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Focus Article, *Mendeleev Commun.*, 2017, **27**, 213–223
Mendeleev Communications

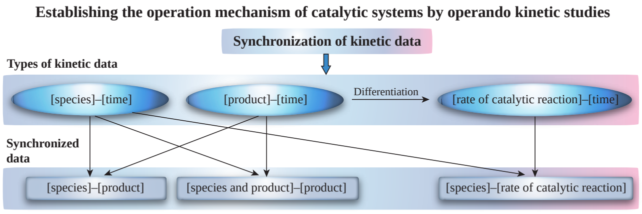
Kinetic aspects of operando studies: state-of-the-art and unexplored possibilities

Alexander F. Schmidt,* Anna A. Kurokhtina and Elizaveta V. Larina

Department of Chemistry, Irkutsk State University, 664003 Irkutsk, Russian Federation.
Fax: +7 3952 201 307; e-mail: aschmidt@chem.isu.ru

DOI: 10.1016/j.mencom.2017.05.001

Operando spectroscopy is one of the most effective tools for investigating catalytic systems, providing unique experimental data that has long been required for kinetic studies of catalytic reactions. However, the utilization of kinetic methods in operando studies is frequently not taken into account. To address this issue, this article provides a discussion of the current status, problems, and prospects of operando kinetic studies of complex catalytic reactions.



Introduction

Complex catalytic processes usually exhibit very complicated dynamics[1,2] due to the coupling between numerous elementary steps inside catalytic cycles and the formation, deactivation, and reactivation of active species proceeding outside the main catalytic cycles. Therefore, obtaining reliable data on the fundamental aspects of such reactions is a challenge which requires a set of physical and physicochemical approaches and methods to be used for fundamental investigations. Undeniably, the development of physical investigation methods considerably influences the progress of chemical science, as exemplified by the use of spectroscopic studies in catalysis. Initially, all spectroscopic methods in catalytic investigations were applied as *ex situ* techniques only, generally providing information on the initial (catalyst precursor) or final (after a catalytic reaction) state of catalysts. Despite the importance of this information, it does not shed light on the dynamics of the reaction. Therefore, *in situ* measurements were used as next-stage physicochemical methods for characterizing catalytic reactions. Initially, most of these studies were carried out under model conditions, *i.e.*, at low substrate/catalyst ratios, in the presence of stabilizing ligands and in the absence of catalytic system components, and under other conditions that do not allow the catalyst to achieve high turnover numbers. Subsequently, spectroscopic investigations of catalysts were directly performed under reaction conditions as a breakthrough due to to the possibility of tracking the catalyst state changes (at least for observable catalyst forms) during substrate-to-product conversion.

Currently, *in situ* catalyst states under real reaction conditions can be studied *via* the following techniques (Section S1, Online Supplementary Materials): X-ray absorption (XAS, EXAFS and XANES),[3,4] Raman spectroscopy,[5] IR spectroscopy (TIRS, DRIFTS, ATR-IRS and PM-IRRAS),[6] UV-VIS spectroscopy,[7,8] NMR spectroscopy,[9,10] and electron microscopy (ETEM, ESTEM and EELS/STEM).[11–13]

However, the identification of a catalyst form by *in situ* measurements is still insufficient to determine its role in catalytic reactions. In particular, additional information on the temporal profiles of catalytic activity is required and thus the measurement of substrate conversions as functions of time is necessary. Recently, an approach to simultaneous spectroscopic investigation of catalyst transformation and catalytic reaction progress under real conditions has been suggested, termed operando spectroscopy.[14] The operando methodology gains popularity for investigating catalytic

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Alexander F. Schmidt received his PhD and Dr. Sci. (Chemistry) degrees from Irkutsk State University in 1992 and 2003, respectively. He worked at the groups of Professor E. Lindner at the University Tübingen (Germany) in 1992–1993, Professor W. Keim at the RWTH Aachen (Germany) in 1999, and Professor K. Kohler at Technical University of Munich (Germany) in 2006. He became a Full Professor in 2005. He is currently a head of Chair of Physical and Colloidal Chemistry of Irkutsk State University. His research interests focus on the kinetics and mechanisms of catalytic reactions. He has authored about 150 scientific publications.

Anna A. Kurokhtina received her PhD degree under the guidance of Professor A. F. Schmidt at the Irkutsk State University in 2011. She is currently an associate professor at Chair of Physical and Colloidal Chemistry of this university. Her current scientific interests focus on palladium-catalyzed cross-coupling reactions. She has authored about 60 scientific publications.

Elizaveta V. Larina received her master's degree under the guidance of Professor A. F. Schmidt at the Irkutsk State University in 2013. She is currently a post-graduate fellow of this university. Her current scientific interests focus on palladium-catalyzed cross-coupling reactions. She has authored about 40 scientific publications.

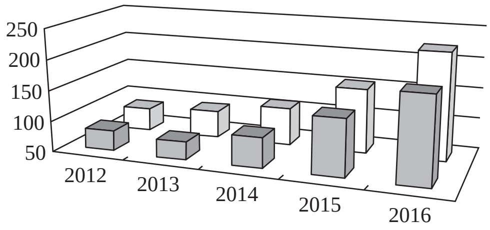


Figure 1 Number of publications containing the term ‘operando spectroscopy’ in titles, abstracts, or keywords, as indexed in the Web of Science (white) and Scopus (grey) in 2012–2016.

reactions mechanisms, as exemplified by the growing number of papers indexed in the Web of Science and Scopus over the last years (Figure 1). Moreover, several recently published special issues of journals specializing in catalysis were devoted to operando techniques.[15–17] The above facts indicate the great interest of the catalytic community in operando investigations into catalytic reaction mechanisms.

However, an analysis of the literature related to operando spectroscopy reveals that the importance of applying kinetic methods in the operando studies of catalytic reactions is underestimated. In addition, the operando methodology opens new possibilities for kinetic studies by providing unique experimental data applicable to not only quantitative kinetic methods (*i.e.*, the kinetic modeling of a complete reaction mechanism) but also simple qualitative methods used in the visualization-based interpretation of kinetic data.

Here, we attempt to specify the concept of operando methodology with regard to kinetic investigations into catalytic processes, in particular, to elucidate the role of the species identified in an operating catalytic system and to establish a reliable operation mechanism.

Concept of operando studies

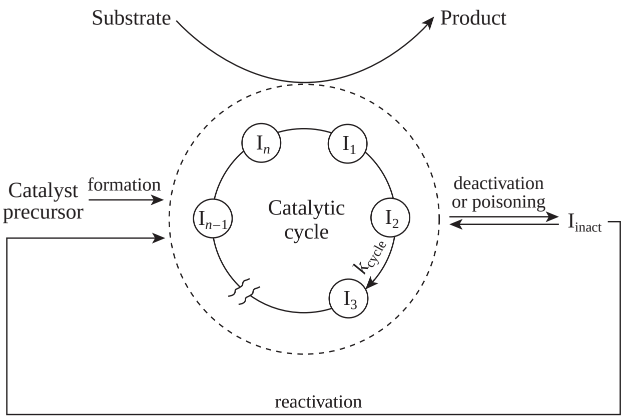
Previously,[5] when the term ‘operando spectroscopy’ was introduced, the concept of operando spectroscopy was represented by spectroscopic studies of catalysts (catalytic systems) under real reaction conditions, where simultaneous determination of structure/composition and activity/selectivity[5] was implemented to obtain fundamental information on the [structure/composition]–[activity/selectivity] relationship.[17,18] The rate constant or free activation energy should be used as a main fundamental descriptor of catalytic activity instead of commonly used turnover frequency (TOF, reaction rate divided by catalyst amount). However, the complexity of catalytic reactions, which proceed *via* a large number of consequent-parallel elementary steps, makes the determination of all involved rate constants practically impossible. Therefore, to describe such systems, an effective apparent constant k_{app} could be introduced, being a proportionality coefficient in the following empirical equations:

$$[\text{rate}] = k_{\text{app}}[\text{active species amount}]^n,$$

$$[\text{TOF}] = k_{\text{app}}[\text{active species amount}]^{n-1}.$$

Therefore, to achieve the main goal of operando studies, *i.e.*, obtaining fundamental information on [structure/composition]–[activity/selectivity] relationships,[5,14] the [active species amount]–[activity] and similar relationships are required to evaluate apparent rate constants.

The current knowledge in the field of catalysis does not leave any doubt that the interaction of a catalyst precursor loaded in a reactor with a reaction medium initiates numerous transformations of the above catalyst to produce a number of species. Thus, the postulate that ‘the catalyst is any product of catalyst precursor conversion identified in the reaction mixture’ is evidently incorrect since not only active but also inactive catalyst species can occur among the detected products. Nevertheless, this logic is rather frequently and unconsciously used in publications, impacting on the development of operando study concepts. Inactive species play a role no less important as compared to active species due to affecting the amounts of the latter and, consequently, influencing the performance of the catalytic system by being involved in the following processes: (i) formation of active species from catalyst precursor, (ii) deactivation/poisoning (formation of inactive species from active ones), and (iii) reactivation of active species (iterative formation of active species from inactive ones) (Scheme 1).



Scheme 1 Schematic diagram of key processes occurring in a catalytic system.

As the reaction proceeds, the amounts of active and inactive species formed from a catalyst precursor are subjected to considerable variation. Therefore, to obtain information on the [structure/composition]–[activity/selectivity] relationship and to establish correlations such as [species amount]–[activity], both catalytic reaction rate measurements (*i.e.*, the formation rate of substrate conversion products) and the temporal variation of the amount of supposedly catalytically active species are required. Nevertheless, the operando spectroscopy-related literature does not extensively describe the temporal profiles of such catalyst-derived species. Below, we demonstrate that identifying the roles of observable species (active or inactive) in catalysis and, consequently, obtaining [structure/composition]–[activity] relationships using operando studies is impossible without the simultaneous kinetic control of the amounts of catalytic reaction and catalyst precursor transformation products.

Catalyst selectivity, frequently considered as a necessary attribute of operando spectroscopy,[5,18] is also determined by the relative activities of a catalytic system in the formation of several but not one products. The activity of a catalyst in the formation of different products is directly connected with its so-called differential selectivity (see below). However, note that the percentage of operando spectroscopic studies on catalyst selectivity is very low, measurements of differential selectivity not being reported at all.

Therefore, in our opinion, to control catalytic activity, operando studies should focus not only (and not as much) on *in situ* spectroscopic detection and identification of catalyst transformation products along with the simultaneous kinetic control of substrate conversion products but also on the simultaneous kinetic control of observed catalyst species. In other words, the *in situ* spectroscopic detection and identification of catalyst species are only a tool providing information on the kinetics of catalyst transformations and their roles in the catalytic system, which can only be obtained by the analysis of kinetic data. The kinetic data make it possible to elucidate the roles of species (active or inactive) observed by the used method and to determine their contribution to either product formation or total substrate conversion (when the same product can be produced *via* several routes).

For the above reasons, the term operando spectroscopy is not completely well turned, emphasizing *in situ* spectroscopic studies of the working catalyst and ignoring the requirement of obtaining kinetic data to establish the roles of observed species. In addition, a possibility to study the operating catalyst under real conditions *via* not only spectroscopic methods but also different versions of *in situ* electron microscopy has recently appeared.[11,12,19–21] Moreover, a certain confusion arises when, for instance, papers describing any *in situ* spectroscopic study are termed as operando studies, even if spectroscopy is only used for the kinetic control of catalytic reaction products[22] or a spectroscopic investigation of the catalyst with simultaneous measurement of its performance is carried out, but data on activity/selectivity are not taken into account when drawing conclusions.[23–25] As the goal of operando studies is not only the identification of catalyst transformation products but also their mandatory kinetic control with simultaneous kinetic control of catalytic reaction products, a better definition of such investigations could be ‘operando kinetics’ or ‘operando kinetic studies of a catalyst’.

Goals and tasks of operando studies

To achieve the main strategic goal of obtaining information on [structure/composition]–[activity] relationships, the operando investigations should and can solve tasks that can be divided into two closely associated groups. Tasks of the first group aim at gaining novel fundamental knowledge on full mechanisms operating in catalytic systems where the roles of observed catalytic species are precisely identified, whereas those of the second group have more applied aspects and are determined by the needs of chemical industry (*i.e.*, the commercialization of new catalytic processes and optimization of known ones).

The above fundamental knowledge on full mechanisms operating in catalytic systems means not only establishing the mechanism of the catalytic cycle providing the largest contribution to the formation of desired catalytic reaction products, but also determining the mechanisms of coupled processes influencing the activity and selectivity of the catalytic system, *i.e.*, the formation/deactivation/iterative reactivation of active species (Scheme 1). This group of processes can be properly defined as catalyst transformations occurring outside the main catalytic cycle. The importance of any knowledge on these processes (*e.g.*, their kinetics) is accounted for by the fact that the ratio of their rates directly determines the amount of active species and, consequently, the activity of the catalytic system in the formation of products, finally defining selectivity. In addition, the dynamic properties of these processes are responsible for the possible non-stationary catalyst amount in the course of the catalytic reaction. Since the catalytic cycle and catalyst transformations occurring outside it can influence each other due to process coupling, each of them may be a limiting factor for catalytic activity.

The applied aspect of operando studies features the construction of more reliable kinetic models that can play a key role in the development and optimization of processes.[6] The tasks of kinetic chemical process modeling always face the problem of kinetic data deficiency mainly caused by the existence of unobservable components due to either their ultra-low concentration (short lifetime) or the absence of suitable detection methods at the disposal of a research group. The low concentration of unobservable components that do not make any significant (*i.e.*, that exceeding the experimental error) contribution to material balance does not mean that these components play an insignificant role in the catalytic system. Excellent evidence illustrating this point is provided by the successful examples of catalytic reactions using ultra-low catalyst loadings (ppm and ppb orders of magnitude),[26–28] which are considerably lower than the detection limit of the most sensitive methods usually used in operando studies. Kinetic data deficiency is a perennial problem even in view of the continuously developed analytical methods, making it necessary to provide as many dimensions for kinetic measurements as possible to construct reliable kinetic models. Partially, this task is indeed solved by operando studies, which provide the experimental observation of catalyst transformation products along with those of substrate conversion.

To attain the two goals of operando studies, it is necessary to solve technical problems related to the simultaneous identification and kinetic control of products and intermediates of the two types of processes operating in a catalytic system. The first type represents catalyst transformations under real conditions outside the main catalytic cycle, and the corresponding kinetic data is hereinafter referred to as the type 1 kinetic data. The second type represents catalyst transformations occurring in the main catalytic cycle, where catalytic reaction products are formed, and is hereinafter referred to as the type 2 kinetic data. The synchronization of both types of kinetic data can help to elucidate the role of a given species observed in the test catalytic system, *i.e.*, whether it is the active catalyst or is necessary for active catalyst formation (positive role in catalysis), or whether it is a deactivated form of the catalyst or plays a key role in catalyst deactivation (negative role in catalysis). In our opinion, the simultaneous acquisition of two types of kinetic data is actually the main experimental task of the operando kinetic studies of catalytic processes (operando kinetics). The solution of this task unequivocally leads to the appearance of a set of important technical issues arising from the modification of the process for reactors that enable synchronous acquisition of kinetic information from *in situ* characterization and reaction kinetics from real-time product analysis.[6,24,29,30]

Requirements of operando studies

Operando studies significantly rely on the construction of special reactors[6,16,31] that provide the possibility of simultaneous implementation of various *in situ* techniques, on the one hand, and ensure that reaction conditions are identical to those in conventional reactors (including industrially used ones), on the other hand. In contrast to *ex situ* measurements, *in situ* techniques exclude the uncontrolled influence of measurement conditions on the results of such measurements. For instance, *ex situ* analyses involve the removal of a solvent and other compounds from the reaction mixture, heating the samples and exposing them to a vacuum or strong electric fields, *etc*. Such manipulations (especially, for the analysis of highly reactive catalytically active substances) can in theory result in an erroneous understanding of the processes operating in a real catalytic system and in contradictory conclusions based on the results of implementing different methods.

However, note that the tendency of performing all measurements using *in situ* techniques only can result in an unjustified complication of equipment and, as a consequence, in its high cost. In reality, some of these measurements can be carried out using *ex situ* methods, providing results well-suited for their purpose. For instance, the analyses of the liquid and/or gas phases of reaction mixtures to determine the amounts of stable compounds present therein aiming at measuring the activity and selectivity of the catalytic system can be performed *ex situ* by periodical sampling for GC or GC-MS analysis. If a large number of products are formed in a catalytic reaction, methods involving prior component separation are considerably better suited than *in situ* spectroscopic measurements of such multi-component systems.

Another requirement of operando studies is the reproduction of the reaction mixture composition. Researchers are willing to decrease the substrate/catalyst ratio (*i.e.*, to increase the catalyst content of the reaction mixture) to achieve higher quality of the spectroscopic data and solve problems resulting from the insufficient detection limit of the methods. Unfortunately, this compromise of operating catalytic systems under model conditions instead of real ones can dramatically affect the results. Examples of the strong influence of a substrate/catalyst ratio on catalyst transformations outside the main catalytic cycle, which determine the amount of active species, have been known for a long time. For instance, different variants of the above influence were observed for cross-coupling reactions.[1,32–36] If the substrate participates in the formation and/or reactivation of active species (*e.g.*, metallic Pd leaching under the action of aryl halides), the substrate/catalyst ratio becomes the major factor determining the active species amount. Another reason for the importance of the substrate/catalyst ratio can be the formation of reactive substances in a side reaction, which can serve, for example, as additional ligands.[37] In such cases, the properties of the catalytic system become dependent on catalyst turnover numbers, which can be limited by the substrate/catalyst ratio.

On the kinetic control of catalyst transformations in operando kinetic studies

Before determining the necessity of kinetic measurements in operando studies elucidating the operation mechanism of catalytic systems, it is useful to define the term ‘reaction mechanism’. The reaction mechanism concept includes two components:[1] a set of steps (usually called the mechanistic reaction scheme) that determines the mechanism structure, *i.e.*, the interplay of reactants and intermediate species; and information on the structures/compositions and reactivities of all reactants and intermediates, which determines the chemical (or physicochemical) component of the reaction mechanism. Importantly, no hierarchical subordination between these two components exists, and they are equally necessary for establishing the reaction mechanism.[1]

Since no assumption concerning a reaction mechanism can be considered reliable ‘until it is shown to be consistent with the observed kinetics’,[38] kinetic investigations are necessary for establishing a reaction mechanism. Regarding the operation mechanism of catalytic systems, ‘the most compelling evidence for the identity of the true catalyst will always be kinetic in nature’,[39] and only then the two types of kinetic data on catalyst transformations outside and inside the main catalytic cycle can be used to construct hypotheses of the role of one or another catalyst species in catalysis.[40] Nevertheless, in numerous recently published operando studies, attempts to collect type 1 kinetic data and synchronize it with the type 2 kinetic data are relatively sparsely undertaken, even if this is possible from the technical (experimental) point of view. For instance, among 22 selected research papers dealing with operando spectroscopy published in 2011–2016,[9,23,25,41–59] kinetic dependences such as [amount of catalyst species detected]–[observed activity] were obtained as a result of such synchronization in less than half of them,[9,42,44–47,49,51,59] and measurements of selectivity and its synchronization with type 1 kinetic data (correlation of selectivity with the amount of catalyst species observed) were reported in only one paper.[49] Most frequently, investigations termed ‘operando spectroscopy’ by the authors are limited to simultaneous *in situ* spectroscopic/microscopic studies of catalyst transformation products and temporal profile measurements of substrate conversion products (type 2 kinetic data), that indeed nominally corresponds to the accepted definition of operando spectroscopy.[5,14] However, the above temporal profile measurements become useless when not synchronized with type 1 kinetic data since, in this case, they are not used to achieve the goal of operando studies, *i.e.*, establishing the roles of observed species in catalysis.

At this time, no experimental verifications of hypotheses concerning the role of one or another compound detected in catalytic substrate conversion are attempted. The detection of catalyst transformation products does not *per se* mean that such species play an important (and especially positive) role in catalysis with respect to activity/selectivity. However, this hypothesis is very often accepted by default. The role of detected species can be negative, neutral or insignificant. Kinetic studies are the only tool to determine the catalytic role of substances, which are experimentally observed by *in situ* techniques, and usually require additional specifically designed experiments. In only few papers, the researchers considered the theoretical possibility of another unobservable species being the true active catalyst, even though kinetic evidence was obtained for the participation of another species observed under real catalytic conditions. This situation is possible if the amount of unobservable species linearly depends on that of observed species due to the intrinsic properties of the catalytic system,[44] forcing researchers to support their conclusions by additional experimental evidence. The excellent examples reflecting the exact approach to operando kinetic studies were provided.[45–49,51]

In our opinion, the absence of kinetic measurements and/or synchronization of two types of kinetic data in operando studies means that establishing the composition and structure of reaction intermediates and products is still considered to be sufficient evidence of the reaction mechanism. Actually, obtaining complete information on the composition and structure of all chemical system components is necessary but insufficient for establishing the reaction mechanism since this information does not allow the mechanistic reaction scheme to be determined and only makes it possible to reveal the chemical (or physicochemical) component of the reaction mechanism.[1]

From a mathematical viewpoint, data on the composition of all reactants/intermediates allows one to unambiguously determine the obligatory set of linearly independent stoichiometric equations required to find all possible equations of component material balance, describing the ratios between the amounts of components during the reaction. The mathematical problem of searching linearly independent stoichiometric equations based on the above composition-related data is reduced to solving a system of linear algebraic equations determining the composition of reaction components (*i.e.*, the molecular matrix of the system; see Section S2). The obtained solution provides a set of stoichiometric equations describing transformations that possibly occur in the system (*i.e.*, the stoichiometric matrix of the system; see Section S2). The stoichiometric matrix is sufficient for establishing all material balance equations describing the ratios between the amounts of components at any reaction time. However, the above matrix is only one of an infinite number of related linearly dependent matrices that also conform to the observed component composition. The problem of finding the correct set of stoichiometric equations corresponding to real reaction mechanism steps based on the knowledge of component composition has no solution. Note that an analogous conclusion is also correct for the practically unattainable hypothetic situation when the composition of all reaction system components is known (see Section S3). Therefore, the effective operando studies of catalytic systems cannot be reduced to operando spectroscopic detection of catalyst transformation products and establishing their structure and composition since additional data is necessary to determine their roles.

As demonstrated below, such data should not be limited to kinetic information on catalyst transformations inside the catalytic cycle (catalytic system activity, *i.e.*, type 2 data) since knowing the kinetics of catalyst transformations outside the catalytic cycle is required to suggest an adequate reaction mechanism.

Catalytic system activity: synchronization of type 1 integral kinetic data with type 2 differential kinetic data

Since one can detect and characterize the composition and structure of only a catalyst species with initially unclear functions and a high probability of other unobservable species playing an important role in catalysis exists, the measurement of catalytic reaction rate (*i.e.*, the rate of substrate conversion into products) is the only opportunity to establish the rates of the catalytic cycle steps. Indeed, in a steady state of the catalytic cycle (quasi-stationarity), the rates of all its steps are equal to each other and to the accumulation rate of a product formed in the catalytic cycle. Thus, even when the real-time observation of all catalytic cycle intermediates is impossible or only some of them can be observed, the measurement of the rate of product accumulation (*i.e.*, the catalytic reaction rate) allows one to obtain unequivocal information on the rates of all catalytic cycle steps.

The differentiation of type 2 integral raw kinetic data providing information on catalytic cycle rates and knowing the concentrations of observed catalyst transformation products (type 1 integral raw kinetic data) at the same reaction times enable the determination of the roles of these species in catalysis by the synchronization of these data types. In this case, the synchronization of types 1 and 2 kinetic data means the procedure of matching raw integral kinetic data such as [species amount]–[time] with differential kinetic data on the catalytic cycle such as [catalytic reaction rate]–[time] (Scheme 2, **A**).

Synchronization of kinetic data (Scheme 2, **A**) can result in the following outcomes.

Example 1. The positive linear dependence of the amount of the detected species on the rate of catalytic reaction product formation [Figure 2(*a*)] that is independent of the amount of catalyst loaded into the reactor. This behavior implies that the catalytic reaction exhibits first-order kinetics with respect to the concentration of the observed species and serves as a convincing indicator for either the participation of this species as a catalytic cycle intermediate directly in the product formation step (*i.e.*, active species) or its involvement in fast exchange equilibria with such intermediates.[49] Notably, being involved in the fast equilibrated exchange with the catalytic cycle intermediate, these species are outside the catalytic cycle and are inactive. However, the fast exchange between active and inactive species makes them kinetically indistinguishable because of the identical regularities of their concentration changes.

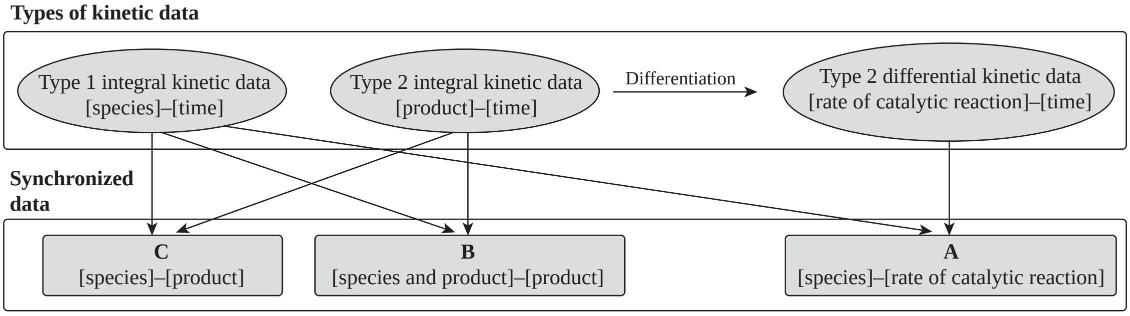
Example 2. The positive nonlinear dependence of the amount of the detected species on the rate of catalytic reaction product formation [Figure 2(*b*)], *i.e.*, linearity of the ln[reaction rate] *vs.* [amount of detected species] plot with a slope between one and two that is independent of the amount of catalyst loaded into the reactor. This behavior implies that the catalytic reaction order with respect to the observed species is greater than one but less than two, and it can result from the existence of steps that exhibit nonlinear kinetics with respect to intermediates (for instance, those of the second order) involved in the sequence of catalytic cycle steps.

Such a behavior is a convincing indicator for the participation of the observed species as a catalytic cycle intermediate either directly in the step of product formation (*i.e.*, active species) or in fast exchange equilibria with such intermediates. The reaction order with respect to the active species in such cases can vary from one to two depending on the ratio of the rates of linear and nonlinear catalytic cycle steps. When the second order reaction step nonlinear in relation to intermediates is rate-determining, the reaction order with regard to the observed species can also be very close to an integer value of two.

Example 3. Nonlinear, including quasi-cyclic, dependences (with both positive and negative sections) of the amount of the detected species on the rate of catalytic reaction product formation are observed [Figure 2(*c*)–(*h*)]. Such dependences can appear once the observed species are either catalytic cycle intermediates (*i.e.*, active species), or the species involved in a fast exchange equilibrium with such intermediates, or inactive species outside the catalytic cycle. Nevertheless, when the amounts of species and the catalytic reaction rates are measured precisely, the functions of these species in catalytic systems can be reliably established.

Example 3.1. If extensive curve sections with positive dependences of the amount of species on the catalytic reaction rate and short sections with negative dependences at quasi-cyclic curves [Figure 2(*c*),(*d*)] are present, the observed species are catalytic cycle intermediates or are involved in a fast exchange equilibrium with such intermediates. At the same time, the quasi-cyclic character of the curve implies that the catalytic reaction product is not formed in the step where the species in question are involved.

Based on the theoretical concept of catalytic reaction kinetics, for a stable steady-state (quasi-stationary) set of catalytic cycle steps, an increase in the amount of any intermediate should be accompanied by an increase in the rates of all steps where it is involved, consequently, leading to an increased rate of product formation. *Vice versa*, a decrease in the amount of any catalytic cycle intermediate should be accompanied by a decrease in the rates of all steps where it is involved, consequently leading to a decreased product formation rate. Thus, the amount of observed species has a positive dependence on the product formation rate. However, at particular reaction times, the phase of increased catalytic cycle intermediate amounts caused by the domination of catalyst formation/reactivation over its deactivation is succeeded by the phase of their decreased amounts when the deactivation of active species becomes dominant over their formation/reactivation. At that point in time, short sections exhibiting negative dependences appear in the plots of [amount of observed species] *vs.* [rate of product formation], being caused by insignificant distinctions of time points when different reaction intermediates



Scheme 2 Synchronization of types 1 and 2 kinetic data.

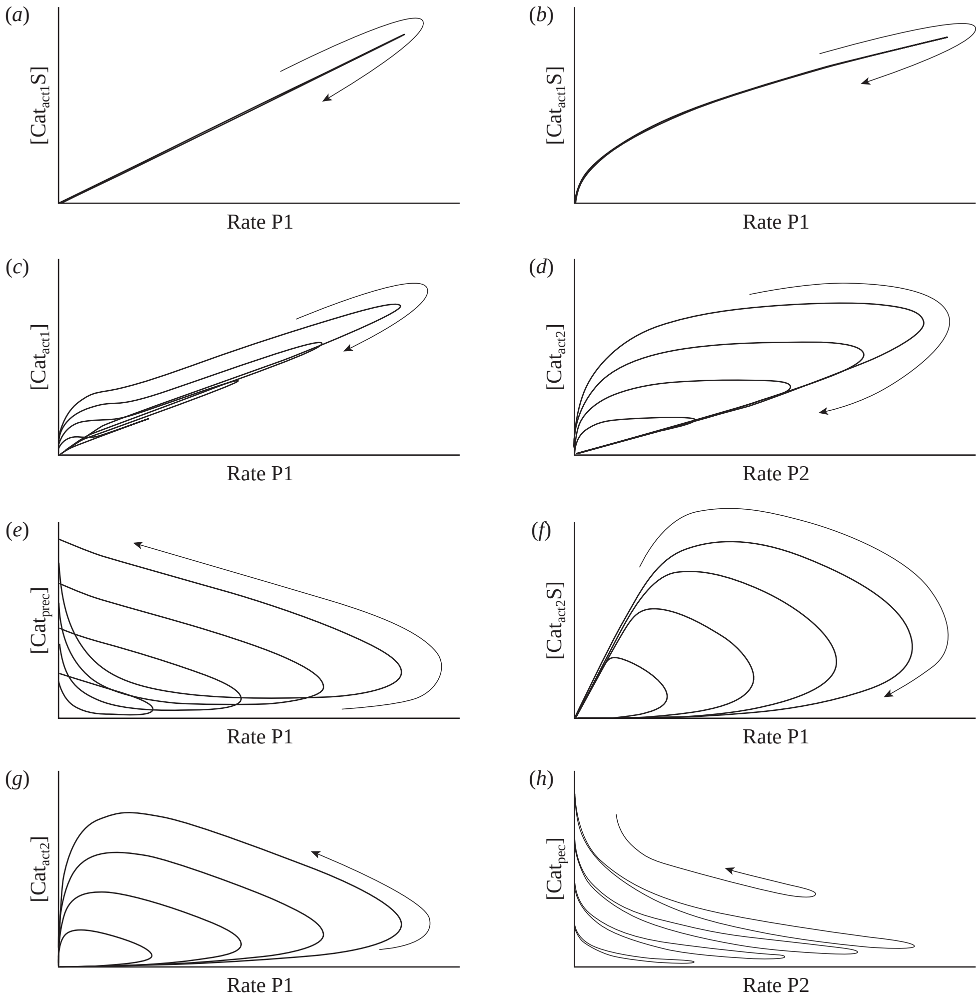


Figure 2 Simulation of [species amount]–[catalytic reaction rate] dependences for catalyst species playing different roles in the catalytic conversion of substrate S to products P1 and P2 proceeding through two catalytic cycles of the Michaelis–Menten type (see Section S4). Simulations represent the results of calculations using four different catalyst precursor loadings. The reaction progress is indicated by arrows. Explanations for cases (*a*)–(*h*) are provided in the main text. Cat$_{prec}$ denotes inactive catalyst precursor; Cat$_{act1}$and Cat$_{act1}$S denote the intermediates (active species) of the catalytic cycle where product P1 is formed; Cat$_{act2}$ and Cat$_{act2}$S denote the intermediates (active species) of the catalytic cycle where product P2 is formed; rate P1 is the formation rate of product P1; rate P2 is the formation rate of product P2. The data presented hereinafter were simulated using the Gepasi 3.10 program.[60,61] For a detailed description of simulation procedures, see Section S4.

achieve their maximal concentrations. Therefore, if the observed species is an intermediate that does not directly participate in the step of the reaction product formation (see Examples 1 and 2), the time when it achieves its maximal concentration does not coincide with that for the intermediate participating directly in the product formation step and directly determining its rate. This transition phase is succeeded by a decrease in both the amounts of all catalytic cycle intermediates and the reaction rate, resulting in a positive dependence of the amount of observed species on the reaction rate.

Example 3.2. Extensive sections exhibiting negative dependences of the amount of species on the catalytic reaction rate [Figure 2(*e*)–(*h*)] imply that these species are not catalytic cycle intermediates and are not involved in fast exchange equilibria with such intermediates, but exist outside the main catalytic cycle, *i.e.*, are inactive in the catalytic cycle of product formation. However, these species can actively participate in the formation of other products in other catalytic cycles (see Section S4).

Indeed, an increase in the amount of the observed species with a simultaneous decrease in the catalytic reaction rate (and *vice versa*) can only occur when these species do not act as intermediates of the catalytic cycle and exist outside it.

A similar analysis of operando kinetic studies data can be carried out for the family of homo- and cross-coupling reactions of aryl halides with different reagents in the presence of ligand-free catalytic systems (see Section S5). Operando kinetic studies based on *in situ* UV-VIS spectroscopy revealed that significant amounts of $[PdX_4]^{2-}$ complexes (X = halide) were formed under real catalytic conditions in all reactions considered. The acquirement and synchronization of types 1 and 2 kinetic data unequivocally indicated that the formed $[PdX_4]^{2-}$ complexes were not the intermediates of catalytic cycles producing cross-coupling products and existed outside them.

For instance, the dependence of $[PdI_4]^{2-}$ concentration on the product formation rate was obtained for the direct arylation of indole by iodobenzene [Figure 3(*a*)] using a ligand-free catalytic system. In line with the above reasoning (Example 3.2), this dependence can indicate that $[PdI_4]^{2-}$ is an inactive species in the formation of 2-phenylindole since there are extensive sections exhibiting a negative dependence of $[PdI_4]^{2-}$ concentration on 2-phenylindole formation rate. The formation of such complexes results from the homocoupling of iodobenzene to produce biphenyl.[62] As biphenyl was observed as a by-product in the above reaction, the quasi-cyclic dependence of $[PdI_4]^{2-}$ concentration on the main product (2-phenylindole) formation rate indicates that $[PdI_4]^{2-}$ is formed in a side reaction (biphenyl formation) rather than in the reaction leading to main product (2-phenylindole) formation.

The negative dependence of $[PdI_4]^{2-}$ concentration on the rate of product formation (Example 3.2) observed in the Suzuki

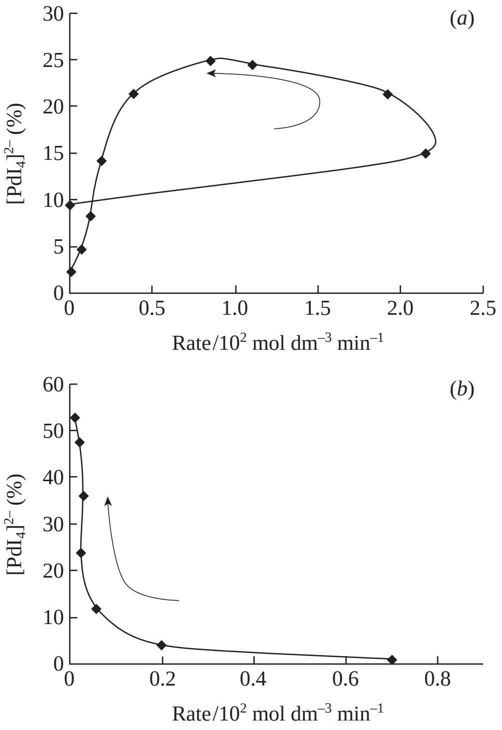


Figure 3 Percentage of $[PdI_4]^{2-}$ (relative to a maximum possible concentration under the reaction conditions) (*a*) *vs.* the rate of 2-phenylindole formation in the direct arylation of indole by iodobenzene using $PdCl_2$ as a catalyst precursor and (*b*) *vs.* biphenyl formation rate in the Suzuki reaction of iodobenzene using $PdCl_2$ as a catalyst precursor (the reaction progress is indicated by arrows).

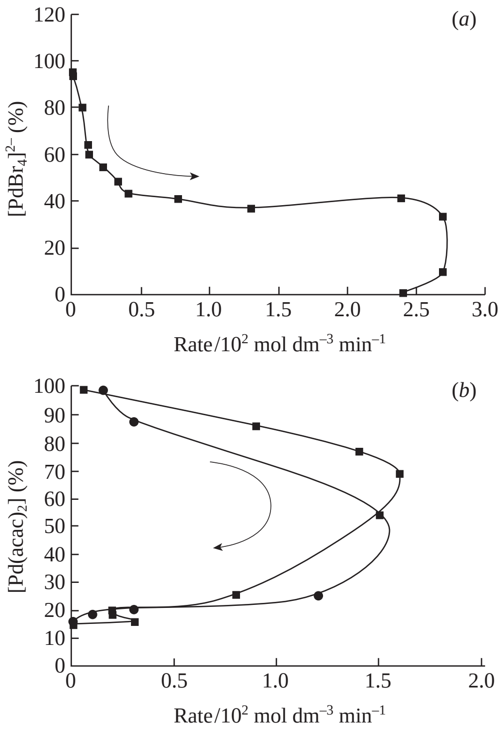


Figure 4 (*a*) Percentage of $[PdBr_4]^{2-}$ (relative to a maximum possible concentration under the reaction conditions) *vs.* stilbene formation rate in the Heck reaction of styrene and benzoic anhydride using NaBr-containing catalytic system and $PdCl_2$ as a catalyst precursor and (*b*) percentage of $Pd(acac)_2$ (relative to a maximum possible concentration under the reaction conditions) *vs.* rates of (●) biphenyl and (■) benzene formation in the reductive homocoupling of iodobenzene (the reaction progress is indicated by an arrow).

reaction of iodobenzene [Figure 3(*b*)] indicates that this species stayed outside the main catalytic cycle, and an analogous pattern was obtained for the Heck reaction with aromatic carboxylic acid anhydrides [Figure 4(*a*)]. Therefore, the formation of $[PdI_4]^{2-}$ in these processes represents the deactivation of active species. Indeed, the Heck and Suzuki reactions in the presence of ligand-free catalytic systems are accompanied by the deactivation of active palladium(0) species due to the formation of $[PdX_4]^{2-}$ complexes.[63,64] Therefore, the previously suggested role of $[PdX_4]^{2-}$ complexes in Heck and Suzuki reactions fully agrees with the data obtained by operando kinetic studies.

A negative dependence of the amount of $Pd(acac)_2$ on the product formation rate (Example 3.2) was observed for the reductive homocoupling of iodobenzene to produce biphenyl accompanied by a side reaction of its reduction using HCOONa as a reducing agent [Figure 4(*b*)], and a similar dependence was also obtained for benzene, which was formed along with expected biphenyl [Figure 4(*b*)]. Such a behavior unambiguously points to the absence of any catalytic activity of $Pd(acac)_2$.

Catalytic system selectivity: synchronization of types 1 and 2 integral kinetic data

Despite the initially postulated necessity of measuring not only the activity but also the selectivity of the catalytic system in operando spectroscopic studies,[5,14] a minor number of studies provide selectivity data. Moreover, such cases involved the so-called integral selectivity of catalytic systems (see below), and the data were never synchronized with the kinetics of catalyst transformations. Probably, the importance of selectivity data (particularly differential selectivity, see below) is not currently evident and requires additional arguments.

Selectivity reflects the ability of a catalyst to favor a certain reaction over other undesirable reactions. It is essential to distinguish between differential and integral selectivities, the difference being caused by a distinction between differential and integral data in chemical kinetics. Differential data operate with instantaneous reaction rates (*i.e.*, derivatives of the substance amount *vs.* time plots) at certain reaction times, while integral data deal with the corresponding amounts of substances. The differential selectivity of a catalyst for the desired product is often understood as the ratio of its formation rate to the sum of formation rates of all reaction products at a certain reaction time. Integral selectivity does not reflect the relative rate of desired product formation, but represents the ratio of the desired product amount to the sum of amounts of the products formed, *i.e.*, the relative amount of the desired product. Therefore, in contrast to integral selectivity, differential selectivity is directly related to the instantaneous rates of product formation. Differential selectivity measurements have a number of advantages over catalytic activity measurements, and they allow one to elucidate the fine mechanistic details of reactions with complex product compositions and reactions involving catalyst transformations outside the catalytic cycle (*e.g.*, formation, deactivation, and/or poisoning of active species).[40,65] The main advantage of differential selectivity in comparison with catalytic activity protocols is its independence of the total amount of truly active species. Thus, the changes of differential selectivity in discriminatory experiments can be unambiguously attributed to changes in the nature of the active species. Conversely, the change of catalytic activity can be attributed to changes in the amount and/or nature of active species. The clarification of these two alternative responses of the catalytic activity to changes in the catalytic system is impossible once the active species are experimentally unobservable by *in situ* spectroscopic techniques. Thus, differential selectivity measurements are best suited for *in situ* operando kinetic investigations.

One of the factors hampering the application of kinetic approaches based on differential selectivity instead of catalytic activity is a number of technical difficulties in measuring the absolute formation rates of several products needed to be known at any time to estimate selectivity. New opportunities for implementing the differential selectivity methodology are opened *via* analyzing the so-called phase trajectories of the formed products,[65] which allow one to easily visualize changes in reaction selectivity using raw integral kinetic data. In complex reactions, phase trajectories provide a clear visualization of the basic kinetic patterns of the test process. For reactions where the substrate is converted into several products, it is possible to plot the dependences of one product yield *vs.* that of another one to obtain the phase trajectories. The slope of the tangent to any point of the phase trajectory equals the ratio of product formation rates at this time point and represents differential selectivity.[65] The shape of the phase trajectory, determined by the kinetics of product buildup, is a very specific and sensitive parameter. A discrepancy in phase trajectories due to varying the catalyst precursor or adding some additives to the reaction mixture unambiguously indicates a change in the nature of the catalytically active species making a major contribution to substrate conversion. Conversely, the phase trajectory overlap becomes possible only when differential selectivity values are identical at any reaction moment, thus indicating that the nature of the catalyst remains the same.

The type 1 kinetic data can be synchronized with the differential selectivity data for catalytic reaction products by plotting phase trajectories such as [observed species and product amount]–[product amount] (Scheme 2, **B**). For instance, in the reaction of styrene with benzoic anhydride, carbonyl-containing products (*i.e.*, chalcone and dihydrochalcone) are formed along with expected stilbene (see Section S5). A comparison of the phase trajectory of $[PdBr_4]^{2-}$ synchronized on dihydrochalcone and those of chalcone and stilbene [Figure 5(*a*)] clearly show that qualitative changes in the catalytic system occur when the concentration of $[PdBr_4]^{2-}$achieves a maximum and steady-state value at the end of the reaction. These changes are reflected in the changes of differential selectivity for catalytic reaction products (*i.e.*, changes of phase trajectory slopes).

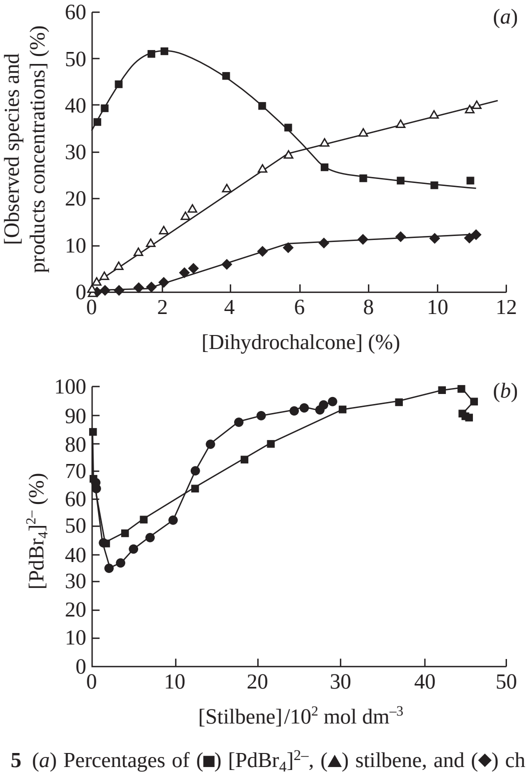


Figure 5 (*a*) Percentages of (■) $[PdBr_4]^{2-}$, (▲) stilbene, and (◆) chalcone (relative to a maximum possible concentrations under the reaction conditions) *vs.* percentage of dihydrochalcone using $PdCl_2$ as the catalyst precursor and (*b*) percentage of $[PdBr_4]^{2-}$ (relative to a maximum possible concentration under the reaction conditions) *vs.* concentration of stilbene using (■) Na_2PdBr_4 and (●) $PdBr_2$ as catalyst precursors in the Heck reaction of styrene with benzoic anhydride.

Elucidation of the roles of observable catalyst species using phase trajectories

In operando kinetic studies, the phase trajectory methodology can be used to analyze the differential selectivity for catalytic reaction products and to establish the regularities of changes in the ratio between the rates of catalyst transformations and the catalytic reaction by synchronizing types 1 and 2 kinetic data. The advantage of this approach is that only raw kinetic data such as [species amount]–[time] (type 1 integral kinetic data) and [product amount]–[time] (type 2 integral kinetic data) are needed for synchronization (Scheme 2, **C**). Thus, in contrast to the situation when data on catalytic activity are used for synchronization (Scheme 2, **A**), differentiation of type 2 integral kinetic data (*i.e.*, differentiation of the temporal profiles of reaction product formation) is not required to obtain dependences such as [activity]–[reaction time], allowing one to verify the proposed roles of catalyst species.

Establishing inactive species. Example 1. Phase trajectories, *i.e.*, the dependences of the amount of catalyst species on the amount of a certain reaction product, are positive and linear, and they do not change when the total catalyst amount changes [Figure 6(*a*)]. In such a case, the observed species is inactive and is directly formed from the active one as a result of irreversible deactivation (Scheme 1).

Indeed, if a coupling knot of the catalytic cycle and active species deactivation exists (Scheme 1), the rates of coupled steps are described by the following equations:

$$r_{\text{deact}} = k_{\text{deact}}[\text{I}],\ \ r_{\text{cycle}} = k_{\text{cycle}}[\text{I}],$$

where k_{deact} and k_{cycle} are the apparent rate constants of the deactivation of active species [I] and the catalytic reaction, respectively.

The ratio between the above rates becomes

$$r_{\text{deact}}/r_{\text{cycle}} = k_{\text{deact}}/k_{\text{cycle}}$$

and is found to be independent of the amounts of species and any other components. This determines the linear character of the phase trajectory (*i.e.*, the unchanged slope of the tangent to the phase trajectory) plotted as [species amount]–[catalytic reaction product amount] and its independence of any other factors influencing the amount of active species during the reaction.

Example 2. Phase trajectories are positive saturation dependences, with their leads coinciding at variable catalyst amounts [Figure 6(*b*)]. In this case, the observed species is inactive, but its deactivation is reversible (Scheme 1). Indeed, the corresponding equations describing the rates of the catalytic reaction and deactivation are as follows:

$$r_{\text{deact}} = k_{\text{deact+}}[\text{I}] - k_{\text{deact–}},\ \ r_{\text{cycle}} = k_{\text{cycle}}[\text{I}],$$

where k_{cycle} is the apparent rate constant of the catalytic reaction, and $k_{\text{deact+}}$ and $k_{\text{deact–}}$ are rate constants of direct and reverse deactivation, respectively.

In this situation, the ratio between the rates is

$$r_{\text{deact}}/r_{\text{cycle}} = (k_{\text{deact+}}[\text{I}] - k_{\text{deact–}})/k_{\text{cycle}}[\text{I}].$$

The selected equilibrium of deactivation–activation results in the zero numerator of the above equation at some time points and leads to a horizontal section of the phase trajectory [Figure 6(*b*)].

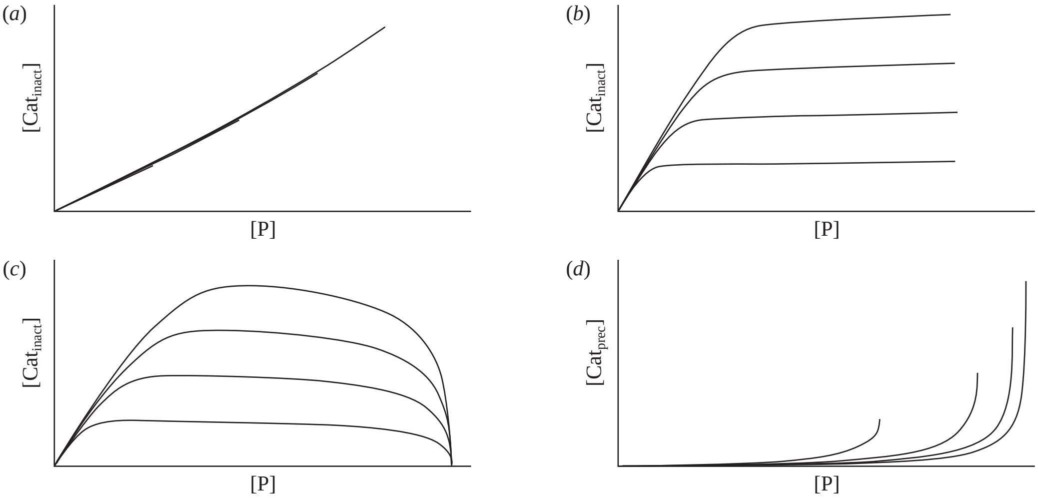


Figure 6 Simulated [species amount]–[product amount] dependences for inactive catalyst species in the catalytic conversion of substrate S to product P at four different loadings of the catalyst precursor (see caption for Figure 2). Cat_{prec} denotes inactive catalyst precursor; Cat_{inact} denotes inactive species resulted from active species deactivation. (*a*) The observed species is inactive in P formation and is formed directly from the active species as a result of irreversible deactivation; (*b*) the observed species is inactive in P formation and is formed directly from the active species as a result of slow reversible deactivation; (*c*) the observed species is inactive in P formation and is formed directly from the active species as a result of irreversible deactivation; however, it can be reactivated as a result of a sequence of steps; (*d*) the observed species is inactive in P formation and is formed indirectly from the active species as a result of irreversible deactivation through a set of steps. For a detailed description of simulation procedures, see Section S6.

The linearity of phase trajectories and their independence of the catalyst amount at the beginning of the reaction are evident under $k_{deakt+}[I] \gg k_{deakt-}$. Indeed, in this case, the above equation is transformed as follows:

$$r_{deact}/r_{cycle} = k_{deact+}[I]/k_{cycle}[I] = k_{deact+}/k_{cycle}.$$

Consequently, the derivatives of phase trajectories become constant and independent of the catalyst amount, *i.e.* they manifest linear and constant leads at variable catalyst amounts.

Example 3. If deactivation is irreversible but active species reactivation is possible as a result of a sequence of steps involving the substrate (Scheme 1), the phase trajectory of an inactive species can be represented as a curve with a maximum [Figure 6(*c*)]. At the same time, similarly to the case of reversible deactivation, these curves can have linear leads coinciding at variable catalyst amounts. The decreased concentration of inactive species at the end of the reaction results from the conversion of the observed inactive species into other inactive species, whose subsequent conversion slows down with the consumption of the substrate required for reactivation.

Example 4. If deactivation is irreversible and the observed inactive species are formed from the active ones indirectly, *i.e.*, in a set of consecutive steps, the phase trajectories exhibit a horizontal section at the reaction onset, whose slope subsequently increases [Figure 6(*d*)]. The extent of the horizontal sections depends on the catalyst loading. Indeed, if inactive species formation results from the deactivation of catalytic cycle intermediates, the initial amount of inactive species is equal to zero. The increased amount of active species due to their formation from the catalyst precursor induces the formation of both catalytic reaction products and inactive species resulting from the above step sequence, reflected in an induction period of the phase trajectory (*i.e.*, the section characterized by the increase of tangent slope) with a horizontal section at the lead. Note that, after the induction period and an increase in the amount of the species observed, subsequent maxima can appear in the phase trajectory if reactivation proceeds.

The phase trajectory corresponding to Example 1 was obtained for the reductive homocoupling of iodobenzene to produce biphenyl in the presence of $Pd(acac)_2$ as a catalyst precursor, where the reaction stopped after the maximal concentration of $[PdI_4]^{2-}$ was reached due to the full deactivation of active species.[62] A positive linear dependence of the amount of $[PdI_4]^{2-}$ on the amount of biphenyl was obtained, corresponding to the case when the observed species are inactive and are formed directly from the active one as a result of irreversible deactivation [Figure 7(*a*)]. At the same time, the phase trajectory for benzene formation (proceeding along with the expected biphenyl production) exhibited an induction period [Figure 7(*a*)]. This result indicates that the observed inactive species are indirectly formed from the active ones, *i.e.*, *via* a set of consecutive steps

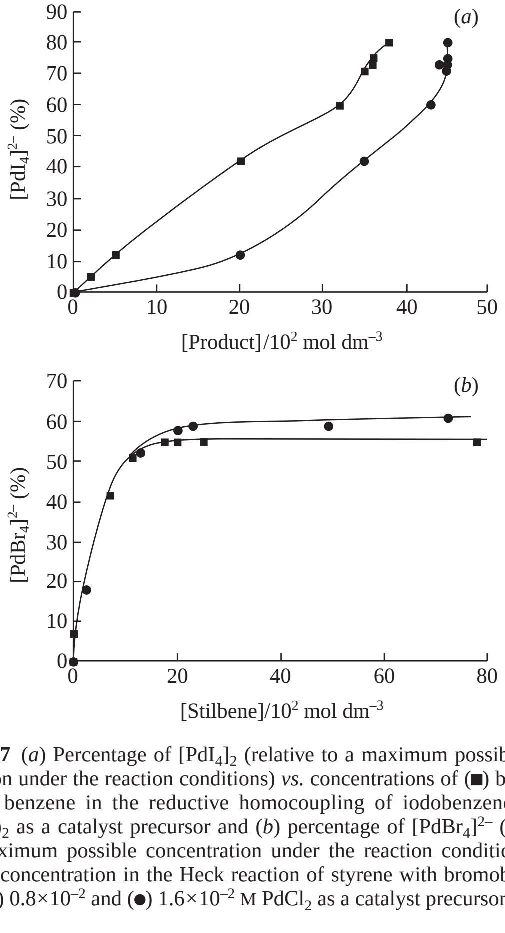


Figure 7 (*a*) Percentage of $[PdI_4]_2$ (relative to a maximum possible concentration under the reaction conditions) *vs.* concentrations of (■) biphenyl and (●) benzene in the reductive homocoupling of iodobenzene using $Pd(acac)_2$ as a catalyst precursor and (*b*) percentage of $[PdBr_4]^{2-}$ (relative to a maximum possible concentration under the reaction conditions) *vs.* stilbene concentration in the Heck reaction of styrene with bromobenzene using (■) 0.8×10^{-2} and (●) 1.6×10^{-2} M $PdCl_2$ as a catalyst precursor.

(Example 4). Notably, the formation of biphenyl and benzene occurred *via* different active species,[62,66] in agreement with the different types of phase trajectories obtained.

Experimental dependences perfectly illustrating the situation described in Example 2 were obtained for the Heck reaction of bromobenzene [Figure 7(*b*)]. The phase trajectories in $[PdBr_4]^{2-}$–stilbene concentration coordinates (see Section S5) obtained by varying the concentration of the catalyst precursor ($PdCl_2$) showed overlapping leads, in agreement with the accepted viewpoint that the formation of $[PdBr_4]^{2-}$ is one of the directions of active species deactivation for the Heck reaction using ligand-free catalytic systems.[63,64]

Phase trajectories corresponding to Example 3 were obtained in the direct arylation of indole with iodobenzene [Figure 8(*a*)]. The dependences of $[PdI_4]^{2-}$ concentration on that of 2-phenylindole obtained for various precursor concentrations clearly marked maxima and matched leads. Taking the above reasoning into account, we conclude that the deactivation of active species to $[PdI_4]^{2-}$ was irreversible; however, these species could be reactivated.

The irreversible deactivation of active species in the absence of reactivation possibilities (Example 4) can be concluded from the phase trajectory of the Suzuki reaction with iodobenzene [Figure 8(*b*)]. Indeed, the concentration of $[PdI_4]^{2-}$ continuously increased in the course of the reaction, exhibiting a maximum at the point when the reaction completely stopped,[67] which indicated irreversible deactivation of active species.

A more complicated pattern was observed in the reaction between styrene and benzoic anhydride with $PdBr_2$ or Na_2PdBr_4 as catalyst precursors [Figure 5(*b*)]. The negative dependence of the $[PdBr_4]^{2-}$ concentration at the reaction onset cannot be due to the active species in the formation of stilbene. The subsequent rise of the phase trajectory resulted from the irreversible deactivation of active species to form $[PdBr_4]^{2-}$ (Example 1).

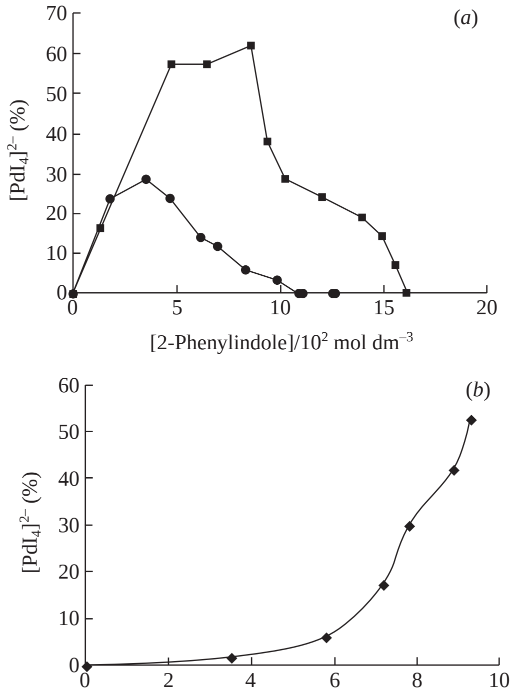


Figure 8 Percentage of $[PdI_4]^{2-}$ (relative to maximum possible concentration under the reaction conditions) (*a*) *vs.* concentration of 2-phenylindole in the direct arylation of indole by iodobenzene using (●) 1.6×10^{-2} and (■) 3.2×10^{-2} M levels of the catalyst precursor ($PdCl_2$) and (*b*) *vs.* concentration of biphenyl in the Suzuki reaction with iodobenzene using $PdCl_2$ as a catalyst precursor.

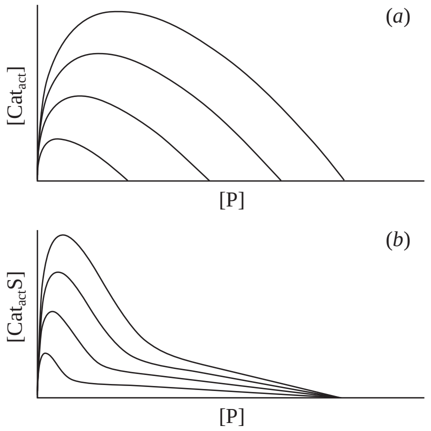


Figure 9 Simulation of [species amount]–[product amount] dependences for active catalyst species in the catalytic conversion of substrate S to product P for four different loadings of the catalyst precursor (see caption for Figure 2). The observed species (*a*) Cat_{act} and (*b*) $Cat_{act}S$ are active in P formation. See Section S7 for a detailed description of simulation procedures.

Establishing active species

Example 1. Non-linear phase trajectories with maxima exhibiting the following features: (i) presence of vertical sections; (ii) intersection with the *x* axis at the end of the reaction; and (iii) dependence on the total catalyst loading (Figure 9). In this case, the observed species is either the active one or is involved in a fast exchange equilibrium with the active species, and the formation and deactivation of active species proceeds in the catalytic system.

Indeed, if the active species are formed from a catalyst precursor, their initial amounts are zero. An increase in the amount of active species resulting from its formation should induce the appearance of the catalytic reaction product, that is reflected in phase trajectories with an induction period (trajectory sections with decreasing slopes) and a vertical slope at the reaction onset (Figure 9). Note that, in the case of active species, the slope of the phase trajectory, initially vertical and decreased subsequently, allows one to distinguish between the phase trajectories of active and inactive species, the latter one exhibiting either a finite positive slope at the reaction onset [Figure 6(*a*)–(*c*)] or an almost horizontal slope at the reaction onset followed by an increase [Figure 6(*d*)]. The disappearance of active species, *e.g.*, as a result of irreversible deactivation, should terminate the catalytic reaction, as the intersection of the phase trajectory with the *x* axis proves.

Conclusion

Operando studies present a powerful methodology for investigating catalytic systems. However, the importance of the simultaneous kinetic control of catalytic reaction products and spectroscopically observed catalyst species is frequently not taken into account. Therefore, the vast possibilities of the operando methodology are not used in full. We demonstrated that different ways of synchronizing integral and differential kinetic data on the accumulation of reaction products with kinetic data on the concentrations of different (*i.e.*, active and inactive) catalyst species can provide important information on the fundamental aspects of catalytic system operation. Note that the operando approach affords information on both the main catalytic cycle and the processes occurring outside it (*i.e.*, the formation, deactivation, and reactivation of active species). As illustrative examples, different dependences obtained *via* these synchronizations were applied to cross-coupling and related reactions.

This work was supported by the Russian Foundation for Basic Research (grant no. 16-29-10731). Experimental data for the reaction of styrene with benzoic anhydride were obtained in the framework of a project supported by the Russian Science Foundation (no. 14-13-00062).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.05.001.

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Received: 9th February 2017; Com. 17/5172