Mechanism for Antibody Catalysis of the Oxidation of Water by Singlet Dioxygen

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Recently Wentworth et al. report the surprising result that antibodies (and T-cell receptors, TCR) efficiently catalyze the conversion of molecular singlet oxygen ($^1O_2$) plus water to hydrogen peroxide (HOOH). In this paper, we use quantum chemical (QC) methods (B3LYP Density Functional Theory) to delineate the plausible mechanisms for this efficient conversion of water to HOOH. We find two reasonable pathways. In Pathway I
(a) $H_2O$ catalyzes the reaction of $^1O_2$ with a second water to form HOONO,
(b) HOONO reacts with $^1O_2$ to form HOO-HOOO,
(c) HOO-HOOO rearranges to HOOH-OOO that subsequently reacts with $H_2O$ to form two HOOH plus $^1O_2$ or $^3O_2$.
Pathway II differs in that step b is replaced with HOONO forming a dimer that decomposes to form the intermediate in c plus $H_2O$, which then proceeds to similar products. For a system with $^{18}O H_2O$, these mechanisms leads to a 3:1 ratio of $^{16}O:^{18}O$ in the product HOOH for Pathway I and 2.2:1 for Pathway II. This is in good agreement with the ratio 2.2:1 observed in isotope experiments by Wentworth et al. These mechanisms can lead to two HOOH per initial $^1O_2$ or one, depending on whether the product of step c is $^1O_2$ or $^3O_2$. This is in good agreement with the experimental result of 2.0.

We then used the QC structures for products and transition states with the HierDock docking and molecular dynamics procedure to search for sites in the antibody that would stabilize the reaction intermediates. Indeed, we find such sites in the barrel-like interface of light and heavy chains of the antibody and TCR, a structure unique to these systems.

These results provide a plausible mechanism for the chemistry and provide an explanation of the special character of antibodies responsible for this unexpected chemistry. These results suggest a number of experimental tests and provide a guideline for how to build biomimetic nanoscale systems to producing HOOH (or HOOOH).

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Figure 1. Pathways investigated for $^{1}\text{O}_2$ catalysis of H$_2$O to HOOH. The red circled numbers refer to equations in the main text.

Figure 2. Gas phase structures for various clusters and transition states discussed in Section 3
Figure 3 (a) One of the possible binding regions for HOH catalysis in the Fab. This picture shows the HOOOH dimer clustering region in purple. This is at the interface of the V_H and V_L in region 2. The ordered crystallographic waters are shown in half bonds. The yellow circled part in the inset is the magnified part in this figure. (b) A 90° rotation about the z axis shows Gln38 from V_L and Gln39 from V_H making a hydrogen bond network at the mouth of the barrel. Region A is the left region in both figures. The inset in the figure shows the barrel like structure that we find to be critical to this catalysis.