

Splitting of the nonlinear temperature dependence of selection processes into the temperature dependencies of the single reaction pathways

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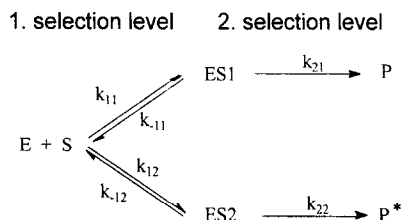
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Abstract

The paper describes a concept, which allows the determination of the temperature dependencies of the single reaction pathways in a selection process based on brutto-activity and selectivity measurements. © 1997 Elsevier Science B.V.

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Selection processes play an important role in chemistry. Typical examples are the regioselection (hydroformylation) or enantioselection (asymmetric hydrogenation and asymmetric dihydroxylation, respectively). In general, products of these reactions are formed over two reaction pathways ¹ according to Scheme 1. The result of the first selection level is the formation of intermediates and the further reaction in the second selection level leads to the products.



Scheme 1. General scheme for a selection process.

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¹ These and all following considerations refer to only two reaction pathways and intermediates, respectively, e.g., using ligands containing C₂-symmetry for enantioselection. If using C₁-symmetric selection inducing ligands the number of possible intermediates increases to four. The formation of each product results from independent processes.

Pressure and temperature are freely adjustable parameters to make distinctions between the reaction pathways as far as possible. Temperature does not necessarily have a uniform influence as known for a long time. The plot of the logarithmic product ratios as function of the reciprocal of temperature (modified Eyring-plot) can show a nonlinear dependence. For different selection processes extrema are often observed in the form of maxima or minima [1,2]. A detailed interpretation of this nonlinear temperature dependence on the basis of the empirically found *isoinversion principle* is given in Ref. [3,4]. Whereas the experimental behaviour is interpreted by Scharf et al. that different selection levels show changing dominance in various temperature areas, Ridd [5,6] makes a change of the rate limiting steps between the selection levels responsible for the 'transition region'. In Ref. [7] it was shown that the nonlinearity of logarithmic product ratios is caused by the nonlinear behaviour of the logarithmic intermediate ratios. Further investigations led to the conclusion that a quantification of the conditions of an extremum, or in a more general sense of deviations from linearity, is dependent on the reason that leads to the nonlinear behaviour. This means that there is no unified equation describing such nonlinearities [8]. Reasons for the experimentally observable nonlinearity of the logarithmic product ratio as a function of the reciprocal of temperature may be (a) disturbed intermolecular equilibria, (b) direct intramolecular exchange of intermediates, or (c) the dissociation of a ligand during the reaction, irrespective of whether the ligand has a decisive influence on the selection or not [7,8]. Thereby the temperature depending logarithmic product ratio is only an overall effect. The temperature dependence of single reaction pathways can be totally different. The disturbance of the intermolecular preequilibria, one reason for the nonlinear temperature dependence, can have a greater influence on especially one of the both reaction pathways. In those cases in which selection is the result of an exceptional reactivity of one intermediate the disturbance of intermolecular preequilibria can affect especially one of the both reaction pathways. This is known for the examples of the thermodynamically less stable *minor* complex in the case of asymmetric hydrogenation [9] and also for the systems which can be described by the concept of 'ligand accelerating catalysis' (LAC) described recently by Sharpless [10]. The temperature dependence for the formation of each product which allows a deeper insight in mechanistical courses has not been reported in the literature so far. The problem seems to be the fact that one either follows the decrease of the educt, or a measured quantity which is proportional to the total amount of product like time dependent consumption of hydrogen in a hydrogenation reaction, instead of observing the single reaction products.

This work aims at the presentation of a concept that allows the determination of the temperature dependence of each reaction pathway in a selection process from the overall activity and the experimentally available product ratios at various temperatures. Thus, it should be possible to assign the contribution of single reaction pathways to the even nonlinear temperature dependence of the logarithmic product ratios.

Based upon the statements of Halpern concerning the catalytic asymmetric hydrogenation [9] we were able to show that the basic form of the Michaelis–Menten-equation (Eq. (1)) is valid, irrespective of the model extensions like disturbed intermolecular equilibria, intramolecular exchange processes between intermediates or the possibility of four stereoisomeric intermediates when using C_1 -symmetrical ligands, respectively [11].

$$-\frac{d[H_2]}{dt} = \frac{k_{\text{obs}} \cdot [E_0] \cdot [S]}{K_M + [S]} \quad (1)$$

The macroscopically determinable rate constant k_{obs} corresponds to the sum of all rate constants of the rate determining last step, each multiplied with the mole fraction of the catalyst substrate

complexes. The reciprocal of the macroscopically observable Michaelis constant K_M corresponds on the other hand to the sum of all reciprocals of the single Michaelis constants. This is shown in Eqs. (2a) and (2b) for the simplest model depicted in Scheme 1.

$$k_{\text{obs}} = \frac{(k_{21} \cdot (k_{11}/(k_{-11} + k_{21})) + k_{22} \cdot (k_{12}/(k_{-12} + k_{22})))}{(k_{11}/(k_{-11} + k_{21}) + k_{12}/(k_{-12} + k_{22}))} = \frac{(k_{21} \cdot K_{\text{ES1}} + k_{22} \cdot K_{\text{ES2}})}{(K_{\text{ES1}} + K_{\text{ES2}})} = \frac{(k_{21} \cdot [\text{ES1}] + k_{22} \cdot [\text{ES2}])}{([\text{ES1}] + [\text{ES2}])} \quad (2a)$$

$$K_M = \frac{1}{(K_{\text{ES1}} + K_{\text{ES2}})} = \frac{1}{(k_{11}/(k_{-11} + k_{21}) + k_{12}/(k_{-12} + k_{22}))} \quad (2b)$$

The quotient of both constants which are to be determined leads to Eq. (3):

$$k_{1\text{storder}} = \left(k_{21} \cdot \frac{k_{11}}{k_{-11} + k_{21}} + k_{22} \cdot \frac{k_{12}}{k_{-12} + k_{22}} \right) = (k_{21} \cdot K_{\text{ES1}} + k_{22} \cdot K_{\text{ES2}}) \quad (3)$$

This value is the same one as resulting from the Michaelis–Menten-equation in the case of a very low substrate concentration and/or a high value for K_M ($S \ll K_M$). Macroscopically it's a first order reaction, taking account of the initial catalyst concentration $[E_0]$ leads to a rate constant according to Eq. (3).

If the discussed selection process is not a catalytic one but a stoichiometric reaction analogous relations can be derived if certain preconditions are fulfilled. The following Eqs. (4)–(7) depict the decrease of the educt $[E]$ in a stoichiometric reaction according to Scheme 1, validity of the 'steady state' approximation for the intermediates assumed.

$$\frac{d[E]}{dt} = -(k_{11} \cdot [E] \cdot [S]) - (k_{12} \cdot [E] \cdot [S]) + \frac{k_{-11} \cdot k_{11} \cdot [E] \cdot [S]}{k_{-11} + k_{21}} + \frac{k_{-12} \cdot k_{12} \cdot [E] \cdot [S]}{k_{-12} + k_{22}}$$

with

$$[\text{ES1}] = \frac{k_{11} \cdot [E] \cdot [S]}{k_{-11} + k_{21}} \quad \text{and} \quad [\text{ES2}] = \frac{k_{12} \cdot [E] \cdot [S]}{k_{-12} + k_{22}} \quad (4)$$

After transformation according to Eqs. (5) and (6), Eq. (7) is obtained for the decrease of $[E]$.

$$\frac{d[E]}{dt} = -(k_{11} \cdot [E] \cdot [S]) \cdot \left(1 - \frac{k_{-11}}{k_{-11} + k_{21}} \right) - (k_{12} \cdot [E] \cdot [S]) \cdot \left(1 - \frac{k_{-12}}{k_{-12} + k_{22}} \right) \quad (5)$$

$$\begin{aligned} \frac{d[E]}{dt} = & -(k_{11} \cdot [E] \cdot [S]) \cdot \left(\frac{k_{-11} + k_{21}}{k_{-11} + k_{21}} - \frac{k_{-11}}{k_{-11} + k_{21}} \right) \\ & - (k_{12} \cdot [E] \cdot [S]) \cdot \left(\frac{k_{-12} + k_{22}}{k_{-12} + k_{22}} - \frac{k_{-12}}{k_{-12} + k_{22}} \right) \end{aligned} \quad (6)$$

$$-\frac{d[E]}{dt} = \left(k_{21} \cdot \left(\frac{k_{11}}{k_{-11} + k_{21}} \right) + k_{22} \cdot \left(\frac{k_{12}}{k_{-12} + k_{22}} \right) \right) \cdot [E] \cdot [S] = k_{1\text{storder}} \cdot [E] \cdot [S] \quad (7)$$

The problem can be reduced easily to a pseudo first order reaction using an excess of $[S]$. Finally a totally analogous relation can be found for stoichiometric reactions as for the corresponding catalytic course of the selection process as in Eq. (3).

Regarding catalytic or stoichiometric selection processes, these principally well known derivations demonstrate that under special conditions the sum of rate constants for the rate limiting last step multiplied each with the corresponding reciprocal Michaelis constant results in activity.

The product ratio of a selection process according to Scheme 1 can be described by Eq. (8) ²:

$$\frac{[P]}{[P^*]} = \frac{k_{21} \cdot ES1}{k_{22} \cdot ES2} = \frac{k_{21} \cdot K_{ES1}}{k_{22} \cdot K_{ES2}} = \frac{k_{21} \cdot (k_{11}/(k_{-11} + k_{21}))}{k_{22} \cdot (k_{12}/(k_{-12} + k_{22}))} \quad (8)$$

Comparison of Eqs. (3) and (8) shows that they contain the sum and on the other hand the ratio of values typical for one reaction pathway. Combination of the results from brutto-activity measurements and selectivity for different temperatures allows the determination of interesting values, see Eq. (9). These can be plotted in dependence on temperature, e.g., after Eyring.

$$k_{22} \cdot \left(\frac{k_{12}}{k_{-12} + k_{22}} \right) = \frac{k_{1st\ order}}{([P]/[P^*] + 1)} \quad \text{and} \quad k_{21} \cdot \left(\frac{k_{11}}{k_{-11} + k_{21}} \right) \\ = (k_{1st\ order}) - k_{22} \cdot \left(\frac{k_{12}}{k_{-12} + k_{22}} \right) \quad (9)$$

In this way it should be possible to reduce the nonlinear temperature dependence of logarithmic product ratios to its component contributions of the single reaction pathways and to gain more information about the mechanistic course of a reaction ³.

Without detailed explanations the introduced concept may be transferred analogously to additional intramolecular exchange processes (a literature composition concerning the asymmetric hydrogenation as the best investigated selection process can be found in Ref. [11]) and to more than two reaction pathways, respectively. In the latter case, for example as result of using C₁-symmetric ligands, only the contribution of one product, which may be formed in two independent ways to the nonlinear temperature dependence of the logarithmic product ratio is determinable.

A problem for the practical application of the introduced concept consists in the following. In some selection processes, like the asymmetric hydrogenation, the rate constants of the rate limiting second selection level, the oxidative addition of hydrogen, contain the concentration of hydrogen [H₂]. In such cases isobaric conditions considerably simplify the kinetic analysis. If the rate constant containing the constant [H₂] becomes high enough to disturb one or both of the preequilibria, enantioselection is then dependent on [H₂]-pressure, the influence of the temperature dependent pure rate constant cannot be distinguished from the influence of temperature dependent [H₂]-solubility. Therefore, selection processes containing only one rearrangement on the second selection level are much more suitable for the introduced investigations. The asymmetric dihydroxylation of olefines with OsO₄ complexed with chiral amines as catalyst found by Sharpless (for a review see Ref. [13]) is a selection process which the nonlinear temperature dependence is described for [2]. Eventually, additional statements concerning the intermediates ⁴ of this preparatively important selection process can be given by means of the concept suggested here.

² This equation is not valid if the formation of the intermediates is rate determining. A detailed discussion of these conditions can be found in Refs. [9,12].

³ The same result is obtained if a measured product proportional value (e.g., the brutto hydrogen consumption during an asymmetric hydrogenation) is split according to the observed selectivity (which is constant during the experiment) and the hydrogen consumption of each enantiomeric product analyzed.

⁴ According to Sharpless an osmaoxetan is the intermediate. Corey favors at present an 'Olefine-complex' [14]. The experimentally observable nonlinear temperature dependence of the logarithmic product ratio is in accordance with both ideas of the intermediate, because in both cases its formation is defined over a preequilibrium. Recently published theoretical studies on the intermediates can be found in Refs. [15–17].

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