[3+2] versus [2+2] Addition of Metal Oxides Across C=C Bonds. Reconciliation of Experiment and Theory

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ABSTRACT

The reaction of a metal oxide with a double bond is the initial step in the osmium-catalyzed *cis*-dihydroxylation of olefins. The mechanism of the addition of osmium tetraoxide and rhenium(VII) oxides across C=C bonds was controversial. Early work indicated a [3+2] addition, and later kinetic studies suggested an initial [2+2] addition, whereas recent quantum-chemical calculations showed the [3+2] addition to be favored. Experiment and theory have now become reconciled. In this Account, we discuss recent contributions to the mechanistic debate as well as future challenges.

Addition of Osmium Tetraoxide Across C=C Bonds

Transition-metal-complex-mediated oxygen-transfer reactions are of considerable importance in chemistry, both in the industrial arena and under laboratory conditions. The *cis*-dihydroxylation of olefins using osmium tetraoxide[1,2] is a prominent example which gives hydrocarbons with vicinal functional groups from readily accessible starting materials. The presence of a transition metal agent implies the use of homogeneous catalysis. Improved methods such as biphasic catalytic systems and immobilization techniques combine a high selectivity and relatively mild reaction conditions with a good separability of catalyst and product. Up to two stereogenic centers can be generated in a single reaction. The *cis*-dihydroxylation of prochiral olefins using osmium tetraoxide as catalyst together with asymmetric amine ligands as chiral auxiliaries shows a very high enantioface selectivity. The importance of the reaction is demonstrated by the fact that the 2001 Nobel Prize[3] in Chemistry was awarded for the development of chirally catalyzed oxidation reactions.

Figure 1 shows a catalytic cycle of *cis*-dihydroxylation mediated by osmium tetraoxide.[2,4] The reaction was discovered by Hoffmann[5] in 1912. In the late 1930s at Marburg, Criegee[6] developed the amine ligand-assisted reaction. Sharpless and co-workers employed chiral amines, thus achieving asymmetric dihydroxylation.[7] Since this breakthrough in the early eighties, the reaction has been further developed with recent contributions from the Beller,[8] Bäckvall,[9] Choudary,[10] Jacobs,[11] and Sharpless[12] laboratories toward an improvement of the catalytic oxidation chain and methods of catalyst immobilization. A recent highlight is also the catalytic oxidative C=C cleavage method using osmium tetraoxide, as reported by the Borhan group.[13]

Given the common use of the *cis*-dihydroxylation reaction in state-of-the-art chemical synthesis, it is some-

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Gernot Frenking studied chemistry at the universities Aachen, Kyoto, and TU Berlin, where he received his Ph.D. in 1979. After obtaining his Habilitation in Theoretical Organic Chemistry at the TU Berlin in 1984, he moved to the USA. Following one year as a visiting scientist in the group of Professor Henry F. Schaefer, III, at the University of California (Berkeley), he became a senior scientist at the Stanford Research Institute (SRI International) in Menlo Park, California. In 1989 he returned to Germany and became an Associate Professor for Computational Chemistry at the Philipps Universität Marburg. In 1998 he was appointed Full Professor for theoretical chemistry. His current research interests lie in the field of theoretical inorganic chemistry. Major topics are the nature of the chemical bond in inorganic compounds, particularly in transition metal complexes, and reaction mechanisms of transition metal catalyzed reactions.
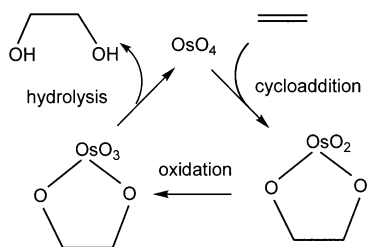
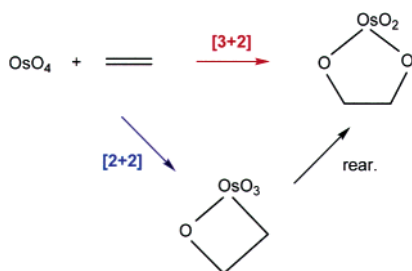**FIGURE 1.** Example of a primary catalytic cycle of *cis*-dihydroxy-lation.

FIGURE 2. Concerted (top) vs stepwise (bottom) formation of the formation of the five-membered metallacycle (metalla-2,5-dioxolane).

what astonishing that its fundamental mechanism remained unclear for several decades. Böeseken[14] proposed in 1922 a concerted [3+2] pathway where an O=Os=O moiety adds across the C=C bond (Figure 2, top). The formal product of the [3+2] addition, a five-membered metallacycle (osma-2,5-dioxolane), was experimentally characterized; its hydrolysis gives the diol.[1] The concerted [3+2] mechanism was challenged in 1977: Sharpless and co-workers[15] postulated a stepwise mechanism via a cyclic organometallic intermediate (metalla-2-oxetane) in the reaction of chromyl chloride (CrO$_2$Cl$_2$) with olefins as well as in the related reaction of osmium tetraoxide. According to this suggestion, the intermediate four-membered metallacycle (metalla-2-oxetane) is formed via [2+2] addition of an Os=O functionality across the C=C bond. Then the intermediate rearranges to the five-membered metallacycle (Figure 2, bottom). Evidence for this stepwise mechanism was provided by non-linear Eyring plots of enantioselectivity as a function of the reciprocal of temperature for asymmetric dihydroxylations.[16] However, Corey[17,18] and others supported a Michaelis−Menten kinetics with an initial metal coordination of the olefin and subsequent [3+2] addition.

The controversy about the reaction mechanism of the OsO$_4$ addition to olefins was finally solved with the help of modern quantum chemical methods. Due to improved methods and steadily increasing computational resources, computational chemistry is now an important tool for the clarification of reaction mechanisms involving transition metal compounds.[19] Geometric structures and energies of transition states can be calculated. Not only the rate-determining event but the entire profile of a multiple-step mechanism can be considered. Alternative mechanisms can be compared with each other. Insight into the origin of activation barriers can be gained by the analysis of the electronic structure of transition states.

In 1996 and 1997, three independent groups presented quantum chemical results on the reaction mechanism of the reaction of OsO$_4$ with ethylene. Frenking,[20] Morokuma,[21] Ziegler,[22] and co-workers gave the answer to the long-standing question in unison. The activation energy of the [2+2] addition is calculated to be very high (>39 kcal/mol), whereas the activation energy for the [3+2] addition is much smaller (<10 kcal/mol), indicating that the reaction follows the concerted [3+2] mechanism. The Houk, Sharpless, and Singleton[23] laboratories compared computed and measured kinetic isotope effects and corroborated the concerted reaction course.

Addition of Rhenium(VII) Oxides Across C=C Bonds

The experimental and theoretical characterization of the [3+2] transition state for the addition of OsO$_4$ oxide to simple olefins[23] is not yet the end of the story. There are other substrates and other metal oxides, for which similar reactions were investigated, aiming at the replacement of the volatile, toxic, and expensive osmium tetraoxide by alternative oxidants. Rhenium is adjacent to osmium in the periodic table. Herrmann and co-workers[24,25] showed that rhenium(VII) compounds are highly active oxygen-transfer catalysts. Gable et al.[26] reported that pentamethyl cyclopentadienyl trioxorhenium(VII) (Cp*ReO$_3$) only reacts with strained olefins, leading to the five-membered metallacycles. In the case of unstrained olefins, cycloreversion of the metallacycles giving Cp*ReO$_3$ and the olefin was observed.

In the mid-1990s, Gable and co-workers[27−29] presented a series of kinetic studies on the mechanism of these reactions. A homolytic cleavage of a C−O bond upon cycloreversion was shown to be unlikely because of the high stereospecificity of the reaction, even when metalla-2,5-dioxolanes derived from styrene or cycloalkenes were investigated. This argument together with similar activation barriers measured in different solvents and a relatively small Hammett ρ value of 0.48 in the cycloreversion of para-substituted 3-phenyl-metalla-2,5-dioxolanes[29] indicated that a heterolytic cleavage of a C−O bond does also not take place. The concerted [3+2] mechanism and stepwise pathways via a metalla-2-oxetane or a coordinated epoxide remained as mechanistic alternatives. Gable et al.[27] observed a considerable effect of ring strain in the C=C bond of cycloalkenes on the activation enthalpy of cycloaddition, whereas ring strain has a comparably small effect on the activation enthalpy of cycloreversion. They[27] concluded that the reaction follows a stepwise pathway via a metalla-2-oxetane. This mechanism seemed to be supported by a conformational analysis of metalla-2,5-dioxolanes, which suggested that a staggered form accelerates the fragmentation of these metallacycles, whereas an eclipsed form had been anticipated to accelerate a concerted cycloreversion.[28] From a chemist's viewpoint, these kinetic studies[27−29] belong to the highlights of the research field.
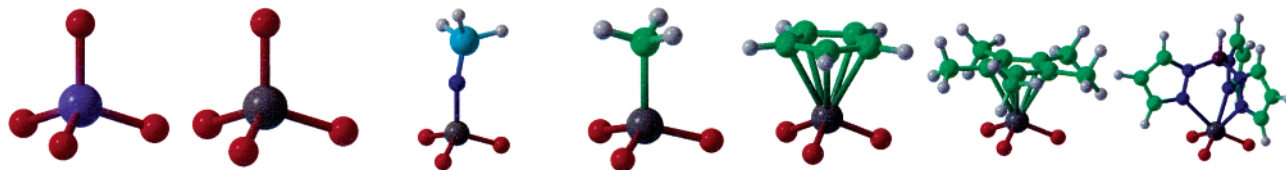
FIGURE 3. Metal oxides of the type LMO$_3$ used in a systematic quantum chemical study. OsO$_4$, ReO$_4^-$, (H$_3$PN)ReO$_3$, MeReO$_3$, CpReO$_3$, Cp*ReO$_3$, and TpReO$_3$.
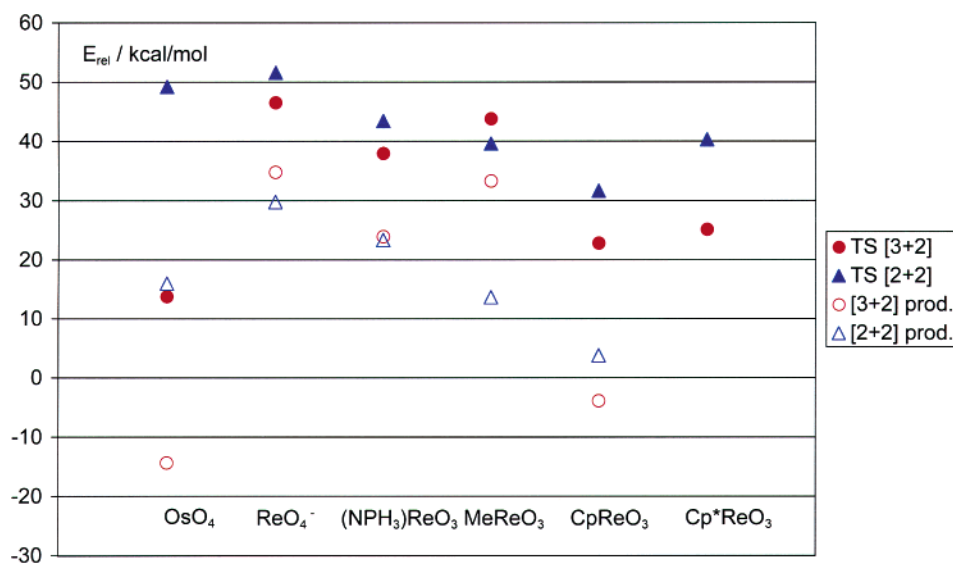

FIGURE 4. Calculated activation energies (filled symbols) and reaction energies (empty symbols) for the [3+2] and [2+2] addition of metal oxides to ethylene. Data compiled from refs 31 and 32.

However, the mechanistic proposal was again challenged by quantum chemical calculations. The Rappé group[30] and others[31,32] investigated the addition of metal oxides to ethylene using density functional theory (DFT). To gain a more complete view, a series of metal oxides shown in Figure 3 was considered, connecting OsO$_4$ and Cp*ReO$_3$ in a logical manner. Figure 4 displays the theoretically predicted activation energies (filled symbols) and reaction energies (empty symbols) for the [3+2] and [2+2] addition of the metal oxides to ethylene.[31,32] The energies were calculated at the B3LYP level of theory, which is a Hartree−Fock density-functional-theory (DFT) hybrid functional. Differences between the structures and energies calculated at B3LYP and other DFT levels are small. The most challenging task is apparently to predict the relative energy of the [3+2] products, where considerable method and basis-set effects were observed. Relative energies of selected structures investigated at B3LYP show a good agreement with those at the highly correlated CCSD(T) ab initio level.[32]

The calculations show that, in contrast to the reaction of OsO$_4$, the [2+2] and [3+2] barriers for the isoelectronic perrhenate (ReO$_4^-$), phosphoraneiminatotrioxo rhenium (VII) (NPH$_3$ReO$_3$), and methyltrioxo rhenium(VII) (MeReO$_3$) are very high but comparable in energy. It is interesting to note that, in case of MeReO$_3$, the [2+2] barrier becomes slightly lower than the [3+2] barrier. Are these metal oxides appropriate models for Cp*ReO$_3$, and do the theoretical investigations thus confirm the experimental
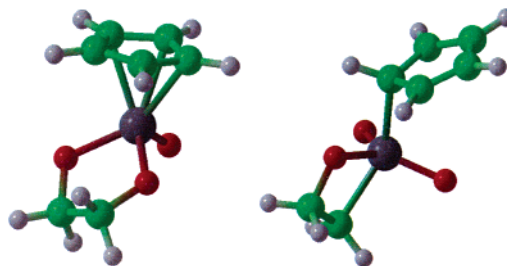

FIGURE 5. Cyclopentadienyl (Cp) as a stereoelectronic mediator that can adopt η^3 (left) and η^1 (right) binding modes as well.

suggestion of a [2+2] pathway? Calculation of the CpReO$_3$ reaction shows that the [2+2] barrier remains high, whereas the [3+2] transition state is strongly stabilized in comparison with that of MeReO$_3$.[32] The calculated transition structures revealed an explanation for the somewhat surprising result. While the methyl substituent shows the η^1 binding mode, Cp is a stereoelectronic mediator which can adopt η^5, η^3, and η^1 bonding modes. The bonding mode η^5 was observed in the reactant, η^3 in all [3+2] structures, and η^1 in all [2+2] structures (Figure 5).[31] The investigation of the Cp*ReO$_3$ system was computationally demanding, so only selected structures were considered. The calculations revealed a smaller tendency of Cp* to the η^1 coordination mode and thus a destabilization of the [2+2] pathway relative to that of the cyclopentadienyl system. These studies lead to the con-
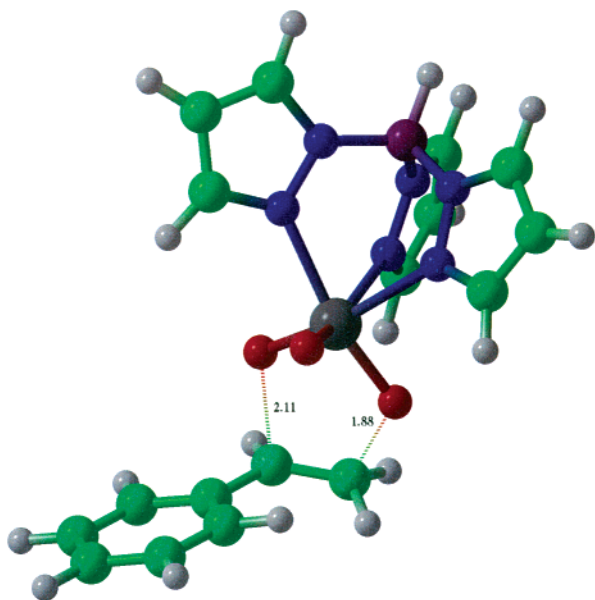
FIGURE 6. Calculated transition structure for the [3+2] addition of TpReO$_3$ to styrene, showing a large extent of asymmetry. Interatomic distances in Å. Cf. ref 33.

clusion that Cp*ReO$_3$ reacts with simple olefins via the concerted [3+2] mechanism.[31,32]

Gable and co-workers[33] recently accomplished a reconciliation of experiment and theory. [(Tris(3,5-dimethylpyrazolyl) hydridoborato] trioxo rhenium(VII) (Tp'ReO$_3$)[34] was chosen as the metal oxide in studies of cycloreversion because its derivatives have been used as catalysts for the deoxygenation of epoxides in the presence of phosphines as oxygen acceptors.[35] Catalytic systems based on the corresponding Cp* compounds are deactivated by the formation of oligonuclear complexes.[36] Kinetic isotope effects indicated a highly asynchronous cleavage in the cycloreversion of the metalla-2,5-dioxolanes, which could have pointed toward a stepwise mechanism. However, Gable et al.[33] also presented a quantum chemical analysis of the transition state. This remarkable [3+2] transition structure is displayed in Figure 6. It shows a large extent of asymmetry, with the C–O distance to the terminal carbon of styrene (1.88 Å) being much shorter than the C–O distance to the vicinal carbon (2.11 Å). Asynchronous transition states of other oxygen-transfer reactions were recently discovered, for instance, in the epoxidation of butadiene with organic and inorganic peroxides.[37,38] The *cis*-dihydroxylation of olefins by permanganate was computationally shown by Houk and Strassner[39] to follow a concerted [3+2] mechanism, with asymmetric transition states predicted in the case of α,β-unsaturated carboxylic acids.[40,41] Inspection of the frontier-orbital coefficients of the substrate rationalizes the asynchronous formation of two C–O bonds with π-conjugated double bonds.[42] This concept seems to be generally applicable to regioselectivity issues in organometallic catalysis.[43] Finally, studies by Limberg[44,45] and by Torrent and Ziegler[46,47] about the reaction of chromyl chloride (CrO$_2$Cl$_2$) and permanganyl chloride (MnO$_3$Cl) with C=C bonds should be mentioned, which indicate a variety of reaction paths including olefin
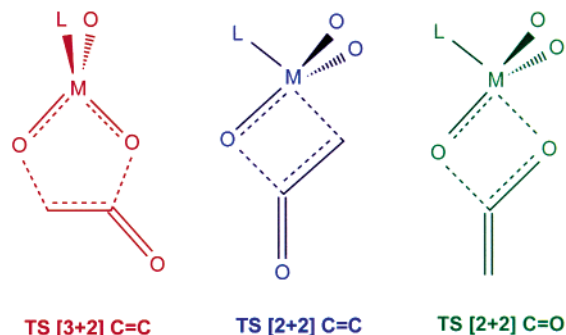

FIGURE 7. Multiple reaction paths in metal oxide additions to ketene, represented by their transition states. Both the metal M and the ligand L have a strong effect on the peri- and chemoselectivity of the reaction.

epoxidation from an oxo functionality.[48] Theory and experiment showed that the [2+2] mechanism of SO$_3$ with C=C bonds is favored over the [3+2] mechanism.[49]

Future Challenges

The enantio- and diastereoselectivity in the asymmetric *cis*-dihydroxylation of olefins using osmium tetraoxide were computationally studied by the Maseras,[50] Norrby,[51] and Chapleur[52] groups using quantum chemical calculations combined with a force field (QM/MM), a transition-state force field based on quantum chemical calculations (QM → MM), and molecular dynamics simulations (MD). However, the origin of the remarkable temperature dependence of the enantioface selectivity reported by Göbel and Sharpless[16] has not been understood entirely. We hope that fully quantum mechanical calculations of the reaction profile at different temperatures using the Car–Parrinello method (CPMD)[53] will give the answer. This computationally expensive project is in progress.

Attempts to understand the origin of the [3+2] and [2+2] activation energies have accompanied the clarification of reaction mechanisms by quantum chemical calculations. One important concept is the electronic character of oxygen transfer, i.e., whether the oxidant attacks the substrate in an electrophilic or nucleophilic manner.[54] A prominent example of an experimental probe is the chemoselective oxidation of thianthrene 5-oxide suggested by Adam et al.[55] A quantum chemical probe was also recently developed. Decomposition schemes,[56–59] for example, the charge decomposition analysis (CDA),[59] reveal the relative importance of donor and acceptor interactions in the transition states and thus present a measure of the electronic character of the reaction.[60–62] The [3+2] activation energies can be elucidated using this concept: It was shown[32] that more electrophilic metal oxides are more reactive to olefins. OsO$_4$ and rhenium oxides can be electrophilic or nucleophilic, depending on the substrate. This electronic flexibility of the transition state supports Gable's[33] observation of a dichotomous behavior in Hammett studies of the cycloextrusion of para-substituted styrenes from rhena-2,5-dioxolanes. Electron-deficient and electron-releasing functionalities induce a decrease ($\rho = 1.13$) and increase ($\rho = -0.65$) of electron density at the
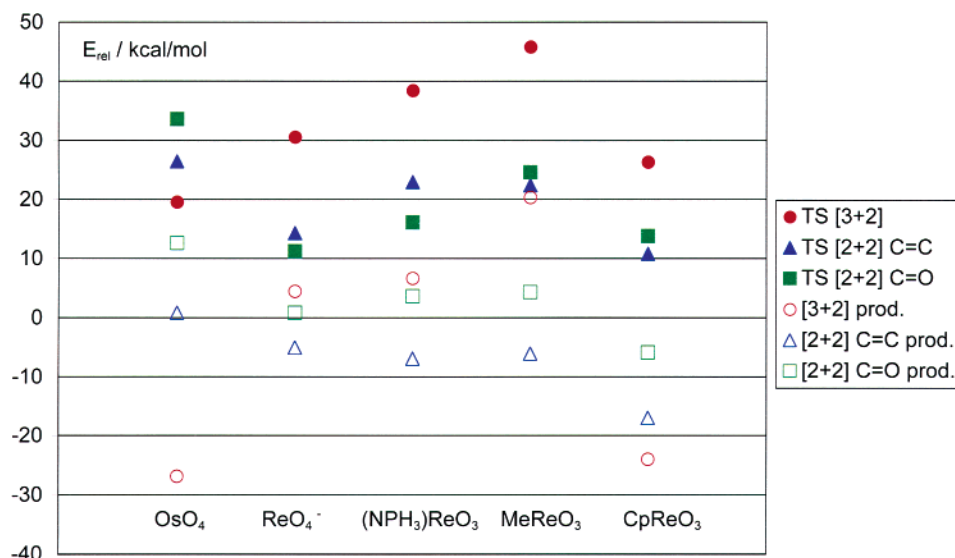
FIGURE 8. Calculated activation energies (filled symbols) and reaction energies (empty symbols) for the [3+2] and [2+2] addition of metal oxides to ketene. Data compiled from ref 32.

reaction center, respectively. Gisdakis and Rösch[63] successfully predicted the [3+2] barriers of metalla-analogous cycloadditions from thermodynamic data using Marcus theory. In contrast, a rational approach to the [2+2] barriers is more difficult. Here, the electronic character measured by orbital interactions provides limited insight. This can be understood by the fact that a [2+2] addition of a metal oxide with a C=C bond is charge-controlled rather than orbital-controlled.[64]

The question as to whether there is any [2+2] addition of a metal oxide of the type LMO_3 across a C=C bond is intriguing. One idea is to consider a specifically activated substrate. Due to its unique electronic structure, ketene is prone to undergo [2+2] cycloadditions. Note that the carbonyl moiety of ketene is not an innocent bystander but actively mediates a Hückel topology in the transition state.[65] Given the industrial importance of [2+2] reactions of organic molecules with the heterocumulene,[66] mechanistic studies of metal-oxide additions to ketenes are not only of academic interest. Recent mechanistic density functional calculations[32] on the peri-, chemo-, stereo-, and regioselectivity in the reaction of OsO_4 and $LReO_3$ with ketene predict a variety of reaction paths shown in Figure 7, with the thermodynamic preference frequently differing from the kinetic preference. Osmium tetraoxide again favors the [3+2] pathway, whereas the [2+2] barriers are predicted to be lowest for the rhenium oxides (Figure 8). The [2+2] addition across the C=O moiety is competitive to the [2+2] addition across the C=C moiety, in particular when rhenium oxides of the $LReO_3$ type with hard ligands L are involved.[32] However, reactions of metal oxides with phenylketenes might loose their concertedness; further experimental studies are in progress. Furthermore, a competing diradical pathway was recently discussed by Ujaque et al.[67] in the dihydroxylation of protoanemonin, an olefin having a diradical mechanism in the Diels–Alder reaction.

Potential biological targets of metal oxides are the C=C bonds of the nucleobases. Earlier experimental work[68,69]

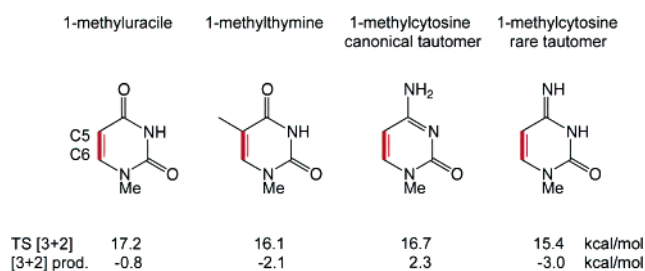|	1-methyluracile	1-methylthymine	1-methylcytosine canonical tautomer	1-methylcytosine rare tautomer	
TS [3+2]	17.2	16.1	16.7	15.4	kcal/mol
[3+2] prod.	-0.8	-2.1	2.3	-3.0	kcal/mol

FIGURE 9. Pyrimidine bases as potential biological targets of osmium tetraoxide. [3+2] activation and reaction energies taken from ref 70.

showed a reactivity of OsO_4 toward the C5=C6 bonds of pyrimidine nucleotides, particularly thymidine derivatives, thus implying the chemical recognition of DNA mismatch by using metal oxides. Quantum-chemical calculations[70] reveal considerable differences in the thermodynamics of the osmylation of 1-methyl-protected pyrimidine derivatives, whereas similar activation energies of approximately 15 kcal/mol are predicted for the [3+2] addition of osmium tetraoxide to these substrates (Figure 9). The reaction with the rare N4-imino tautomer of 1-methylcytosine shows the smallest activation energy.[70] In contrast, the reaction of metal oxides with the C4=C5 bond of purines would involve an expensive breakdown of a fused aromatic system.

Current research also focuses on the chemistry of superheavy metal oxides. The first chemical characterization of the group-8 transactinide-element hassium by the synthesis of its tetraoxide[71] raised the question as to whether the chemistry of a 5d transition metal and that of its 6d transactinide congener are similar or different. The similarity of the adsorption enthalpies of OsO_4 (−9 kcal/mol) and HsO_4 (−11 kcal/mol) on silicon nitride surfaces determined via an elaborated technique provides valuable insight.[71] However, the consideration of adsorption enthalpies does not ultimately convince a chemist. While the experimental investigation of the chemistry of

superheavy elements is difficult because the elements are produced via nuclear fusion on a one-atom-per-time scale and the isotopes decay rapidly, state-of-the-art relativistic quantum chemistry conquers the lower blocks of the periodic table more readily.[72,73] Ongoing work aims to predict the mechanism of the addition of recently reported hassium[71] and bohrium[74] oxides to ethylene, and a comparison with the chemistry of the lighter metal oxides seems interesting.

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