Theoretical model explaining the relationship between the molecular mass and the activation energy of the enzyme revealed by a large-scale analysis of bioinformatics data

Piotr H. Pawlowski and Piotr Zielenkiewicz
Institute of Biochemistry and Biophysics of the Polish Academy of Sciences, Warszawa, Poland

A general dependence of the enzyme catalytic rate on its mass was revealed when a statistical analysis of 17065 records from the EMP database was performed. The estimated activation energy of the catalytic process decreases asymptotically with the enzyme molecular mass increase. The proposed theoretical model postulates the existence of an intermediate complex of the enzyme and the departing product. It allows for the explanation of the discovered mass-energy relationship, as an effect of the global enzyme–product interactions during complex dissociation. Fitted parameters of the model seem to be in agreement with those widely accepted for the van der Waals energy of molecular interactions. Their values also agree with the picture of the hydrogen bonding in the catalytic process and suggest that surface walk can be the favorable way of the product departure.

Key words: turnover, catalysis, enzyme, molecular mass, statistics

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Appendix 1

According to eqn. 23 and eqn. 24 the global energy of enzyme-product interactions energy, $U_{glo}$, can be calculated as

$$U_{glo} = -\sum_{ij} 2e_{ij} \left( \frac{d_{ij}^*}{d_{ij}} \right)^6,$$

(A.1.1)

where appropriate components of the sum are taken for the $i$-th atom of enzyme and the $j$-th atom of product, separated by the distance $d_{ij}$. Other symbols denote: $e_{ij}$, an absolute value of minimal energy of van der Waals interactions, and $d_{ij}^*$, the interatomic distance of the van der Waals minimum.

Assumed in the Theoretical model, the homogeneity of enzyme and product, and equality of London atomic interactions allow for the replacement of the above, point-like, characteristics of the system by continuous ones, and the appropriate sum by the double-volume integral

$$U_{glo} = -2e(d^*)^6 n_en_p \int \int \frac{\delta V_E \delta V_P}{d^6}. $$

(A.1.2)

In the above formula, $\delta V_E$ and $\delta V_P$ are infinitesimal elements of the enzyme (E) and the product (P) volume, respectively. $n_E$ and $n_P$ are the densities of atoms. Parameters $e$ and $d^*$ are constant values of the indexed ones. Variable $d$ is the distance between given points of the enzyme and the product.
For a spherical product of radius $R_p$, relatively small compared to the enzyme characteristic dimension, we can neglect the change in the considered distance $d$ related to the change of the location in the product. For this reason, we may treat distances from different points of the enzyme to different points of the product as measured only to a chosen single point of the latter, for example, its center. As a result, integration inside product becomes trivial, and leads to the formula

$$U_{\text{glo}} = -\frac{8\pi\varepsilon(d^*)^6}{3} n_en_p R_p^3 \int_0^{d_0} \frac{\delta V_E}{d_0^6},$$  \hspace{1cm} (A.1.3)

where we introduced $d_0$, which denotes the distance from a given point of the enzyme to the product center.

For assumed geometry of the model (Fig. 4), and for the half-immersed product displacement $\lambda$ from the enzyme center, the easiest way to calculate the defined integral (A.1.3) is to use Cartesian coordinates $x, y, z$, with origin at the center of the product, the $y$ axis oriented perpendicularly towards the enzyme body, and the $z$ axis going through the product and enzyme centers. These coordinates additionally were related to the set of spherical variables $\rho, \theta, \phi$ (Fig. 8). In the proposed model, the point $(0, 0, -\lambda)$ represents the position of the bound-state product.

Now, for $\lambda < R_E - R_p$, when integrating using the spherical variables, one obtains:

$$U_{\text{glo}} = -\frac{8\pi\varepsilon(d^*)^6}{3} n_en_p R_p^3 \int_0^{\rho_{\text{max}}} \int_0^{\theta_{\text{max}}} \frac{1}{\rho^4} \sin(\theta) \delta \theta \delta \rho \int_0^{\phi_{\text{max}}} \delta \phi,$$ \hspace{1cm} (A.1.4)
where the upper limit of the radial integration $\rho_{\text{max}}$ is

$$\rho_{\text{max}} = \sqrt{R_E^2 - \lambda^2 \sin^2(\Theta) - \lambda \cos(\Theta)}. \quad \text{(A.1.5)}$$

When one calculates the azimuthal and radial integrals in formula A.1.4, one gets:

$$U_{\text{glo}} = \frac{8\pi^2 e(d^*)^6 n_E n_p R_p^3}{9} \int_0^\pi \sin(\Theta) \delta(\Theta) \left\{ \frac{1}{\left[ R_E^2 - \lambda^2 \sin^2(\Theta) - \lambda \cos(\Theta) \right]^3} - \frac{1}{R_p^3} \right\}.$$  \quad \text{(A.1.6)}$$

In the above expression, the expansion of the function in the curly brackets $\{}$ in a Maclaurin series up to the power of 2 (with respect to $\lambda$) allows for approximate polar integration. Then

$$U_{\text{glo}} = U_{\text{glo}}(0) + \frac{16\pi^2 e(d^*)^6 n_E n_p R_p^3}{3R_E^2} \lambda^2, \quad \text{(A.1.7)}$$

where the energy of global interactions in the enzyme center, $U_{\text{glo}}(0)$, equals
\[ U_{glo}(0) = \frac{16\pi^2 e(d^*)^6}{9} n_E n_P R_P^3 \left( \frac{1}{R_E^3} - \frac{1}{R_P^3} \right). \]  
(A.1.8)

If the geometric distance between the bound-state site and the site where the product is crossing the barrier for its release, equals \( \zeta \), the respective difference in energy is

\[ \Delta U_{glo} = \frac{16\pi^2 e(d^*)^6}{3 R_E^2} n_E n_P R_P^3 \zeta^2. \]  
(A.1.9)

**Appendix 2**

Assuming that the mean number of bonds of a certain type which have to be broken during the considered process is \( n_b \), the change in the energy of local interactions \( \Delta U_{loc} \) can be written as:

\[ \Delta U_{loc} = n_b e_b , \]  
(A.2.1)

where \( e_b \) is a single-bond energy. Then, the standard deviation \( \sigma_g \) of the discussed energy can be simply calculated as:

\[ \sigma_g = \sigma_{n_b} e_b , \]  
(A.2.2)

Assuming Poisson distribution of the number of bonds, one may put
Thus,

$$\sigma_n = \sqrt{n_b}.$$  \hspace{1cm} (A.2.3)

Finally,

$$\sigma_G = \sqrt{n_b} e_b$$ \hspace{1cm} (A.2.4)

The set of obtained equations describes the relations between microscopic and macroscopic parameters of the system. We have

$$e_b = \frac{\sigma_G^2}{\Delta U_{loc}}$$

$$n_b = \frac{\Delta U_{loc}}{e_b}$$ \hspace{1cm} (A.2.6)