends in the Tc or Re distances to the S atoms are well respected within and between both complexes. The average deviation of the distances of complexes **1** and **2** given in Table 1 is 0.0393 Å, which can be considered as very satisfactory for this level of theory.

Table 2 compares selected B3LYP/LANL2DZ theoretical angles with those of the X-ray results for the Tc and Re complexes given in Figure 2. From this table, it can be seen that these calculated results again show fair agreement in comparison with the X-ray results.

The calculations mentioned above were all done for a singlet state. The energy for the lowest triplet state was calculated at its corresponding equilibrium geometry and was considerably higher than that of the singlet state for both complexes. For the Tc complex, the difference between the singlet (−1967.414 49 au) and triplet (−1967.393 85 au) energies amounts to 13.0 kcal mol^{-1}. For the Re complex, the corresponding values are −1966.467 69 au, −1966.436 51 au, and 19.6 kcal mol^{-1}. We therefore concluded to perform the calculations on all of the remaining complexes in their singlet states.

III.2. Stability Patterns. Thermodynamic quantities such as the reaction energy (ΔE) permit the comparison of the stability

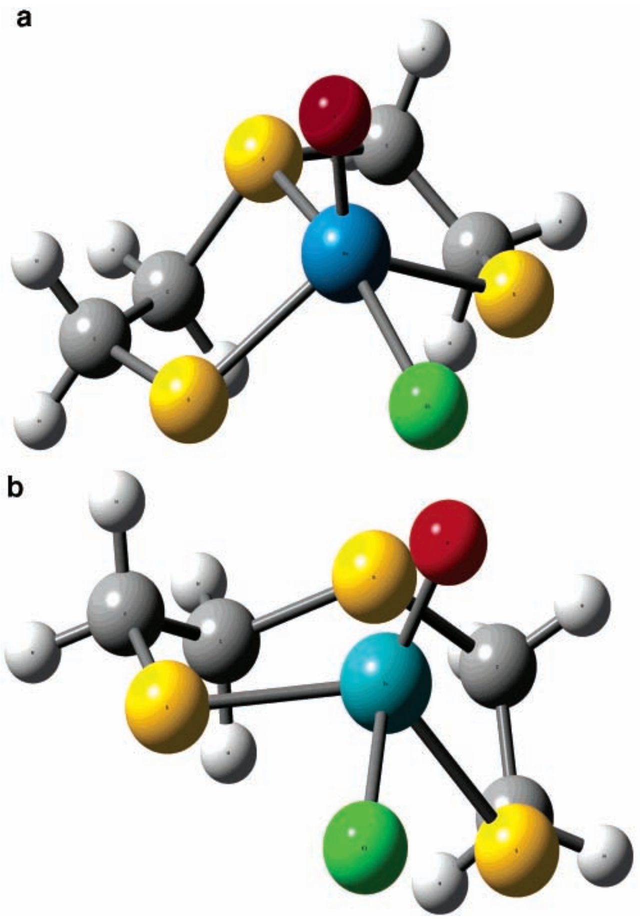

Figure 2. (a) Chloro(3-thiapentane-1,5-dithiolato)oxorhenium(V) (**1**). (b) Chloro(3-thiapentane-1,5-dithiolato)oxotechnetium(V) (**2**).

TABLE 1: Comparison of Selected Theoretical Bond Distances in Re Complex 1 and Tc Complex 2 at the B3LYP/LANL2DZ Level with Those of the X-ray Results (Distances are in Å)

bond	B3LYP/Lan2DZ	X-ray
	Re Complex **1**	
Re−O	1.686	1.705
Re−S(3)	2.328	2.260
Re−S(1)	2.329	2.272
Re−S(2)	2.410	2.295
Re−Cl(1)	2.388	2.372
	Tc Complex **2**	
Tc−O(1)	1.676	1.659
Tc−S(1)	2.328	2.278
Tc−S(3)	2.332	2.279
Tc−S(2)	2.445	2.349
Tc−Cl(1)	2.382	2.360

TABLE 2: Comparison of the B3LYP/LANL2DZ Angles (Degrees) in Re Complex 1 and Tc Complex 2 at the B3LYP Level with Those of the X-ray Results

angle	B3LYP/Lan2DZ	X-ray
	Re Complex **1**	
O(1)−Re−S(1)	119.5	114.1
O(1)−Re−S(3)	120.4	115.2
S(3)−Re−S(1)	120.0	130.7
O(1)−Re−S(2)	95.6	101.8
S(3)−Re−S(2)	86.6	86.3
S(1)−Re−S(2)	85.2	86.3
O(1)−Re−Cl(1)	102.2	102.0
S(3)−Re−Cl(1)	84.9	84.3
S(1)−Re−Cl(1)	84.5	83.3
S(2)−Re−Cl(1)	162.0	157.2
	Tc Complex **2**	
O(1)−Tc−S(1)	120.2	116.2
O(1)−Tc−S(3)	120.2	115.4
S(1)−Tc−S(3)	119.4	128.3
O(1)−Tc−S(2)	95.1	101.6
S(1)−Tc−S(2)	86.4	84.7
S(3)−Tc−S(2)	85.6	84.9
O(1)−Tc−Cl(1)	103.6	104.5
S(1)−Tc−Cl(1)	84.7	84.1
S(3)−Tc−Cl(1)	84.2	83.5
S(2)−Tc−Cl(1)	160.1	153.8

TABLE 3: Calculated Energy of Substitution for the Metal Complexes Derived from 1 and 2 with Varying Ligand L (Values in au) in the Gas Phase and in an Aqueous Solution

Re complexes	ΔE		Tc complexes	ΔE	
	gas phase	solution		gas phase	solution
ReSSS	0	0	TcSSS	0	0
ReSNS	0.1319	0.1332	TcSNS	0.1320	0.1459
ReONS	0.1364	0.1345	TcONS	0.1408	0.1504
ReSOS	0.1433	0.1475	TcSOS	0.1469	0.1507
ReOSS	0.1501	0.1476	TcOSS	0.1549	0.1533
ReOOS	0.1576	0.1552	TcOOS	0.1599	0.1582
ReONO	0.1618	0.1565	TcONO	0.1665	0.1624
ReOSO	0.1659	0.1646	TcOSO	0.1714	0.1702
ReOOO	0.1687	0.1652	TcOOO	0.1718	0.1732

sequence of a series of Re and Tc complexes via the above-mentioned substitution reaction $\mathrm{MOL_1 + L_2 \rightarrow MOL_2 + L_1}$, with $\Delta E = [E(\mathrm{MOL_2}) + E(\mathrm{L_1})] - [E(\mathrm{MOL_1}) + E(\mathrm{L_2})]$. The results are given in Table 3. [Note that Re complex **1** and Tc complex **2** were taken as references; therefore, $\mathrm{L_1}$ equals SSS (shorthand notation for the SSS ligand), whereas $\mathrm{L_2}$ equals SNS, ONS, OSS, ONO, OSO, OOO, OOS, and SOS, the fourth ligand always being Cl (cf. Figure 1; W = Cl)].

Note that, in principle, complexes of the types NEN, OEN, and SEN [E = O, S, $\mathrm{N(CH_3)_3}$] could also be considered corresponding to X = NH in the ligand $\mathrm{L_2}$ ($\mathrm{XH{-}CH_2{-}CH_2{-}E{-}CH_2{-}CH_2{-}XH}$) mentioned above. However, these cases were not retained because they involve a hydrogen transfer to the complex that can be considered as an unwanted side effect of the ligand-substitution reaction under consideration.

For computational simplicity, ΔE values are used in our study instead of ΔG values. It should, however, be mentioned that, in a very recent study on ligand-exchange reactions of the system $[\mathrm{Tc(CO)}_i(\mathrm{H_2O})_{6-i}]^+$ ($i = 0{-}6$), in which the total number of particles is unchanged before and after reaction, the approximation $\Delta G \approx \Delta E$ has been put forward because the entropies of the reactants and products are approximately the same.[35]

From Table 3, we can deduce that all of the ΔE values are positive, indicating that ReSSS and TcSSS are the most stable complexes. The sequences of stability for the two metal complexes are the same. This agrees with the highly similar properties of Tc and Re and their place in the periodic table. Table 3 underlines the role of the ligand in complex stability: the more S donors there are, the more stable the complexes are. For ligands containing three identical X and Y atoms, the sequence of stability is SSS > OOO, in agreement with the results found by Liu et al. in studying the Tc complexes using SAS values.[16−18] The stability sequence in an aqueous medium obtained with the PCM model is completely identical to that of the gas phase for both Tc and Re. The results show a very high correlation ($r^2 = 0.997$ for Re and $r^2 = 0.988$ for Tc), the slopes of the curves being close to 1 (1.013 for Re and 0.996 for Tc). Consequently, in the remaining part of the paper, the discussion on stability sequences will be limited to the gas-phase data.

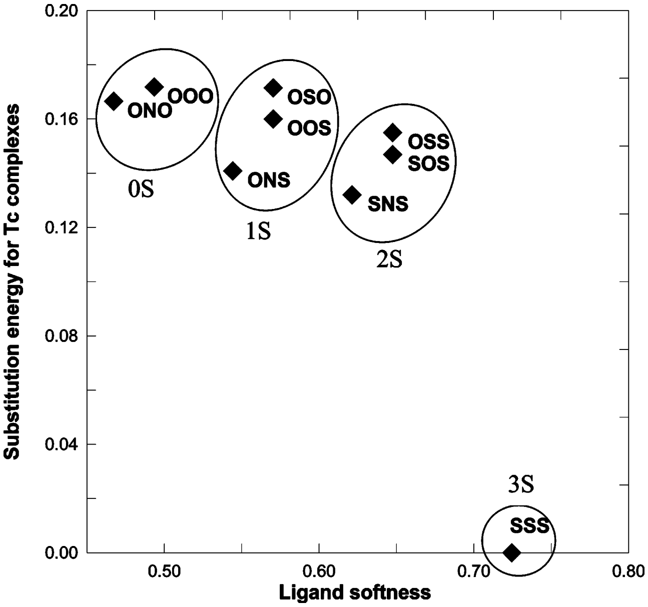

Figure 3. Correlation between ligand-substitution reaction energy, ΔE (in au), and ligand softness for the Tc(V) complexes (in eV^{-1}); note the clustering of the ligands with 3-, 2-, 1-, and 0S atoms.

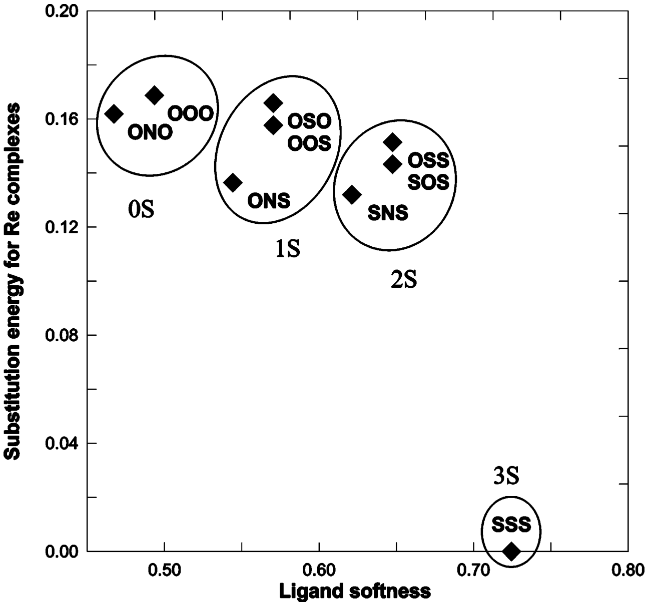

Figure 4. Correlation between ligand-substitution reaction energy, ΔE (in au), and ligand softness for the Re(V) complexes (in eV^{-1}); note the clustering of the ligands with 3-, 2-, 1-, and 0S atoms.

Figures 3 and 4 give the correlations between the energy of the ligand-substitution reaction and the softness of the ligand for Re and Tc complexes, respectively. The softness of the ligand represents an approximate value of the softness of the varying part of the group $XH-CH_2-CH_2-E-CH_2-CH_2-XH$, with $E = O$, $N(CH_3)$, or S and $X = S$ or O, calculated as the sum of the E and X atoms' softness taken from ref 20, on the basis of the *softness additivity principle*.[36]

From Figures 3 and 4, it is obvious that the behaviors of Re and Tc, concerning the stabilities of their complexes, show a comparable pattern. Generally spoken, increasing the softness of the ligand stabilizes the complexes.

This global ligand softness is, in view of the hardness values for S, O, and N (4.14, 6.08, and 7.23 eV,[20] respectively), expected to be essentially governed by the number of S atoms. This feature clearly shows up when, in Figures 3 and 4, clusters are drawn corresponding to the S content of the ligand: an increasing stability upon increasing S content clearly emerges for the relative position of the clusters, the "3S" Re complex **1** and "3S" Tc complex **2** being by far the most stable ones.

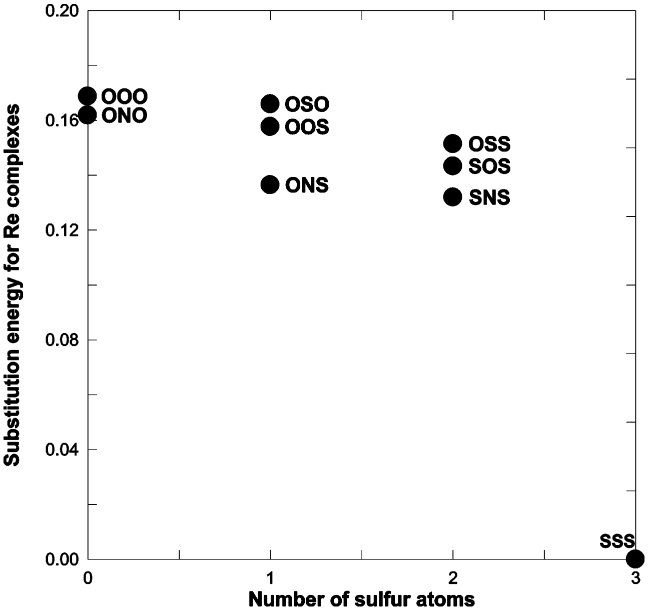

Figure 5. Ligand-substitution reaction energy (in au) vs the number of S atoms for the Re(V) complexes.

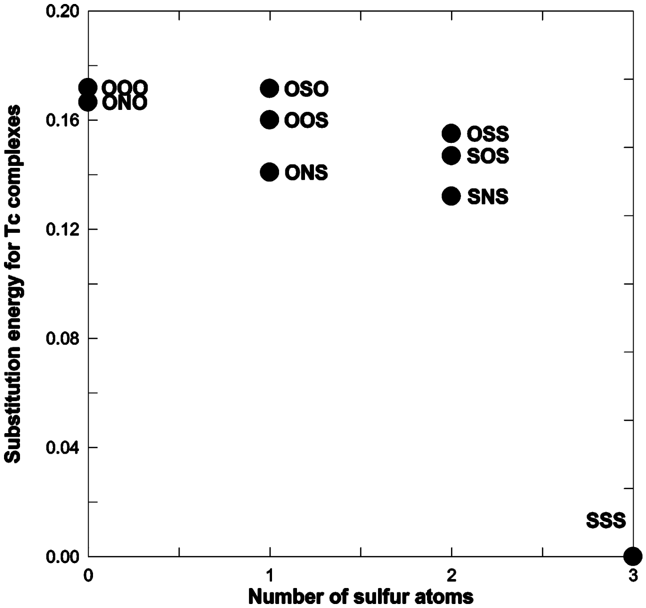

Figure 6. Ligand-substitution reaction energy (in au) vs the number of S atoms for the Tc(V) complexes.

To refine the picture of the relationship between complex stability and the nature of the ligand, we plotted, in Figures 5 and 6, the ligand-substitution ΔE versus the number of S atoms showing the "fine structure" of the stabilization energies for different ligands with the same number of S atoms.

In the case of 2 S atoms, the stability sequence SNS > SOS > OSS gives an indication that a terminal S atom contributes to the stability of the complexes to a larger extent than when the S atom occupies the central position. As a change in coordination occurs between a terminal S atom and the central S atom (Figure 1), the central S atom can be expected to be *more* positively charged as opposed to the terminal one. When this effect is mimicked, it is therefore rewarding to look at the softness of the cation, in the case of the central atom, for discussing the fine structure of the stability sequence.

These values can easily be obtained by extending the working equation

$$S = \frac{1}{I_1 - A} \tag{1}$$

(I_1 being the first ionization energy and A being the electron affinity) from neutral atoms to cations. Then, eq 1 becomes

$$S_{\text{cation}} = \frac{1}{I_2 - I_1} \tag{2}$$

where I_2 is the second ionization energy.

Using the data from ref 37, one obtains the following hardness sequence for O, N, and S, including both neutral atoms and cations:

$$\begin{array}{lcccccc} & S^0 \ll & O^0 < & S^{+1} < & N^0 < & N^{+1} \ll & O^{+1} \\ \eta = & 4.14\ (\text{eV}) & 6.08 & 6.48 & 7.23 & 7.53 & 10.75 \end{array}$$

The softness of the central S atom is strongly diminished when compared to that of the terminal atom, explaining the SNS > SOS > OSS sequence in the stability of the "2S" ligand complexes.

The hardness sequence clearly shows that two values are "outliers" of the 6−7.5 eV hardness region: (1^0) the neutral S atom and (2^0) the positively charged O atom. The fact that the positively charged S atom (modeling the central S atom in the ligand) is surpassed in softness only by both its neutral counterpart and the neutral O atom has as immediate consequence that the number of S atoms is still, in this more refined scheme, the main ordering parameter.

The higher hardness for the positive oxygen atom disfavors the position of oxygen as the central ligand because it is then three-coordinated. It is remarkable that, whereas the neutral O atom is less hard than the neutral N atom, this sequence is inverted for the cations, and the difference is, moreover, much more pronounced.

This phenomenon finds its origin essentially in the much higher second ionization energy of oxygen as compared to that of nitrogen [35.12 eV (O^+) vs 29.60 eV (N^+)],[37] which can be ascribed to its $s^2p_xp_yp_z$ configuration. The relative stability of the half-filled subshell is apparent from the higher first ionization energy of N versus O. Combined with the relatively close first ionization energies [13.62 eV (N) vs 14.53 eV (O)], this yields, via eq 2, a much higher hardness for O than for N.

In summary, on the basis of a first-order coordination-effect correction to the isolated atom softness additivity model, we can say that, for (1^0), in globo, the more S atoms there are, the higher the stability and, for (2^0), a central O atom strongly disfavors stability.

These observations can now be easily applied to the 0S and 1S clusters in Figures 5 and 6. In the 0S clusters, it is clear that the stability sequence ONO > OOO reflects the unfavorable situation of a central O atom when compared to that of a central N atom. In the case of the 1S complexes, the following stability sequence is obtained in the Re case: ONS > OOS > OSO.

When OOS and OSO are compared, the destabilizing effect of the central oxygen overrules the stabilizing effect of the terminal S. In those cases where a N or O atom is central (ONS and OOS), O leads to further destabilization. The situation for Tc is identical to the Re case (cf. Figures 5 and 6). As a whole, these results account for the stability sequence of Tc complexes with three identical chelating atoms, SSS > OOO, found by Liu et al. using SAS values.[16−18]

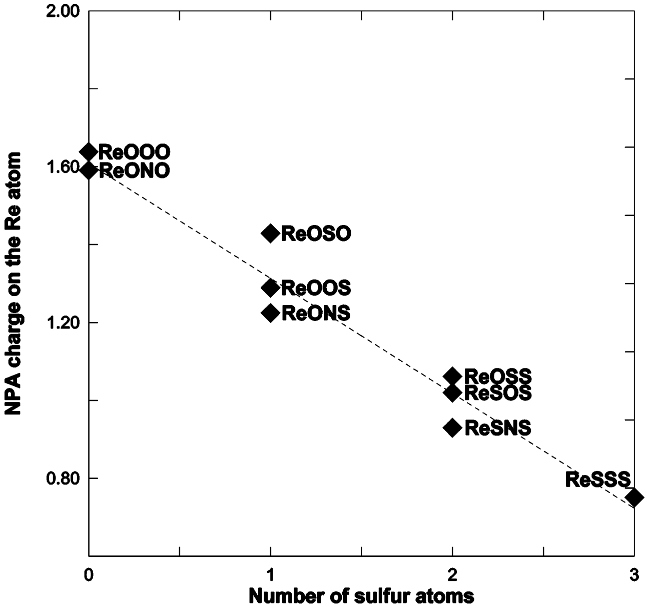

Figure 7. NPA charge on the Re atom vs the number of S atoms for the Re(V) complexes.

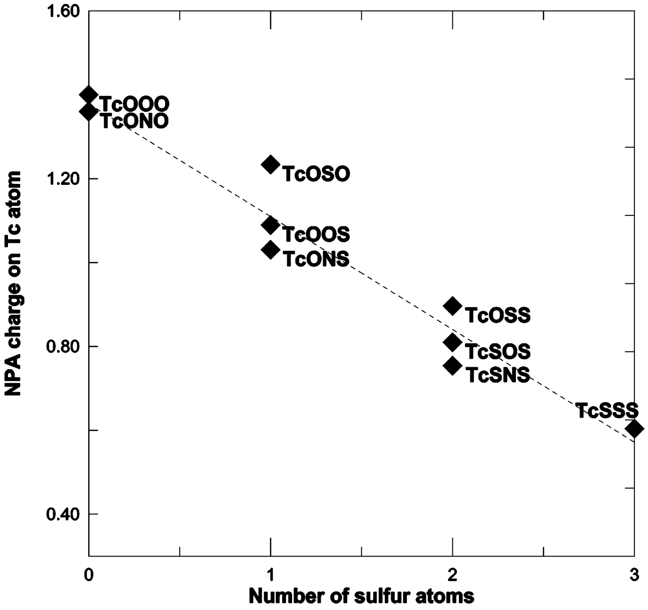

Figure 8. NPA charge on the Tc atom vs the number of S atoms for the Tc(V) complexes.

Moreover, NPA charges on the M atom show a good correlation with the number of S atoms in the metal complex (Figures 7 and 8). The analysis of these values shows that the positive charge upon M (M = Re and Tc) decreases when the number of S atoms increases, its evolution being 0S > 1S> 2S > 3S and O > N > S. The NPA charge on the M atom can, therefore, be considered to be an indicator of the stability of those complexes. Figures 9 and 10 give the correlations between the substitution ΔE and the NPA charges on Re and Tc. Note that the NPA charges are systematically shifted downward when passing from Re to Tc. The higher hardness of Re, opposing charge transfer, might be one of the factors accounting for this difference.

To study the relative stability of Re complexes versus that of Tc complexes, we have used a simple substitution reaction

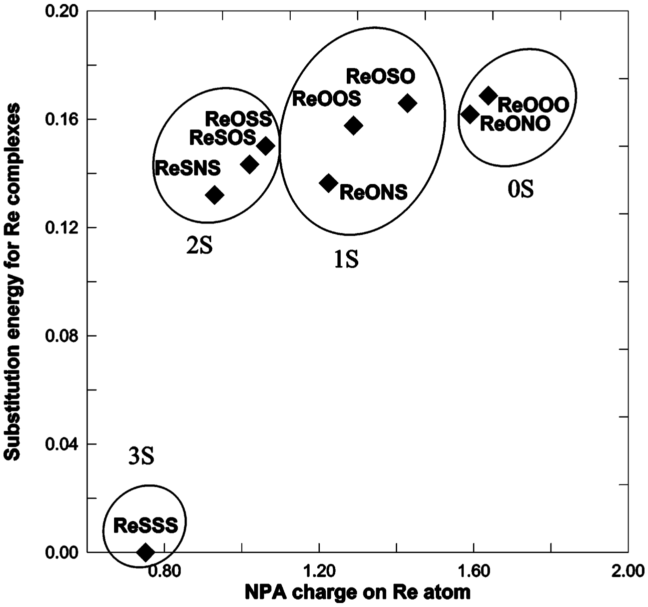

Figure 9. Ligand-substitution reaction energy (in au) vs the NPA charge on the Re atom for the Re(V) complexes.

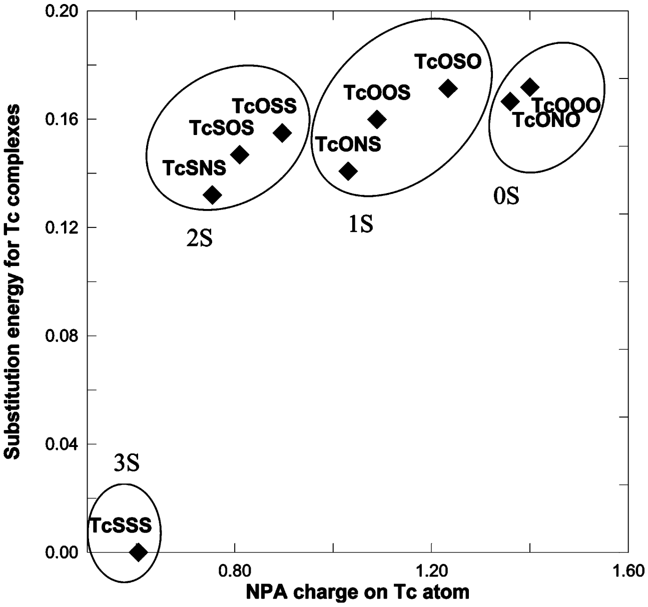

Figure 10. Ligand-substitution reaction energy (in au) vs the NPA charge on the Tc atom for the Tc(V) complexes.

TABLE 4: Calculated Transmetalation Energy, ΔE (in au), for Varying Ligands

ligands	ΔE	ligands	ΔE
SSS	0.03748	OOS	0.03899
SNS	0.03660	ONO	0.04121
ONS	0.04097	OSO	0.04193
SOS	0.03545	OOO	0.04559
OSS	0.04013		

of the type ReOL + Tc → TcOL + Re, L being the same series of ligands used before. ΔE is given as $[E(\text{TcOL}) + E(\text{Re})] - [E(\text{ReOL}) + E(\text{Tc})]$, $E(\text{MOL})$ being the energy of the complex. $E(\text{Re})$ and $E(\text{Tc})$ are the energy values of a Re and a Tc atom, respectively, at their lowest energy for a sextet multiplicity [$E(\text{Re}) = -78.845\,59$ au and $E(\text{Tc}) = -79.948\,43$ au].

Table 4 gives the energies of the transmetalation reaction with varying ligands. From this table, we can see that all of the energies are positive. This indicates that the reaction is favored in the reverse sense, TcOL + L → ReOL + L, and that all ligands prefer Re to Tc. This might be due to the differences in their polarizability or softness. This is also in agreement with the values found in Table 3: $\Delta E(\text{TcOL}) > \Delta E(\text{ReOL})$. These results indicate that Re complexes are more stable than their Tc analogues and are in agreement with experimental results.[16−18] Note, however, that these results cannot be related to the findings of labeling chemistry, where it is not thermodynamics that rules the reaction but the kinetics of reduction, which in routine "^{99}Tc conditions" occurs much more slowly.

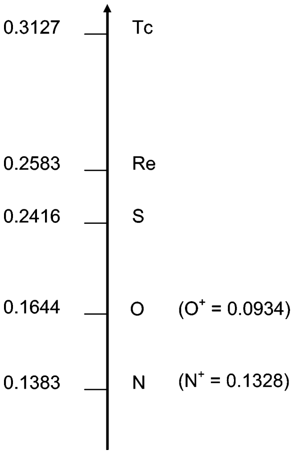

Figure 11. Ordering of softnesses of the relevant atoms. Values are taken from ref 20, except for those of Tc, O^+, and N. Correction for the central chelating atom inverts the O−N sequence. All values are in eV^{-1}.

TABLE 5: Softness Values for the Elements Surrounding Tc in the Periodic Table (Values in eV^{-1})

Cr S= 0.3267	**Mn** S= 0.2688	**Fe** S= 0.2624
Mo S= 0.3225	**Tc** S= ?	**Cr** S= 0.3333
W S= 0.2793	**Re** S= 0.2583	**Re** S= 0.2631

III.3. Interpretation in Terms of the HSAB Principle. The trends obtained above for the ligand-substitution and transmetalation reactions can be interpreted within the context of conceptual DFT using the HSAB principle. The HSAB principle proposes that reactions will occur most readily between species matching in hardness or softness.[24,38]

As stated above, the "experimental" atomic softness values can be obtained via the relationship in eq 1, where I and A are the experimental ionization energy and electron affinity values, respectively, represented in Figure 11.

For Tc, no experimental value is available; a value was calculated by interpolating the softness trend of the neighboring group of atoms in the periodic table.

From Table 5, we can see that Mo is softer than W and Ru is softer than Os. By analogy, we can then propose that Tc is softer than Re. The softness of Tc can be extracted by a simple proportionality between the softness values of those atoms. Indeed, we assume that the ratio of the global softness values of Tc and Re is equal to the ratio of the softness values of Mo and W and also equal to the ratio of the softness values of Ru and Os. We hereby concentrate on rows 5 and 6 because only when comparing row 5 with row 6 does the f-orbital effect appear.

$$\frac{S(\mathrm{Tc})}{S(\mathrm{Re})} \approx \frac{S(\mathrm{Mo})}{S(\mathrm{W})} \approx \frac{S(\mathrm{Ru})}{S(\mathrm{Os})} \tag{3}$$

An estimation of the softness of Tc can then be obtained as

$$S(\mathrm{Tc}) \approx S(\mathrm{Re})\,\frac{\dfrac{S(\mathrm{Mo})}{S(\mathrm{W})} + \dfrac{S(\mathrm{Ru})}{S(\mathrm{Os})}}{2} \tag{4}$$

leading to a value of 0.3127.

Note that in groups 6−8 of the periodic table, as is also the case in columns 4−6, the softness decreases when passing from the fifth to the sixth period. This behavior is at first somewhat counterintuitive because one might think that softness would increase monotonically when going down in the periodic table, as is the case for the main-group elements in the upper rows. However, it is well-documented that a lot of properties (among others, atomic radii,[39] which are expected to reflect polarizability and softness[40,41]) show an "anomalous behavior" for periods 4−6. It is common to ascribe this effect to the so-called lanthanide contraction, which refers to the fact that, in the third-row transition metals, the 4f shell can be considered as corelike because of its compactness.[42]

As can be seen from Figure 11, the principle of softness matching (i.e., looking for the smallest softness difference between the acceptor and donor atoms)[25c,d,38] perfectly explains the above-mentioned sequence for the ligand-substitution reaction, SSS > OOO, in line with the experimental results.

Softness matching also explains the sequence of transmetalation reaction energies. Figure 11 shows that the two transition metals are softer than the S, O, and N atoms and S is softer than O and N. Because Re is softer than Tc, the smallest local softness difference occurs between Re and S. From the HSAB principle, it can be inferred that the smaller the values of this difference, the smaller the transmetalation energies should be. This is demonstrated in Table 5, where the transmetalation energies of the complexes decrease with an increasing amount of S in the chelator.

The results show a close analogy with a recent study of the authors on the complexation reaction of tin halides $Sn(CH_3)_3X$ with halide ions Y^-, with X and Y = F, Cl, Br, and I,[43] where it was found that the complexation energies become more negative when the softness difference between the acceptor atom in the Lewis acid (Sn) and the donor atom in the Lewis base Y becomes smaller, in agreement with the HSAB principle.

In conclusion, the HSAB principle points out that all of the ligands prefer Re to Tc, in agreement with the results given in Figure 11. The softness difference between Re and each atom X is smaller than the difference in softness between Tc and the same atom X, but both Re and Tc prefer S to other atoms such as O and N (this is confirmed by the smallest softness difference between Re and S).

IV. Conclusions

DFT calculations employing the B3LYP functional and the LANL2DZ basis set have been performed on several mixed [3 + 1] Re and Tc complexes. A test of the ability of the methodology to offer a fair description of the geometry of these complexes was performed by fully optimizing the two complexes **1** and **2**. It was shown that the results show fair agreement with X-ray data. The stability of the complexes of a given metal, Re or Tc, was evaluated using a simple substitution reaction. The calculated reaction energies, ΔE's, for the reaction $MOL_1 + L_2 \rightarrow MOL_2 + L_1$ were successfully correlated with the softnesses of the ligands. The number of S atoms and the presence of a three-coordinated central oxygen atom turn out to be the main stabilizing and destabilizing factors, respectively. This analysis also shows that, for ligands containing three identical X and Y chelating atoms, the sequence of stability is SSS > OOO, in agreement with the results found by Liu et al. using SAS values. The results when passing from Re to Tc are identical, and the sequences are unchanged when passing from the gas phase to an aqueous solution.

The relative stability of Re complexes versus that of Tc complexes was studied using a simple transmetalation reaction of the type $ReOL_1 + Tc \rightarrow TcOL_2 + Re$ and shows that all of the ligands prefer Re to Tc, indicating that Re complexes are thermodynamically more stable than their Tc analogues. When the newly presented Tc softness value is used, the principle of softness matching (i.e., looking for the smallest softness difference between the acceptor and donor atoms in a Lewis acid−base reaction) also perfectly explains the sequence of transmetalation reaction energies. The latter is important for in vivo stability because $^{186/188}$Re is used for systemic radionuclidic "tumor-specific" therapy, and the free perrhenate should dramatically increase the radiation dose to normal tissues.

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Supporting Information Available: Geometries (Cartesian coordinates) and energies of all of the complexes and the $HX-CH_2-CH_2-Y-CH_2-CH_2-XH$ [X = S, O; Y = O, $N(CH_3)$, S] compounds. NPA charges on the Re and Tc atoms (Figures 7−10). This material is available free of charge via the Internet at http://pubs.acs.org.

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