

Three-experiment method for the elucidation of the rate-limiting step in catalytic reactions. Theoretical considerations

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Introduction

The elucidation of the nature of the rate-limiting step is the major question in mechanistic studies of any chemical reaction. A routine procedure for the determination of the rate-limiting step using the orders in reagents may lead to false conclusions when in a catalytic reaction catalyst deactivation and regeneration processes take place [1,2]. Therefore, the usage of the method of competitive reactions has become indispensable. Recently, this approach has been widely used for obtaining Hammett correlations (in particular for the Heck reaction [3,4,5,6,7,8,9,10]). However, an employment of only competitive experiments (with two or more competing substrates) for determination of the Hammett parameters (ρ) and, consequently, the rate-limiting step has led to a certain confusion. For example, it has been incorrectly asserted that absolutely all of the catalytic cycle steps influence the reaction selectivity (usually, a measurable parameter of competitive experiments); the influence of the nature of a substituent on the selectivity of competitive reactions is considered as the influence of substituent on the rate of noncompetitive reactions; the parameters ρ of Hammett correlations obtained in competitive experiments are suggested to be concurrent with the corresponding parameters of the noncompetitive reactions. In our opinion, there is a misunderstanding of the fact that the results of the competitive and noncompetitive reactions may dramatically differ from one another. However, elucidation of these differences is of great importance for discrimination of alternative mechanistic hypotheses. Nevertheless, such differences have never been analyzed (except work [11]) for the Heck reaction.

Herein we demonstrate that the method of competitive reactions, despite its obvious advantages in mechanistic investigations, does not reveal full details of the rate-determining step, and sometimes is totally useless in this respect.

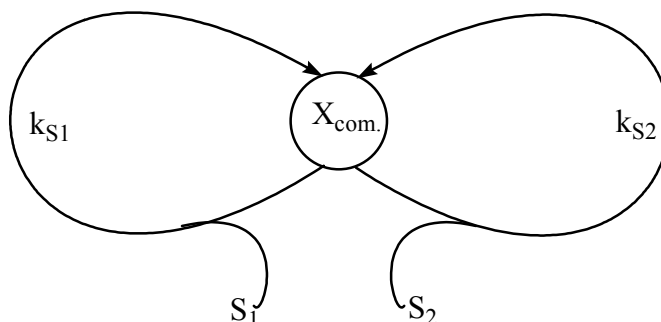
Discussion

Let us consider all possible cases arising for the pair of substrates S1 and S2 in a catalytic reaction when three experiments (one competitive and two noncompetitive) are carried out. The use of equal concentrations in all the experiments is advantageous, since it does not require the determination of the exact dependences of the reaction rate on the substrate and catalyst concentrations. In addition, this approach leads to a simplification of the kinetic equations comprising the constant reagent concentrations. It is also convenient to accept that the substrates do not differ considerably in their steric and electronic properties and, as a consequence, the nature of the rate-limiting step in all the cases is the same. All of the following speculations assume that the rate-limiting step is much slower than other reaction steps. This allows treatment of all fast reversible steps as quasi-equilibrium. In this case all the conclusions drawn from further

theoretical considerations are independent on the number of intermediates in the catalytic cycle.

Limiting case 1. *Competing substrates react with a common intermediate participating in the rate-determining step of the catalytic cycle (scheme 1).*

Scheme 1



In this case, the rates of noncompetitive experiments are described by the simplest equations

$$r_{S1} = k_{S1}[Cat]_Z, \quad r_{S2} = k_{S2}[Cat]_Z, \quad \text{where } [Cat]_Z \text{ is the total catalyst concentration.}$$

The combination of two catalytic cycles for a competitive experiment leads to the two-pathway reaction mechanism involving just one common intermediate (scheme 1). The total reaction rate obtained from the competitive experiment will be equal to the sum of the rates of the noncompetitive experiments

$$r_{S1+S2} = (k_{S1} + k_{S2})[Cat]_Z; \quad r_{S1+S2} = r_{S1} + r_{S2} \quad (1)$$

Moreover, the ratio of the reaction rates (further denoted by L) obtained from the competitive experiment will be equal to the ratio of the rate constants for the slowest steps ($L = k_{S1}/k_{S2}$). The introduction of the parameter L is useful for further consideration because the classical method of competitive reactions is limited just by the determination of L as a ratio of yields of two reaction products.

If the Hammett constants can be employed for the description of the reactivity of the used substrates, the parameters ρ determined from the competitive and noncompetitive experiments will be entirely the same. Actually, for noncompetitive experiment

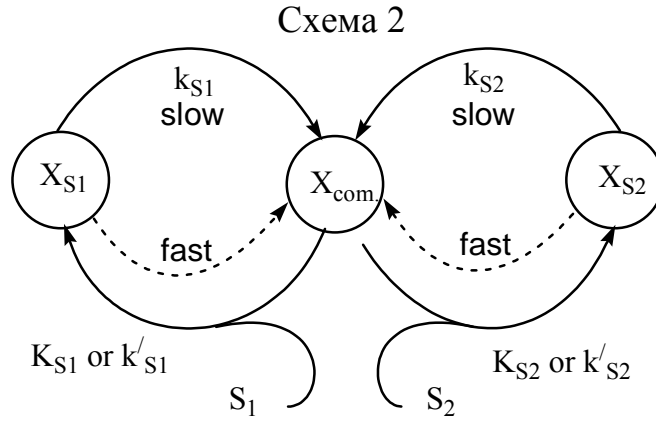
$$\text{Log} \frac{r_{S1}}{r_{S2}} = \text{Log} \frac{k_{S1}}{k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2})$$

Where, σ_{S1} and σ_{S2} are substituent constants in S1 and S2.

And for competitive experiment

$$\text{Log} L = \text{Log} \frac{k_{S1}}{k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2})$$

If the substrates react with the common intermediate that participates only in the fast step (Scheme 2), two cases may arise.



k'_{s1}, k'_{s2} and K_{s1}, K_{s2} are the rate constants of fast irreversible and the equilibrium constants of fast reversible steps respectively.

Limiting case 2.1. *The competing substrates react with the common intermediate that participates in the fast irreversible step (scheme 2). The noncompetitive experiment rates are the same as in the case 1*

$$r_{s1} = k_{s1}[Cat]_{\Sigma}, \quad r_{s2} = k_{s2}[Cat]_{\Sigma}$$

The detailed derivation of the steady-state kinetic rate law for the competitive reaction, with respect to the case 2.1, is given in [11]. The main feature of this equation is that it contains the rate constants (more exactly their ratio) of the two fast competitive steps

$$r_{s1+s2} = \frac{(L+1)k_{s1}k_{s2}[Cat]_{\Sigma}}{Lk_{s2} + k_{s1}} \quad (2)$$

The parameter L in this case, reflects the ratio of the rate constants of the fast irreversible steps (k'_{s1} and k'_{s2}) having a common intermediate ($L = k'_{s1}/k'_{s2}$).

Importantly, the parameters ρ determined from both competitive and noncompetitive experiments can be different since they are connected through a different combination of rate constants. For the noncompetitive experiment

$$\text{Log} \frac{r_{s1}}{r_{s2}} = \text{Log} \frac{k_{s1}}{k_{s2}} = \rho(\sigma_{s1} - \sigma_{s2}),$$

and for the competitive one

$$\text{Log} L = \text{Log} \frac{k'_{s1}}{k'_{s2}} = \rho'(\sigma_{s1} - \sigma_{s2})$$

Limiting case 2.2. *the competing substrates react with the common intermediate participating in the fast reversible step (scheme 2).*

The quasi-equilibrium approximation can be applied to the fast reversible step, and as a result the rates of noncompetitive experiments can be expressed as

$$r_{s1} = \frac{K_{s1}k_{s1}[Cat]_{\Sigma}}{1 + K_{s1}}, \quad r_{s2} = \frac{K_{s2}k_{s2}[Cat]_{\Sigma}}{1 + K_{s2}}$$

and the total rate of the competitive experiment as

$$r_{s1+s2} = \frac{(K_{s1}k_{s1} + K_{s2}k_{s2})[Cat]_{\Sigma}}{1 + K_{s1} + K_{s2}} = \frac{(L+1)K_{s2}k_{s2}[Cat]_{\Sigma}}{1 + K_{s1} + K_{s2}} \quad (3)$$

The parameter $L = \frac{K_{S1}k_{S1}}{K_{S2}k_{S2}}$ in this case involves the rate constants of the slow steps and the equilibrium constants for the preceding fast steps. As previously, it is equal to the ratio of rates for two pathways in competitive experiment.

Obviously, if the quasi-equilibrium is shifted towards the intermediate participating in the rate-determining step ($K_{S1}, K_{S2} \gg 1$), then the cases 2.2 and 2.1 will become kinetically indistinguishable. This is clear for noncompetitive experiments

$$r_{S1} = \frac{K_{S1}k_{S1}[Cat]_{\Sigma}}{1 + K_{S1}} \approx k_{S1}[Cat]_{\Sigma}, \quad r_{S2} = \frac{K_{S2}k_{S2}[Cat]_{\Sigma}}{1 + K_{S2}} \approx k_{S2}[Cat]_{\Sigma}$$

However, when $K_{S1}, K_{S2} \gg 1$, the rate equation of the competitive experiment (3) can easily turn into the equation (2). Thus, the distinction between the cases 2.1 and 2.2 is just dependant on the parameter L . Clearly, the conclusions, concerning the difference of the parameters ρ obtained from the competitive and noncompetitive experiments, drawn above for the case 2.1 can be now used for the case 2.2. (when $K_{S1}, K_{S2} \gg 1$).

When opposite condition $K_{S1}, K_{S2} \ll 1$ is true, the quasi-equilibrium will be shifted towards the common intermediate reacting with the substrate, so the rate equation of the competitive experiment turns into

$$r_{S1+S2} = \frac{(K_{S1}k_{S1} + K_{S2}k_{S2})[Cat]_{\Sigma}}{1 + K_{S1} + K_{S2}} \approx (K_{S1}k_{S1} + K_{S2}k_{S2})[Cat]_{\Sigma}$$

And for noncompetitive experiment

$$r_{S1} = \frac{K_{S1}k_{S1}[Cat]_{\Sigma}}{1 + K_{S1}} \approx K_{S1}k_{S1}[Cat]_{\Sigma}, \quad r_{S2} = \frac{K_{S2}k_{S2}[Cat]_{\Sigma}}{1 + K_{S2}} \approx K_{S2}k_{S2}[Cat]_{\Sigma}$$

Subsequently, $r_{S1+S2} = r_{S1} + r_{S2}$, which is similar to equation 1. Thus, the kinetics is indistinguishable for the case 2.2 (when $K_{S1}, K_{S2} \ll 1$) and case 1 (equation 1). Moreover, the Hammett equation indicates for these cases that the parameters ρ obtained from competitive and noncompetitive reactions coincide. Actually, for noncompetitive reaction

$$\text{Log} \frac{r_{S1}}{r_{S2}} = \text{Log} \frac{K_{S1}k_{S1}}{K_{S2}k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2})$$

and for competitive

$$\text{Log} L = \text{Log} \frac{K_{S1}k_{S1}}{K_{S2}k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2})$$

The obtained equations allow prediction of the rate ratio of the three reactions (one competitive, and two noncompetitive) which can be observed in the experiment. As shown, the cases 2.1, and 2.2 (when $K_{S1}, K_{S2} \gg 1$) are described by just one equation (2). The assumption that the first substrate (S1) in noncompetitive experiment is more reactive ($r_{S1} > r_{S2}$) leads to a conclusion that $k_{S1} > k_{S2}$. Hence for the cases 2.1 and 2.2 (when $K_{S1}, K_{S2} \gg 1$), when $k_{S1} > k_{S2}$, it is reasonable to write down the following

$$\frac{r_{S1}}{r_{S1+S2}} \approx \frac{Lk_{S2} + k_{S1}}{Lk_{S2} + k_{S2}} > 1$$

It is possible to show that the corresponding relation r_{S2}/r_{S1+S2} is be less than one. Thus, for the mechanism involving quasi-equilibrium steps (case 2.2., when $K_{S1}, K_{S2} \gg 1$) and for the mechanism involving irreversible steps (case 2.1.), the competitive

experiment rate must have an intermediate value as compared to those for noncompetitive experiment rates. With regard to the magnitude of the sum of the noncompetitive experiment rates (the maximum possible rate of competitive experiment for the considered mechanisms) we obtain the following rate sequence

$$r_{S1} + r_{S2} \succ r_{S1} \succ r_{S1+S2} \succ r_{S2}$$

As it has already been shown that $r_{S1+S2} = r_{S1} + r_{S2}$ for the cases 1 and 2.2 (when $K_{S1}, K_{S2} \ll 1$). Consequently, the rate sequence of the three experiments is dramatically different, i.e.

$$r_{S1} + r_{S2} = r_{S1+S2} \succ r_{S1} \succ r_{S2}$$

Finally, when $K_{S1}, K_{S2} \ll 1$ and $K_{S1}, K_{S2} \gg 1$ are not realized (e.g. K_{S1}, K_{S2} are not very small and not very high) the third rate sequence

$$r_{S1} + r_{S2} \succ r_{S1+S2} \succ r_{S1} \succ r_{S2}$$

becomes possible.

Conclusions

Consequently, on the basis of only three experiments with a pair of substrates one can draw the following conclusions

1. If the rate of competitive experiment is lower than the sum of the rates of two noncompetitive experiments the competitive substrates do not participate in the rate-determining step of the catalytic cycles.
2. If the rate of competitive experiment is lower than the sum of the rates of two noncompetitive experiments, but higher than the reaction rate for the most reactive substrate (of the two), the substrates participate in the fast reversible steps and the major part of the catalyst must exist in the form of intermediates formed before the substrates enter the catalytic cycle (the equilibrium constants have small values).
3. If the rate of competitive experiment is lower than the rate of the reaction of the most reactive substrate, but higher than that for the less active one, this may indicate involvement of the substrates either in the fast irreversible or in the fast reversible steps. Noteworthy, in the last case, the major part of the catalyst must exist in the form of intermediates of the catalytic cycle that are formed after the substrates enter the catalytic cycle (the equilibrium constants have high values). In this case, the parameters ρ of the Hammett correlations determined from competitive and noncompetitive experiments have different values.
4. If the rate of competitive experiment has a value either higher than the sum of the rates of noncompetitive experiments or lower than the rate of the reaction of the less active substrate, this disagrees with considered mechanisms. However, this fact itself is important for the discrimination of alternative mechanistic hypotheses.

Apparently, the employment of several pairs of substrates increases the reliability of the predictions, especially, in demonstration of the quantitative adequacy of the mechanistic hypothesis. A mechanistic study of the Heck reaction based on the approach formulated above is in progress.

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