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STUDY OF EXTRACTION EQUILIBRIA IN THE REACTION OF ALKALINE HYDROLYSIS OF ACTIVATED AMINO ACID ESTERS

BADANIE RÓWNOWAG EKSTRAKCJI W REAKCJI ZASADOWEJ HYDROLIZY AKTYWOWANYCH ESTRÓW AMINOKWASÓW

Abstract: Correlation between observed kinetic effects of phase-transfer catalytic reaction of the alkaline hydrolysis of 4-nitrophenyl ester of *N*-benzyloxycarbonylglycine-4 in the two-phase system chloroform-borate buffer pH = 10 and a content of ionic forms of catalyst was investigated. The phosphonium salts QX (X = Cl^-, Br^-, I^-) shows high catalytic reactivity. Dependence of the reaction kinetics discussed in the framework of the extraction mechanism with a competitive extraction of a nucleophile OH^-, nucleofuge 4-$NO_2C_6H_4O^-$ and anion $X^-$of the phase-transfer catalyst.

Keywords: phase-transfer catalysis, kinetics, hydrolysis, quaternary phosphonium salts, branched catalytic cycle, extraction equilibria

Introduction

Phase-transfer catalysis (PTC) is a new effective method of an organic chemistry, theoretical bases of which are now being intensively developed. PTC is widely used in the recycling process of ecotoxicants and highly toxic substances, successfully implemented in the reactions of "green chemistry", used for the synthesis of medicinal substances and for different applications in industry [1-5]. Despite the wide practical application of PTC-reactions in industry their theoretical description is incomplete [6, 7]. Those PTC systems cannot be explained by classical theoretical positions hence they are of special interest. Investigation of the mechanisms of PTC processes and topology of these reactions is of major relevance. For example, among the reactions which can be carried out under PTC conditions the reactions of S_N2-type are promising for study, in particular, the alkaline

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hydrolysis of the esters in the two-phase system aqueous base solution/organic phase [8]. Similar to PTC/OH^- - systems with two anions are usually described by Starks scheme, presented in Figure 1 [9].

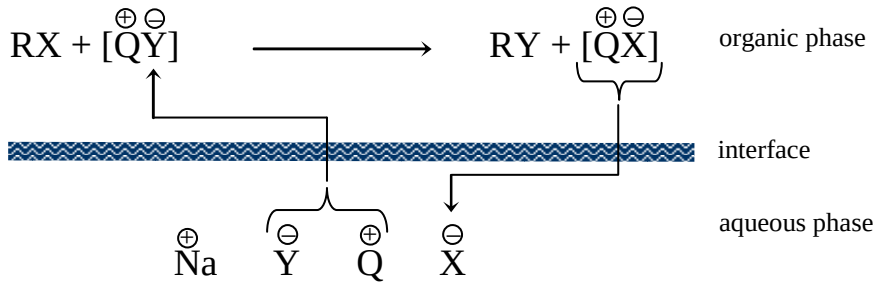

Fig. 1. Schematic representation of the mechanism of phase-transfer catalysis by Starks

Figure 1 shows a simple scheme of the PTC process, which involves only two anions: the nucleophile (Y^-) and the counter-ion (also the departing group X^-) of the initial form of catalyst. In the common case processes are more complex and involve three and more anions. The catalytic cycle in this case is branched or includes a feedback trough a new ion pair QZ-reaction product (Fig. 2) [10].

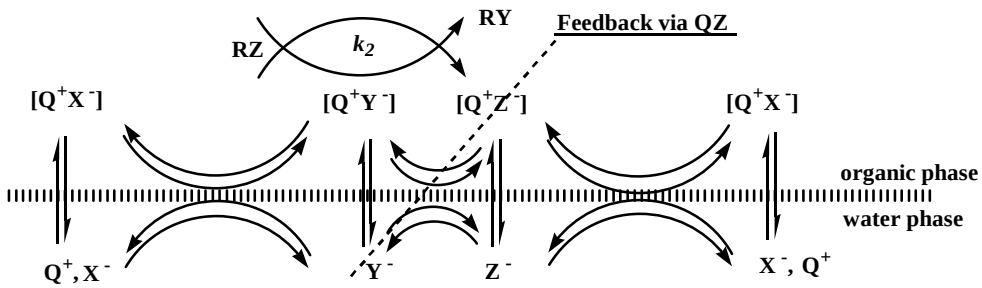

Fig. 2. Schematic representation of PTC process with feedback. QX is the initial form of phase-transfer catalyst, RZ is substrate, Y^- is nucleophile, X^- is the counter-ion of phase-transfer catalyst, QY is active form of phase-transfer catalyst, RY is reaction product, Z^- is nucleofuge

Substrate RZ transforms into reaction product RY under the influence of the active ion pair QY. Catalyst cation Q^+ releases and can bind to a nucleofuge as a new ionic pairs QZ. As can be seen from Figure 2, organic phase contains three ion pairs: QX, QY and QZ. Ion exchange in these pairs is equilibrium process and competitive interaction of three anions for the formation of an ion pair with the cation (Q^+) of the catalyst occurs. As a result, in the catalytic cycle appears the branch point - cation catalyst. It is seen from the scheme (see Fig. 2) that accumulation of active ion pair QY for the formation of the product RY is desirable, *ie* kinetics of the reaction depends on the concentration. The active catalytic form QY arises in reactions (1) and (2):

$$Y_w^- + QZ_o \rightleftharpoons QY_o + Z_w^- \quad (1)$$

$$Y_w^- + QX_o \rightleftharpoons QY_o + X_w^- \quad (2)$$

where the indices "o" and "w" designate the organic and water phases respectively. These two equilibria are mainly determined the quasistationary concentration of QY_o, and consequently, the efficiency of the catalysis.

In summary, the scheme with a branched catalytic cycle includes the following stages:

1. Distribution of the catalyst QX between the aqueous and organic phases

$$QX_o \rightleftharpoons Q_w^+ + X_w^- \quad (3)$$

2. Exchange of anions in the reaction system - nucleophile Y^-, nucleofug Z^-, with phase-transfer catalyst QX in the aqueous phase and their transfer in the form of ion pairs QX, QY and QZ in organic phase

$$\begin{aligned} Q_w^+ + X_w^- &\rightleftharpoons QX_o \\ Q_w^+ + Y_w^- &\rightleftharpoons QY_o \\ Q_w^+ + Z_w^- &\rightleftharpoons QZ_o \end{aligned} \quad (4)$$

3. Chemical interaction of ether RZ with active form of a phase-transfer catalyst QY in the organic phase to form a reaction product RY

$$RZ_o + QY_o \xrightarrow{k_{app}} QZ_o + RY_w \quad (5)$$

4. Competitive interaction of ion pairs and diffusion through the phase interface (equations (1) and (2)).

According to the equation (1) the formation of the active ion-pair QY occurs, which switched in the catalytic cycle and can interact with the substrate RZ (reaction (5)). According to the reaction (2) the initial form of the catalyst QX can be created which like QY can again participate in the catalytic cycle. For the desired reaction (5) an accumulation of the ion pair QZ in the reaction mixture is extremely undesirable since it leads to poisoning of the catalyst.

As seen from Figure 2, the catalytic effect of a phase-transfer catalyst QX lies in its ability to form an active ion pair QY and transfer it into the organic phase. It is obvious that this ability depends on the nature of the cation of a phase-transfer catalyst Q^+ and competitive extraction equilibria. Also hydrophilic/lipophilic balance of ion pairs has a significant effect on their extraction capacity [11]. The cation of the catalyst must be sufficiently lipophilic to form ion pairs with anions and effectively moves into the organic phase. Such interaction should not be strong to realize exchange of nucleofuge with formation of a new "active" form of the catalyst. For the reaction (5) quasistationary concentration of "active" ion pair QY precisely determined by equilibria (1) and (2).

Thereby it seems interesting to investigate the extraction equilibrium of branched catalytic cycle on example of alkali hydrolysis reaction of the activated ester of N-substituted amino acids in the two-phase (liquid/liquid) system in the presence of quaternary onium salts and also distribution patterns of nucleofuge Z^-, cation phase-transfer catalyst Q^+ and the counter-ion $X^- = Cl^-, Br^-, I^-$ in the separated aqueous and organic phases of the model PTC-reaction. As a catalysts which can easily exchange with the anions of the reaction mixture the salts of quaternary phosphonium $(Ph)_4P^+X^-$ ($X^- = Cl^-, Br^-, I^-$) were selected.

In this paper the distribution of the reactants and the reaction products of alkaline hydrolysis of 4-nitrophenyl ester of *N*-benzyloxycarbonylglycine (RZ) were studied in a two phase system chloroform-borate buffer pH = 10.0 and kinetic regularities are compared with the extraction equilibria and the factors influencing the effectiveness of the catalysts.

Materials and methods

Materials

4-nitrophenol was recrystallized from water, mp 387 K, [12]: mp 387 K. *N*-benzyloxycarbonylglycinate (Reanal) tetraphenylphosphoniumchloride ("MERC-Schuchardt"), tetraphenylphosphonium bromide ("MERC-Schuchardt"), tetraphenylphosphonium iodide ("Fluka"), 4-nitrophenyl ester of *N*-benzyloxycarbonyl-glycine ("Sigma") were used without additional purification. Solvents were purified by standard procedures [12].

Technique of kinetic experiment

Kinetic measurements were conducted in thermostatically controlled glass vessel with hashing system at temperature of 298 K, equal volumes of borate buffer pH 10 and chloroform were brought and added hinge plates of the catalyst and *N*-benzyloxycarbonylglycine 4-nitrophenyl ester. The moment of addition of ether was considered as the beginning of kinetic measurements. Through certain periods of time the sampling from a water and organic phase was made. To terminate chemical process the reaction mixture was transferred to 0.1 M solution of nitric acid and quantitative determination of reagents was done. Standard borate buffer was prepared by the standard procedure described elsewhere [12]. As a phase-transfer catalysts were used quarternary phosphonium salts - tetraphenylphosphonium chloride (Ph_4PCl), tetraphenylphosphonium bromide (Ph_4PBr) and tetraphenylphosphonium iodide (Ph_4PI). The control of the reaction rate was carried out spectrophotometrically at l = 260 nm. Experimental data were processed with first order equation: $\ln[a/(a - x)] = k_{app} \cdot t$, where: a - initial concentration of ether [M], x - the current concentration of a product [M], k_{app} - a reaction rate constant in two-phase system [s^{-1}], t - time [s].

Quantitative definition of substances

Determination of 4-nitrophenol and tetraphenylphosphonium cations was carried out spectrophotometrically. Optical density was measured on Specord S-300 (Germany) at the wavelength of λ = 315 nm for 4-nitrophenol and at λ = 269 nm and λ = 276 nm for tetraphenylphosphonium salts. Concentration of 4-nitrophenol and a tetraphenylphosphonium cation in aqueous and organic phases was calculated according to calibration charts. Halide ions (X^- = Cl^-, Br^-, I^-) was determined potentiometrically with use of corresponding ion-selective electrodes.

All experiments of extraction and kinetic measurements were carried out under the following conditions: two-phase system chloroform-borate buffer pH = 10 (volume ratio 1:1). The temperature of reaction mixture was T = 298 K, hashing speed of 900 rpm. Tetraphenylphosphonium salts $Ph_4P^+ X^-$ (X = Cl^-, Br^-, I^-) with various anions, were used as phase-transfer catalysts. In order to estimate the catalytic activity of salts in the hydrolysis

of *N*-benzyloxycarbonylglycine 4-nitrophenyl ester we examined its kinetics at a constant substrate concentration ($5 \cdot 10^{-3}$ M) on variation of the concentration of catalyst.

Results and discussion

Alkaline hydrolysis of *N*-benzyloxycarbonylglycine 4-nitrophenyl ester (RZ) in two-phase system proceeds according to the following stoichiometric equation:

$$\underset{\text{RZ}}{C_6H_5CH_2OC(O)NHCH_2COOC_6H_4NO_2\text{-}4} + 2OH^- \xrightarrow[\text{cat, T = 298 K}]{\text{pH = 10}} C_6H_5CH_2OC(O)NHCH_2COO^- + 4\text{-}NO_2C_6H_4O^- + H_2O \quad (6)$$

Tetraphenylphosphonium halides are effective catalysts, according to Figure 3, the reaction rate decreases among $Cl^- > Br^- > I^-$. Observed increase of rate constant k_{app} with increase of the Ph_4PX catalyst (C_{cat}) concentration indicates an increment of hydroxide ion transfer in organic phase where actually the desired reaction (6) [13] runs. With an increase in of hydrophobicity of the phase-transfer catalyst in the range $Ph_4PCl > Ph_4PBr > Ph_4PI$ the transfer of hydroxide ion from aqueous to organic phase decreases which is related to a steric effect. Unfortunately, it is impossible to determine the relative contributions of the hydrophobic effect due to the lack of the data on hydroxide ion distribution between aqueous and organic phases [9].

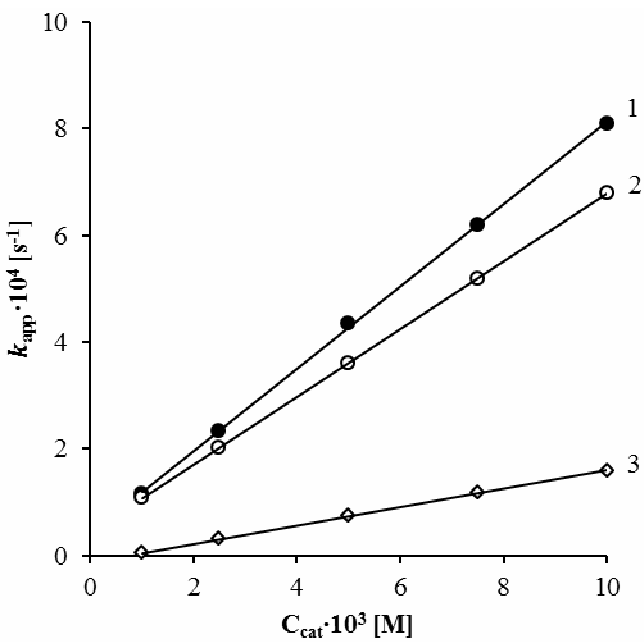

Fig. 3. Dependence of reaction rate constants k_{app} of alkaline hydrolysis of *N*-benzyloxycarbonylglycine 4-nitrophenyl ester in two-phase system chloroform-borate buffer pH = 10 from the concentration of the catalyst $(Ph)_4PX$, X = Cl^-(1), Br^- (2), I^-(3), 298 K

In the presence of the tetraphenylphosphonium salts three types of semi-logarithmic kinetic curves in the first-order reaction coordinates was observed [14]. During catalysis with tetraphenylphosphonium bromide was obtained linear dependence, with tetraphenylphosphonium chloride obtained kinetic dependence is of the "poisoning" effect of the catalyst, and with tetraphenylphosphonium iodide the effect of "auto acceleration" was found [14]. To find out the cause of the observed phenomena, the distribution of the cationic and anionic parts of the phase-transfer catalyst and the reaction product (4-nitrophenol) between the aqueous and organic phases was studied. Quantitative characteristics of distribution of the tetraphenylphosphonium cations and halide ions between the aqueous and organic phases were partition coefficients, calculated by the following equations:

$$K_{o/w}^{Ph_4P^+} = \frac{\left[Ph_4P^+\right]_o}{\left[Ph_4P^+\right]_w} \tag{7}$$

$$K_{o/w}^{Hal^-} = \frac{C_o^{Hal^-}}{C_w^{Hal^-}} \tag{8}$$

where: $K_{o/w}^{Ph_4P^+}$ - tetraphenylphosphonium cation partition coefficient; $[Ph_4P^+]_o$ and $[Ph_4P^+]_w$ - concentration tetraphenylphosphonium cation in the organic and aqueous phases [M]; $K_{o/w}^{Hal^-}$ - distribution ratio of halide ions between the aqueous and organic phases; $C_o^{Hal^-}$ and $C_w^{Hal^-}$ - the concentration of halide ions in organic and aqueous phases [M], respectively.

Figure 4 shows relation of tetraphenylphosphonium cation distribution with concentration of resulting reaction product (4-nitrophenol), calculated on the total volume of the two-phase system. As can be seen, in the absence of RZ ester a small amount of phase-transfer catalyst located in the aqueous phase whereas most part is in chloroform. Obtained results are in good agreement with literature data [12], chloroform is a good solvent for the phosphorus salts extraction. Tetraphenylphosphonium halides Q^+X^- (X = Cl, Br, I) have sufficiently expressed polar and nonpolar parts. They are diphilic, and characterized by solubility in both organic and aqueous phases. Depending on the content of lipophilic 4-nitrophenol the value of $K_{o/w}^{Ph_4P^+}$ changes in reaction medium.

On the site of the kinetic curve, wherein the ether has reacted for less than 50% (~4000 s), the content of Ph_4P^+ in phases varies insignificantly. The tendency of accumulation tetraphenylphosphonium cation in the organic phase occurs. At the next site the conversion of ester is more than 50%, and a tetraphenylphosphonium is predominantly located in organic phase. It is supposed that the lipophilic cation Ph_4P^+ forms ion pair with the reaction product - 4-nitrophenol $\{Ph_4P^+||4\text{-}NO_2Ar^-\}$ and remains in organic phase.

Thus, the extraction of tetraphenylphosphonium - cation in the form of ion pair from the aqueous phase into organic phase occurs due to the accumulation of 4-nitrophenol anion. Such changes in the reaction system may cause decrease of the reaction rate which exhibit so-called “catalyst poisoning” effect.

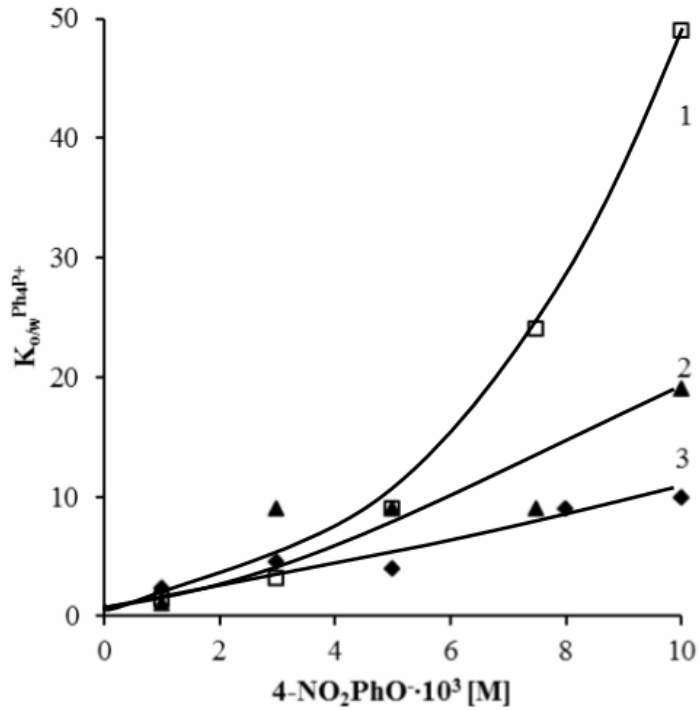

Fig. 4. Dependence of the distribution of tetraphenylphosphonium cation $K_{o/w}^{Ph_4P^+}$ between phases at varying concentrations of 4-nitrophenol anion [4-NO_2PhO^-] in two-phase system of chloroform-borate buffer pH = 10, 297 K. [Ph_4PCl] = $5\cdot10^{-3}$ M (1); $1\cdot10^{-3}$ M (2); $1\cdot10^{-2}$M (3)

According to potentiometric measurements it was found that the content of chloride - ion in the reaction system decrease in the organic phase, and increase in aqueous phase when the concentration of 4-nitrophenol increases in the range of $5\cdot10^{-4}$-$1\cdot10^{-2}$ M. This phenomenon can be explained by the high hydrophilicity of Cl^- - ion. The last displaces from the organic phase of more lipophilic 4-nitrophenol - ion. Similar phenomena have been described in [15]. According to [5] in PTC reactions with several nucleophiles each anion displaced quantitatively from the organic phase by neighbor from right in the row: SO_4^{2-}, F^-, OH^-, Cl^-, Br^-, I^-. Considering that in experiment a small amount of catalyst tetraphenylphosphonium chloride ($1\cdot10^{-4}$-$1\cdot10^{-2}$ M) were used, it was determined that the concentration of halides in the organic phase during the reaction is negligible. Such a phenomenon can be explained by the fact that the transition of anions in the organic phase without hydration shell is thermodynamically unfavorable [10]. As can be seen in the case of completed hydrolysis of the ester RZ, the chloride ion transforms completely into the aqueous phase. This means that the concentration of the ion pair catalyst/tetraphenylphosphonium chloride in the volume of the organic phase is low. As a result it was observed decrease of the reaction rate at high conversion degrees of the *N*-benzyloxycarbonylglycine 4-nitrophenyl ester.

The content of bromide-ion in the aqueous and organic phases during the reaction does not change significantly and remains at a constant level. Bromide ion resides predominantly in the aqueous phase. Concentration of 4-nitrophenol anion in the organic phase increases with increase of the total concentration of tetraphenylphosphonium iodide in the reaction mixture.

In all the examined cases there are areas of high and low reaction rate. Based on the kinetic data it can be concluded that the change of the nucleophile content during the process is unlikely a single reason for changes of the investigated reaction rate. Catalyst poisoning by accumulation of the product (4-nitrophenol), is seems to give a major contribution to rate changes. It is worth noting that the total redistribution of I^- and OH^- anions aside of $\{Q^+\|^-OAr\}$ ion pair occurs at sufficiently low concentrations of 4-nitrophenol, that leads to a halt of the catalytic process.

Conclusions

Thus, phase-transfer reaction of alkaline hydrolysis of *N*-benzyloxycarbonylglycine 4-nitrophenyl ester in the two-phase system (chloroform-borate buffer) passes through the extraction mechanism with the rate-limiting step of chemical interaction in the bulk of organic phase. Kinetic curves in a coordinates of the pseudo-first order equation characterized by a higher velocity at the initial stages, which can be related to a competitive extraction of reactive OH^- nucleophile which forms during reaction of nucleofuge ($4\text{-}NO_2C_6H_4O^-$) and phase-transfer catalyst anion X^- (X = Cl, Br, I). In a context of the extraction mechanism the nature of phase-transfer catalyst plays a crucial role at the stage of the anion extraction from the aqueous into the organic phase.

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BADANIE RÓWNOWAG EKSTRAKCJI W REAKCJI ZASADOWEJ HYDROLIZY AKTYWOWANYCH ESTRÓW AMINOKWASÓW

Abstrakt: Zbadano korelację pomiędzy obserwowanym efektem kinetycznym przejścia fazowego katalitycznej reakcji zasadowej hydrolizy estru 4-nitrofenylowego *N*-benzyloksycarbonylglycyny-4 w dwufazowym układzie chloroform-bufor boranowy, pH = 10, z zawartością jonowych form katalizatora. Sole fosfoniowe QX (X = Cl^-, Br^-, I^-) wykazują wysoką aktywność katalityczną. Zależności kinetyki reakcji przeanalizowano w ramach mechanizmu ekstrakcji z konkurencyjną ekstrakcją nukleofilu OH^-, grupą odchodzącą 4-$NO_2C_6H_4O^-$ i anionem X^- katalizatora przejścia fazowego.

Słowa kluczowe: kataliza przejścia fazowego, kinetyka, hydrolizy, czwartorzędowe sole fosfoniowe, rozgałęziony cykl katalityczny, równowagi ekstrakcji