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Outer-Sphere Oxidation of the Superoxide Radical Anion

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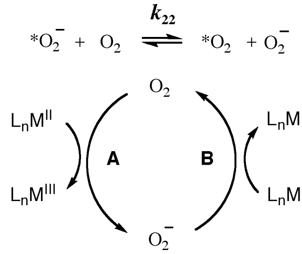
Efforts to use the Marcus model to describe oxidations of the superoxide radical anion (O_2^-) by transition-metal complexes have failed dramatically, with discrepancies between theory and experiment spanning 13 orders of magnitude. As a result, the prevailing view is that these reactions involve some complex interactions that are not yet understood. We now show that once the familiar form of the Marcus cross relation (MCR) is modified to allow for the relatively small size of O_2^-, excellent agreement is obtained between theory and experiment. This simple finding dispels the decades of uncertainty surrounding these reactions and provides a reliable method for determining whether oxidations of O_2^- occur via inner- or outer-sphere pathways. More generally, the modified MCR is applicable to any homogeneous electron-transfer process characterized by significant differences in size between electron donors and acceptors.

The superoxide radical anion is one of several reactive oxygen species present at low concentrations during the cellular metabolism of O_2. To protect against these toxic species, metalloenzymes, such as the manganese, iron, and copper/zinc superoxide dismutases, catalyze their conversion to hydrogen peroxide and O_2. This involves direct binding of O_2^- to metal ions in the active sites of these enzymes.[1] In addition, it has long been thought that O_2^- is converted directly to O_2 by outer-sphere electron transfer to transition-metal complexes, and two early reports lent indirect support for this mechanism.[2] One hallmark of such processes is their compliance with the Marcus model for outer-sphere electron transfer.[3] Indeed, O_2 oxidations of hydroquinones[2c] and phenols,[2d] and the reverse reactions, which involve reductions by O_2^-, obey the log K vs log k relationships required by the Marcus model. However, while application of the Marcus cross relation (MCR) to O_2 oxidations of metal complexes supports an outer-sphere mechanism, this has not been the case for reductions of metal complexes by O_2^-.[4]

Scheme 1



The observed rate constant, k_{22}, for electron exchange between O_2^- and O_2 in water (Scheme 1) was measured by Lind and Merényi[5a] and is 450 ± 160 M^{-1} s^{-1}. When the MCR is used to estimate k_{22} from rate data for reactions of outer-sphere electron-donor complexes with O_2 (A in Scheme 1), calculated k_{22} values are consistently 1−3 orders of magnitude too small.[4,6] Because of this consistency, the outer-sphere nature of these reactions is not questioned.[6] By contrast, when the MCR is applied to reactions of likely outer-sphere complexes with O_2^- (path B), calculated k_{22} values vary by 13 orders of magnitude.[4]

In 1993, Merényi and Lind[5b] argued that small k_{22} values calculated for reactions of *organic* donors with O_2 could be attributed to differences in size between the donors (ca. 7−13 Å in diameter) and O_2, whose O−O bond length is 1.21 Å.[7] To explain problematic reactions of superoxide with metal complexes, it has been suggested that O_2^- (O−O bond

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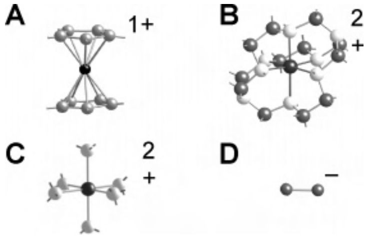

Figure 1. Scale models of representative inorganic complexes and O_2^-. Models A−C (in ball-and-stick notation, with approximate H-atom positions on C and N atoms indicated by sticks) represent (respectively) Cp_2Fe^+ (Cp = cyclopentadiene),[4,10a] $Co(sep_3)^{2+}$ (sep = sepulchrate = 1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]eicosane;[4,10bc] the dark spheres are C atoms, and the lighter ones are N atoms) and $Ru(NH_3)_6^{2+}$.[4,10d] Model D shows the relative size of O_2^- (O−O bond distance = 1.33 Å). Models A−C were created using published CIF files.[10a,c,d]

distance = 1.33 Å)[8] is specifically solvated in water, so that its effective size is much larger than that of O_2.[4,7,8] Moreover, quantum-mechanical calculations[9] argued that the self-exchange rate constant (k_{22} in Scheme 1)[5a] may be inherently unsuitable for evaluation by the MCR.

A reasonable starting point for evaluating the above proposals is to begin with Merényi and Lind's demonstration[5b,c] that differences in size (effective radii, r; Figure 1) play a significant role and to extend these arguments to reactions of O_2^-.

For this, we derived a general form of the MCR that, by algebraic addition of a single experimentally accessible term, quantitatively accounts for differences in size between electron donors and acceptors. This was then applied to data for reactions between outer-sphere donors and O_2 (path A in Scheme 1) and then to reactions between outer-sphere acceptors and O_2^- (path B).

The familiar form of the MCR is obtained by assuming that the reorganization energy of the cross reaction, λ_{12}, is the average of the reorganization energies of the individual self-exchange reactions, i.e., that $\lambda_{12} = (1/2)(\lambda_{11} + \lambda_{22})$. When $r_1 \neq r_2$, the *inner-sphere component* of the reorganization energy of the cross reaction can still be expressed as an average: $\lambda_{12(\text{in})} = (1/2)(\lambda_{11(\text{in})} + \lambda_{22(\text{in})})$. However, the outer-sphere (solvent) reorganization energies are no longer additive; i.e., $\lambda_{12(\text{out})} \neq (1/2)(\lambda_{11(\text{out})} + \lambda_{22(\text{out})})$. This is because $\lambda_{12(\text{out})}$ is a function of the radii, r_1 and r_2, respectively, of the donor and acceptor (eq 1, where η is the refractive index and D_s is the static dielectric constant).[3b]

$$\lambda_{12(\text{out})} = (ne^2)\left(\frac{1}{2r_1} + \frac{1}{2r_2} - \frac{1}{r_1 + r_2}\right)\left(\frac{1}{\eta^2} - \frac{1}{D_s}\right) \qquad (1)$$

For $r_1 \neq r_2$, a modified MCR was obtained by first defining the reorganization energy of the cross reaction as shown in eq 2, in which Δ is defined as shown in eq 3.

$$\lambda_{12} = (1/2)(\lambda_{11} + \lambda_{22} + 2\Delta) \qquad (2)$$

$$\Delta = (ne^2)\left(\frac{1}{2r_1} + \frac{1}{2r_2} - \frac{1}{r_1 + r_2}\right)\left(\frac{1}{\eta^2} - \frac{1}{D_s}\right) - \frac{1}{2}(\lambda_{11(\text{out})} + \lambda_{22(\text{out})}) \qquad (3)$$

Table 1. Radii and Rate Constants[4,6] for 14 Electron Donors

entry	electron donor[a]	effective radius[b] (Å)	k_{calc} ($M^{-1}\ s^{-1}$)	k_{obs} ($M^{-1}\ s^{-1}$)
1	$Ru^{II}(NH_3)_5phen^{2+}$	4.5	5.4×10^{-3}	7.7×10^{-3}
2	$Ru^{II}(NH_3)_5isn^{2+}$	4.5	5.8×10^{-2}	1.1×10^{-1}
3	$Ru^{II}(NH_3)_5(4\text{-vpy})^{2+}$	4.5	1.7×10^{-1}	5.7×10^{-1}
4	α-$PW_{12}O_{40}^{4-}$	5.6	9.6×10^{-1}	1.4
5	α-$SiW_{12}O_{40}^{5-}$	5.6	25	8.5
6	α-$AlW_{12}O_{40}^{6-}$	5.6	1.4×10^{2}	24
7	$Co^{II}(sep)^{2+}$	4.5	1.3×10^{2}	43
8	$Ru^{II}(NH_3)_6^{2+}$	3.4	59	63
9	$Cr^{II}(5\text{-Clphen})_3^{2+}$	6.8	9.7×10^{4}	2.5×10^{5}
10	$Cr^{II}(bpy)_3^{2+}$	6.8	3.4×10^{5}	6.0×10^{5}
11	$Cr^{II}(phen)_3^{2+}$	6.8	4.9×10^{5}	1.5×10^{6}
12	$Cr^{II}(5\text{-Mephen})_3^{2+}$	6.8	8.3×10^{5}	2.2×10^{6}
13	$Cr^{II}(4,4'\text{-}Me_2bpy)_3^{2+}$	6.8	8.1×10^{6}	1.4×10^{7}
14	$Cr^{II}(4,7\text{-}Me_2bpy)_3^{2+}$	6.8	8.1×10^{6}	2.5×10^{7}

[a] Abbreviations: phen = 1,10-phenanthroline; isn = isonicotinamide; vpy = vinylpyridine; sep = sepulchrate; bpy = 2,2′-bipyridine. [b] Except for the Keggin anions (entries **4**−**6**), these are the "radii equivalent to the sphere of equal volume" equal to $(1/2)(d_1d_2d_3)^{1/3}$, where d_1, d_2, and d_3 are the diameters of the complexes along three orthogonal axes.[11]

Equation 2 removes $\lambda_{11(\text{out})}$ and $\lambda_{22(\text{out})}$ by subtraction and, in their place, inserts eq 1. When eq 2 is used to derive the MCR (see the Supporting Information, SI), its familiar form, eq 4, is retained. Now, however, $\ln f_{12}$ and W_{12} (eqs 5 and 6) include Δ (but are otherwise unchanged).

$$k_{12} = (k_{11}k_{22}K_{12}f_{12})^{1/2}W_{12} \qquad (4)$$

$$\ln f_{12} = \frac{[\ln K_{12} + (w_{12} - w_{21})/RT]^2}{4\ln(k_{11}k_{22}/Z^2) + \left(w_{11} + w_{22} - \frac{\Delta}{2}\right)/RT} \qquad (5)$$

$$W_{12} = \exp\left[-\left(w_{12} + w_{21} - w_{11} + w_{22} - \frac{\Delta}{2}\right)/2RT\right] \qquad (6)$$

The observed rate constant, k_{22} (450 $M^{-1}\ s^{-1}$), and eqs 3−6 were used to calculate rate constants, k_{12}, for 14 reactions between inorganic complexes and O_2.[4,6] The 14 electron donors and their effective radii are listed in Table 1.

The effective radii of the donors, r_1, were used in eq 1 to calculate $\lambda_{11(\text{out})}$ values for use in eq 3. For $\lambda_{22(\text{out})}$ in eq 3 (associated with self-exchange between O_2 and O_2^-), a value of 28.5 kcal mol^{-1} was obtained from $\lambda_{22(\text{total})} = \lambda_{22(\text{in})} + \lambda_{22(\text{out})}$ by using $\lambda_{22(\text{total})} = 45.5$ kcal/mol[5a] and $\lambda_{22(\text{in})} = 17$ kcal/mol.[9] Next, a *single value* of r_2 (specific to outer-sphere reactions of O_2) was obtained by fitting calculated k_{12} values (eqs 4−6) to observed rate constants, using the unique value of r_2 as *the only adjustable variable*.

The best fit, and excellent agreement in Table 1 and Figure 2, was obtained by setting $r_2 = 2.5$ Å. This agreement not only confirms Merényi and Lind's suggestion[5b,c] regarding

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Table 2. Radii of Electron Acceptors and Relative Magnitudes of Work Terms,[a] w_{ij}, and $\Delta/2$ for Their Oxidations of O_2^-

entry	electron acceptor[b]	effective radius[c] (Å)	w_{11} (kcal mol^{-1})	w_{12} (kcal mol^{-1})	$\Delta/2$ (kcal mol^{-1})	k_{calc} (M^{-1} s^{-1})	k_{obs} (M^{-1} s^{-1})
7′	$Co^{III}(sep)^{3+}$	4.5	1.46	−1.04	2.95	2.7	8.7×10^{-1}
a	$Fe^{III}(edta)(H_2O)^-$	3.0	0.49	0.35	2.95	5.2×10^4	2.0×10^4
8′	$Ru^{III}(NH_3)_6^{3+}$	3.4	2.28	−1.35	2.19	1.7×10^5	2.0×10^5
b	$Fe^{III}Cp_2^+$	5.0	0.00	−0.56	3.30	3.8×10^6	8.6×10^6
2′	$Ru^{III}(NH_3)_5isn^{3+}$	4.5	1.46	−1.04	2.95	1.1×10^8	2.2×10^8
1′	$Ru^{III}(NH_3)_5phen^{3+}$	4.5	1.46	−1.04	2.95	1.7×10^9	3.5×10^9

[a] Work terms not listed are zero. [b] Abbreviations: edta = ethylenediamine tetraacetate; Cp = cyclopentadienyl. [c] Effective radii are calculated as in Table 1.[11]

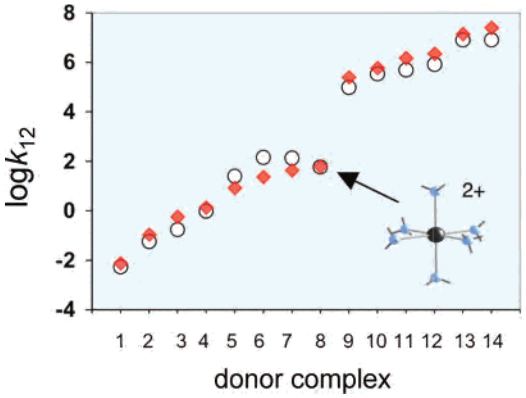

Figure 2. Observed (red diamonds) and calculated (circles) rate constants for reactions of O_2(aq) with the 14 one-electron donors in Table 1. Complex **8** is highlighted (structure and arrows) because its outer-sphere character and kinetic parameters are well established.

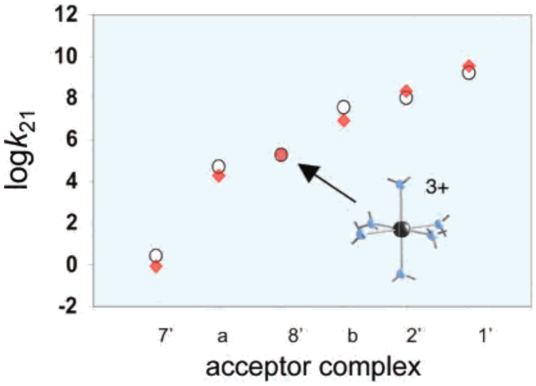

Figure 3. Observed (red diamonds) and calculated (circles) rate constants for reactions of O_2^-(aq) with the electron acceptors listed in Table 2. Complex **8′** is highlighted for the reasons given in the caption of Figure 2.

the importance of the donor size but also, for the first time, provides a reliable method (eqs 3−6) for accurately predicting rates of outer-sphere electron transfer to O_2. In addition, the effective radius, r_2 (=2.5 Å), is consistent with previously calculated values.[5a,9]

Next, the effective radius, r_2 (2.5 Å), was used in eqs 3−6 to calculate the rate constants, k_{21}, for reactions of outer-sphere inorganic complexes with O_2^-. All other parameters (including $k_{22} = 450$ M^{-1} s^{-1})[5a] were taken directly from the literature.[4] *No adjustable variables whatsoever were included.*

Of the 14 complexes listed in Table 1 and Figure 2, rate constants for reactions between four of these (i.e., the oxidized forms of **1**, **2**, **7**, and **8**) and O_2^- have been determined experimentally.[4] These obviously outer-sphere complexes were used, along with two others[4] (entries a and b; see Table 2), to give the results in Figure 3.

Given the problematic nature of reactions between metal complexes and O_2^-, the results in Figure 3 were somewhat surprising: previously calculated k_{22} values[4] for these six reactions spanned 8 orders of magnitude. (See the SI for comments on three problematic reactions: oxidations by $(Co(en)_3^{3+}$, $Fe(CN)_6^{3-}$, and $Mo(CN)_8^{3-}$.) It is appropriate to point out that Bakac and Espenson[4] studied this problem prior to Lind and Merényi's[5a] publication of an experimentally measured value for k_{22}. Without a reliable value for k_{22}, the present analysis simply could not be done.

Inspection of the functional dependence of k_{calc} on Δ (eqs 5 and 6) shows why relative size is particularly important in reactions of charged species. The correction, Δ, is linearly combined with the Coulombic work terms, w_{11}, w_{12}, and w_{21}. Hence, both W (an inverse exponential function of these sums) and f are significantly altered by inclusion of Δ (Table 2).

In conclusion, once differences in size are taken into account, rate constants for reactions between outer-sphere electron-acceptor complexes and O_2^- comply with the Marcus model. This simple finding dispels the decades of uncertainty surrounding these reactions and provides a reliable method for determining whether oxidations of O_2^- occur via inner- or outer-sphere pathways. Moreover, the excellent agreement obtained using a *single value* of r_2 in both Figures 2 and 3 implies that the hydrodynamic radius of O_2^- (at pH values well above the pK_a of HO_2) may not be substantially larger than that of O_2. More generally, eqs 3−6 apply to any homogeneous electron-transfer process characterized by significant differences in size between donors and acceptors.

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Supporting Information Available: Derivation of eqs 4−6, calculation of the results in Figures 2 and 3, w_{ij} and $\Delta/2$ for reductions of O_2 (Table S1), oxidations of O_2^- by three additional complexes, and comment on reactions of phenoxyl radicals and O_2^-. This material is available free of charge via the Internet at http://pubs.acs.org.

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