PERSPECTIVES: CHEMISTRY

Harnessing the Power of Diatomics

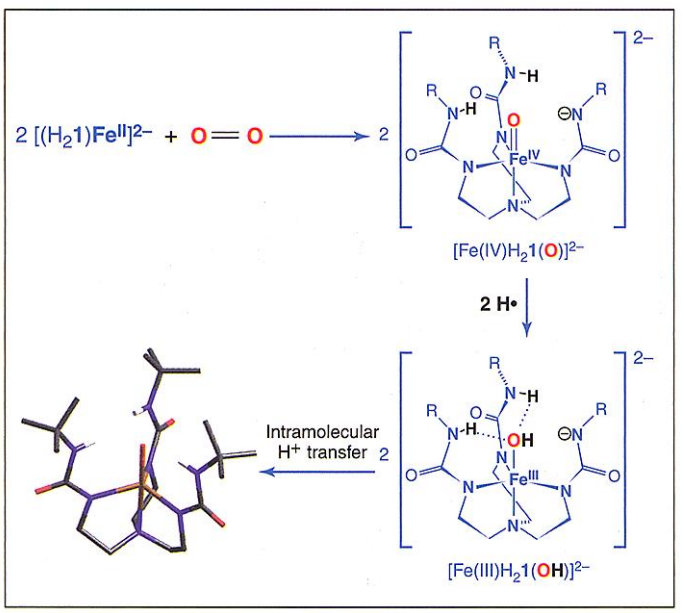
H. Holden Thorp

When a diatomic molecule is broken up into its constituent atoms, these very energetic atoms can subsequently react to form additional bonds, providing a large driving force for reaction. Diatomic molecules such as H_2, O_2, and N_2 can therefore serve as high-energy reactants. Consider, for instance, the oxidation of methane to methanol:

$$2\ H_3C{-}H + O{=}O \rightarrow 2\ H_3C{-}O{-}H$$

In this transformation, one O=O double bond and two C–H bonds are broken, and two C–O bonds and two O–H bonds are formed. The reaction has a large negative enthalpy (it releases a lot of energy), making the process favorable. Despite this potential thermochemical power, however, diatomic molecules often fail to undergo productive chemistry because the energy needed to break the diatomic bond is also high. Both synthetic and biological catalysts may be used to overcome this kinetic barrier, and these often contain transition metal ions, which react with diatomic molecules and create metal-atom bonds (*1*). These intermediates deliver one atom of the diatomic molecule to the substrate through a pathway whose kinetic barrier is lower than that of the uncatalyzed process. In this issue, MacBeth *et al.* make use of a synthetic nonheme iron complex to provide a striking example of such a reaction (*2*).

The formation of metal-atom intermediates has advantages other than simply overcoming the barrier of diatomic bond cleavage (*1*). The ancillary ligands bonded to the metal ion influence the electronic properties of the metal ion in such a way that the coordinated atom remains sufficiently reactive, a feature that inorganic chemists call "inner-sphere" effects. In addition, the microenvironment of the coordinated atom can be engineered to control the electronic and geometric interactions between the atom and additional reactants, and these are termed "outer-sphere" effects (*3*). Manipulation of both inner- and outer-sphere properties of a metal-atom moiety allows the reactivity of an atom to be tuned.



Efficient capture. In the system by MacBeth *et al.*, two iron complexes react with oxygen to form metal-oxo intermediates; these react further with abstract hydrogen atoms to form an Fe(III)-OH complex. In the final step, a proton is transferred from the hydroxo ligand to a base in the outer sphere to form the crystallographically characterized Fe(III)-oxo complex.

Several metalloenzymes react with diatomic molecules to form metal-atom intermediates. For example, the enzyme hydrogenase activates H_2 by forming metal-hydride bonds (*4*), and the enzyme nitrogenase is believed to activate N_2 through formation of metal nitrido species (*5*). The heme enzymes cytochrome P_{450} and peroxidase and the nonheme enzyme methane monooxygenase (MMO) form what are believed to be metal-oxo intermediates (*6*, *7*). These enzymes, however, form only a single metal-oxo unit from each O_2 molecule, the second oxygen atom being converted to water:

$$M^{n+} + O{=}O + 2H^+ + 2e^- \rightarrow M^{(n+2)+}{=}O + H_2O$$

The conversion of one oxygen atom of O_2 to water means that a portion of the available thermochemical power of the O_2 molecule is lost, if the goal is selective oxidation of an organic substrate. Of course, many enzymes produce water because only one metal ion is present at the active site, allowing only one metal-oxo moiety to be formed. But even enzymes with two or more metal ions often produce water because the spatial arrangement of the metal ions precludes their working in concert. A small molecule catalyst has the advantage that it can in principle capture both oxygen atoms through homogeneous reaction between two metal complexes and a O_2 molecule:

$$2M^{n+} + O{=}O \rightarrow 2M^{(n+2)+}{=}O$$

Cleaving the O–O bond of dioxygen with a nonheme iron complex is perhaps more challenging than with an iron porphyrin. This is because heme groups can form radical cations that stabilize oxidized intermediates and facilitate the cleavage step. In contrast, in nonheme enzymes, such as MMO, the metal ions must undergo redox chemistry controlled only by inductive effects from the ancillary ligands (*7*). MacBeth *et al.* now report (*2*) a nonheme iron complex that reacts with O_2 to produce two equivalents of a metal-oxo complex, which subsequently react to abstract hydrogen atoms (see the figure). In previous studies of nonheme systems, metal-oxo intermediates were implicated but not structurally characterized (*8*).

A notable feature of this system is the formation of two equivalents of the metal-oxo complex from one equivalent of O_2. MacBeth *et al.* have accomplished this goal by designing a ligand that incorporates two essential features: an appropriate set of nitrogen donor ligands to bind the iron ion (the inner sphere) and the proper microenvironment to interact with the coordinated oxygen atom (the outer sphere). In particular, the outer sphere was engineered to form hydrogen bonds between the ligand and the resulting metal-oxo group, an arrangement that has been implicated as a stabilizing factor in some enzyme active sites (*9*).

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The study by MacBeth *et al.* also represents the first structural characterization of a monomeric metal-oxo complex of iron. The complex that is isolated is not the initially formed Fe(IV) species, which results directly from splitting O_2. Rather, it is an Fe(III)-O complex that forms after transfer of a hydrogen atom to the intermediate complex (see the figure). The long Fe–O bond (1.8 Å) is consistent with an Fe(III) ion and an oxide ligand, formally O^{2-} (*10*). The ligand provides a proton acceptor in the outer sphere of the complex that participates in the net hydrogen atom transfer process and stabilizes the oxide ligand by formation of hydrogen bonds.

The question of whether hydrogen atoms are transferred intact or with concomitant partitioning into an electron and a proton has important kinetic implications (*11*). The new iron compounds of MacBeth *et al.* are particularly well suited for probing these pathways because proton acceptors are intimately involved in the outer-sphere chemistry of their reactive metal ion centers. The complexes thus elegantly mimic the ability of some enzymes to influence both inner and outer coordination spheres of a metal ion.

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12. I thank T. N. Sorrell, J. L. Templeton, M. R. Gagne, and V. A. Szalai for comments on this manuscript.

PERSPECTIVES: IMMUNOLOGY

Lymphocyte Survival—Ignorance Is BLys

Yacine Laâbi and Andreas Strasser

Members of the tumor necrosis factor receptor (TNFR) superfamily and their ligands are critical regulators of immune responses (*1*). They can be divided into two groups according to their intracellular structure and the types of signaling proteins that they activate. Death receptors (Fas, TNFR1, DR3, DR4, DR5, and DR6) contain a death domain through which they bind to adapter proteins such as TRADD (TNFR-associated death domain) or FADD (Fas-associated death domain)/MORT1, triggering apoptosis through recruitment and activation of caspase-8. Members of the other group (TNFR2, CD30, and CD40) lack a death domain. They bind TRAF (TNFR-associated factor) and activate c-Jun NH_2-terminal kinase (JNK) and the transcription factor Rel/NF-κB, thereby promoting cell survival, proliferation, and differentiation (*1*).

The functional distinction between these two groups is not absolute. Some receptors lacking death domains can trigger apoptosis by inducing the expression of membrane-anchored TNF ligand and by signaling through TNFR1 (*2*). Paradoxically, death receptors can also promote proliferation under certain circumstances. For example, TNFR1 is essential for liver regeneration after partial hepatectomy (*3*), and signaling through FADD is required for mitogen-induced T lymphocyte proliferation (*4–6*).

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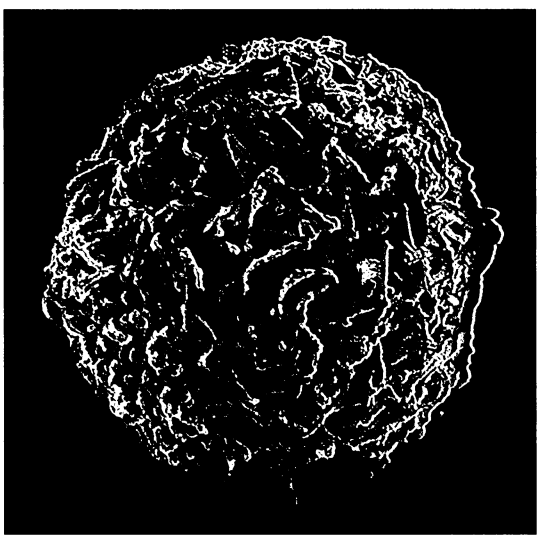
A flurry of recent papers now report that two newly identified receptors, TACI and BCMA, and their ligands BAFF/BLys (THANK/TALL-1) and APRIL (*7–11*), have joined the TNFR superfamily. These receptors and their ligands specifically regulate the survival, proliferation, and differentiation of B lymphocytes (*12–16*). Like CD40 ligand (CD40L), BAFF and APRIL promote survival of B cells, and, in collaboration with signals from the B cell antigen receptor (BCR), they also regulate their proliferation and differentiation. Both ligands are produced by monocytes, dendritic cells, and activated T cells. BAFF and APRIL are more closely related to each other than to any member of the TNF family, and each binds with high affinity to both BCMA and TACI (*12–16*). These two receptors are expressed on resting and activated B cells (*12–17*). In addition, TACI has been found on activated T cells (*18*), indicating that BAFF and APRIL may regulate T cell activity. Overexpression of BCMA activates the transcription factors Rel/NF-κB, JNK, Elk-1, and p38 kinase (*19*). When bound to its ligand, TACI activates Rel/NF-κB and NF-AT (*13–16, 18, 19*).



Scanning electron micrograph of a B cell.

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Distinct pathways leading to programmed cell death are activated through ligation of death receptors by ligand or through antigen receptor cross-linking in the absence of costimulatory signals. Fas-induced apoptosis requires FADD and caspase-8 and is not regulated by the Bcl-2 protein family (see the figure) (*4*, *20*, *21*). In contrast, apoptosis induced by ligation of BCR is mediated by different caspases and is controlled by Bcl-2 family members (*22*). Signals from antigen receptors and TNFR superfamily members synergize to promote lymphocyte proliferation and differentiation (*22*). In B cells, this is achieved (at least in part) by each signaling pathway inhibiting the proapoptotic activity of the other pathway. BCR ligation activates expression of FLIP (*23*), a competitive inhibitor of caspase-8 that blocks death receptor–induced apoptosis (*24*). Conversely, ligation of CD40, TACI, or BCMA triggers expression of Bcl-2–related proteins that inhibit apoptosis induced by BCR ligation (*7–9, 22*).

The transcription factor Rel/NF-κB is essential for survival and proliferation of B cells (*25*). It is likely that Rel/NF-κB–me-