Relativity as a Synthesis Design Principle: A Comparative Study of [3 + 2] Cycloaddition of Technetium(VII) and Rhenium(VII) Trioxo Complexes with Olefins

Henrik Braband, Michael Benz, Bernhard Spingler, Jeanet Conradie,* Roger Alberto,* and Abhik Ghosh*

ABSTRACT: The difference in [3 + 2] cycloaddition reactivity between fac-[MO₃(tacn)]⁺ (M = Re, ⁹⁹Tc; tacn = 1,4,7-triazacyclononane) complexes has been reexamined with a selection of unsaturated substrates including sodium 4-vinylbenzenesulfonate, norbornene, 2-butyne, and 2-methyl-3-butyne-2-ol (2MByOH). None of the substrates was found to react with the Re cation in water at room temperature, whereas the ⁹⁹Tc reagent cleanly yielded the [3 + 2] cycloadducts. Interestingly, a bis-adduct was obtained as the sole product for 2MByOH, reflecting the high reactivity of a ⁹⁹TcO-enediolato monoadduct. On the basis of scalar relativistic and nonrelativistic density functional theory calculations of the reaction pathways, the dramatic difference in reactivity between the two metals has now been substantially attributed to differences in relativistic effects, which are much larger for the 5d metal. Furthermore, scalar-relativistic ΔG values were found to decrease along the series propene > norbornene > 2-butyne > dimethylketene, indicating major variations in the thermodynamic driving force as a function of the unsaturated substrate. The suggestion is made that scalar-relativistic effects, consisting of greater destabilization of the valence electrons of the 5d elements compared with those of the 4d elements, be viewed as a new design principle for novel ⁹⁹mTc/Re radiopharmaceuticals, as well as more generally in heavy-element coordination chemistry.

INTRODUCTION

Technetium-99m, a metastable nuclear isomer of technetium-99, is the most commonly used radioisotope in medicine, and the demand for ⁹⁹mTc radiopharmaceuticals with novel biodistribution properties is considerable.¹⁻⁴ A common early step toward the development of these products involves model chemistries with ⁹⁹Tc and Re. Although the two elements are chemically very similar, they exhibit quantitative differences in reactivity, reflecting the somewhat greater stability (and lower reduction potentials) of the higher oxidation states of Re. In a seminal finding, Pearlstein and Davison in the 1980s showed that fac-[⁹⁹TcO₃(μ-μ₃,μ₅-O)] complexes undergo [3 + 2] cycloadditions with olefins to yield ⁹⁹TcO-diolate derivatives.³ The analogous ReO-diolate species, in contrast, were found to be unstable, undergoing the opposite reaction when thermalized. We built on this finding to develop fac-[⁹⁹mTcO₃(μ-μ₃,μ₅-O)] complexes as aqueous-phase labeling agents for olefins.⁶⁻⁸ The factors underlying the difference in reactivity between the two group 7 elements, however, have remained obscure. Physicochemical measurements at the Tromso laboratory on analogous pairs of 4d and 5d metalloccorroles,⁹⁻¹¹ including those involving Mo¹²/W,¹³ ⁹⁹Tc²¹/²³O²⁻/²⁵O,¹⁵ Ru²¹V²³/²⁵N²⁷, and Ag³⁰Au³¹,³²⁻³⁴ suggested that relativistic effects might partly explain the difference in cycloaddition reactivity between ⁹⁹mTc/⁹⁹Tc and Re.²⁰

Unfortunately, little is known about the importance of relativistic effects for transition-metal reactivity.²¹⁻²³ For most of the 20th century, relativistic effects were not considered important for chemistry. Indeed, in 1929, Paul Dirac asserted that the only imperfections remaining in quantum mechanics “give rise to difficulties only when high-speed particles are involved, and are therefore of no importance in the consideration of atomic and molecular structure and ordinary chemical reactions in which it is, indeed, usually sufficiently accurate if one neglects relativity variation of mass and velocity and assumes only Coulomb forces between the various electrons and atomic nuclei.”²⁴ This view started changing only in the 1970s.²⁵,²⁶ Today the importance of relativistic effects is well recognized for the static properties of sixth- and...
seventh-period elements.\textsuperscript{27} Relativity thus accounts for such well-known effects as the liquid state of Hg\textsuperscript{28} and the yellow color of elemental Au\textsuperscript{29} and Cs as well as a host of less well-known effects in heavy-element chemistry.\textsuperscript{30–33}

\section{RESULTS AND DISCUSSION}

\textbf{Synthetic and Reactivity Studies.} With the above as the backdrop, we chose to perform a comparative study of \textit{fac-} \{MO$_3$(tacn)\}$_+$ (M = Re, $^{99}$Tc; tacn = 1,4,7-triazacyclononane) complexes with respect to their [3 + 2] cycloaddition reactivity with a selection of unsaturated substrates including sodium 4-vinylbenzenesulfonate, norbornene, 2-butyne, and 2-methyl-3-butyn-2-ol (2MBByOH; Scheme 1). Because we already knew from our recent work that \textit{fac-}[$^{99}$TcO$_3$(tacn)]$^+$ reacts with a broad range of olefins to yield $^{99}$TcO-diolate products, we focused here particularly on complexes of the type \textit{fac-} \{MO$_3$(tacn)\}X (X = Cl, BPh$_4$).\textsuperscript{34} We verified that the Re complexes do not react with olefins and alkynes, as indeed was expected from Pearlstein and Davison’s original observations.\textsuperscript{6} Because alkynes had not been examined as substrates until now, we chose to examine the interaction of the water-stable complex \textit{fac-}[$^{99}$TcO$_3$(tacn)]Cl$^-$ with the water-soluble propargylic alcohol 2MBByOH. After the addition of 2 equiv of the propargylic alcohol to an aqueous solution of \textit{fac-}[$^{99}$TcO$_3$(tacn)]Cl$^-$, a quick color change was observed from yellow to green. After stirring for 2 h at room temperature, the dinuclear complex \{[$^{99}$TcO$_3$(tacn)]$_2$(2MBByOH)$\}$Cl$_2$ was isolated as the sole product following removal of all volatiles under high vacuum. No mononuclear intermediate was detected by either high-performance liquid chromatography (HPLC) or NMR. This finding suggests that the expected $^{99}$TcO-endiolate intermediate acts as a highly reactive substrate for a second equiv of \textit{fac-}[$^{99}$TcO$_3$(tacn)]$^+$ to yield the observed bis-adduct (Scheme 2).

The Fourier transform infrared spectrum of \{[$^{99}$TcV(O)O$_2$(tacn)]$_2$(2MBByOH)$\}$Cl$_2$ understandably indicated the formation of two diastereomers in a 2:1 ratio (Scheme 3).\textsuperscript{36} Slow evaporation of an aqueous solution of the product in the presence of excess KBr led to crystallization of the major diastereomer of \{[$^{99}$TcV(O)O$_2$(tacn)]$_2$(2MBByOH)$\}$Br$_2$ (isomer 1 in Scheme 3). Single-crystal X-ray diffraction analysis (Table 1 and Figure 1) revealed an intramolecular N4—H···O7 hydrogen bond, which, along with less overall steric crowding, appears to be responsible for the formation of isomer 1 as the major product. In contrast to the [3 + 2] cycloadducts of \textit{fac-}[$^{99}$TcO$_3$(tacn)]$^+$ with alkynes, slow decomposition of isomer 1 of the bisadduct (formation of \{[TcO$_4$]$^+$\}) was observed over days.

\textbf{Theoretical Modeling.} Relativistic and nonrelativistic density functional theory (DFT) calculations (typically with large all-electron STO-TZ2P basis sets; see Experimental Section for details) were used to investigate the [3 + 2] cycloaddition of the cationic complexes \{MO$_3$(tacn)$\}$+$ (M = Tc, Re) with four different olefins, namely, propene, dimethylketene, 2-butyne, and norbornene, in acetonitrile (MeCN) as a solvent (Table 2). Relativity was taken into account either via effective core potentials (ECPs) or with a scalar-relativistic treatment with the zeroth-order regular approximation (ZORA). Two-component spin–orbit relativistic calculations were undertaken in a few cases as random checks on the quality of the ECP and scalar-relativistic results; the latter results were indeed found to be adequate, with minimal differences relative to the spin–orbit calculations. The data in Table 1 led to the following conclusions.

Relativistic calculations indicate dramatically lower (in an algebraic sense) reaction free energies ($\Delta G$) and free energies of activation ($\Delta G^\ddagger$) for Tc than for Re, consistent with the experimentally observed difference in reactivity between the two metals. These translate to substantially “earlier” transition states for Tc than for Re; in other bonds, key bonds affected by the reaction are rather similar in length to the starting materials for the Tc reactions compared with the Re reactions (Figure 2). In sharp contrast, nonrelativistic calculations (B3LYP$_{rel}$ and PBE0$_{rel}$ in Table 2) indicate similar $\Delta G$ and $\Delta G^\ddagger$ values for the two metals. The fact that these generalizations hold regardless of the exchange-correlation functional and the organic substrate indicates that the difference in reactivity between the two metals is largely a relativistic effect.

The above interpretation is supported by computations of the adiabatic electron affinities (EAs) for the M(VII) $d^0$ complexes MeTc$^{VII}$O$_3$ and MeRe$^{VII}$O$_3$ (Me = methyl). At the scalar relativistic level, the B3LYP values are 3.44 and 2.79 eV, respectively, i.e., the EA of the Tc(VII) complex is 650 meV higher than that of the Re(VII) complex. The scalar-relativistic PBE0 values are similar, 3.31 and 2.65 eV, as are the...
PBE-D2ECP values, 3.67 and 3.02 eV. At the nonrelativistic level, the B3LYP EAs are 3.64 and 3.32 eV, while the PBE0 EAs are 3.51 and 3.20 eV, respectively, which translates to a difference of just over 300 meV between the two metals. These results prove that the difference in the EAs or reduction potentials between the Tc(VII) and Re(VII) species is substantially ascribable to the relativistic destabilization of the Re 5d orbitals relative to the Tc 4d orbitals. Much the same considerations should apply to the cycloaddition reaction of interest in this study because it also involves a reduction, albeit a two-electron one, of the M(VII) centers.

Another key observation from Table 2 is that the ΔG values, which decrease along the series propene > norbornene > 2-butyne > dimethylketene, reflect dramatic variations in the thermodynamic driving force as a function of the olefinic substrate. In fact, for propene, all of the relativistic methods yield positive ΔG values, consistent with the experimental observation that simple, unstrained olefins do not react with cationic [ReVIIIO3]+ reagents at room temperature. Interestingly, much smaller variations are observed among the ΔG values for dimethylketene and norbornene. In fact, for propene, all of the relativistic methods yield positive ΔG values, consistent with the experimental observation that simple, unstrained olefins do not react with cationic [ReVIIIO3]+ reagents at room temperature. Interestingly, much smaller variations are observed among the ΔG values for dimethylketene and norbornene. Overall, our results underscore the need for substantial additional benchmarking of different functionals vis-à-vis transition-metal-mediated redox reactions, especially for 4d and 5d elements.

### CONCLUSION

In earlier studies of metalloporphyrin-type compounds, we concluded that the difference in redox potential between

---

**Table 1. Crystal Data and Structure Refinement for [{99TcV(O)O2(tacn)}2(2MByOH)]Br2·2H2O**

| Property                        | Value         |
|---------------------------------|---------------|
| empirical formula               | C₁₁₇H₄₂Br₂N₆O₉₂₀Tc₂ |
| diffractometer                  | Xcalibur, Ruby diffractometer |
| wavelength (Å)                  | 0.71073       |
| fw                              | 833.58        |
| cryst syst                      | monoclinic    |
| space group                     | P2₁/c         |
| a (Å)                           | 16.5494(7)    |
| b (Å)                           | 13.3552(5)    |
| c (Å)                           | 14.509(2)     |
| α (deg)                         | 90            |
| β (deg)                         | 114.955(11)   |
| γ (deg)                         | 90            |
| volume (Å³)                     | 2903.1(6)     |
| Z                               | 4             |
| density (calc) (g cm⁻³)         | 1.907         |
| temperature (K)                 | 183.1         |
| abs coeff (mm⁻¹)                | 3.758         |
| F(000)                          | 6632          |
| cryst size (mm³)                | 0.234 × 0.145 × 0.075 |
| cryst description               | green block   |
| θ range for data collection (deg)| 2.715−30.508 |
| index ranges                    | −23 ≤ h ≤ 23, −19 ≤ k ≤ 19, −19 ≤ l ≤ 20 |
| refinl collected                | 41201         |
| indep refinls                   | 8809 [R(int) = 0.0396] |
| refin obsd                      | 7686          |
| criterion for observation       | I > 2(I)      |
| completeness to θ = 25.242° (%) | 99.0          |
| abs corr                        | semiempirical from equivalents |
| max and min transmmt            | 1.000 and 0.789 |
| data/restraints/param           | 8809/6/362    |
| GOF on F²                       | 1.054         |
| final R indices (I > 2σ(I))     | R1 = 0.0469, wR2 = 0.1202 |
| R indices (all data)            | R1 = 0.0550, wR2 = 0.1250 |
| largest diff peak and hole (e Å⁻³) | 2.533 and −2.461 |
| CCDC                            | 2071332       |

---

**Figure 1.** Thermal ellipsoid (50% probability) plot for [{99TcV(O)-O₅(tacn)}₂(2MByOH)]Br₂. Bromide ions and water molecules have been omitted for clarity. Selected bond distances (Å) and angles (deg): Tc1−O1 1.661(3), Tc1−O2 1.926(3), Tc2−O4 1.665(3), Tc2−O5 1.946(3), Tc1−N8 2.163(4), Tc1−N9 2.175(4), Tc1−N10 2.295(4), Tc2−N11 2.185(3), Tc2−N12 2.147(4), Tc2−N13 2.250(4); O1−Tc1−O2 112.86(16), O2−Tc1−O3 81.73(12), O4−Tc2−O5 108.23(16), O5−Tc2−O6 81.42(12), O2−C13−O5 107.6(3), O3−C14−O6 108.8(3).
analogous 4d and 5d complexes is largely attributable to scalar relativistic effects, much as calculated for $\Delta G$ and $\Delta G^\dagger$ values in the present study. The greater relativistic destabilization of the valence electrons of the 5d elements compared with those of the 4d elements thus may be viewed as a reliable design principle for novel $^{99m}$Tc radiopharmaceuticals, as well as more

Table 2. Scalar-Relativistic and Nonrelativistic DFT Energetics (eV) for Different Substrates in CH$_3$CN

| substrate       | metal | B3LYP$^{scalar}$ | B3LYP$^{non}$ | PBE0$^{scalar}$ | PBE0$^{non}$ | OPBE0$^{scalar}$ | OPBE0$^{non}$ | PBE-D2ECP$^b$ |
|----------------|-------|-----------------|---------------|----------------|-------------|-----------------|---------------|--------------|
| propene        | Tc    | −0.38           | 0.83          | −0.77          | 1.09        | −0.91           | 1.13          | −1.31        | 0.98         | −0.71         | 1.46         | −0.48         | 0.59         |
|                | Re    | 1.28            | 1.86          | −0.81          | 1.10        | 0.33            | 1.69          | −1.38        | 0.98         | 0.54          | 2.01         | 0.55          | 1.09         |
| dimethylketene | Tc    | −1.44           | 1.28          | −1.83          | 1.17        | −2.02           | 1.20          | −2.42        | 1.10         | −1.77         | 1.62         | −1.47         | 0.50         |
|                | Re    | −0.21           | 1.91          | −1.74          | 1.05        | −0.76           | 1.77          | −2.41        | 0.92         | −0.50         | 2.32         | −0.41         | 0.93         |
| 2-butyne       | Tc    | −1.20           | 1.35          | −1.62          | 1.26        | −1.76           | 1.25          | −2.18        | 1.14         | −1.58         | 1.61         | −1.35         | 0.70         |
|                | Re    | −0.21           | 1.91          | −1.50          | 1.25        | −0.48           | 1.74          | −2.10        | 1.09         | −0.30         | 2.07         | −0.21         | 1.11         |
| norbornene     | Tc    | −0.73           | 1.10          | −1.14          | 0.92        | −1.25           | 0.98          | −1.67        | 0.83         | −1.00         | 1.35         | −0.96         | 0.32         |
|                | Re    | 0.48            | 1.67          | −1.20          | 0.80        | −0.02           | 1.49          | −1.77        | 0.66         | 0.24          | 1.87         | 0.07          | 0.73         |

$^a$Obtained with ADF. $^b$Obtained with Gaussian.

Figure 2. Ball-and-stick diagrams, with key distances (Å), for the optimized PBE-D2ECP stationary points for the [3 + 2] cycloaddition of [MO$_3$(tacn)]$^+$ and norbornene. M = Tc (left), Re (right).
generally in heavy-element coordination chemistry. In other words, higher-valent technetium species such as pertechnetate or fac-[99TcO4]1− derivatives should be much more easily reduced (i.e., accept electrons in their 4d orbitals) than isoelectronic Re species (where electrons would be added to 5d orbitals). This prediction—in this case, a postdiction—is nicely illustrated by the facile synthesis of 99mTc(1) organometallic compounds via the reduction of pertechnetelement (UPLC) solvents were formic acid (0.1% in Millipore water) (solvent heavy/element coordination compounds.

We look forward to seeing additional applications of TeAP, 15 min, 75 °C. TEAP; 3 mg, 0.18 mmol). Analytical data are in agreement with the literature.

A solution of [ReO3(tacn)](BPh4) (36 mg, 0.05 mmol) in MeCN (3.0 mL) was added the olefin or alkane of interest (0.5 mmol), and the reaction mixture was stirred for 2 h at room temperature, followed by UPLC–MS analysis. If no reaction was observed, the temperature was raised to 85 °C for 2 h, and the reaction mixture was again analyzed by UPLC–MS. We found no evidence for the formation of a [3 + 2] cycloadduct for either norborne or 2-butene.

Reactions of [ReO3(tacn)]Cl in Water with Alkenes and Alkynes.

Of a [3 + 2] cycloadduct was confirmed by UPLC-Ms analysis. If no reaction was observed, the temperature was raised to 85 °C for 2 h, and the reaction mixture was again analyzed by UPLC–MS. We found no evidence for the formation of a [3 + 2] cycloadduct for either 2MBrOH or sodium 4-vinylbenzenesulfonate.

Synthesis of [(99TcO)2(tacn)](2MBrOH)Cl2.

A yellow solution of [99TcO3(tacn)]Cl (6.23 mg, 0.02 mmol) in dd-water (1.0 mL) was added 2MBrOH (4 μL, 0.04 mmol), resulting in a rapid color change to green. After stirring for 2 h at room temperature, the solvent and other volatiles were removed under high vacuum, affording [(99TcO3(tacn)](2MBrOH)Cl2 in quantitative yield. IR (cm−1): 3456s, 3412s, 3120m, 2991w, 2913w, 2845w, 2050w, 1675w, 1411w, 1484w, 1455w, 1422w, 1381w, 1356w, 1286w, 1246w, 1230w, 1174w, 1110w, 1064m, 1041m, 967s, 931m, 847m, 837m, 802w, 746w, 716w, 676w, 621w, 601w, 565w, 525w, 467w, 436v. H NMR (500 MHz, D2O): δ 8.11 (s, CH isomer 1, 1 H), 7.58 (s, CH isomer 2, 1 H), 7.37–7.22 (m, tacn, 36 H), 1.60 (s, CH isomer 1, 1 H), 1.45 (s, CH isomer 2, 3 H), 1.24 (s, CH isomer 2, 3 H). 13C NMR (125 MHz, D2O): δ 129.21 (O,CRR, 1 C), 123.94 (CH isomer 1, 2 C), 120.07 (CH isomer 1, 1 C), 57.94–45.21 (tacn, 6 C), 28.02 (CH isomer 2, 1 C), 26.98 (CH isomer 1, 2 C), 25.07 (CH isomer 2, 1 C). See Scheme 3 for a definition of isomers 1 and 2.

Crystals of [(99TcO3(tacn)](2MBrOH)Br2, suitable for single-crystal X-ray diffraction analysis were obtained by slow evaporation of an aqueous solution of the product in the presence of excess KBr.

X-ray Structure Analysis.

Crystallographic data were collected at 183(2) K with Mo Kα radiation (λ = 0.7107 Å) monochromatized with graphite on an Oxford Diffraction Xcalibur system with a Ruby detector. Suitable crystals were covered with oil (Infinum V8512, formerly known as Paratone N), mounted atop a glass fiber, and immediately transferred to the diffractometer. The Crystallography program suite was used for data collection, semiempirical absorption correction, and data analysis. The structure was solved with direct methods using SIR9244 and refined by full-matrix least-squares methods on F2 with SHELXL-201845 using the Olex2 GUI.46 The refinement was done with anisotropic thermal parameters for all non-H atoms, unless otherwise indicated. The positions of the H atoms were calculated using the “riding” atom option in SHELXL-2018. More details on data collection and structure calculations are given in Table 1 and in the crystallographic information file.

Computational Methods.

The majority of DFT calculations (including full geometry optimizations in the presence of a solvent) were carried out with the ADF 2018 program system.47 Relativistic effects were taken into account with the ZORA48 method, applied both as a scalar correction and with spin–orbit coupling at the two-component level. A parallel set of calculations were carried out with the same basis set but with a nonrelativistic Hamiltonian. Specially optimized all-electron ZORA STO-TZ2P basis sets were used throughout. A variety of exchange-correlation functionals were tested, including OLYP,50 B3LYP,51–53 PBE0,54 and OPBE.55 The potential influence of dispersion corrections was examined, and, in general, they did not make a significant difference. Our results therefore generally refer to the primitive functionals. Zero-point energy and thermal corrections (vibrational, rotational, and translational) were made to the electronic energies in the calculation of the
thermodynamic parameters. Enthalpies ($H$) and Gibbs free energies ($G$) were calculated from

\[ U = E_d + E_{\text{nucl}} \]  
(1)

\[ H = U + RT \]  
(2)

\[ G = H - TS \]  
(3)

where $U$ is the gas-phase thermodynamic energy, $E_d$ the total electronic energy, and $E_{\text{nucl}}$ the nuclear internal energy (sum of the vibrational, rotational, and translational energies and the zero-point energy correction); $R$ is the ideal gas constant, $T$ the temperature, and $S$ the entropy. $S$ was calculated from the temperature-dependent partition function in ADF at 298.15 K. Solvent effects were taken into account with COSMO (conductor-like screening model)\(^{56-58}\) as implemented\(^2\) in ADF. The type of cavity used is Esurf,\(^{60}\) and the solvent used was MeCN ($\epsilon = 37.5$; $\sigma$ = 2.76).

The Gaussian 16 program\(^1\) was used for the PBE-D2\(^{62,63}\) calculations. The basis set was 6-311G(d,p) on all nonmetal atoms and LANL2DZ with an ECP augmented with one f-polarization function on Re ($0.869$) and Tc ($1.134$). The polarizable continuum model (PCM)\(^64\) as its integral equation formalism variant (IEFPCM)\(^65\) was used for solvent (MeCN) calculations in Gaussian.

■ ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.1c00995.

Selected spectra, additional crystallographic details, and optimized DFT coordinates (PDF)

Accession Codes
CCDC 2071332 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Jeanet Conradie — Department of Chemistry, UiT—The Arctic University of Norway, Tromsø N-9037, Norway; Department of Chemistry, University of the Free State, Bloemfontein 9300, South Africa; orcid.org/0000-0002-8120-6830; Email: conradj@ufs.ac.za

Roger Alberto — Department of Chemistry, University of Zurich, Zürich 8057, Switzerland; orcid.org/0000-0001-5978-3394; Email: Ariel@chem.uzh.ch

Abhik Ghosh — Department of Chemistry, UiT—The Arctic University of Norway, Tromsø N-9037, Norway; orcid.org/0000-0003-1161-6364; Email: abhik.ghosh@uit.no

Authors

Henrik Braband — Department of Chemistry, University of Zurich, Zürich 8057, Switzerland

Michael Benz — Department of Chemistry, University of Zurich, Zürich 8057, Switzerland

Bernhard Spingler — Department of Chemistry, University of Zurich, Zürich 8057, Switzerland; orcid.org/0000-0003-3402-2016

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.inorgchem.1c00995

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grant PZ00P2_126414 of the Swiss National Science Foundation, Grant 262229 of the Research Council of Norway, and Grants 129270 and 132504 of the South African National Research Foundation to J.C.

■ REFERENCES

(1) Abram, U.; Alberto, R. Technetium and rhenium: coordination chemistry and nuclear medical applications. J. Braz. Chem. Soc. 2006, 17, 1486–1500.

(2) Eckelmann, W. C. Unparalleled Contribution of Technetium-99m to Medicine Over 5 Decades. J. Am. Coll. Cardiol. Cardiovasc. Imaging 2009, 2, 364–368.

(3) Jürgens, S.; Herrmann, W. A.; Kühn, F. E. Rhenium and technetium based radiopharmaceuticals: Development and recent advances. J. Organomet. Chem. 2014, 751, 83–89.

(4) Papagiannopoulos, D. Technetium-99m radiochemistry for pharmaceutical applications. J. Labelled Compd. Radiopharm. 2017, 60, 502–520.

(5) Pearlstein, R. M.; Davison, A. Allene—glycol interconversion with technetium and rhenium oxo complexes. Polyhedron 1988, 7, 1981–1989.

(6) Tooyama, Y.; Braband, H.; Spingler, B.; Abram, U.; Alberto, R. High-Valent Technetium Complexes with the $[^{99}\text{TcO}_3]^-$ Core from in situ Prepared Mixed Anhydrides of $[^{99}\text{TcO}_4]^-$ and Their Reactivities. Inorg. Chem. 2008, 47, 257–264.

(7) Braband, H.; Tooyama, Y.; Fox, T.; Alberto, R. Syntheses of High-Valent fac-$[^{99}\text{TcO}_3]^-$ Complexes and $[3 + 2]$ Cycloaditions with Alkenes in Water as a Direct Labelling Strategy. Chem. - Eur. J. 2009, 15, 633–638.

(8) Braband, H.; Tooyama, Y.; Fox, T.; Simms, R. F.; Forbes, J.; Valliant, J. F.; Alberto, R. fac-$[^{99}\text{TcO}_3(tacn)]^-$: A Versatile Precursor for the Labelling of Pharmacophores, Amino Acids and Carbohydrates through a New Ligand-Centred Labelling Strategy. Chem. - Eur. J. 2011, 17, 12967–12974.

(9) Ghosh, A. Electronic Structure of Corrole Derivatives: Insights from Molecular Structures, Spectroscopy, Electrochemistry, and Quantum Chemical Calculations. Chem. Rev. 2017, 117, 3798–3881.

(10) Alemayehu, A. B.; McCormick, L. J.; Vazquez-Lima, H.; Ghosh, A. Relativistic Effects on a Metal–Metal Bond: Osmium Corrole Dimers. Inorg. Chem. 2019, 58, 2798–2806.

(11) Alemayehu, A. B.; Thomas, K. E.; Einrem, R. F.; Ghosh, A. The Story of 5d Metalcorroles: From Metal-Ligand Misfits to New Building Blocks for Cancer Phototherapeutics. Acc. Chem. Res. 2021, Article ASAP. DOI: 10.1021/acs.accounts.1c00290.

(12) Alemayehu, A. B.; Vazquez-Lima, H.; McCormick, L. J.; Ghosh, A. Relativistic effects in metalcorroles: comparison of molybdenum and tungsten biscores. Chem. Commun. 2017, 53, S830–S833.

(13) Alemayehu, A. B.; Vazquez-Lima, H.; Gagnon, K. J.; Ghosh, A. Tungsten Biscores: New Chiral Sandwich Compounds. Chem. - Eur. J. 2016, 22, 6914–6920.

(14) Einrem, R. F.; Braband, H.; Fox, T.; Vazquez-Lima, H.; Alberto, R.; Ghosh, A. Synthesis and Molecular Structure of $^{99}\text{Tc}$ Corroles. Chem. - Eur. J. 2016, 22, 18747–18751.

(15) Einrem, R. F.; Gagnon, K. J.; Alemayehu, A. B.; Ghosh, A. Metal-Ligand Misfits: Facile Access to Rhenium-Oxo Corroles by Oxidative Metallation. Chem. - Eur. J. 2016, 22, S17–S20.

(16) Alemayehu, A. B.; Vazquez-Lima, H.; Gagnon, K. J.; Ghosh, A. Stepwise Deoxygenation of Nitrite as a Route to Two Families of Ruthenium Corroles: Group 8 Periodic Trends and Relativistic Effects. Inorg. Chem. 2017, 56, S285–S294.

(17) Alemayehu, A. B.; Gagnon, K. J.; Terner, J.; Ghosh, A. Oxidative Metallation as a Route to Size-Mismatched Macrocyclic Complexes: Osmium Corroles. Angew. Chem., Int. Ed. 2014, 53, 14411–14414.
(18) Thomas, K. E.; Vazquez-Lima, H.; Fang, Y.; Song, Y.; Gagnon, K. J.; Beavers, C. M.; Kadish, K. M.; Ghosh, A. Ligand Noninnocence in Coinage Metal Corroles: A Silver Knife-Edge. Chem. - Eur. J. 2015, 21, 16839–16847.

(19) Thomas, K. E.; Alemayehu, A. B.; Conradie, J.; Beavers, C. M.; Ghosh, A. Synthesis and Molecular Structure of Gold Triarylcorroles. Inorg. Chem. 2011, 50, 12844–12851.

(20) Metal oxidation states are omitted henceforth, unless essential for the purposes of clarity.

(21) Gorin, D. J.; Tost, F. D. Relativistic effects in homogeneous gold catalysis. Nature 2007, 446, 395–403.

(22) Demissie, T. B.; Garabato, B. D.; Ruud, K.; Kozlowski, P. M. Mercury Methylation by Cobalt Corrinoids: Relativistic Effects Dictate the Reaction Mechanism. Angew. Chem., Int. Ed. 2016, 55, 11503–11506.

(23) Takashima, C.; Ikabata, Y.; Kurita, H.; Takano, H.; Shibata, T.; Nakai, H. Relativistic Effect on Homogeneous Catalytic Reaction by Cationic Iridium Catalysts. J. Comput. Chem., Jpn. 2019, 18, 136–138.

(24) Dirac, P. A. M. Quantum Mechanics of Many-Electron Systems. Proc. R. Soc. London A 1929, 123, 714–733.

(25) Pitzer, K. S. Relativistic effects on chemical properties. Acc. Chem. Res. 1979, 12, 271–76.

(26) Pyykö, P.; Desclaux, J. P. Relativity and the periodic system of elements. Acc. Chem. Res. 1979, 12, 276–281.

(27) Pyykö, P. Relativistic Effects in Chemistry: More Common Than You Thought. Annu. Rev. Phys. Chem. 2012, 63, 45–64.

(28) Mews, J.-M.; Schwertfeger, P. Exclusively Relativistic: Periodic Trends in the Melting and Boiling Points of Group 12. Angew. Chem., Int. Ed. 2021, 60, 7703–7709.

(29) Pyykö, P. Theoretical chemistry of gold. Angew. Chem., Int. Ed. 2004, 43, 4412–4456.

(30) Ghosh, A.; Conradie, J. The Valence States of Copernicium and Flerovium. Eur. Eur. J. Inorg. Chem. 2016, 2016, 2989–2992.

(31) Conradie, J.; Ghosh, A. The Blue–Violet Color of Pentamethylbismuth: A Visible Spin-Orbit Effect. ChemistryOpen 2017, 6, 15–17.

(32) Demissie, T. B.; Conradie, J.; Vazquez-Lima, H.; Ruud, K.; Ghosh, A. Rare and Nonexistent Nitrosyls: Periodic Trends and Relativistic Effects in Ruthenium and Osmium Porphyrin-Based [MNO] Complexes. ACS Omega 2018, 3, 10513–10516.

(33) Pershina, V.; Ilić, M. Carboxyl compounds of Tc, Re, and Bh: Electronic structure, bonding, and volatility. J. Chem. Phys. 2018, 149, 204306.

(34) Conry, R. R.; Mayer, J. M. Oxygen atom transfer reactions of [3 + 2] Cycloadditions. Chem. - Eur. J. 2009, 15, 633–638.

(41) Herrmann, W. A.; Roesky, P. W.; Kühn, F. E.; Scherer, W.; Kleine, M. Heterolyse von ReO3− Erzeugung und Stabilisierung des Kations [ReO4]2−. Angew. Chem. 1993, 105, 1768–1770.

(42) Wieghardt, K.; Pomp, C.; Nuber, B.; Weiss, J. Syntheses of [LRe(CO)3]+ and [LRe(NO)(CO)2]2+ and their oxidative decarboxylation product [LReO3]−. Crystal structure of [LReO3]Cl (L = 1,1,1-triaza-4,7-cyclononane). Inorg. Chem. 1986, 25, 1659–1661.

(43) CrysAlisPro Software System; version 171.32; Oxford Diffraction Ltd.: Oxford, UK.

(44) Almonte, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Molterini, A. G. G.; Polidori, G.; Spagna, R. SIR97: A new tool for crystal structure determination and refinement. J. Appl. Crystallogr. 1999, 32, 115–119.

(45) Sheldrick, G. M. Crystal Structure Refinement with SHELXL. Acta Crystallogr., Sect. C. Struct. Chem. 2015, C71, 3–8.

(46) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLE2X: a complete structure solution, refinement and analysis program. J. Appl. Crystallogr. 2009, 42, 339.

(47) te Velde, G.; Bickelhaupt, F. M.; Baerends, E. J.; Fonseca Guerra, C.; van Gisbergen, S. J. A.; Snijders, J. G.; Ziegler, T. Chemistry with ADF. J. Comput. Chem. 2001, 22, 931–967.

(48) van Lente, E.; Baerends, E. J.; Snijders, J. G. Relativistic regular two-component Hamiltonians. J. Chem. Phys. 1993, 99, 4597.

(49) Handy, N. C.; Cohen, A. J. Left-right correlation energy. Mol. Phys. 2001, 99, 403–412.

(50) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron-density. Phys. Rev. B: Condens. Matter Mater. Phys. 1988, 37, 785–789.

(51) Becke, A. Density-functional exchange-energy approximation with correct asymptotic behaviour. Phys. Rev. A: At., Mol. Opt. Phys. 1988, 38, 3098–3100.

(52) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. Results Obtained with the Correlation Energy Density Functionals of Becke and Lee, Yang and Parr. J. Chem. Phys. Lett. 1989, 157, 200–206.

(53) Perdew, J. P.; Ernzerhof, M.; Burke, K. Rationale for mixing exact exchange with density functional approximations. J. Chem. Phys. 1996, 105, 9982–9985.

(54) Adamo, C.; Barone, V. Toward reliable density functional methods without adjustable parameters: The PBE0 model. J. Chem. Phys. 1999, 110, 6158–6170.

(55) Schwart, M.; Ehlers, A. W.; Lammertsma, K. Performance of the OPBE exchange-correlation functional. Mol. Phys. 2004, 102, 2467–2474.

(56) Klatt, A.; Schüttmann, G. COSMO: A New Approach to Dielectric Screening in Solvents with Explicit Expressions for the Screening Energy and Its Gradient. J. Chem. Soc., Perkin Trans. 2 1993, 799–805.

(57) Klatt, A. Conductor-like Screening Model for Real Solvents: A New Approach to the Quantitative Calculation of Solvation Phenomena. J. Phys. Chem. 1995, 99, 2224–2235.

(58) Klatt, A.; Jonas, V. Treatment of the outlying charge in continuum solvation models. J. Chem. Phys. 1996, 105, 9972–9981.

(59) Pye, C. C.; Ziegler, T. An implementation of the conductor-like screening model of solvation within the Amsterdam density functional package. Theor. Chem. Acc. 1999, 101, 396–408.

(60) Pascual-Ahuir, J. L.; Silla, E.; Tuñón, I. GEPOL: An improved description of molecular surfaces. III. A new algorithm for the computation of a solvent-excluding surface. J. Comput. Chem. 1994, 15, 1127–1138.

(61) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. J.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidio, F.; Goings, J.; Pinaud, O.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.
Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Ochterski, J. W.; Fox, D. J. Gaussian 16, revision C.01; Gaussian, Inc.: Wallingford, CT, 2016.

(62) Perdew, J. P.; Burke, K.; Ernzerhof, M. Generalized gradient approximation made simple. Phys. Rev. Lett. 1996, 77, 3865−3868; Errata: Phys. Rev. Lett. 1997, 78, 1396−1396.

(63) Grimme, S. Semiempirical GGA-type density functional constructed with a long-range dispersion correction. J. Comput. Chem. 2006, 27, 1787−1799.

(64) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. J. Phys. Chem. B 2009, 113, 6378−6396.

(65) Skyner, R. E.; McDonagh, J. L.; Groom, C. R.; van Mourik, T.; Mitchell, J. B. O. A review of methods for the calculation of solution free energies and the modelling of systems in solution. Phys. Chem. Chem. Phys. 2015, 17, 6174−6191.