THE HALDANE RELATIONSHIP ENZYMES & EQUILIBRIUM

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Many students have difficulty in distinguishing between the static equilibrium concept first encountered in chemistry A⇌B, and the dynamic equilibrium of steady-state concept usually encountered in biology A↔B⇌C⇌D↦E. If the static equilibrium A⇌B favours the formation of a large excess of B, how is it that enzymes can act to maintain a high concentration of A in the presence of low concentrations of B? Haldane[1] resolved this question when he derived the relationship between the static equilibrium constant (Keq) and the dynamic equilibrium parameters for an enzyme reaction (Km and Vmax). His relationship in its simplest form is:

$$Keq = \frac{V_f \cdot Km_b}{V_b \cdot Km_f}$$

where the subscripts f and b refer to the forward and back reactions respectively. For the derivation of this relationship the reader should consult a text-book on enzyme kinetics[2]. The usefulness of this relationship is that it enables the student to see how enzymes can evolve which can give high maximum velocities in either the forward or the backward direction within the thermodynamic constraint imposed by the equilibrium constant. This evolution is achieved by tailoring the relative sizes of the Km's for the two directions.

It is my experience that the following graphical presentation of the Haldane relationship is a help to the student. If the two velocity curves for the forward and backward velocities of an enzyme catalysis are superimposed as in Fig. 1 then

$$Keq = \frac{area \ X}{area \ Y}$$

This ratio can be maintained constant while individual maximum velocities for the forward and backward reactions (V_f and V_b) can be varied by the choice of suitable values for the Michaelis constants (Km_f and Km_b). Figures 1a and 1b represent two enzymes, both of which catalyze the reaction A⇌B for which the Keq = 3. The first enzyme (I) in figure 1a favours the forward direction over the backward direction, and so the enzyme has evolved with an appropriate ratio of Km_b/Km_f. The highest Vmax for this enzyme is therefore in the same direction as the flow towards equilibrium. Figure 1b shows the same reaction catalyzed by another enzyme (II) which has evolved to give highest maximum velocity in the direction away from equilibrium. The thermodynamic constraint, Keq, is constant as shown by the ratio of areas, but the highest maximum velocity is now in the back direction. This has been attained by the evolution of a higher Km_b/Km_f ratio than for the first enzyme.

The Michaelis constant (Km) is frequently a good measure of the "looseness" of binding of a substrate to the enzyme since it often approximates the dissociation constant of the enzyme-substrate complex. The price that is paid to attain a high maximal velocity in a given direction is in the relative "looseness" of binding of substrate and product to the enzyme. Binding of A to enzyme II is "tighter" than to enzyme I. Therefore when enzyme II is catalyzing

the reaction B → A at maximum velocity it is more susceptible to product inhibition by A than enzyme I would be under similar conditions. The importance of the continual removal of inhibitory products (excretion) and the continual supply of substrate (nutrition) to the maintenance of the steady-state in biology can be presented to students in a fresh way through illustration of the Haldane relationship.

REFERENCES

[1] Haldane, J. B. S., "Enzymes", Longmans, London, 1930, p. 80.

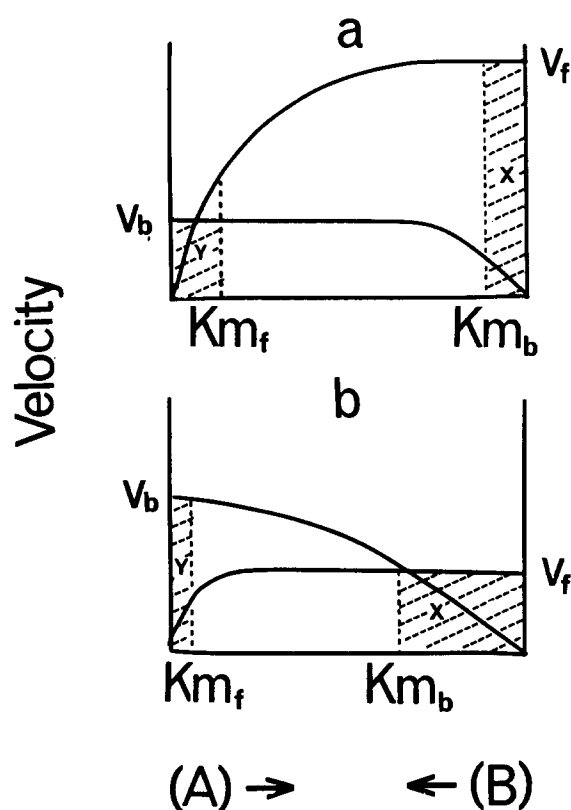[2] Plowman, K. M., "Enzyme Kinetics", McGraw-Hill, New York, 1973.

Figure 1. Superimposed velocity curves for two enzymes (I and II) catalyzing the same reaction A⇌B for which the equilibrium constant Keq = 3.0. Fig. 1a shows enzyme I which gives a higher maximum velocity towards static equilibrium and figure 1b shows enzyme II which gives a higher maximum velocity away from static equilibrium.

Metabolic Pathways Chart, 1976

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The dedication of the author to his chosen task and the generous support by the sponsors has led to an attractive colourful production which will adorn the walls of many laboratories and offices and serve as an invaluable source of information.

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