Oxygen Activation

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Structures of Transition States in Metal-Mediated O_2-Activation Reactions**

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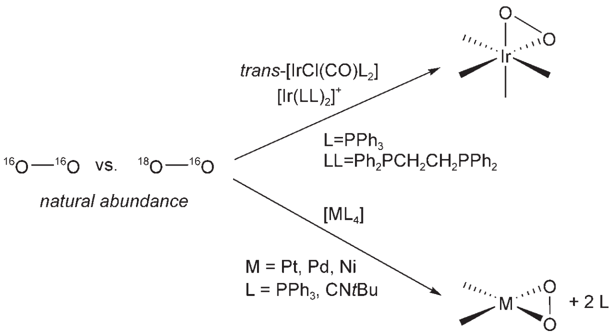
Enrichment of heavy oxygen (^{18}O) from its level at natural abundance is widely used to probe O_2-dependent processes in the atmospheric and biological sciences.[1–4] Here we describe the first application of this technique to O_2-binding reactions of classic inorganic compounds. Competitive ^{18}O kinetic isotope effects (KIEs)[5–7] reflecting the ratio of second-order rate constants for the formation of η^2-peroxide compounds from $^{16,16}O_2$ and $^{18,16}O_2$ ($k_{16,16}/k_{18,16}$) have been determined (Scheme 1). Related measurements on enzymatic reactions[4,8–11] have been interpreted on the basis of equilibrium isotope effects (EIEs) and simple models that neglect variations in the transition-state structure. The present studies suggest that the proposed enzyme mechanisms may need to be reevaluated in light of the sensitivity of ^{18}O KIEs to changes in the height of the free-energy barrier for reactions involving the formation of a metal–O_2 bond.



Scheme 1. Competitive ^{18}O isotope effect on the formation of η^2-peroxo complexes.

Oxygenation of solutions prepared from *trans*-[IrCl(CO)-$(PPh_3)_2$], [Ir(dppe)$_2$]Cl, [Pt(PPh_3)$_4$], [Pd(PPh_3)$_4$], [Ni(PPh_3)$_4$], and [Ni(CN*t*Bu)$_4$] (PPh_3 = triphenylphosphine, dppe = 1,2-bis(diphenylphosphino)ethane, CN*t*Bu = *tert*-*n*-butylisocya-

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nide) affords the corresponding η^2-peroxides $[IrCl(CO)O_2(PPh_3)_2]$, $[IrO_2(dppe)_2]Cl$, $[PtO_2(PPh_3)_2]$, $[PdO_2(PPh_3)_2]$, $[NiO_2(PPh_3)_2]$, and $[NiO_2(CN\textit{t}Bu)_2]$.[12–16] On the basis of early studies on *trans*-$[IrCl(CO)(PPh_3)_2]$ and $[Pt(PPh_3)_4]$,[13,14] concerted oxidative-addition mechanisms have been proposed in which two electrons transfer to O_2 at the same time that two metal–oxygen bonds form.[17,18]

This work describes O_2-binding mechanisms for a series of compounds in "anhydrous" *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO).[19] In most cases, high yields of stable products were obtained, as revealed by $^{31}P\{^1H\}$ and ^1H NMR as well as UV/Vis spectroscopy.[20] Kinetics studies were performed by monitoring the disappearance of the reduced compound (0.05–0.35 mM) upon reaction with a greater than tenfold excess of O_2, either by conventional or stopped-flow UV/Vis spectrophotometry. The irreversible formation of η^2-peroxide products on the time scale of the experiments is reported in terms of the rate constant for O_2 binding (k_{O_2}) in DMF at 25 ± 2 °C unless noted.

Depending on the stability of the reduced compounds in Scheme 1, the reaction mechanisms range from simple to complex, thus making it a challenge to probe the relative energy barriers to O_2 activation. Bimolecular kinetics observed for *trans*-$[IrCl(CO)(PPh_3)_2]$[21] and $[Ir(dppe)_2]Cl$ indicate $k_{O_2} = 0.17 \pm 0.02\,\text{M}^{-1}\,\text{s}^{-1}$ and $2.8 \pm 0.4\,\text{M}^{-1}\,\text{s}^{-1}$, respectively. The slowest reacting complex, *trans*-$[IrCl(CO)(PPh_3)_2]$, has the lowest O_2 affinity ($\Delta G_{298K} = -5.6 \pm 0.2$ kcal mol^{-1} in DMF). No sign of reversible O_2 loss could be detected for any of the other peroxide compounds examined.[22] $[Pt(PPh_3)_4]$, $[Pd(PPh_3)_4]$, $[Ni(PPh_3)_4]$, and $[Ni(CN\textit{t}Bu)_4]$ dissociate in solution to two- and three-coordinate species[14,16,23] which are oxidized 10^2–10^5 times faster than *trans*-$[IrCl(CO)(PPh_3)_2]$. In the simplest case involving a d^{10} metal, disappearance of $[Pt(PPh_3)_4]$ is first order in O_2 and the derived rate constant ($k_{O_2} = 32 \pm 8\,\text{M}^{-1}\,\text{s}^{-1}$) is independent of the PPh_3 concentration. This behavior is consistent with $[Pt(PPh_3)_3]$ being the primary reactive species.[14]

The oxidation of $[Pd(PPh_3)_4]$ is more than 10^3 times faster than that of $[Pt(PPh_3)_4]$ and exhibits more complex kinetics. The reactions are first order with respect to O_2, yet the rate constant ($k_{O_2} = 41\,100 \pm 300\,\text{M}^{-1}\,\text{s}^{-1}$) decreases in response to added PPh_3 until a limiting k_{O_2} value of $2480 \pm 130\,\text{M}^{-1}\,\text{s}^{-1}$ is reached at a PPh_3 concentration of 0.025–0.08 M. This behavior is consistent with a two-term rate law and competitive binding of O_2 to $[Pd(PPh_3)_2]$ and $[Pd(PPh_3)_3]$ (Scheme 2). The first term in the rate law simplifies to k_{O_2} for $[Pd(PPh_3)_2]$ when the reduced species are present in rapid equilibrium and $k_{-1}[L] \gg k_2[O_2]$, whereas the second term gives k_{O_2} for $[Pd(PPh_3)_3]$ at high PPh_3 concentration.

Reactions of $[Ni(PPh_3)_4]$ and $[Ni(CN\textit{t}Bu)_4]$ can also be understood in terms of Scheme 2. In the absence of added PPh_3, the disappearance of $[Ni(PPh_3)_4]$ depends only slightly on the concentration of O_2. This behavior is consistent with dissociation of $[Ni(PPh_3)_3]$ in a kinetically irreversible manner caused by fast trapping of $[Ni(PPh_3)_2]$ by O_2. The addition of PPh_3 (0.15–0.34 M) causes ligand association to compete with O_2 binding and allows the determination of k_{O_2} ($230 \pm 10\,\text{M}^{-1}\,\text{s}^{-1}$) for $[Ni(PPh_3)_3]$. Spectroscopic evidence suggests that $[Ni(PPh_3)_2(DMSO)]$ is the reactive species in DMSO (see Supporting Information), where the reaction is first order in O_2 without added PPh_3, and $k_{O_2} = 3300 \pm 80\,\text{M}^{-1}\,\text{s}^{-1}$. The kinetics of the oxygenation reaction of $[Ni(CN\textit{t}Bu)_4]$ give a linear first-order plot with a nonzero *y*-intercept, which suggests that the rates of ligand dissociation and O_2 binding are comparable, that is, $k_1 \approx k_3[O_2]$. Addition of CN*t*Bu causes the intercept to approach zero but the slope, which corresponds to $k_{O_2} = 3300 \pm 150\,\text{M}^{-1}\,\text{s}^{-1}$, remains unchanged; this is consistent with $[Ni(CN\textit{t}Bu)_3]$ being the reactive species.

$$[ML_3] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [ML_2] + L + O_2 \xrightarrow{k_2} [MO_2L_2]$$

$$[ML_3] + O_2 \xrightarrow{k_3} [MO_2L_2] + L$$

$$-\frac{d[ML_3]}{dt} = \frac{k_1 k_2 [O_2][ML_3]}{k_{-1}[L] + k_2[O_2]} + k_3 [O_2][ML_3]$$

Scheme 2. Kinetic scheme for O_2 binding.

The ^{18}O KIEs for the O_2-binding reactions were determined by a method in which stable-isotope mass spectrometry is used.[1,4] Experiments were performed under conditions of intermolecular competition by introducing a substoichiometric amount of metal compound into a sealed reaction vessel containing natural-abundance O_2. Subsequent to the reaction, isolation and analysis of the O_2 remaining in solution revealed ^{18}O enrichment as a result of a faster consumption of $^{16,16}O_2$ than $^{18,16}O_2$. Data were collected at varying concentrations of metal complex to determine $k_{16,16}/k_{18,16}$ (Figure 1). The ^{18}O KIEs are independent of both the fractional O_2 consumption and the ratio of O_2 consumed per mole of reduced compound. This ratio was 1:1 in most cases but as high as 1.6 ± 0.4:1 for $[Pt(PPh_3)_4]$ and 2.3 ± 0.8:1 for $[Ni(PPh_3)_4]$ because of the catalytic oxidation of PPh_3.[15,24] The $k_{16,16}/k_{18,16}$ ratio is a competitive effect and serves as a probe of all the steps from the encounter of the metal complex with O_2 to the first kinetically irreversible step. Thus, the KIEs in this work reflect O_2 binding concomitant with reduction to peroxide (O_2^{2-}) and are independent of ligand dissociation and subsequent ligand oxidation.

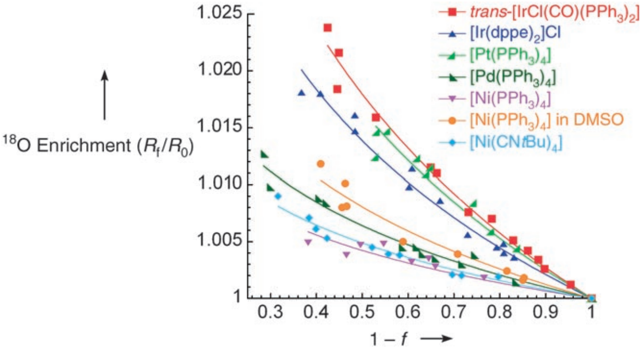

Figure 1. ^{18}O enrichment plot. Data are fitted to the equation: $R_f/R_0 = (1-f)^{((1/(k_{16,16}/k_{18,16}))-1)}$; R_0 and R_f are the $^{18}O/^{16}O$ ratios prior to reaction and at a fractional conversion (f), respectively.

The formation of η^2-peroxide compounds is characterized by $k_{16,16}/k_{18,16}$ values from 1.0069 to 1.0268 (Table 1). The ^{18}O

Table 1: Rate constants for O_2 binding and ^{18}O isotope effects ($\pm 2\sigma$) at 25 ± 2 °C.[a]

Product	k_{O_2} [$M^{-1}s^{-1}$]	$k_{16,16}/k_{18,16}$	ν_{O-O}, sym ν_{M-O}, asym ν_{M-O} ($^{16,16}\nu - {}^{18,16}\nu$) [$cm^{-1}$][f]	$(K_{16,16}/K_{18,16})_{calcd}$
trans-$[IrCl(CO)O_2(PPh_3)_2]$	0.17 ± 0.02	1.0268(37)[e]	858(24), 581(9), 595(9) [g]	1.028
$[IrO_2(dppe)_2]Cl$	2.8 ± 0.4	1.0205(36)[e]	843(25), 547(9), 533(9) [g]	1.028
$[PtO_2(PPh_3)_2]$	32 ± 7	1.0251(51)	827(23), 470(10) 488(10)	1.031
$[NiO_2(PPh_3)_2]$	>230[c]	1.0071(14)	–	1.028[h]
$[NiO_2(PPh_3)_2]$[b]	3000 ± 80[b]	1.0113(27)[b]	–	1.028[h]
$[NiO_2(CNtBu)_2]$	3300 ± 150[d]	1.0069(16)[d,e]	897(25), 560(10), 523(10)	1.026
$[PdO_2(PPh_3)_2]$	41100 ± 300	1.0093(29)[e]	877(23), 496 (10), 487(10)	1.030

[a] In DMF unless noted. [b] In DMSO. [c] k_{O_2} is a lower limit in the absence of added PPh_3 (see text). [d] [CN*t*Bu] = 0–0.088 M. [e] In DMF and DMSO. [f] Refs. [27–29]. [g] $\Delta\nu_{M-O}$ for $[RhCl(CNtBu)O_2(PPh_3)_2]$ in Ref. [28]. [h] Average of $(K_{16,16}/K_{18,16})_{calcd}$ for $[PdO_2(PPh_3)_2]$ and $[Ni(CNtBu)_2O_2]$.

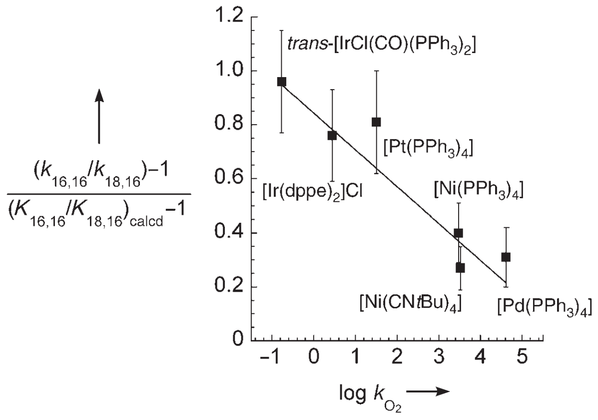

Figure 2. Isotope effects reflecting variation in transition-state structures for O_2 binding.

KIEs are larger for the O_2-binding reactions with third-row metals than for the faster reactions with first- and second-row metals. This range of values is larger than that determined for iron-, copper-, and flavin-containing enzymes, which react with O_2 according to diverse mechanisms.[4] The formation of η^2-peroxide compounds is characterized by ^{18}O KIEs that are less than the EIEs ($K_{16,16}/K_{18,16}$) calculated from Bigeleisen's formalism[25] using normal mode stretching frequencies.[26–29] Although the products are structurally quite different, they exhibit similar shifts of oxygen-isotope-dependent stretching frequencies resulting in a narrow range of $(K_{16,16}/K_{18,16})_{calcd}$ values (1.026 to 1.031; see Table 1 and Supporting Information). The average value is three times greater than that reported for the reduction of O_2 to H_2O_2 (1.0089) and previously used as a benchmark to identify metal–peroxide intermediates in enzymes and O_2-carrier proteins.[4,8–10,26]

Heavy-atom KIEs are conventionally interpreted with transition state theory and the equation, $k_{16,16}/k_{18,16} = (\nu^{\ddagger}_{16,16}/\nu^{\ddagger}_{18,16})(K^{TS}_{16,16}/K^{TS}_{18,16})$, which includes contributions from the reaction-coordinate frequency ($\nu^{\ddagger}$) and the equilibrium constant for the formation of the transition state (K^{TS}).[6] The transition states for η^2-O_2 binding are visualized in terms of structures that are intermediate between the reactant and product states, in which the O–O bond is partially weakened and two new metal–O bonds are partially formed. The results reported here support an assumption that is commonly made when interpreting mechanisms based on ^{18}O KIEs: that $\nu^{\ddagger}_{16,16}/\nu^{\ddagger}_{18,16}$ is approximately 1 and that $K_{16,16}/K_{18,16}$ is the upper limit to $K^{TS}_{16,16}/K^{TS}_{18,16}$ and therefore to $k_{16,16}/k_{18,16}$.[4–7]

For inner-sphere electron transfer (ET), in which new bonds are formed during the redox reaction, the productlike character of the transition state can be defined in terms of the ratio of the ^{18}O KIE to the EIE. The parameter $[(k_{16,16}/k_{18,16})-1]/[(K_{16,16}/K_{18,16})_{calcd}-1]$ is expected to correlate with the barrier height ($\Delta G^{\ddagger} \propto \log k_{O_2}$) when the reaction coordinate includes the reorganization of bonds involving oxygen nuclei.[5] This is precisely the behavior observed in Figure 2, which supports the proposal that the reactions examined occur by oxidative addition of O_2. Alternative mechanisms, such as those involving η^1-superoxide intermediates, are unlikely in view of a) the absence of optically detectable intermediates in the kinetics experiments and b) ^{18}O KIEs that are significantly larger than the EIEs of 1.005 reported for η^1-binding of O_2 to metalloproteins.[4,26] Although the $k_{16,16}/k_{18,16}$ ratio for *trans*-$[IrCl(CO)(PPh_3)_2]$ is very close to that reported for outer-sphere ET,[30] this mechanism can be ruled out because the value of $\Delta G°$ (44.7 kcal mol^{-1}) estimated from one-electron redox potentials[31,32] greatly exceeds the observed $\Delta G^{\ddagger}$ value (18.7 kcal mol^{-1}).

These studies show that ^{18}O KIEs are sensitive probes of transition-state structure in reactions where O_2 binds to a transition-metal center. Consistent with a productlike transition state, a value of $[(k_{16,16}/k_{18,16})-1]/[(K_{16,16}/K_{18,16})_{calcd}-1]$ close to 1 is obtained for *trans*-$[IrCl(CO)(PPh_3)_2]$, the compound which exhibits the slowest and least thermodynamically favorable reaction with O_2. This parameter decreases for the other reactions as the transition state becomes more reactant-like. These reactions are ostensibly more exothermic as k_{O_2} increases systematically over five orders of magnitude. The trend can be explained in the context of the Marcus theory of electron transfer, in which the ^{18}O KIE arises from oxygen nuclear reorganization (λ).[30] As $\Delta G°$ becomes increasingly favorable, the contribution of this term to $\Delta G^{\ddagger}$ decreases as shown in Figure 3.

In summary, competitive ^{18}O KIEs have been used for the first time to probe the binding of O_2 to inorganic compounds. All KIEs are less than the theoretical EIEs calculated from the stretching frequencies of O_2 and the structurally defined η^2-peroxo products. The ^{18}O KIEs decrease as O_2-binding rate constants increase by over five orders of magnitude. This trend indicates that all the reactions occur by the same

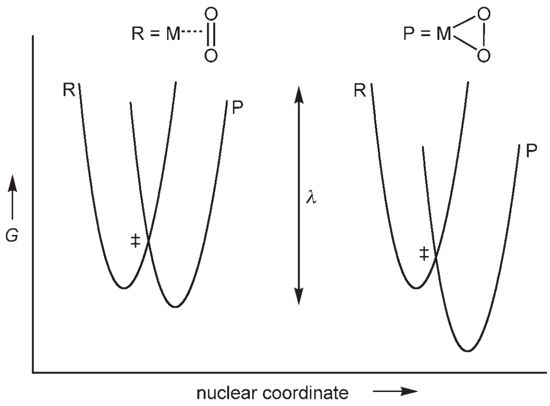

Figure 3. Model for the contribution of λ to the reaction barrier (designated ‡).

mechanism, albeit with measurable differences in the transition-state structure. The correlation of the product-like character of the transition state with the barrier height can be explained in terms of Marcus theory, where an increasingly favorable $\Delta G°$ value decreases the contribution of isotope-dependent nuclear reorganization to $\Delta G^{\ddagger}$. This property appears to differentiate reactions involving inner-sphere ET to O_2 from reactions proceeding by outer-sphere ET, in which ^{18}O KIEs appear to be relatively insensitive to the value of $\Delta G°$.[30] The highly variable ^{18}O KIEs determined in this work for a single class of metal-mediated oxidation reactions underscores the need for benchmarks and relevant models to interpret such measurements upon O_2-activation reactions of metalloenzymes.

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