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Review Article

Rate and equilibrium constants of O_2-binding and O_2 release: "The forward and reverse steps for the ^{T}state → ^{R}state change for human Hb_4/BPG, under standard conditions"

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APPENDIX

Consecutive equivalent first order reactions

Consider a scheme of two consecutive pseudo-first-order reactions with stoichiometry given by

$$Hb_2 + O_2 \xrightarrow[\text{excess } O_2]{k_1} (HbO_2)Hb$$

$$(HbO_2)Hb + O_2 \xrightarrow[\text{excess } O_2]{k_2} (HbO_2)_2$$

The hypothetical macromolecule, Hb_2, is defined to be dimeric, each constituent monomer containing a heme moiety capable of reversibly binding a molecule of either O_2 or CO. The dimeric model is intended to be a simplified model for human hemoglobin. In the presence of excess O_2, $(HbO_2)(Hb)$ is produced as an unstable intermediate in the overall reaction given by

$$Hb_2 + 2\,O_2 \rightarrow (HbO_2)_2$$

We can write the following rate equations, understanding that the rate constants, k1 and k2, are pseudo first-order rate constants, the concentration of O_2 being much greater than the concentration of Hb_2.

$$\frac{d[Hb_2]}{dt} = -k_1[Hb_2] \equiv -k_1'[O_2][Hb_2]$$

$$\frac{d[(HbO_2))Hb]}{dt} = k_1[Hb_2] - k_2[(HbO_2)Hb] \equiv k_1'[O_2][Hb_2] - k_2'[O_2][(HbO_2)Hb]$$

$$\frac{d[(HbO_2)_2]}{dt} = k_2[(HbO_2)Hb] \equiv k_2'[O_2][(HbO_2)Hb]$$

The first of these three equations is solved by the method for a first-order equation. The equation of state for $[Hb_2]$ is

$$[Hb_2] = [Hb_2]_0 \exp(-k_1 t)$$

Substituting the value for $[Hb_2]$ into the second rate equation and rearranging, we obtain a first order linear differential equation.

$$\frac{d[(HbO_2)Hb]}{dt} + k_2[(HbO_2)Hb] = k_1[(Hb_2]_0 \exp(-k_1 t)$$

If $[(HbO_2)Hb)]0=0$, the solution for $[(HbO_2)Hb]$ is

$$[(HbO_2)Hb)] = [Hb_2]_0 \left(\left(\frac{k_1}{k_2 - k_1}\right)(\exp(-k_1 t) - \exp(-k_2 t))\right)$$

The solution for $[(HbO_2)_2]$ can be obtained directly from the mass conservation equations.

$$[Hb_2]_0 = [Hb_2] + [(HbO_2)Hb] + [(HbO_2)_2]$$

$$[(HbO_2)_2] = [Hb_2]_0 - [Hb_2] - [(HbO_2)Hb]$$

Substituting the equations of state for $[Hb_2]$ and $[(HbO_2)Hb]$ into the second mass conservation equation one obtains the equation of state for $[(HbO_2)_2]$.

$$[(HbO_2)_2] = [Hb_2]_0 \left(1 - \exp(-k_1 t) - \left(\frac{k_1}{k_2 - k_1}\right)(\exp(-k_1 t) - \exp(-k_2 t))\right)$$

With the equations of state presented above, it is possible to simulate data for each of the concentrations of the reactants in the conversion of Hb_2 to $(HbO_2)_2$.

Special considerations for models of human hemoglobin

In the case of reaction of a dimeric hemoglobin molecule with, for example, O_2, it would be normal to start with a solution free of O_2. In this case, then, the intermediate, $(HbO_2)Hb$, and the end product, $(HbO_2)_2$, are absent at t=0. The progress curve monitored at an appropriate wavelength in the O_2 difference spectrum. Such monitoring records the time dependence of all intermediates, simultaneously. The time course obtained by spectroscopic procedures, then, is directly proportional to fractional saturation of Hb_2 with O_2. The equation of state for fractional saturation of

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Hb_2 binding sites with O_2 is

$$F = \frac{[(HbO_2)Hb] + 2[(HbO_2)_2]}{2[Hb_2]_0}$$

A rate law based on fractional saturation is readily obtained by substituting the individual rate laws for $(HbO_2)Hb$ and $(HbO_2)_2$ presented above.

$$F = \frac{[Hb_2]_0 (2\exp(-k_2t) - 2\exp(-k_1t)) + 2[Hb_2]_0 (1 + \exp(-k_1t) - 2\exp(-k_2t))}{2[Hb_2]_0}$$

Factoring out common terms and combining similar quantities, the rate law reduces to a first order equation.

$$F = 1 - \exp(-k_2t)$$