

Heck Reactions of Alkenes with Aryl Iodides and Aryl Bromides: Rate-Determining Steps Deduced from a Comparative Kinetic Study of Competing and Noncompeting Reactions

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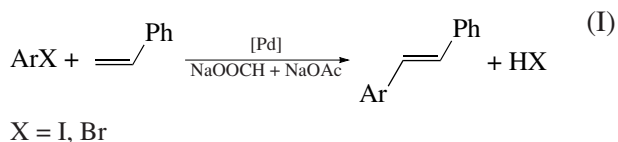
Abstract—Joint kinetic analysis of competition and noncompetition experiments can provide important information and sometimes a direct answer concerning the rate-determining step of a catalytic reaction. Applying this approach to the Heck reaction has demonstrated that alkenes; reactive aryl iodides; and, contrary to the conventional opinion, unactivated aryl bromides participate in rapid steps of the Heck reaction. For aryl iodides, the rate-determining step includes the dissociation of a C–H bond. At the same time, kinetic data for the dissolution of palladium reacting with aryl bromides suggest that the rate of the catalytic reaction is determined by the slow dissolution of palladium aggregates.

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The arylation of alkenes with aryl halides (reaction (I)), which was discovered by Heck [1] and Mizoroki [2] in 1971–1972, has recently become one of the most widely investigated catalytic process [3–6]. In 2000–2004, the Heck reaction was among the key words of 1316 articles published in the journals of the American Chemical Society. By contrast, the number of articles that dealt with this reaction in 1980–1984 was nearly 7 times smaller. It is noteworthy that the proportion of publications focused on the catalysis mechanism in the Heck reaction, including its rate-determining step, has considerably increased. There are many conflicting hypotheses as to the rate-determining step of the Heck reaction. It is sufficient to say that all of the elementary steps constituting the complete catalytic cycle of Heck arylation with an aryl iodide or an activated aryl bromide (oxidative addition of the aryl iodide [7–9], alkene coordination [10], alkene insertion [11–18], and palladium hydride elimination [19–22]) were supposed to be the rate-determining step. All these hypotheses are based on the assumption that the mechanism of the Heck reaction is single-route and reflect Heck’s original ideas of the main catalytic cycle [1]. On the other hand, there is evidence that catalyst deactivation and regeneration processes conjugated with the main catalytic cycle play a significant role in the Heck reaction and are even crucially important in the case of low-reactivity aryl bromide [23–37].

The conventional rate-determining step identification procedure, which uses partial orders of the reaction with respect to reactants, may be misleading when applied to such complicated processes [10, 28]. In view of this, it may be appropriate to use some modification of the method of competing reactions. In recent years, this approach has widely been employed in establishing Hammett relationships between the reaction rate and substituent constants for the Heck reaction [11, 29–35]. However, the data thus obtained are sometimes interpreted without taking into account the fact that the results of competition and noncompetition experiments can differ radically. The difference between competition and noncompetition experimental data is of great significance in the discrimination of hypothetical mechanisms for any process. This difference has never been analyzed for the Heck reaction.

We will demonstrate that, although the method of competing reactions has obvious advantages, it cannot provide complete information about the Heck reaction. Furthermore, because of some specific features of the mechanism of the Heck reaction, it is inapplicable to the identification of the rate-determining step if the results of conventional, noncompetition experiments are not taken into account. We will present new, self-consistent experimental data that, in our opinion, convincingly support our notion of the rate-determining step of Heck arylation with aryl iodides. Furthermore, we will report the first substantiated hypothesis as to the



rate-determining step of the Heck reaction involving aryl bromides, assuming that the reaction proceeds via a multiroute mechanism.

EXPERIMENTAL

Reactions were carried out in *N,N*-dimethylformamide (DMF) under aerobic conditions in a temperature-controlled vessel fitted with a magnetic stirrer. The reaction mixtures were sampled at intervals, and the samples were analyzed on an HP-890 gas-liquid chromatograph using a flame ionization detector, a 15-m-long HP-5 capillary column (Hewlett-Packard), and naphthalene as the internal standard, and temperature-programmed heating from 100 to 250°C. Reaction rates were determined by graphical differentiation of steady-state portions of kinetic curves. The parameters of rate equations were calculated using standard methods of minimization of nonlinear functions (Microsoft Excel 2002). The solvents and chemicals were purified by standard procedures.

Alkene arylation with aryl bromides and aryl iodides. Arylation was carried out at 140°C in 10 ml of DMF, using ArX (10 or 60 mmol), an alkene (10 mmol), NaOAc (11.2 mmol), NaOOCH (1.8 mmol), naphthalene as the internal standard for GLC (2 mmol), and PdCl₂ (0.16 mmol) or the corresponding amount of 4% Pd/C.

Measuring the isotope effect. The reaction was carried out in a temperature-controlled, magnetically stirred vessel by mixing styrene (2.5 mmol), styrene-d₈ (2.5 mmol), PhI (10 mmol), NBU₃ (13 mmol), and PdCl₂ (0.16 mmol) in DMF (10 ml). The reaction was conducted at 80°C. The reaction mixture was sampled at intervals, and the samples were analyzed by GLC and GC-MS (MAT-212 instrument, ionization voltage of 70 eV, anode current of 0.5 mA, 50-m-long SE-30 column, *T* = 100–300°C).

Competition experiments. The competitive arylation of two alkenes (or the arylation of one alkene with two aryl halides) was carried out using the above procedure, but with two reactants.

Interaction of Pd/C with aryl iodides and aryl bromides. The reaction was carried out at 140°C in 10 ml of DMF, using ArBr (60 mmol) or ArI (10 mmol), NBU₄X (0.32 mmol), and 4% Pd/C (0.16 mmol Pd). The reaction mixture was sampled at intervals, and the absorbance of the samples was measured. Knowing the extinction coefficients of the individual compounds present in the mixture, we determined the concentrations of [PdI₄]²⁻ ($\epsilon_{340} = 22750 \text{ l mol}^{-1} \text{ cm}^{-1}$) and [PdBr₄]²⁻ ($\epsilon_{350} = 7812.5 \text{ l mol}^{-1} \text{ cm}^{-1}$).

RESULTS AND DISCUSSION

Theoretical Analysis

Here, we will consider the possible situations that can take place in three different experiments (one com-

petition experiment and two noncompetition ones) for a pair of substrates (S1 and S2) involved in the catalytic reaction. We will assume that the component concentrations are the same in all experiments. It is appropriate to satisfy this condition in kinetic experiments in order to make unnecessary establishing exact relationships between the reaction rate and the substrate and catalyst concentrations. Furthermore, satisfying this condition would simplify the kinetic equations, whose parameters include constant reactant concentrations. We will assume that the substrates do not differ significantly in steric or electronic properties and, therefore, the rate-determining step is invariable. In the analysis presented below, it is assumed that the rate-determining step is much slower than the other steps of the catalytic cycle. It is, therefore, possible to treat all rapid reversible steps as quasi-equilibrium reactions. Note also that, if the catalytic cycle involves more intermediates than are considered in the simple examples given below, the inferences from the kinetic analysis will be essentially the same. We will limit our consideration to the mechanisms that take into account the specific arrangement of the rate-determining, equilibrium, and rapid irreversible steps relative to the step in which the two substrates are in competition in the catalytic cycle of the Heck reaction (see below).

Case 1: The common intermediate, with which both substrates react, is involved in the rate-determining step of the catalytic cycle (Scheme 1). If the rapid step preceding the rate-determining step is irreversible, then all of the catalyst is in the form of X_{com} (Scheme 1) and the rates of the noncompeting processes are described by the simplest equations

$$r_{S1} = k_{S1}[\text{Cat}]_{\Sigma}, \quad r_{S2} = k_{S2}[\text{Cat}]_{\Sigma},$$

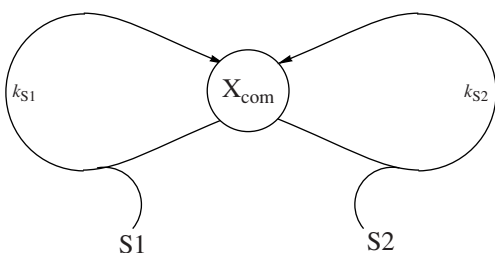
where [Cat]_Σ is the total catalyst concentration.

Note that similar equations will be valid in the case of rapid reversible reactions preceding the rate-determining step if the equilibria in these reactions are shifted to the intermediate X_{com}. The combination of two catalytic cycles in the competition process gives rise to a two-route mechanism such that only one common intermediate should be taken into consideration in the kinetic description of the reaction (Scheme 1).

In the competition experiment, the total conversion rate of the two substrates (*r*_{S1+S2}) is equal to the sum of the rates of the noncompeting reactions:

$$r_{S1+S2} = (k_{S1} + k_{S2})[\text{Cat}]_{\Sigma}; \quad r_{S1+S2} = r_{S1} + r_{S2}. \quad (1)$$

It can be demonstrated that the substrate conversion rate ratio in the competition experiment (*L*) is equal to the ratio of the rate constants of the slow steps (*L* = *k*_{S1}/*k*_{S2}). The parameter *L* will be convenient in further analysis since the classical method of competing reac-



Case 1. k_{S1} and k_{S2} are the rate constants of the slow irreversible steps

Scheme 1.

tions is generally limited to the determination of this parameter from the product yield ratio.

If the reactivity of the substrates S1 and S2 can be described in terms of the Hammett substituent constants, then the values of the reaction parameter ρ derived from the competition and noncompetition experiments will be equal. Indeed, for the noncompetition experiments, we have

$$\log \frac{r_{S1}}{r_{S2}} = \log \frac{k_{S1}}{k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2}),$$

where σ_{S1} and σ_{S2} are substituent constants for the substrates S1 and S2.

For the competition experiment,

$$\log L = \log \frac{k_{S1}}{k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2}).$$

If the common intermediate reacting with both substrates participates in the rapid, not rate-determining, step, then the following two cases are possible.

Case 2a: The common intermediate, with which both substrates react, is involved in an irreversible rapid step of the catalytic cycle (Scheme 2a). Since all of the catalyst is again in the form of the single intermediate (X_{S1} for the substrate S1 and X_{S2} for the substrate S2), the reaction rates in the noncompetition experiments will be described by the following equations (as in case 1):

$$r_{S1} = k_{S1}[\text{Cat}]_{\Sigma}, \quad r_{S2} = k_{S2}[\text{Cat}]_{\Sigma}.$$

The derivation of the corresponding quasi-steady-state rate equation for the competition reaction (Eq. (2)) is detailed in an earlier publication [20].

$$r_{S1+S2} = \frac{(L+1)k_{S1}k_{S2}[\text{Cat}]_{\Sigma}}{Lk_{S2} + k_{S1}}. \quad (2)$$

A specific feature of this equation is that L is the ratio of the rates of rapid, not slow, reactions involving a common intermediate ($L = k'_{S1}/k'_{S2}$). Most of the catalyst in this case is distributed between the intermediates X_{S1} and X_{S2} ($[\text{Cat}]_{\Sigma} \approx [X_{S1}] + [X_{S2}]$).

It is essential that the ρ values derived from the competition and noncompetition experiments may have different magnitudes and signs since they are determined by quite different rate constants. For the noncompetition experiments,

$$\log \frac{r_{S1}}{r_{S2}} = \log \frac{k_{S1}}{k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2}).$$

For the competition experiment,

$$\log L = \log \frac{k'_{S1}}{k'_{S2}} = \rho'(\sigma_{S1} - \sigma_{S2}).$$

Case 2b: The common intermediate, with which both intermediates react, is involved in a reversible rapid step of the catalytic cycle (Scheme 2b). In this case, the quasi-equilibrium approximation is applicable to the reversible rapid step and the reaction rates in the noncompetition experiment are expressed as

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

where $[\text{Cat}]_{\Sigma} \approx [X_{S1}] + [X_{\text{com}}]$ and $[\text{Cat}]_{\Sigma} \approx [X_{S2}] + [X_{\text{com}}]$ for the substrates S1 and S2, respectively. In the competition experiment, the total conversion rate of the two substrates is

$$\begin{aligned} r_{S1+S2} &= \frac{(K_{S1}k_{S1} + K_{S2}k_{S2})[\text{Cat}]_{\Sigma}}{1 + K_{S1} + K_{S2}} \\ &= \frac{(L+1)K_{S2}k_{S2}[\text{Cat}]_{\Sigma}}{1 + K_{S1} + K_{S2}}. \end{aligned} \quad (3)$$

Here, the parameter $L = K_{S1}k_{S1}/K_{S2}k_{S2}$ includes both the rate constants of the slow steps and the equilibrium constants of the preceding rapid steps. As in the previous cases, it is equal to the ratio of the rates of the two routes in the competition experiment. Most of the catalyst is distributed between three intermediates, namely, X_{S1} , X_{S2} , and X_{com} ($[\text{Cat}]_{\Sigma} \approx [X_{S1}] + [X_{S2}] + [X_{\text{com}}]$).

It can be demonstrated that case 2b will be kinetically identical to case 2a if the quasi-equilibrium is shifted to the intermediate participating in the rate-determining step ($K_{S1}, K_{S2} \gg 1$). This is obvious for the noncompetition experiments:

$$\begin{aligned} r_{S1} &= \frac{K_{S1}k_{S1}[\text{Cat}]_{\Sigma}}{1 + K_{S1}} \approx k_{S1}[\text{Cat}]_{\Sigma}, \\ r_{S2} &= \frac{K_{S2}k_{S2}[\text{Cat}]_{\Sigma}}{1 + K_{S2}} \approx k_{S2}[\text{Cat}]_{\Sigma}. \end{aligned}$$

However, it can be demonstrated that the rate equation for the competition experiment (Eq. (3)) also turns into Eq. (2) for $K_{S1}, K_{S2} \gg 1$. The only difference between cases 2a and 2b is in the meaning of the parameter L . Obviously, the conclusion that the competition and noncompetition experiments will lead to different ρ values, which was initially made for case 2a, can be extended to case 2b provided that $K_{S1}, K_{S2} \gg 1$.

If the reverse is true ($K_{S1}, K_{S2} \ll 1$), which means that the quasi-equilibrium is shifted to the common intermediate reacting with the substrate, the rate equation for the competition experiment will appear as

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

The reaction rates in the noncompetition experiments in this case are

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

therefore, $r_{S1+S2} = r_{S1} + r_{S2}$, so, when $K_{S1}, K_{S2} \ll 1$, case 2b is kinetically identical to case 1 (Eq. (1)). From the standpoint of the Hammett equations, this means that the ρ values for the competition and noncompetition experiments will be equal. Indeed, for the noncompetition experiments,

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

for the competition experiment,

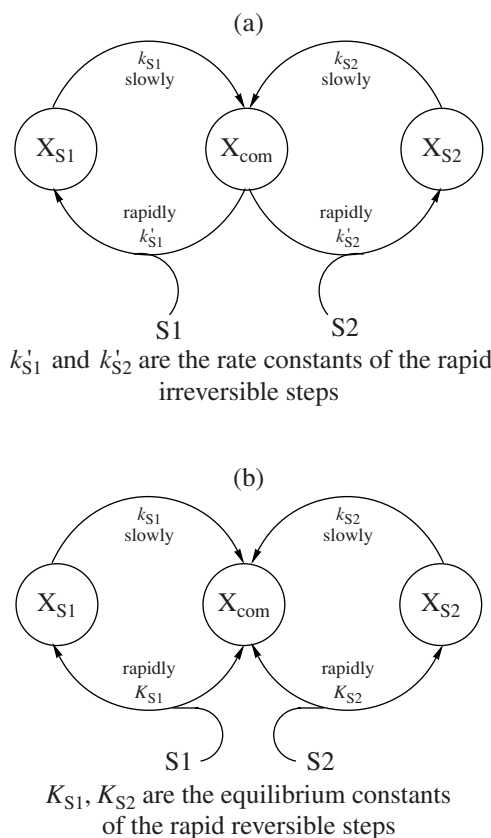
$$\log L = \log \frac{K_{S1}k_{S1}}{K_{S2}k_{S2}} = \rho(\sigma_{S1} - \sigma_{S2}).$$

The equations derived make it possible to compare the reaction rates in the one competition and two noncompetition experiments for the cases considered. As was demonstrated above, for $K_{S1}, K_{S2} \gg 1$, cases 2a and 2b are described by the same rate equation (Eq. (2)). Under the assumption that the first substrate is more active in the respective noncompetition experiment ($r_{S1} > r_{S2}$), we obtain $k_{S1} > k_{S2}$. Hence, the following relationship is valid for cases 2a and 2b under the condition $K_{S1}, K_{S2} \gg 1$:

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

It can be demonstrated that the r_{S2}/r_{S1+S2} ratio is less than unity. Thus, for the mechanism including the quasi-equilibrium (case 2b with $K_{S1}, K_{S2} \gg 1$) and for the mechanism including the irreversible steps (case 2a), the reaction rate in the competition experiments will be intermediate between the reaction rates in the two noncompetition experiments. Taking into consideration the sum of the reaction rates in the noncompetition experiments (which defines the maximum possible rate in the competition experiment for the mechanisms examined), we arrive at the following order of reaction rates:

$$r_{S1} + r_{S2} > r_{S1} > r_{S1+S2} > r_{S2}.$$



Scheme 2.

It has already been shown that $r_{S1+S2} = r_{S1} + r_{S2}$ for cases 1 and 2b (under the condition $K_{S1}, K_{S2} \ll 1$). This implies a quite different order of reaction rates in the three experiments:

$$r_{S1} + r_{S2} = r_{S1+S2} > r_{S1} > r_{S2}.$$

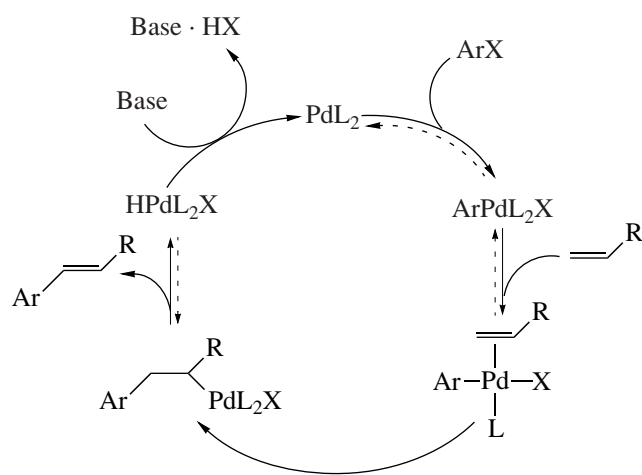
Finally, if K_{S1} and K_{S2} are neither very small nor very large, when neither the condition $K_{S1}, K_{S2} \ll 1$ nor the condition $K_{S1}, K_{S2} \gg 1$ is satisfied, the order of reaction rates will be as follows:

$$r_{S1} + r_{S2} > r_{S1+S2} > r_{S1} > r_{S2}.$$

Thus, from as few as three experiments involving a pair of substrates, we can derive the following inferences:

(1) If the reaction rate in the competition experiment is lower than the sum of the reaction rates in the two noncompetition experiments, then the competing substrates are not directly involved in the rate-determining steps of their catalytic cycles.

(2) If the reaction rate in the competition experiment is lower than the sum of the reaction rates in the noncompetition experiments and is higher than the conversion rate of the more active substrate, then the substrate participates in rapid reversible steps. In this case, most of the catalyst during the process is in the form of intermediates that have formed before the entry of the sub-



Scheme 3.

strate into the catalytic cycle (the equilibrium constants are small).

(3) If the reaction rate in the competition experiment is lower than the conversion rate of the more active substrate and is higher than the conversion rate of the less active substrate, then the substrate participates either in a rapid irreversible step or in a rapid reversible step. In the latter case, most of the catalyst during the process is in the form of intermediates that form after the entry of the substrate into the catalytic cycle (the equilibrium constants are large). In this case, the Hammett parameters derived from the noncompetition and competition experiments have different meanings.

(4) If the reaction rate in the competition experiment is higher than the sum of the reaction rates in the noncompetition experiments or is lower than the conversion rate of the less active substrate, none of the mechanisms examined is valid. Nevertheless, this fact would be of great importance in the discrimination of alternative hypothetical mechanisms.

Obviously, use of several pairs of substrates in these experiments would make the results more reliable, par-

ticularly if it were possible to demonstrate the validity of some mechanistic hypothesis on the quantitative level. The results of the above theoretical analysis were used in our kinetic investigation of the Heck reaction involving aryl iodides and aryl bromides as arylating agents (reaction (I)).

Specific Features of the Mechanism of the Heck Reaction

Before discussing the above results, we will consider the conventional mechanism of the catalytic cycle of the Heck reaction (I) (Scheme 3). This mechanism was suggested by Heck himself [1] and was not radically modified in the more than three decades that followed [3, 4]. The dashed lines in Scheme 3 designate the reverse reactions that can be supposed a priori to take place.

It is significant that only some of the key intermediates appearing in Scheme 3 have been detected experimentally in a real catalytic process [21, 36] or under conditions very similar to the catalytic process conditions [37, 39]. For example, there is no experimental evidence that the formation of an alkene π -complex takes place. This fact is very significant for further analysis since it possibly indicates the low stability of the π -complex. This can be due to either the equilibrium being shifted to the starting alkene and the palladium σ -aryl complex or the high reactivity of the π -complex in subsequent irreversible alkene insertion into the Pd–Ar bond (Scheme 3). The nearly absolute irreversibility of the alkene insertion step is beyond any doubt since the reverse reaction would imply the C–C bond breaking, which is unlikely under the Heck reaction conditions and has never been observed experimentally [40]. Another intermediate that has not been detected experimentally in the catalytic cycle of the Heck reaction is palladium hydride [37–39]. This fact and the high rate of the binding of the resulting acid by the base present in the system allows the arylated alkene formation step to be treated as an irreversible process [20, 34].

Table 1. Rates (r) and selectivities (L) of the competing reactions of iodobenzene with styrene (St), styrene- d_8 (St- d_8), methyl acrylate (MA), and methyl methacrylate (MMA)

Entry	Substrate		Reaction rate, $\text{mol l}^{-1} \text{ min}^{-1} \times 10^2$			L obs. (calc.)
	S1	S2	r_{S1+S2} obs. (calc.)	r_{S1} obs. (calc.)	r_{S2} obs. (calc.)	
1*	St	MMA	3.9(3.9)	3.4(3.4)	9.0(9.0)	4.0(4.1)
2*	St	MA	4.0(4.1)	3.4(3.39)	5.0(4.9)	0.91(0.73)
3*	MA	MMA	5.1(5.3)	5.0(4.9)	9.0(9.0)	5.7(5.6)
4**	St	St- d_8	1.7(1.7)	3.4(3.4)	1.1(1.1)	1.0(1.0)

Note: Rate constants (min^{-1}) used in the calculation: $k_{\text{St}} = 2.11$, $k_{\text{MMA}} = 5.62$, $k_{\text{MA}} = 3.06$, and $k_{\text{St-}d_8} = 0.7$.

* Reaction mixture: DMF (10 ml), alkenes (10 mmol each), PhI (10 mmol), NaOOCH (13 mmol), and PdCl_2 (0.16 mmol). $T = 60^\circ\text{C}$.

** Reaction mixture: DMF (10 ml), styrene (2.5 mmol), styrene- d_8 (2.5 mmol), PhI (10 mmol), NBu_3 (13 mmol), and PdCl_2 (1.6 mmol). $T = 80^\circ\text{C}$.

Table 2. Rates (r) and selectivities (L) of the competing reactions of styrene with PhI (IB), 4-CH₃OC₆H₄I (IA), 4-HOOC₆H₄I (IBA), and 4-NO₂C₆H₄I (INB)

Entry	Substrate		Reaction rate, mol l ⁻¹ min ⁻¹ × 10 ²			L obs. (calc.)
	S1	S2	r_{S1+S2} obs. (calc.)	r_{S1} obs. (calc.)	r_{S2} obs. (calc.)	
1	IB	IA	45.3(42.5)	38.0(38.6)	48.0(48.5)	1.23(1.24)
2	IB	IBA	13.8(12.7)	38.0(38.6)	10.0(10.7)	0.31(0.26)
3	IB	INB	8.3(8.5)	38.0(38.6)	7.0(7.2)	0.25(0.23)
4	IBA	IA	12.7(12.5)	10.0(10.7)	48.0(48.5)	4.7(4.7)

Note: Rate constants (min⁻¹) used in the calculation: $k_{IB} = 24.1$, $k_{IA} = 30.3$, $k_{IBA} = 6.72$, and $k_{INB} = 4.51$. Reaction mixture: DMF (10 ml), aryl iodides (10 mmol each), styrene (10 mmol), NaOAc (11.2 mmol), NaOOCH (1.8 mmol), and PdCl₂ (0.16 mmol). $T = 140^\circ\text{C}$.

Two types of competition experiments, one with two alkenes and the other with two aryl halides, are possible for the Heck reaction.

Competition between Two Alkenes

Although we have already reported experimental data for this variant of competition in Heck arylation with iodobenzene [20], it seems pertinent to discuss them again in the context of this study. It was found for all possible binary combinations between styrene, methyl acrylate, and methyl methacrylate and for the styrene–styrene-d₈ pair that the rate of competing phenylation with iodobenzene is always between the rates of the noncompetition phenylation of the respective alkenes and is described by Eq. (2) (Table 1, calculated data).

Equation (2) will be valid only if the alkene is involved in a rapid reaction step, either the irreversible (case 2a) or the reversible (case 2b with K_{S1} , $K_{S2} \gg 1$). According to the conventional mechanism of the Heck reaction (Scheme 3), this step must be alkene coordination yielding a π -complex. The most popular hypothesis as to the rate-determining step is that alkene coordination is rapid and reversible and the reaction rate is determined by the slow and irreversible alkene insertion step [11–18]. However, as judged from experimental facts only, this hypothesis is implausible. Indeed, the validity of Eq. (2) implies a high concentration of the intermediates that form after the entry of the substrate into the catalytic cycle (case 2b with K_{S1} , $K_{S2} \gg 1$). According to the conventional mechanism of the Heck reaction, these intermediates are alkene π -complexes. However, as was mentioned above, these complexes have never been detected experimentally. Therefore, the most plausible explanation of the validity of the rate equation (2) is that the substrate is involved in a rapid irreversible reaction step. According to the Heck reaction mechanism, this step is alkene insertion.

A significant fact consistent with this inference is the observation of a kinetic isotope effect in noncompeting styrene and styrene-d₈ phenylation reactions [20], including those in the presence of phosphine-containing catalytic systems [21]. In these two cases, the isotope effect value was determined taking into account

the reaction rates in competition experiments. This enabled us to estimate the isotope effects for two steps, namely, the rapid step directly involving the alkene (alkene insertion) and the rate-determining step of the catalytic cycle. The isotope effect value for the insertion step must be equal to the L value for the competition phenylation of styrene and styrene-d₈. According to our data, L is close to unity (Table 1, entry 4). This value of the isotope effect is quite expected since no C–H bond dissociation takes place in the insertion step. Almost at the same time as our publication concerning competing styrene and styrene-d₈ arylation reactions [20] appeared, there was another report on this subject [29], which was limited to L measurements. Performing a large number of replica experiments provided more accurate L data for the competing styrene and styrene-d₈ arylations. The parameter L was found to be somewhat below unity (0.79–0.97) [29]. The slight inverse isotope effect is explicable in terms of the different electronegativities of hydrogen and deuterium [41]. The isotope effect value for the rate-determining step (k_{S1}/k_{S2}) can be determined by solving the set of rate equations for the competing and noncompeting reactions (Table 1, entry 4). Hence, the absolute values of the rate constants k_{S1} and k_{S2} can be determined. According to our measurements, the isotopic effect has a rather large value of ~ 30 [20, 21].

Thus, the hypotheses that alkene coordination and insertion are slow steps are in conflict with the simultaneous kinetic analysis of competition and noncompetition experiments. At the same time the assumption that the step next to irreversible alkene insertion is slow is in excellent agreement with experimental data, including those for the styrene–styrene-d₈ pair. This rate-determining step must result in the dissociation of a C–H bond. However, this conclusion could be accepted as fact only if the high rate of the oxidative addition of the aryl iodide to Pd(0) were confirmed experimentally. This can be done by examining an arylation reaction in which two aryl halides are competing substrates.

Competition between Two Aryl Iodides

It was found that, as in the case of competing alkenes, the rates of the competition reactions of styrene

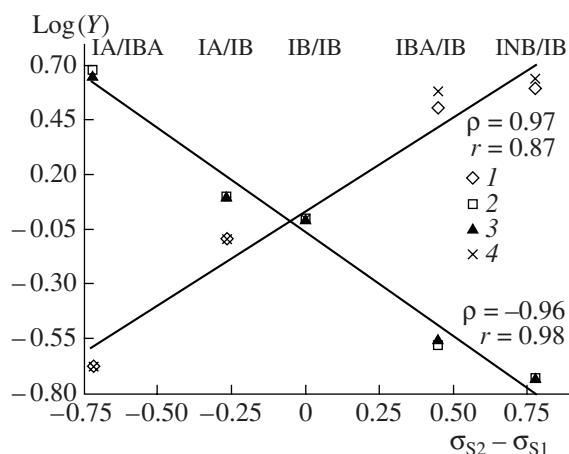


Fig. 1. (1, 2) Hammett relationships for (1) competing ($Y = 1/L$) and (2) noncompeting ($Y = r_{S2}/r_{S1}$) reactions of *para*-substituted aryl iodides with styrene. (3, 4) The same relationships for the (3) k_{S1}/k_{S2} ratio ($Y = k_{S2}/k_{S1}$) and (4) selectivity L (4, $Y = 1/L$) calculated from Eq. (2). For the experimental conditions, see Table 2.

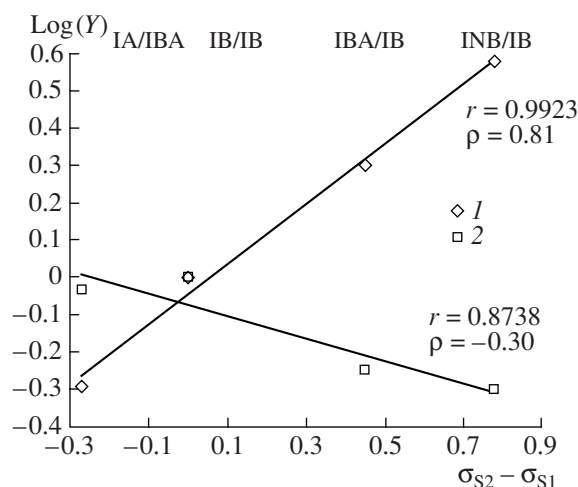


Fig. 2. Hammett relationships for styrene arylation with aryl iodides in the presence of Pd/C according to the results of (1) competition ($Y = 1/L$) and (2) noncompetition ($Y = r_{S2}/r_{S1}$) experiments. For the experimental conditions, see Table 2.

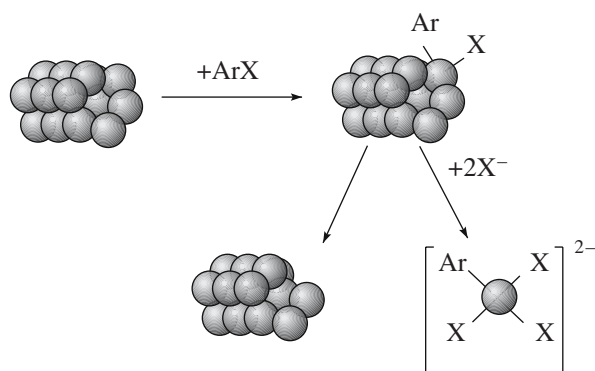
with possible binary combinations between iodobenzene, *p*-iodoanisole, *p*-iodobenzoic acid, and *p*-iodonitrobenzene are intermediate between the reaction rates observed in the respective noncompetition experiments (Table 2) and are adequately described by Eq. (2) (Table 2, calculated data). The use of excess arylating agent and a high temperature (140°C) in these experiments is dictated by the necessity to correctly compare these experiments with the experiments involving aryl bromides, which require these conditions to be established (see the next section).

These results indicate that the aryl iodide, like the alkene, participates in a rapid reversible or a rapid irreversible step of the catalytic cycle. According to the conventional mechanism of the Heck reaction (Scheme 3), this step is the oxidative addition of ArI to Pd(0). This inference is consistent with the above assumption that the step that is next to irreversible alkene insertion and includes C–H bond breaking is slow.

The use of different aryl iodides as competing substrates necessitates use of Hammett relationships in the elucidation of the reaction mechanism, in particular, in the identification of the rate-determining steps. Benhadou et al. [7] were the first to report the parameter ρ for the arylation of unsaturated alcohols with aryl iodides. The value of ρ was derived from noncompetition experiments and was found to be below zero ($\rho = -1.6$). Next, ρ was determined for ethylene arylation from the results of noncompetition experiments [19] and was again found to be well below zero ($\rho = -1.1$). In all later studies [11, 29–34], ρ for the Heck reactions of alkenes with aryl iodides was derived from competition experiments and all authors reported positive ρ values. According to theoretical analysis, the adequacy of Eq. (2) to the data presented in Table 2 permits the ρ

values derived from competition and noncompetition experiments to be different. Therefore, contrary to Boehm and Herrmann's opinion [29], this difference does not indicate any significant disagreement between our data [19] and the results of the competition experiments. Conversely, this difference provides excellent confirmation for the conclusion that the oxidative addition step proceeds at a high rate in the case of aryl iodides. This point is illustrated by the plots of the Hammett relationships for styrene arylation with aryl iodides (Fig. 1) derived from noncompetition experiments (see the r_s values in Table 2) and competition experiments (see the L values in Table 2). As follows from Fig. 1, the ρ values for the noncompetition and competition experiments have opposite signs. Figure 1 also plots the Hammett relationships for the rate constants of the rate-determining steps and selectivity (L) that appear in Eq. (2) and are calculated taking into account reaction rate data from both competition and noncompetition experiments (Table 2). As follows from Fig. 1, the calculated data are in excellent agreement with the experimental data from the competition and noncompetition experiments, illustrating the validity of Eq. (2). Thus, the opposite signs of ρ for the competition and noncompetition experiment are trivially explained by the opposite effects of the substituents on the rapid oxidative addition step and the rate-determining step of the catalytic cycle. Electron-withdrawing substituents are known to speed up the stoichiometric oxidative addition reaction ($\rho > 0$) [42, 43], and this is in full agreement with the results of the competition experiments. At the same time, as follows from our data, electron-donating substituents in the aryl halide accelerate the rate-determining step.

The authors of some publications, including publications dealing with determination of ρ [31, 34], do not

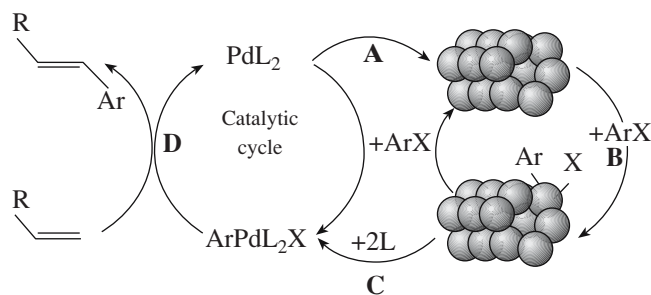


Scheme 4.

rule out a heterogeneous catalytic mechanism of the Heck reaction. In view of this, we carried out experiments using Pd/C as the heterogeneous precursor of the catalyst (Fig. 2). Note that there is good reason to doubt whether the Heck reaction can proceed via a heterogeneous mechanism. Based on the results of experiments in which the solid phase of the catalyst was separated during the catalytic run and on the correlation between the reaction rate and the amount of palladium that has passed from the surface of the heterogeneous precursor into the solution [44], we concluded that the Heck reaction is homogeneous catalytic. Similar conclusions were made for arylation with aryl iodides [23, 24, 45–48], aryl bromides [49–53], and aryl chlorides [54, 55]. It was demonstrated that the aryl halide is responsible for palladium dissolution [23, 24, 44], which, however, takes place only in the presence of potential ligands in the solution. The most efficient dissolution is observed in the presence of halide ions, which are a product of the main catalytic cycle of the reaction [23, 24]. Eventually, we suggested a palladium dissolution mechanism (Scheme 4) [24].

A similar role of the aryl halide in palladium dissolution was reported in other works [45, 56–58], including for colloidal palladium that forms from the catalyst during the Heck reaction [59]. We hold to the mechanism according to which palladium metal aggregates of various sizes (including supported particles) are outside the main catalytic cycle, which makes the main contribution to substrate conversion in the Heck reaction of alkenes with aryl iodides (Scheme 5). It is significant that this mechanism was developed for Heck arylation with aryl iodides without employing the method of competing reactions and was later extended to arylation with aryl bromides [25, 26, 60, 61]. Note also that the authors of a recent review devoted to the Heck reaction [6] also arrived at the conclusion that this reaction proceeds via a homogeneous catalytic mechanism.

The high temperature used in our experiments involving Pd/C, as distinct from our earlier experiments [44], did not allow us to observe the autoacceleration period due to initial palladium dissolution. Nevertheless, there is good reason to assume that it is this pro-



Scheme 5.

cess (Scheme 5, steps B, C), which determines the catalytic activity of the system (the formation of an active catalyst), that raises the parameter p and diminishes the correlation coefficient in the noncompetition experiments (Fig. 2) versus the “homogeneous” experiments (Fig. 1). It is possible that the relationship considered is nonlinear because the effects exerted by the dissolution process on the kinetics of the catalytic reaction are different for electron-donating and electron-withdrawing substituents. At the same time, the Hammett parameters for the competition experiments do not change significantly on passing from the homogeneous catalyst to Pd/C. This is due to the fact that the parameter L in the method of competing reactions is insensitive to the variation of the active catalyst concentration. Thus, the results presented in this section are consistent with the mechanistic hypothesis that catalyst conversion in the Heck reaction takes place outside the catalytic cycle (Scheme 5).

Note that the view that palladium metal dissolution is a catalyst formation process in the case of a heterogeneous precursor and a catalyst regeneration process in the case of a homogeneous precursor is fairly correct only for arylation with aryl iodides. Indeed, it follows from Scheme 5 that palladium metal dissolution under the action of an aryl halide, yielding an oxidative addition product, transforms the step sequence A–D of the Heck reaction into another catalytic cycle (hereafter, the second catalytic cycle). In spite of this, many authors [56, 59, 62, 63] call metallic and/or colloidal palladium only a reservoir of catalytically active compounds. In an earlier publication [25], we also used this formally incorrect definition to describe the role of colloidal palladium. Note, however, that an increase in the Pd(0) aggregation rate can raise the contribution of the second catalytic cycle into the total conversion. This would make the definition of metallic palladium as a catalyst reservoir essentially, not only formally, incorrect.

Obviously, this situation can take place on passing from aryl iodides to aryl bromides, which are less active in the oxidative addition step, implying a higher Pd(0) aggregation rate. Unexpectedly, taking into account the results of competition and noncompetition experiments for Heck arylation with aryl bromides provided the first

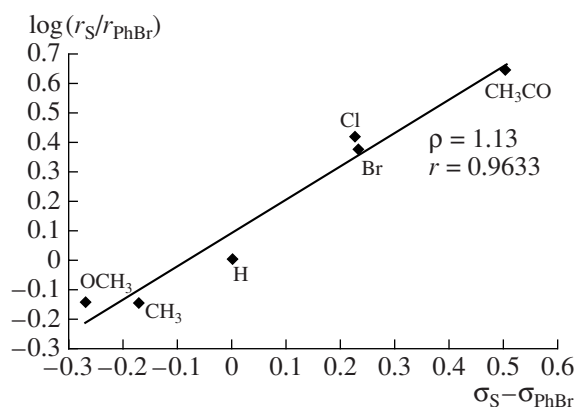


Fig. 3. Hammett relationship for styrene arylation with aryl bromides according to the results of noncompetition experiments. Reaction mixture: DMF (10 ml), ArBr (10 mmol), styrene (10 mmol), NaOAc (11.2 mmol), NaOOCH (1.8 mmol), naphthalene as the internal standard for GLC (2 mmol), and PdCl_2 (0.16 mmol). $T = 140^\circ\text{C}$.

convincing evidence that the second catalytic cycle plays a very significant role in this reaction. Furthermore, this approach led us to revise the conventional notion of the rate-determining step of the Heck reaction for unreactive arylating agents.

Competition between Two Aryl Bromides

For the Heck reactions involving unactivated aryl bromides, as distinct from the same reactions with aryl iodides, the only universally accepted hypothesis as to the rate-determining step is that this step is the oxidative addition of the aryl bromide to $\text{Pd}(0)$ [32, 60, 61, 64, 65]. If this hypothesis is true, then, according to our theoretical analysis (see above), the simplest situation (case 1) takes place. The ρ values derived from competition and noncompetition experiments will coincide. Indeed, the ρ value derived from our noncompetition experiments (Fig. 3) is above zero (~ 1.1), like the ρ values earlier reported for the competing reactions [29, 30, 32–34]. This fact alone radically differentiates aryl bromides from aryl iodides and unambiguously indicates that the Heck reactions of alkenes with aryl iodides and aryl bromides have different rate-determining steps, as was noted in [66].

However, there are facts casting doubt on the hypothesis that the rate-determining step is oxidative addition. These facts include the abnormally small order of the reaction with respect to aryl bromide [67] and the abnormally high sensitivity of the aryl bromide reaction rate to the vigor with which the reaction solution is stirred [27]. These specific features of the reactions involving an aryl bromide cannot be explained in terms of the oxidative addition kinetics and are possibly due to the catalytic process being strongly affected by catalyst conversion outside the main catalytic cycle. Thus, we have an uncertainty typical of kinetic studies

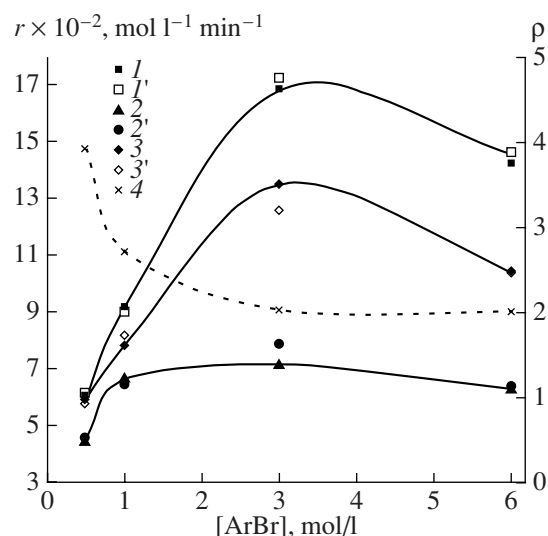


Fig. 4. (1, 2) Observed and (1', 2') calculated rates of non-competing reactions as a function of the (1, 1') bromobenzene and (2, 2') *p*-bromotoluene concentrations. (3) Observed and (3') calculated totals reaction rates and (4) parameter ρ as a function of the sum of the bromobenzene and *p*-bromotoluene concentrations in competition experiments. For the reaction conditions, see the caption to Fig. 3.

in catalysis: some changes in the activity of the catalyst can be explained either by the variation of the rates of reaction steps within the main catalytic cycle or by the variation of catalyst conversion steps outside this cycle. In this case, the researcher needs experimental data allowing one of the alternative hypotheses to be discriminated. It turned out that such data can be obtained by analyzing the results of competition and noncompetition experiments.

A fundamental difference between the kinetics of the competition experiments involving aryl bromides and the same experiments involving aryl iodides is that the parameter L and, therefore, ρ in the former depend strongly on the initial concentrations of the two aryl bromides examined (Fig. 4, curve 4). It was demonstrated by special experiments that, for the iodobenzene + iodoanisole pair, L is invariable over the same substrate concentration range. The sensitivity of the selectivity of the competing reactions to the simultaneous variation of both absolute substrate concentrations can be due to the variation of the contributions of two or more coexisting catalysts to the catalysis. Obviously, this inference is fully consistent with the hypothesis of the coexistence of two catalytic cycles in the Heck reactions of alkenes with aryl bromides.

The total rate of the competing reactions of styrene with bromobenzene and *p*-bromotoluene is intermediate between the rates of the corresponding noncompeting reactions for all aryl bromide concentrations examined (Fig. 4). Equation (2) proved valid for each concentration (Fig. 4, calculated data). According to theoretical analysis, this formally means that the aryl

bromide participates in a rapid, not slow, step, contrary to the conventional opinion. In view of our earlier data [27, 67], the most plausible explanation for the observed kinetics is that the rate-determining step is not in the main catalytic cycle, but is step **B** or **C** (Scheme 5). For aryl bromides, these steps have a stronger effect on catalysis because of the higher Pd(0) aggregation rate. Palladium dissolution actually takes place. This process must include comparatively rapid oxidation of the surface palladium with the aryl bromide and slow palladium dissolution under the action of the halide ions present in the solution (Scheme 4).

In order to verify this hypothesis, we studied the kinetics of formation of the $[\text{PdX}_4]^{2-}$ complexes in solution during the interaction of Pd/C with aryl iodides and aryl bromides in the presence of $[\text{NBu}_4]\text{X}$ as the source of halide ions (Fig. 5). These complexes are believed to result from the conversion of $[\text{ArPdX}_3]^{2-}$ (Scheme 4), which leads to aryl halide reduction products (ArH , Ar-Ar) [23, 24]. In these experiments, Pd/C can be viewed as a rough model of the palladium metal aggregates that form in the course of Heck arylation with aryl bromides. Note that the $[\text{PdX}_4]^{2-}$ formation rate (Fig. 5) is at least 2 orders of magnitude lower than the rate of the catalytic reaction even in the case of iodobenzene, the most active arylating agent. Therefore, the dissolution process can exert a considerable effect on catalytic activity even in the case of iodobenzene. As was mentioned above, this effect was indeed observed in the noncompetition experiments involving Pd/C (Fig. 2). It follows from Fig. 5 that the donor substituents in the aryl halide diminish the formation rate and the maximum concentration of $[\text{PdX}_4]^{2-}$ in the solution. This finding is in agreement with the lower catalytic activity observed in arylation with aryl bromides, for which a stronger effect of the dissolution processes should be expected. The fact that the $[\text{PdBr}_4]^{2-}$ concentration in the solution passes through a maximum during the interaction between Pd/C with PhBr and 4-MeC₆H₄Br is explained by the reducibility of the anionic complex $[\text{NBu}_4]_2[\text{PdX}_4]$ in the DMF + $[\text{NBu}_4]\text{X}$ system, which was discovered by special experiments. Consorti et al. [34], who observed the reduction of Pd(II), explain this similar process by the presence of free tributylamine in the solution as a result of the decomposition of the corresponding ammonium salt (NBu_3 can efficiently reduce $[\text{PdX}_4]^{2-}$ even at much lower temperatures [23]). Thus, the higher and more persistent palladium concentrations in the solution in the case of aryl iodides are due to the high palladium dissolution rate capable of competing with the rates of the continuous palladium reduction and aggregation processes. Accordingly, because of the low dissolution rate in the case of *p*-bromotoluene, only traces of $[\text{PdBr}_4]^{2-}$ appear in the solution.

Thus, the joint kinetic analysis of the competition and noncompetition experiments demonstrated that alkenes and reactive aryl halides participate in rapid steps of the catalytic cycle of the Heck reaction. This is

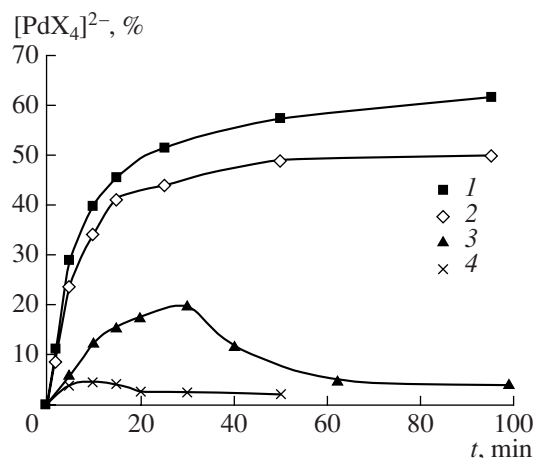


Fig. 5. Time dependence of the $[\text{PdX}_4]^{2-}$ concentration in the solution for the interaction of Pd/C with aryl iodides and aryl bromides in the presence of $[\text{NBu}_4]\text{X}$: (1) PhI, (2) 4-CH₃OC₆H₄I, (3) PhBr, and (4) 4-CH₃C₆H₄Br.

equally true in the case of a heterogeneous precursor of the catalyst (Pd/C). The observed kinetic isotope effect and kinetic data suggest that the rate-determining step of the catalytic cycle is a step including C–H bond dissociation. In the framework of the classical mechanism of the Heck reaction, this step is the β -elimination of palladium hydride. However, any of the experimentally proved C–H bond breaking steps other than classical β -elimination [40, 68, 69] can be rate-determining as well.

By applying the same approach to Heck reactions involving unactivated aryl bromides, we established that, contrary to the conventional opinion, the aryl bromides, like aryl iodides, are involved in rapid steps of the reaction. New kinetic data for palladium dissolution under nearly real catalysis conditions and the earlier views of the functioning of the catalytic system led us to conclude that the rate-determining step is the dissolution of palladium aggregates.

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