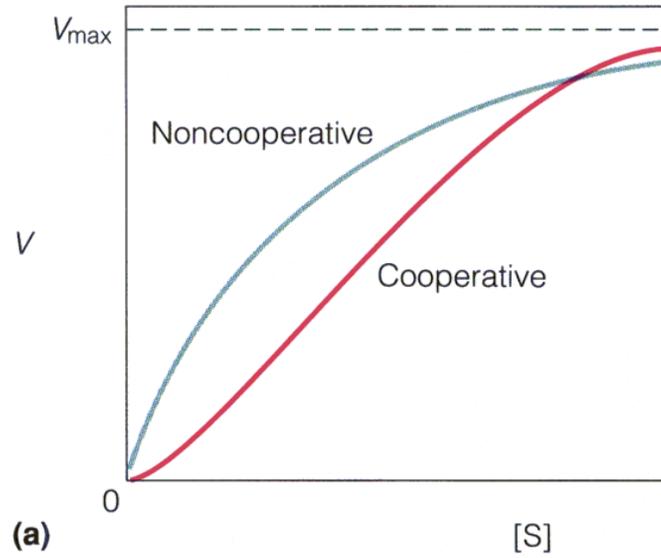
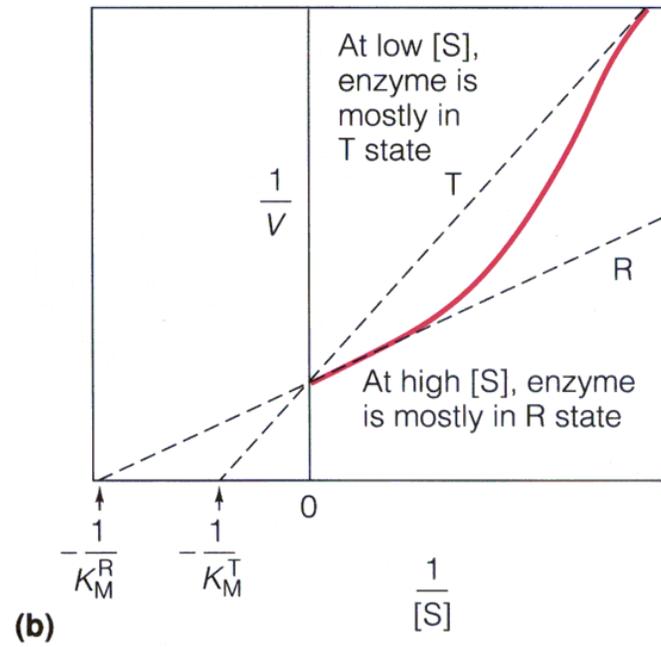


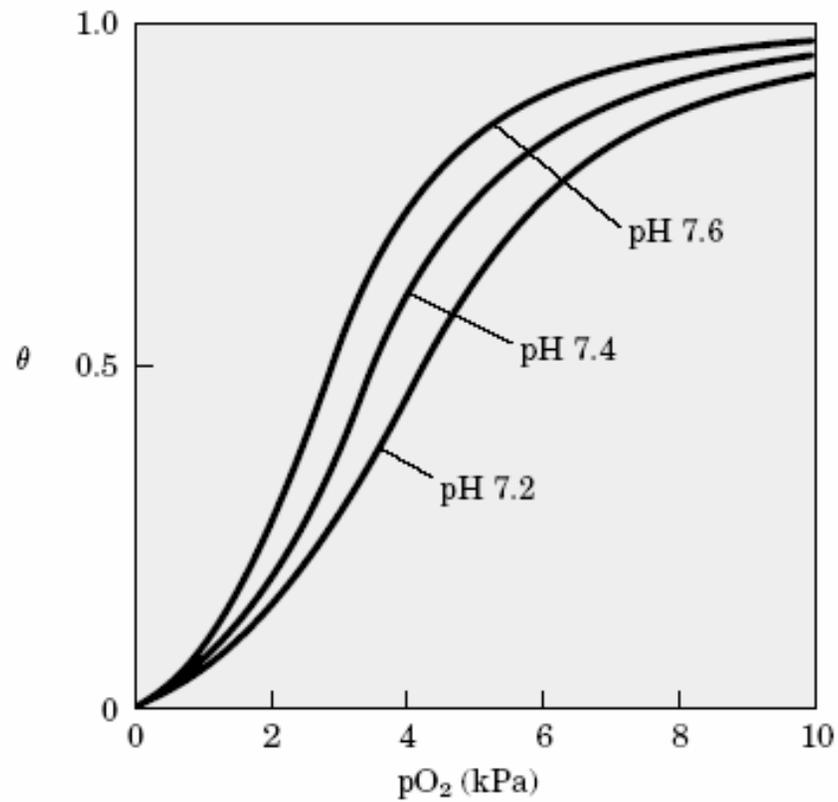
Alosterismo y Cooperativismo



(a)

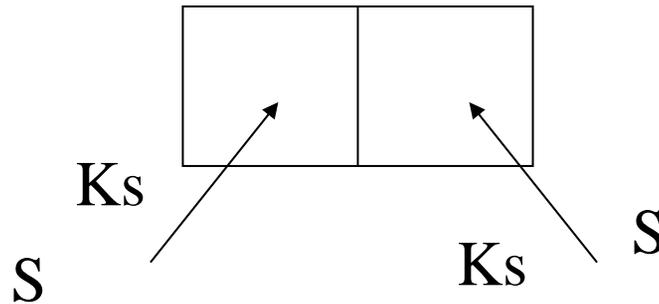


(b)

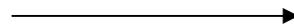


Modelos para explicar el cooperativismo

a. Modelo de Hill



$$v/V_{\max} = \frac{\frac{[S]}{K_s} + \frac{[S]^2}{K_s^2}}{1 + \frac{2[S]}{K_s} + \frac{[S]^2}{K_s^2}}$$



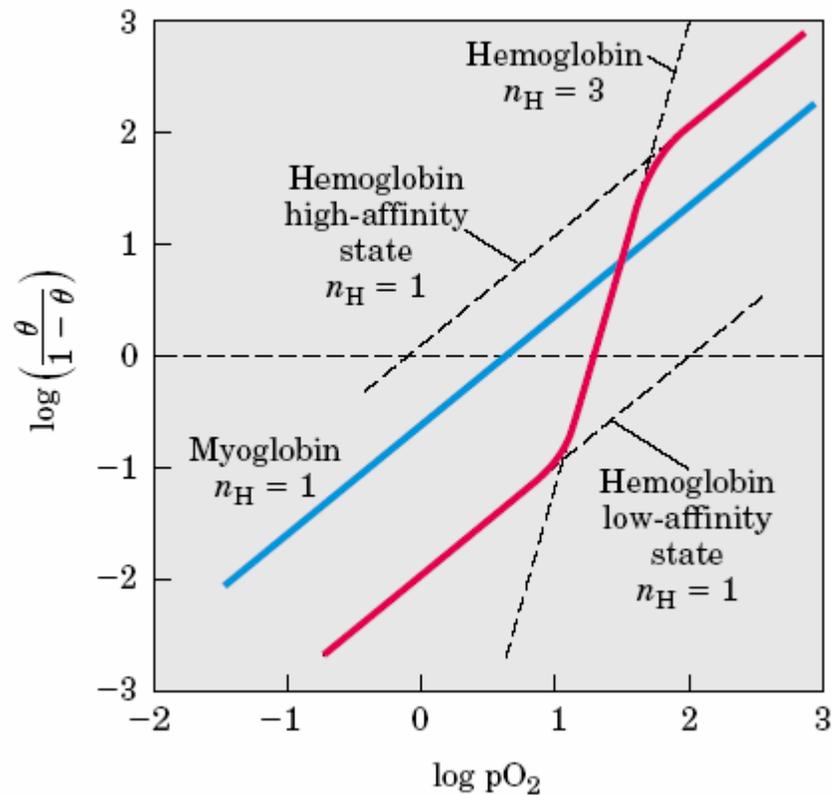
Para n sitios

$$v/V_{\max} = \frac{\frac{[S]}{K_s} \left(1 + \frac{[S]}{K_s} \right)^{n-1}}{\left(1 + \frac{[S]}{K_s} \right)^n}$$

$$v/V_{\max} = \frac{[S]^n}{K_s + [S]^n}$$

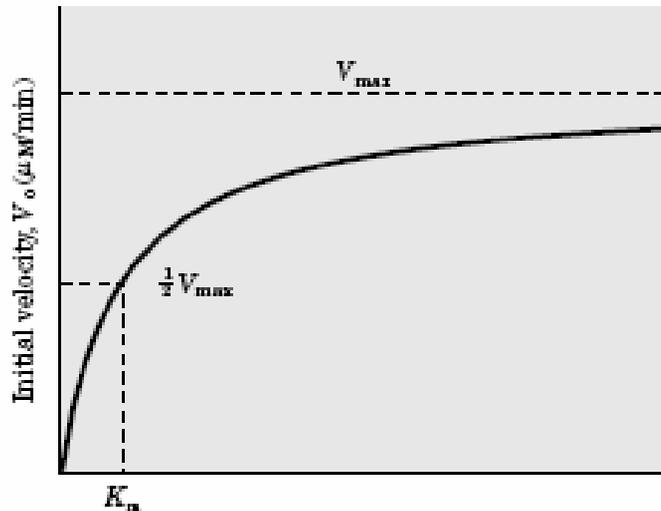
Ecuación de Hill

$$\log\left(\frac{v/V_{\max}}{1 - v/V_{\max}}\right) = n \log(s) - \log K_s$$



Si los n sitios son iguales y tienen la misma K_s y no existe interacción entre ellos, entonces la ecuación anterior se reduce a

$$v/V_{\max} = \frac{[S]}{K_s + [S]}$$



En este caso la enzima tiene **2 sitios** idénticos. Uno no puede distinguir entre 2 moles de enzima con 1 sitio o 1 mol de enzima con 2 sitios independientes.

Qué pasa si los sitios son distintos?

b. Modelo de Adair

Por ejemplo podemos decir que $K_s = aK_s$

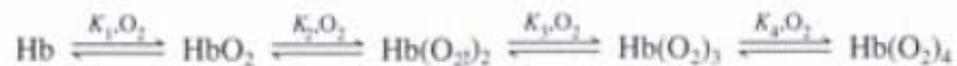
$$v/V_{\max} = \frac{\frac{[S]}{K_s} + \frac{[S]^2}{aK_s^2}}{1 + \frac{2[S]}{K_s} + \frac{[S]^2}{aK_s^2}}$$

Esto no se puede reducir a Michaelis –
Menten y da una curva sigmoidea

Table 10.1 Adair constants for the binding of O_2 to hemoglobin^a

2,3-Diphosphoglycerate (mM)	K_1	K_2	K_3	K_4
	(mmHg)			
0	0.024	~0.074	~0.086	7.4
2.0	0.01	~0.023	~0.008	11.2

^aAt 25°C, pH 7.4, and 0.1-M NaCl. The Adair equation describes the following:

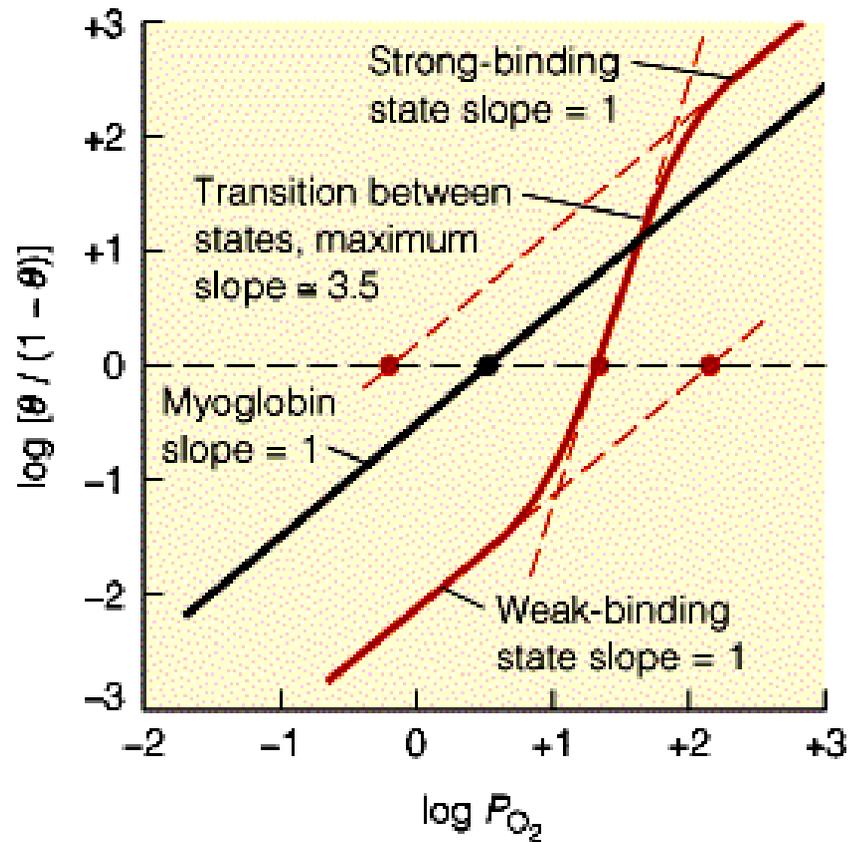


where

$$K_1 = \frac{[\text{HbO}_2]}{[\text{Hb}][\text{O}_2]}, K_2 = \frac{[\text{Hb(O}_2)_2]}{[\text{HbO}_2][\text{O}_2]}, \text{ etc.}$$

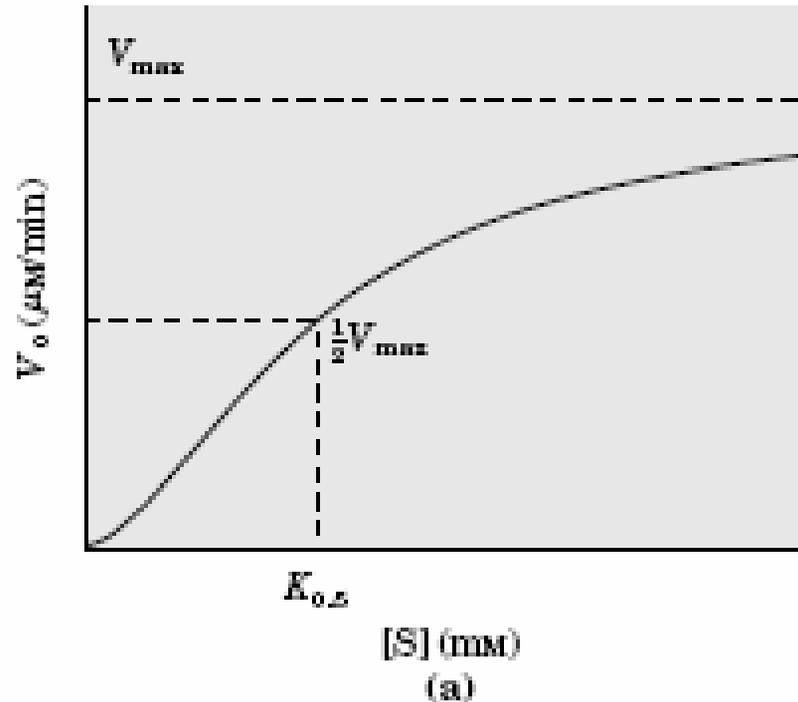
[From I. Tyuma, K. Imai, and K. Shimizu, *Biochemistry* **12**, 1491 (1973).]

Representación de Hill

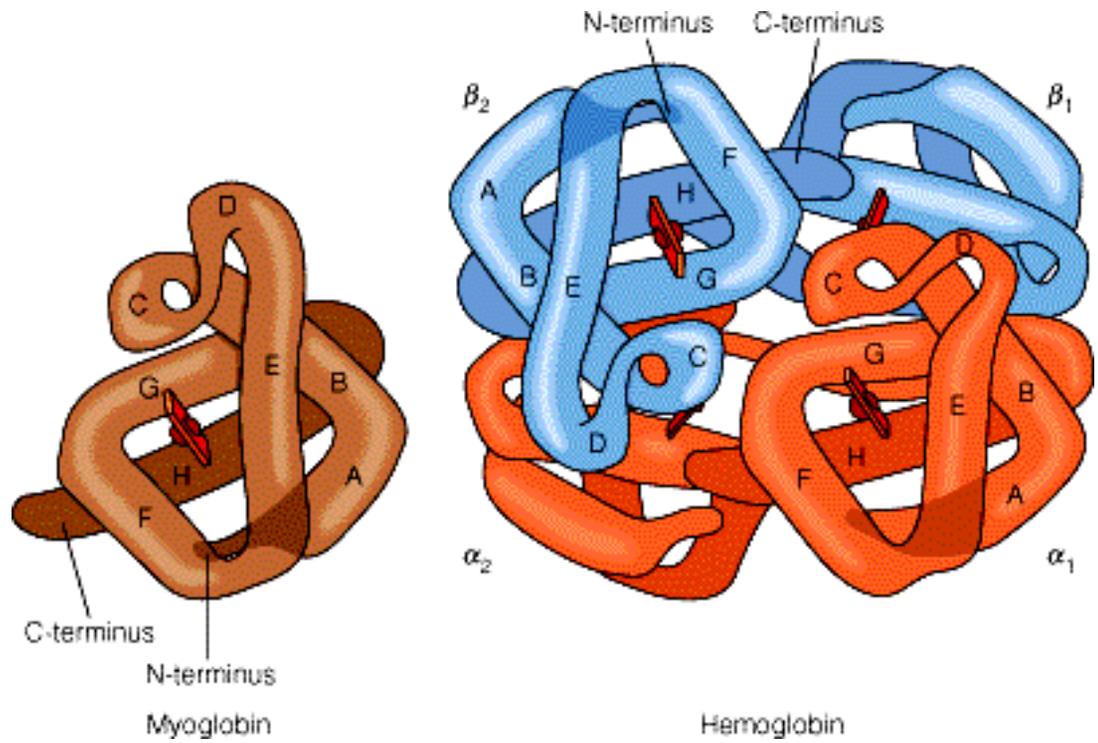


$$v/V_{\max} = \frac{[S]^n}{K' + [S]^n}$$

$$K' = a^A b^B c^C K_s$$

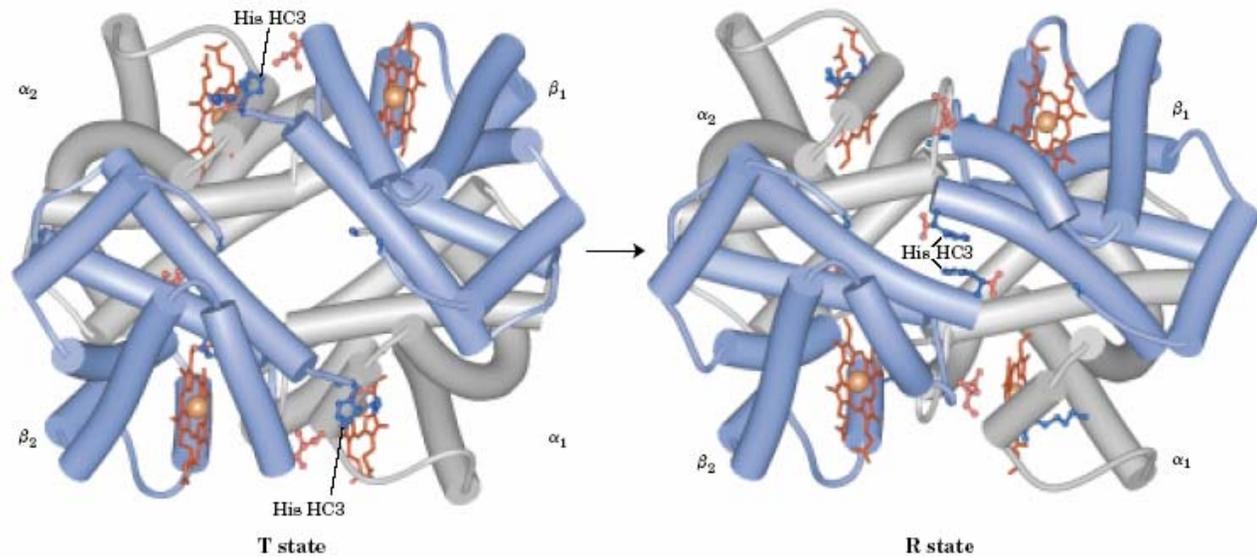


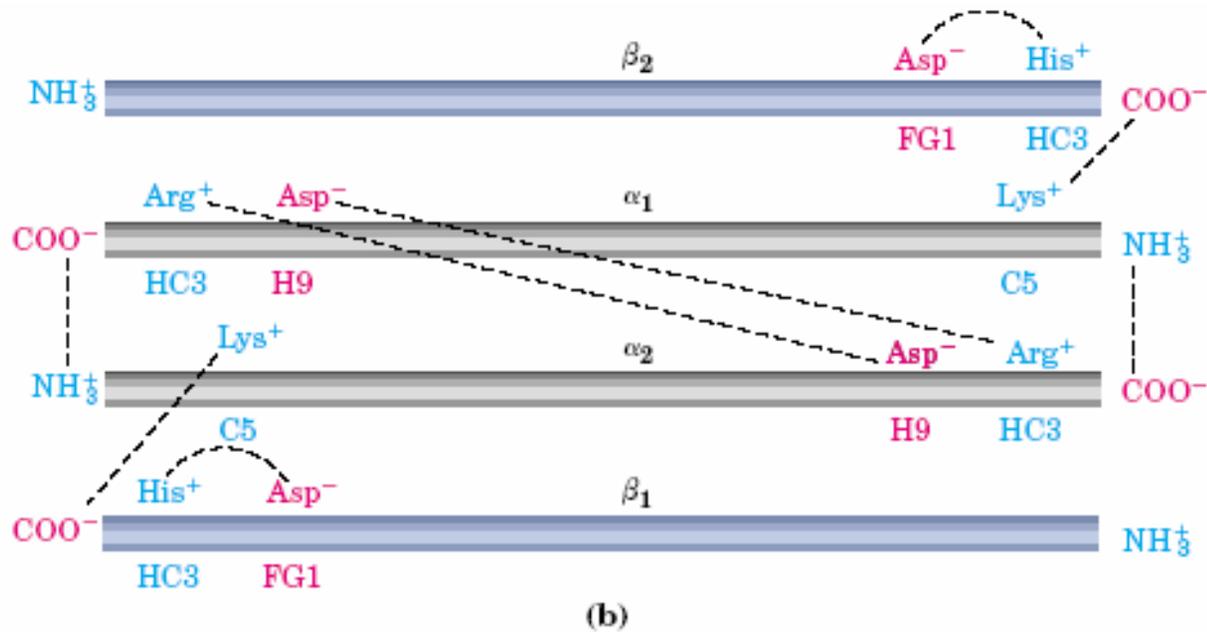
La capacidad que tiene una enzima o proteína de modificar progresivamente la afinidad de sus sitios por el sustrato se denomina **cooperativismo**



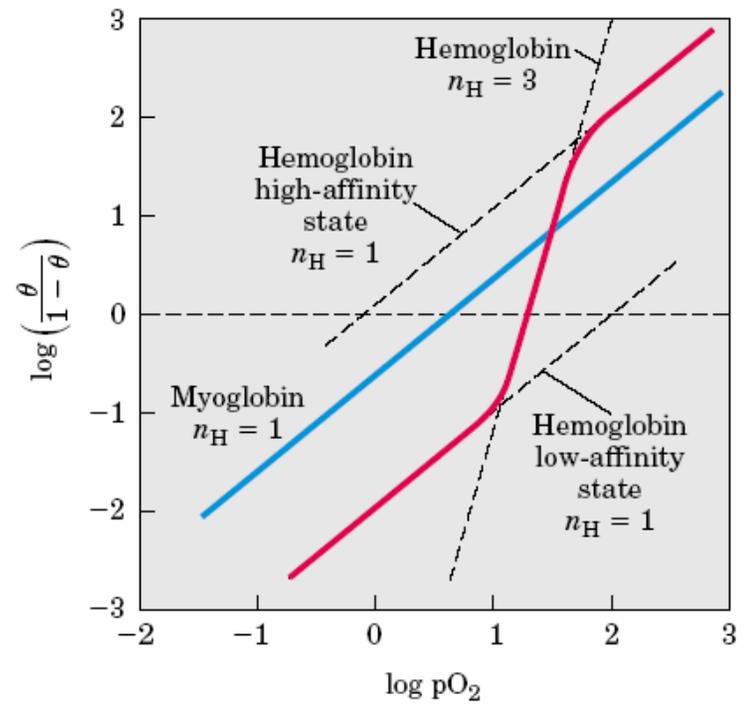
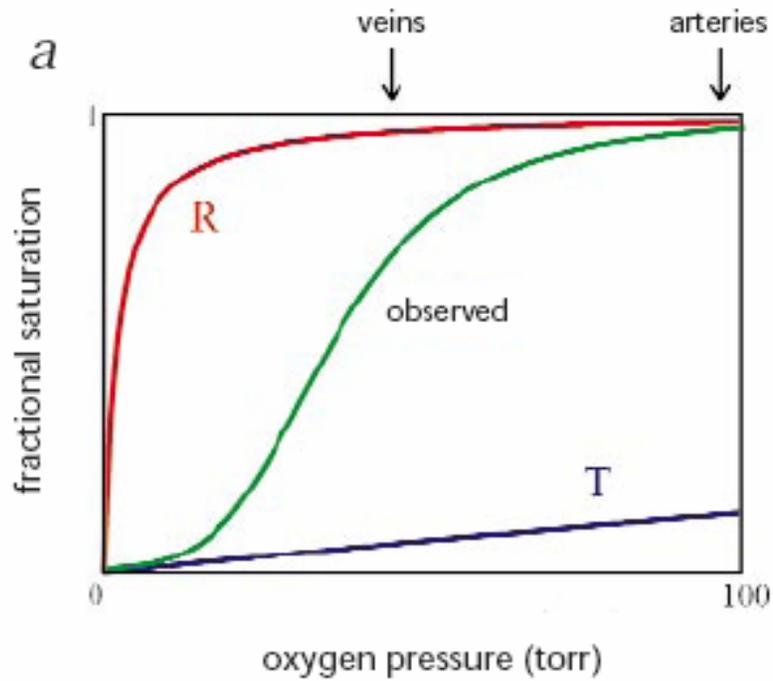


Perutz, 1964 compara la estructura de la oxihemoglobina y la desoxihemoglobina





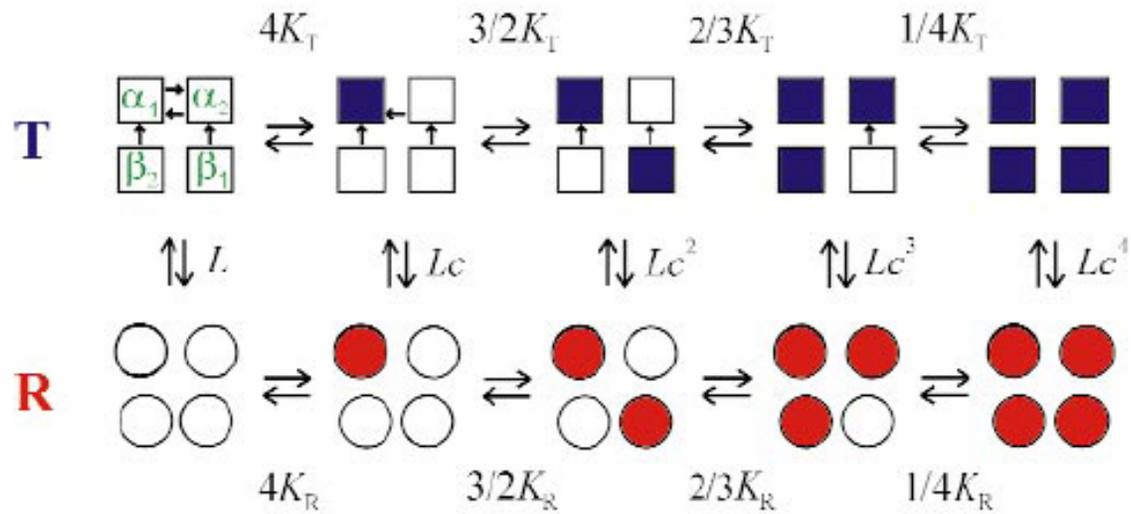
La forma T está estabilizada por puentes salinos



c. Modelo de Monod, Wyman and Changeux, 1965 (MWC)

1. La proteína es un oligómero
2. La proteína existe en un equilibrio entre dos estados: T (tenso) y R (relajado)
3. La forma T tiene la misma constante K_t de unión al sustrato para todos sus sitios
4. La forma R tiene la misma constante K_r de unión al sustrato para todos sus sitios
5. $K_t > K_r$
6. El cooperativismo está dado por la constante de equilibrio entre las formas T y R, la constante alostérica, L.

MWC



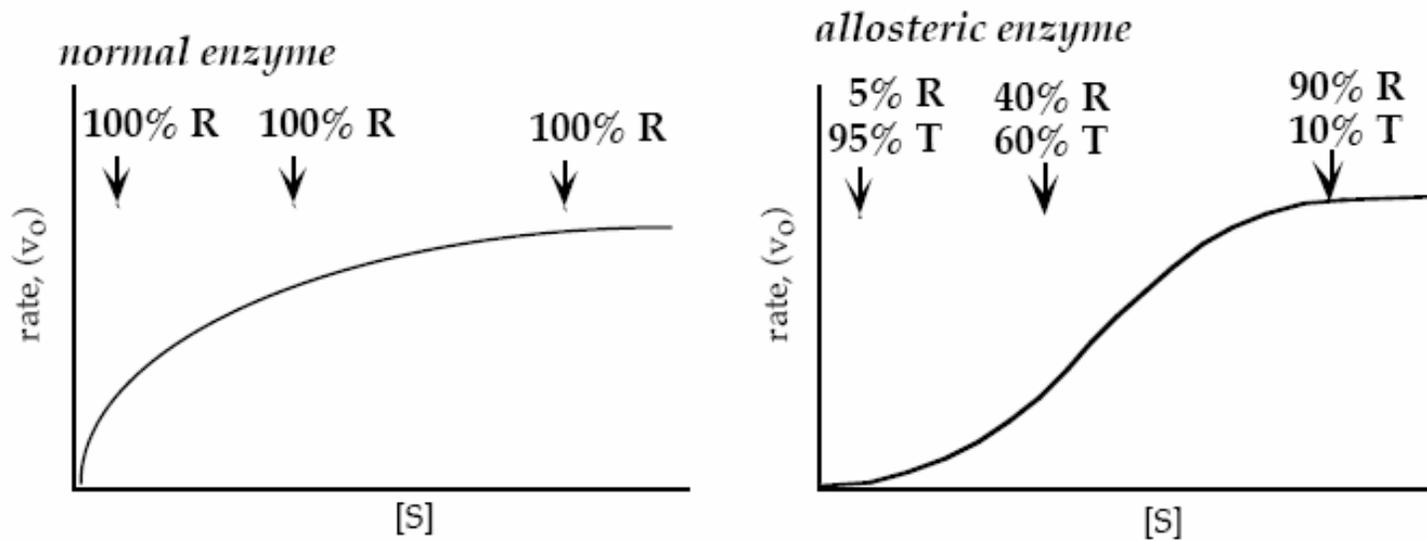


Fig. 18 Per cent of enzyme in the active form.

Alosterismo

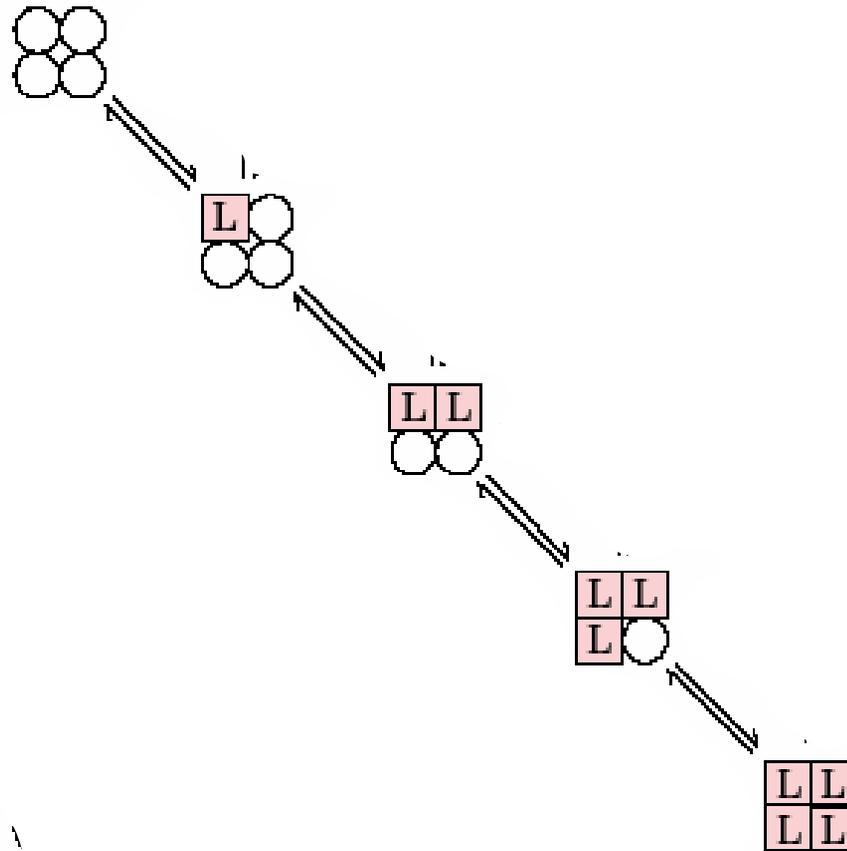
Monod (1963) definió a los ligandos de una enzima que no tuvieran similitud por el sustrato como inhibidores ***alostericos***, y postuló que se unían a sitios distintos de los del sustrato. De ahí el nombre alostéricos por "*otro sitio*"

De esta forma los equilibrios entre las formas T y R se pueden alterar por unión de ***efectores*** positivos o negativos

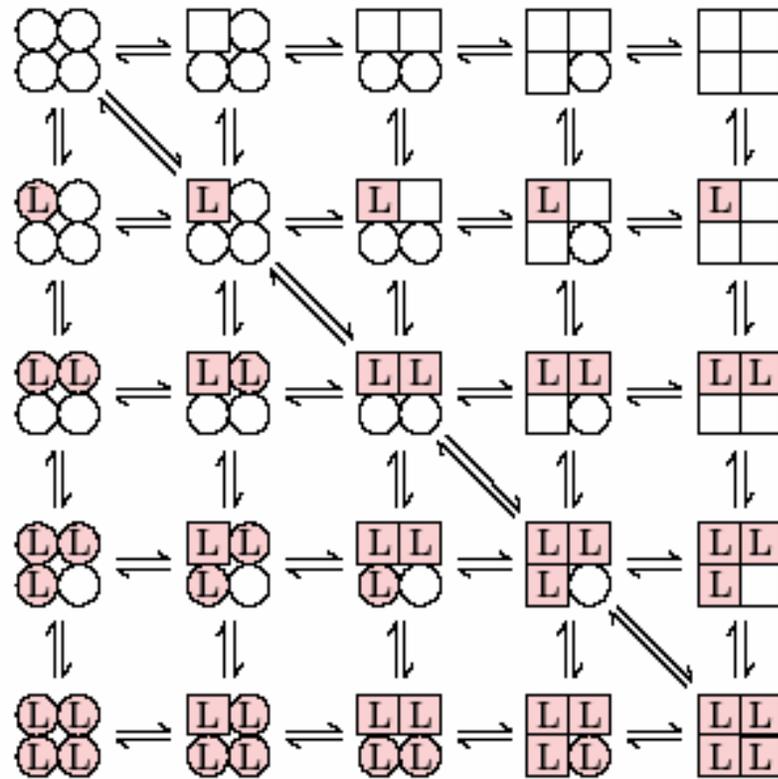
d. Modelo de Koshland, Nemethy and Filmer, 1966 (KNF)

1. En ausencia de ligando la proteína existe como una única conformación
2. Cuando el ligando se une, induce un cambio conformacional que es transmitido al resto de la enzima modificando las constantes de afinidad
3. El modelo de KNF = modelo de ajuste inducido

KNF

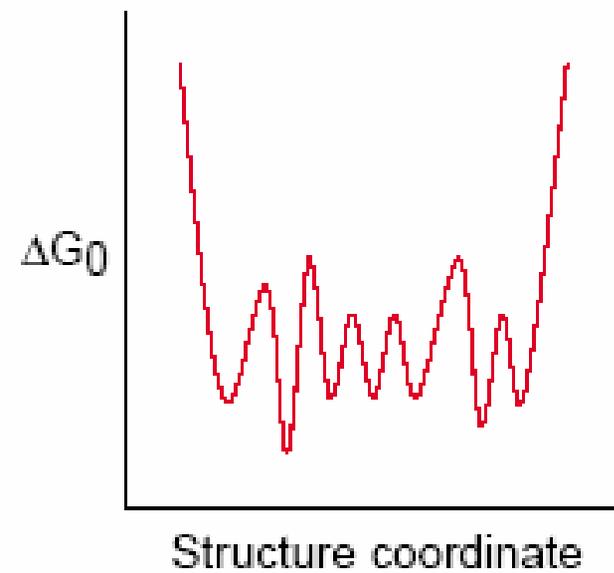


Eigen, 1967



(b) 'New view'

(i) Rugged energy landscape



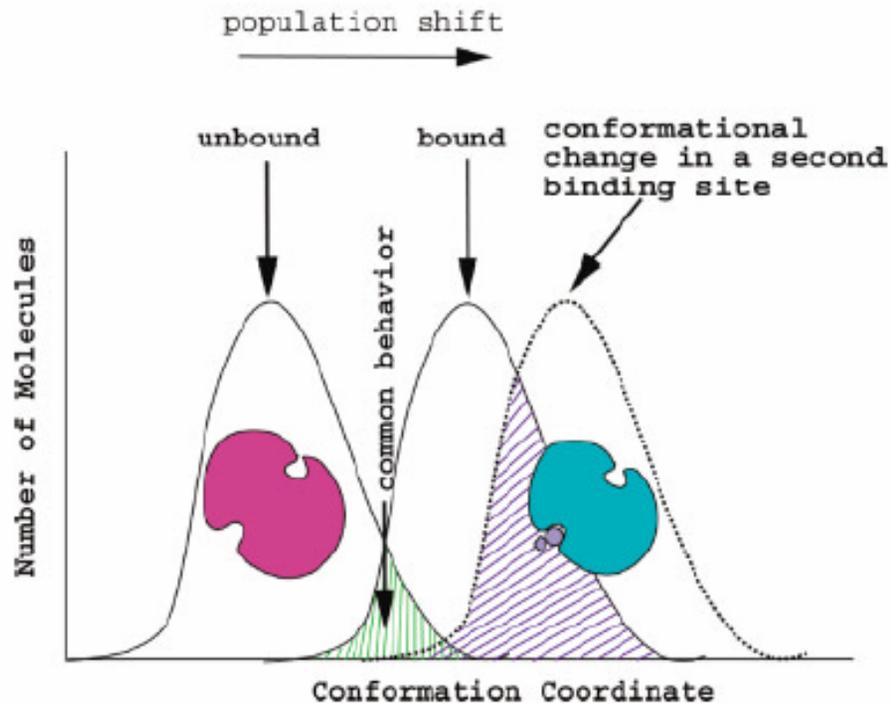


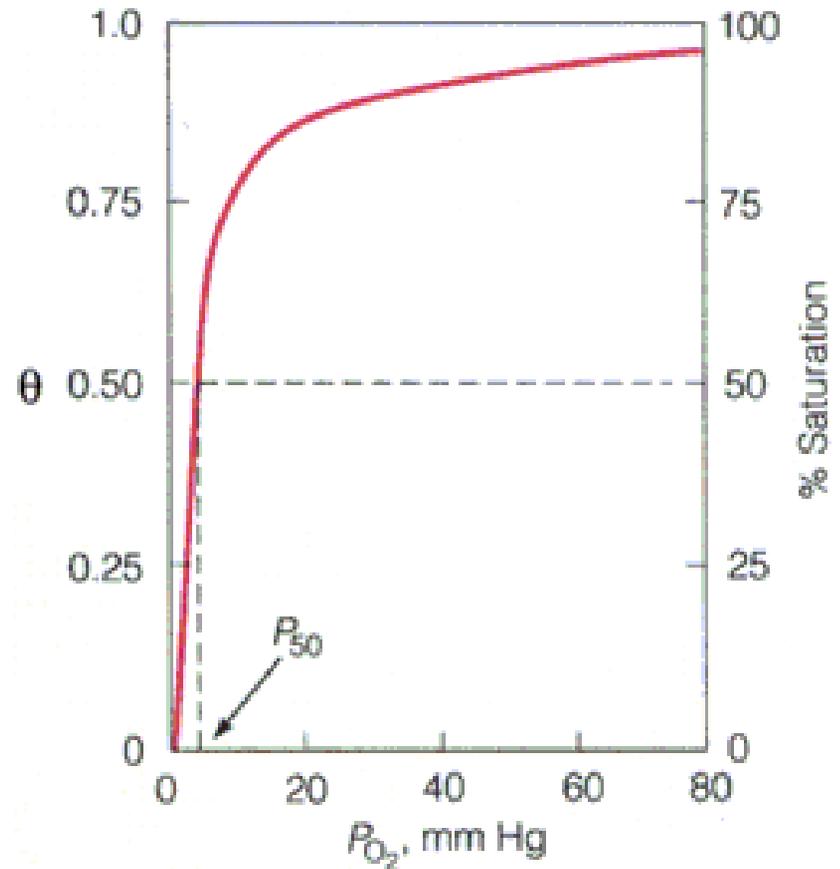
Fig. 2. The "new view" of protein allostery: all proteins are potentially allosteric when thought in terms of population redistribution. Ligand binding leads to a conformational redistribution potentially effecting a conformational change in a second binding site.

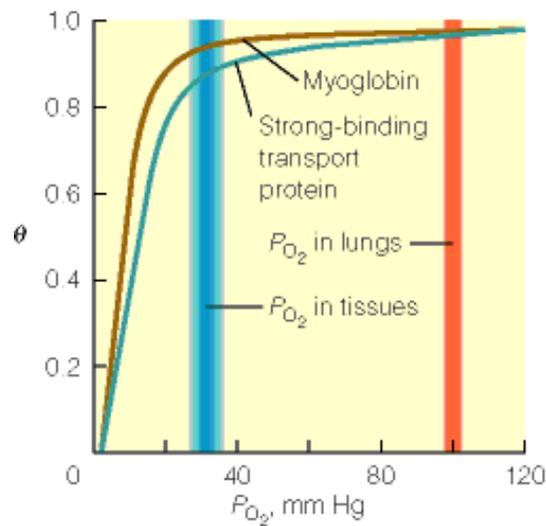
Cuál es la importancia biológica del alosterismo y del cooperativismo?

Relación estructura-función en la Mb y la Hb (Efectos homotrópicos).

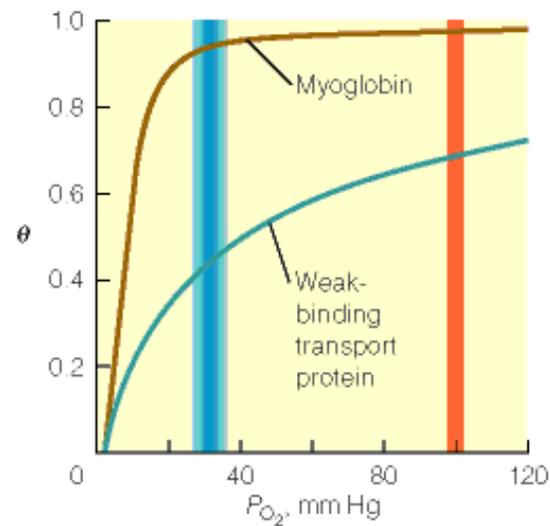
$$\theta = \frac{\text{sites occupied}}{\text{total available sites}}$$

$$\theta = \frac{P_{O_2}}{P_{50} + P_{O_2}}$$

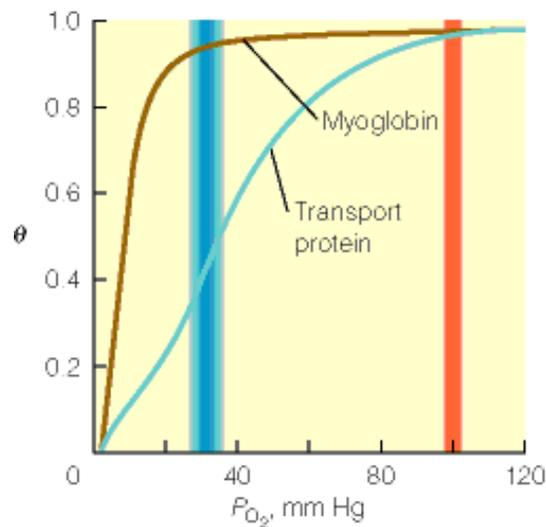




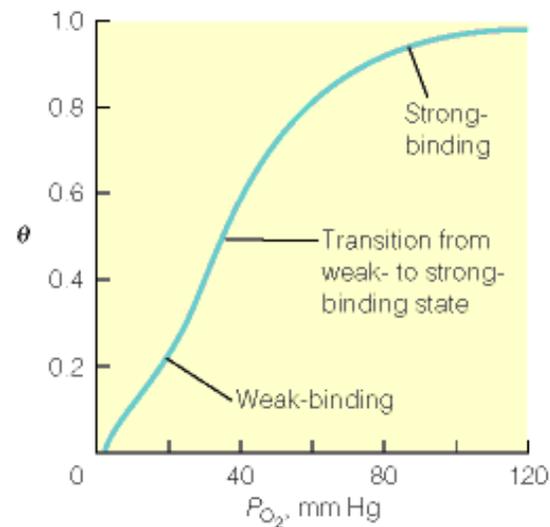
(a) Transport protein efficient in binding but inefficient in unloading (hyperbolic binding curves)



(b) Transport protein efficient in unloading but inefficient in binding (hyperbolic binding curves)

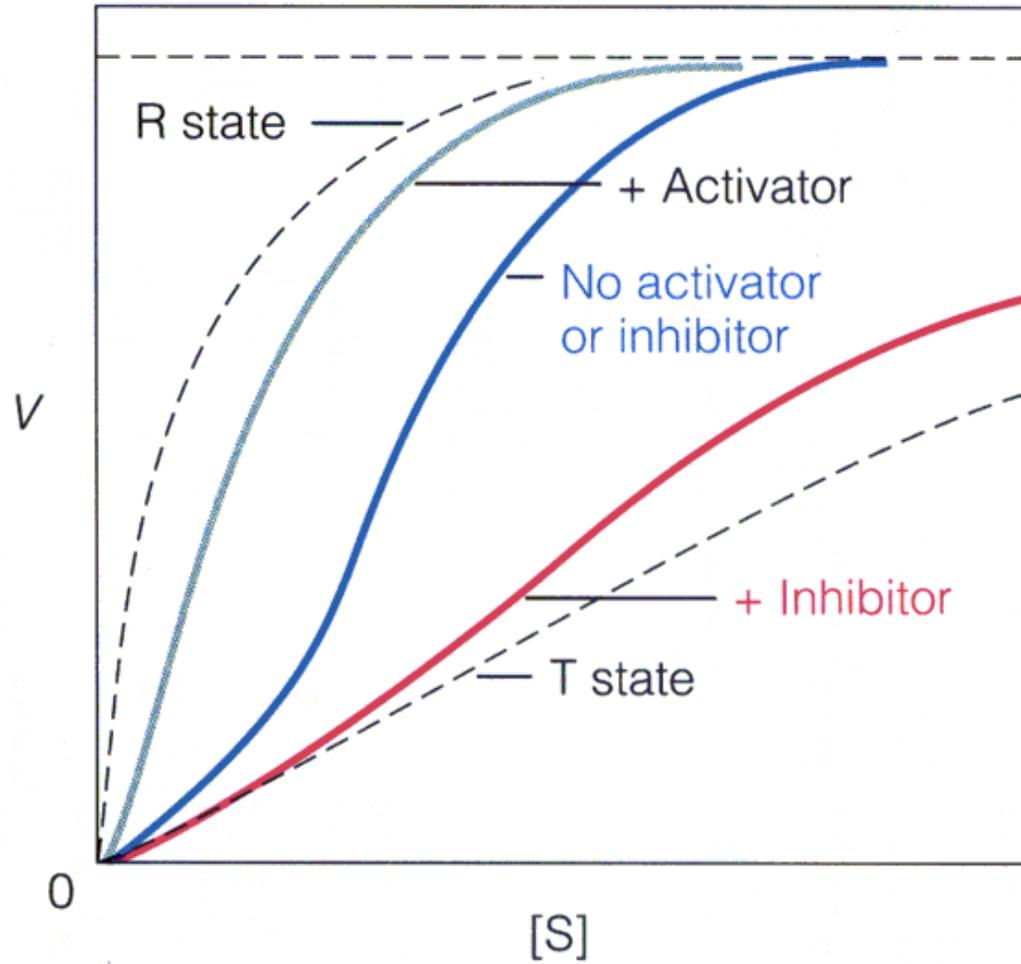


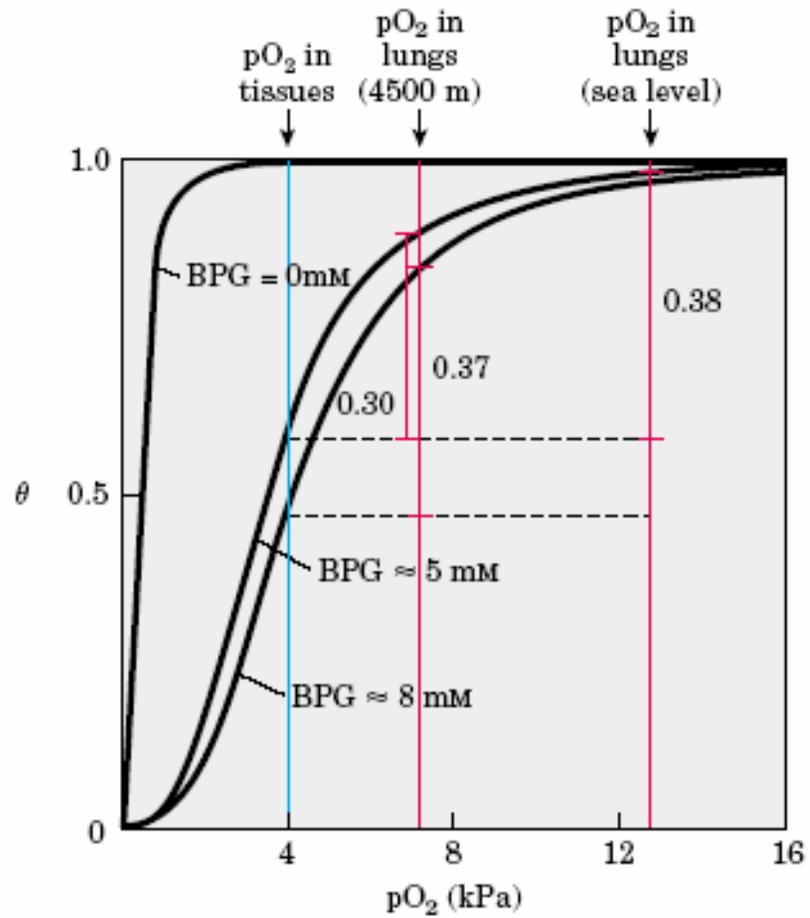
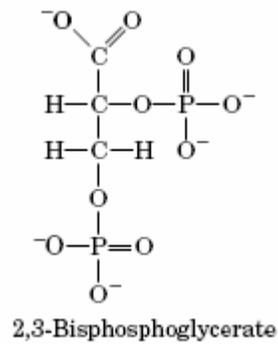
(c) Transport protein efficient in both binding and unloading, because it has a sigmoidal binding curve.



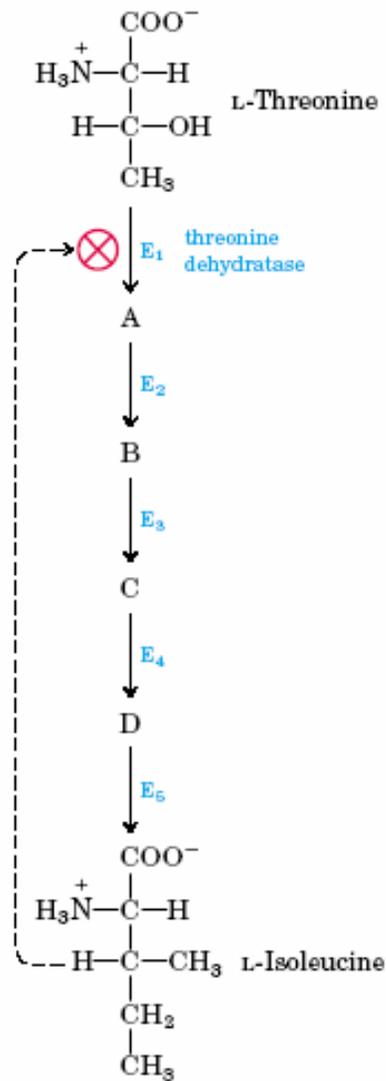
(d) Switch from weak- to strong-binding state explains the sigmoidal curve

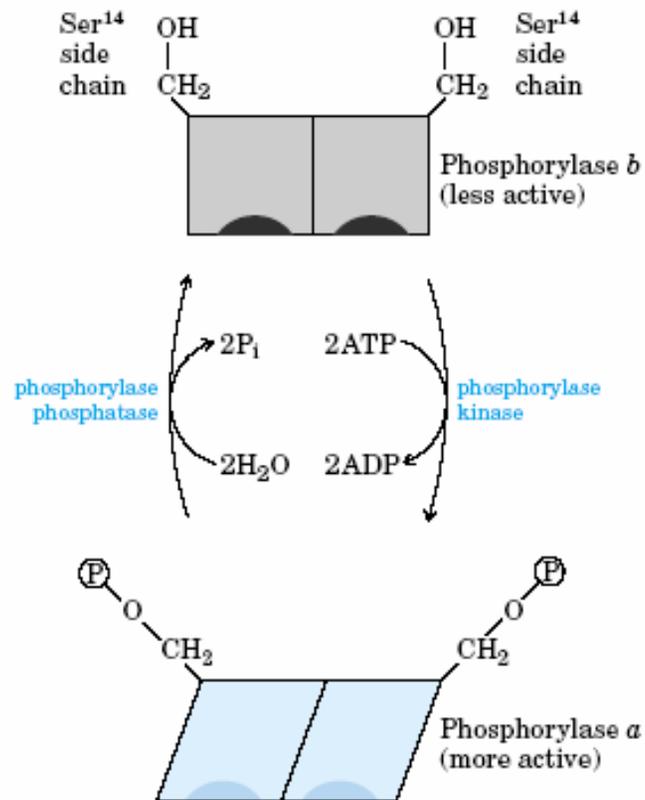
Efectos heterotrópicos

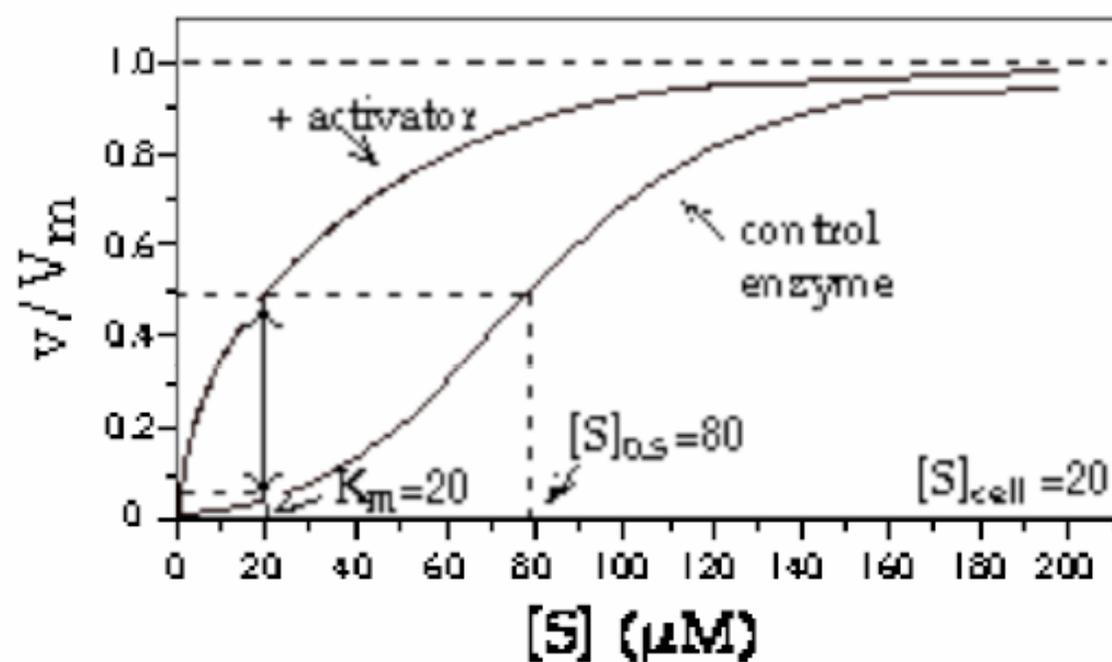




Feedback negativo







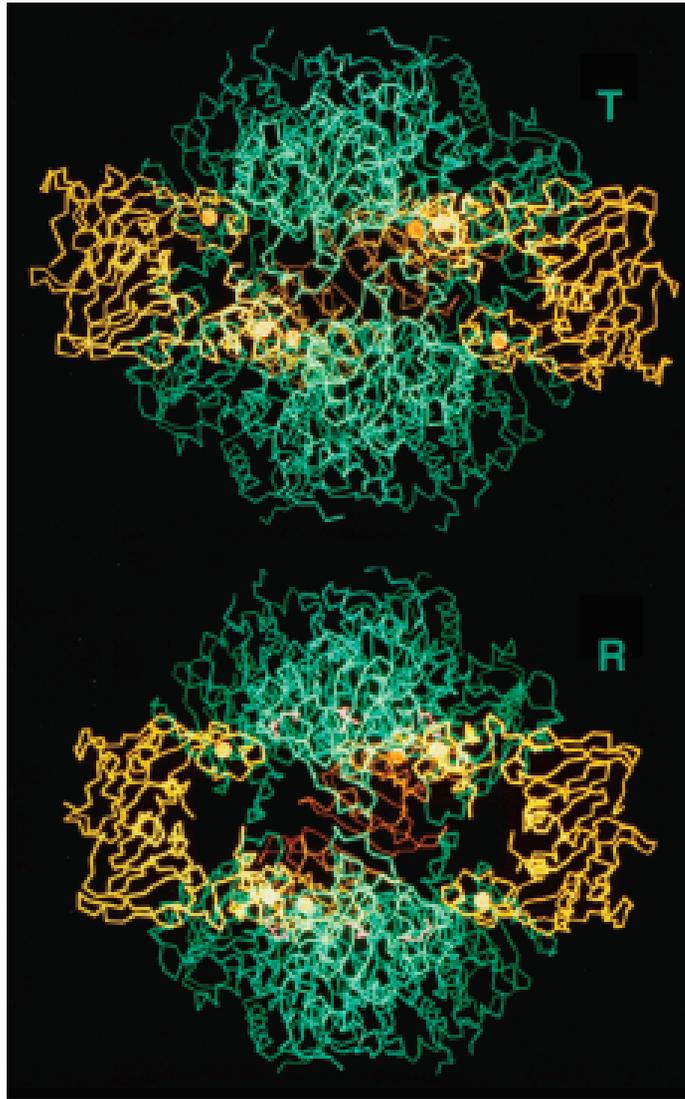


Figure 1. Conformational changes in the protein complex. The top model (T) shows the protein in a relaxed state, while the bottom model (R) shows the protein in a contracted state. The cyan and yellow subunits represent different domains, and the red subunit in the R model indicates a specific conformational change.