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Abstract

A mixture of acetic and 2-methylpropanoic (isobutyric) acids representing non-branched and branched acids, respectively, was catalytically converted to a mixture of ketones in a set of statistically designed experiments (DOE). The selectivity toward the cross-ketonization product was analyzed depending on (a) temperature within 300–450 °C range, (b) molar fraction of each acid in the mixture, from 10% to 90%, and (c) liquid hourly space velocity (LHSV) within 2–12 h⁻¹, and compared against the selectivity toward two symmetrical ketones. Six metal oxide catalysts were tested and ranked on their ability to yield the cross-product as opposed to the self-condensation product. The catalysts were based on either the anatase form of titania or monoclinic form of zirconia and treated with either KOH or K₂HPO₄. The titania catalyst treated by KOH outperformed all other catalysts by providing the cross-selectivity above the statistically expected binomial distribution. The criterion for having a high cross-selectivity in the decarboxylative ketonization is formulated mathematically as the separation of roles of two acids, one being a more active enolic component, and the other being the preferred carbonyl component. According to the suggested criterion, the less branched acetic acid reacts as both the preferred carbonyl and enolic component with untreated catalysts. Therefore, untreated catalysts promote selective formation of the symmetrical ketone, acetone, thereby decreasing the selectivity to the cross-ketone. After alkaline treatment, both the anatase form of titania and monoclinic form of zirconia increase the isobutyric acid participation as the carbonyl component. Acetic acid remains as the preferred enolic component with all treated catalysts, thus increasing the selectivity toward the cross-product in the ketonization of a mixture of carboxylic acids. The condition for achieving a high cross-selectivity by polarizing roles of the two reactants can be extended to other types of cross-condensations.

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CROSS-SELECTIVITY IN THE CATALYTIC KETONIZATION OF CARBOXYLIC ACIDS

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CROSS-SELECTIVITY IN KETONIZATION

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ABSTRACT. A mixture of acetic and 2-methylpropanoic (isobutyric) acids representing non-branched and branched acids, respectively, was catalytically converted to a mixture of ketones in a set of statistically designed experiments (DOE). The selectivity toward the cross-ketonization product was analyzed depending on a) temperature within 300-450 °C range, b) molar fraction of each acid in the mixture, from 10% to 90%, and c) liquid hourly space velocity (LHSV) within 2-12 hr⁻¹, and compared against the selectivity toward two symmetrical ketones. Six metal oxide catalysts were tested and ranked on their ability to yield the cross-product as opposed to the self-condensation product. The catalysts were

based on either the anatase form of titania or monoclinic form of zirconia and treated with either KOH or K_2HPO_4 . The titania catalyst treated by KOH outperformed all other catalysts by providing the cross-selectivity above the statistically expected binomial distribution. The criterion for having a high cross-selectivity in the decarboxylative ketonization is formulated mathematically as the separation of roles of two acids, one being a more active enolic component, and the other being the preferred carbonyl component. According to the suggested criterion, the less branched acetic acid reacts as both the preferred carbonyl and enolic component with untreated catalysts. Therefore, untreated catalysts promote selective formation of the symmetrical ketone, acetone, thereby decreasing the selectivity to the cross-ketone. After alkaline treatment, both the anatase form of titania and monoclinic form of zirconia increase the isobutyric acid participation as the carbonyl component. Acetic acid remains as the preferred enolic component with all treated catalysts, thus increasing the selectivity toward the cross-product in the ketonization of a mixture of carboxylic acids. The condition for achieving a high cross-selectivity by polarizing roles of the two reactants can be extended to other types of cross-condensations.

KEYWORDS: Decarboxylative ketonization; cross-condensation; reaction mechanism; monoclinic zirconia; anatase titania; enolization.

1. INTRODUCTION

Increasing selectivity in catalytic reactions is one of the ultimate goals pursued in the design and preparation of catalysts [1]. Selectivity of chemical reactions can be classified into various types, such as chemo-, regio-, or stereo-selectivity [2]. A common strategy for improving the chemical selectivity of a catalyst is to minimize undesirable reactions by eliminating or blocking improper catalytic sites. In addition, selection of the best process conditions helps discriminate competing reactions. Perhaps, a more challenging problem in the catalyst design is to improve the selectivity toward just one of the several possible isomers in a particular reaction. Such selective catalysts may provide access to regio- or stereoisomers. A stereo selective catalyst must create kinetically favorable conditions for the formation of the preferred stereoisomer.

A less frequent type of selectivity appears in cross-coupling reactions between two reagents. Each reagent may condense either with itself to produce a symmetrical product, or with the other reagent to produce the cross-product. Obviously, each of the two symmetrical products may be produced separately starting from just a single reagent and for that reason often considered as a waste in cross-reactions. The intent of research and development on cross-reactions is to improve the selectivity to the cross-product, as for example, in aldol condensations [3]. Unfortunately, a broadening view on the subject of cross-selectivity combining diverse catalytic reactions has yet to be developed.

An example of an exceptionally high cross-selectivity can be illustrated by a recently discovered selective condensation of two different aldehydes to cross-coupled esters in a Ni(0) catalyzed Tishchenko reaction wherein different electronic factors of the alkyl vs. the

aryl group are responsible for the observed high selectivity [4]. A similar problem of the cross-selectivity exists in the industrial synthesis of unsymmetrical ketones, usually methyl ketones, such as methyl cyclopropyl ketone [5], methyl nonyl ketone [6], methyl isopropyl ketone¹, etc., from a mixture of two carboxylic acids by their cross-ketonization reaction (Scheme 1).

Scheme 1. Product distribution for the cross-ketonization reaction of isobutyric acid, **B**, with acetic acid, **A**.

¹ There has been a surge of interest in the preparation of methyl isopropyl ketone for the past decade. See, for example, [7] available in the English language. The rest of the literature devoted to the preparation of this ketone as the single targeted product, about twenty publications from 1999 to 2012, is in the Chinese language.

The ketonic decarboxylation, also known as the decarboxylative ketonization of carboxylic acids has a long history [8], [9], [10] [11] and several versions, such as a non-catalytic pyrolysis reaction [12], or an industrial scale vapor phase catalytic process [11], [13]. It has been rediscovered several times [8]. The literature on ketonization reactions has been extensively reviewed [9], [10], [11], but the discussion of the cross-selectivity was limited to just a few cases [14], [15], [16]. The interest to ketonization has been recently revived in connection with the bio-oil upgrading [17]. One possibility is to condense acetic acid with bio-derived fatty acids into methyl ketones [6], [18]. In this process it is necessary to minimize consumption of acetic acid into the symmetrical ketone, acetone, which is an undesired by-product. The problem again, is to increase the selectivity to the cross-ketone. The importance of this problem urged us to examine the relative selectivity achieved with different catalysts toward the cross-product in the catalytic ketonization of carboxylic acids. Our goal is to understand the factors governing cross-selectivity and to improve it.

The cross-selectivity is closely related to and depends on the relative reactivity of the two carboxylic acids. In general, a higher degree of branching at the alpha-position decreases the carboxylic acid reactivity in the ketonization reaction [15], [20]. The role of the catalyst, the molar ratio of two acids, and the process conditions affecting the cross-selectivity have not been sufficiently studied.

There are two components used for the construction of any ketone by the decarboxylative ketonization, the acyl group and the alkyl group coming from two different acids. We have recently suggested naming their sources as the carbonyl and enolic

components, respectively by analogy with the aldol condensation [20]. However, unlike the aldol condensation or the Tishchenko reaction in which two cross-products can form, there is only one cross-product possible in the carboxylic acids ketonization reaction (Scheme 1). It has been shown that two different mechanistic pathways exist, and they both lead to the same cross-product [20]. Among two possible combinations for the construction of the cross-ketone, the preferred one is that utilizing the alkyl group from the less branched acid and the acyl group from the more branched acid. Mechanistically, it may occur through the preferred enolization of the less branched acid and its subsequent condensation with the more branched carbonyl component to a beta-ketoacid followed by the loss of CO₂ from the enolic component in the decarboxylation step [20].

The rate-limiting step of the catalytic ketonization has not been confirmed yet, but any variation of the cross-selectivity depending on the catalyst must be explained by the different influence of the employed catalysts on the substituents in the transition state structure. For this reason, cross-reaction becomes a valuable method in the study of the ketonization mechanism. In our previous work on the ketonization mechanism we proposed enolization of carboxylic acids on zirconia [19] and were able to analyze separately the effect of substituents on the reaction rates of the enolic and the carbonyl component [20]. Accordingly, in two competing reactions of a common enolic component with two different carbonyl components, a faster reaction rate is observed for a less substituted carbonyl component (Table 1). The same effect was found for a common carbonyl component reacting faster with a less substituted enolic component. In this approach, the cross-

ketonization conditions are used to separate the effect of substituents on the enolic component from the carbonyl component of the same carboxylic acid.

The cross-selectivity originates from the two competing reactions for each common component leading to the formation of symmetrical vs. non-symmetrical product and consequently controlling the cross-selectivity. For example, the common enolic component, A_e , may yield either the symmetrical ketone, A_eA_c , or a cross-ketone, A_eB_c , with two different carbonyl components, A_c and B_c when the reaction is catalyzed by KOH-treated zirconia (Scheme 1, Table 1). In this study we intended to compare other catalysts on their selectivity to the cross-product and to identify the most selective catalyst for mechanistic studies.

Catalysts for the current study were chosen from the most recent patent literature [21], [22], which specifically targets preparation of unsymmetrical ketones in the cross-ketonization reaction. Acetic acid and 2-methylpropanoic (iso-butyric) acids were chosen as the simplest acids representing a non-branched and a branched acid and being able to enolize.

2. EXPERIMENTAL SECTION

2.1. Materials

Acetic and isobutyric acids with natural isotopes, and isotopically labeled acetic acid, $CH_3^{13}CO_2H$, were purchased from Aldrich. Monoclinic zirconium oxide and anatase form of titania, both in a shape of cylinders, 3-5 mm in length and 3 mm in diameter, were purchased from Alfa Aesar. Zirconia had median pore diameter 160/600 Å and bimodal total

pore volume 0.30 mL/g. Titania featured a median pore diameter of 270 Å and total pore volume of 0.29 mL/g. The BET surface area of all catalyst samples was determined by nitrogen adsorption at 77 K temperature (Appendix A: Supplemental Material, Table A.2).

2.2. Catalyst preparation general procedure

Metal oxide catalysts were prepared according to modified literature procedures [21], [22]. Catalyst pellets, 10 g, were placed in a flask containing 10 mL of 10% aqueous solution of KOH or K₂HPO₄. The flask was sealed and the pressure was reduced to eliminate adsorbed gases. After 1 hour the flask was heated to 60 °C and pellets were soaked for 24 hrs. The solution was drained and the catalyst was washed three times with 20 mL of deionized water, dried at 130 °C for 4 hrs, heated to 450 °C at a 1 °C/min rate and calcined for 2 hrs. Pellets were cut to 1-2 mm in length and used in the continuous flow reactor. A fraction of 0.2-0.75 mm was used for the “inside GC/MS” microreactor.

2.3. Catalysts abbreviation

ZR – untreated zirconia, ZK – KOH treated zirconia, ZP – K₂HPO₄ treated zirconia, TI – untreated titania, TK – KOH treated zirconia, TP – K₂HPO₄ treated titania.

2.4. Continuous flow reactor

A tubular reactor was constructed from a stainless steel tube, 6.4 mm in diameter, 250 mm in length equipped with a thermocouple positioned in the center of the heated zone. The reactor inlet on the top was connected to a preheating line, 1.5 mm in diameter, and 300 mm in length. The outlet on the bottom was connected to a condenser constructed from a jacketed stainless steel tube, 6.4 mm in diameter, and 250 mm in length, chilled by glycol to 0 °C. A metal oxide catalyst, 3.0 mL, was loaded into the reactor at such level as to

have the thermocouple in the center of the catalyst bed. The bottom and the top of the catalyst bed were each filled with Penn State stainless steel packing. The reactor was heated inside an electric furnace, having 25 mm diameter and 210 mm length of the heating space, to temperatures indicated in Table 2. Heating was controlled by the temperature on the furnace through a programmable temperature controller. A mixture of acetic and isobutyric acids at the specified molar ratios, feed rates, and temperatures (Table 2) was introduced to the top of the reactor through the preheated line by the New Era syringe pump, model NE-1000. The reaction was conducted at atmospheric pressure. Deionized water was pumped through the reactor at the end of each run to clean the catalyst. Liquid products formed either one or two phases depending on the acids conversion. Products were collected from the outlet of the condenser. Phases were separated, weighed, and separately analyzed by GC/MS.

2.5. Identification of the products

Product analysis was done by a Thermo Scientific TRACE 1300 gas chromatograph equipped with Restek XTI-5 capillary column, 30m in length, 0.25 mm in diameter, 0.25 mkm phase thickness, FID detector for quantitative analysis and with HP-5 MS UI capillary column, 30 m in length, 0.25 mm in diameter, 0.25 mkm phase thickness, and Thermo Scientific ISQ Single Quadrupole mass selective detector for identification analysis.

2.6. GC quantitative analysis method

Helium carrier gas with a constant column flow, 0.9 ml/min, split mode of injection with a split ratio of 100:1, an oven temperature of 50°C holding for 5 min and then rising 15°C/min were used for the quantitative analysis method. The amounts of all ketone products and

unreacted acids were calculated using the integration of the corresponding peaks relative to the area of the methanol peak added as internal standard. Preliminary calibration of acids and ketones included three levels of their concentration.

2.7. Calculation of the yield and conversion

The yield of ketones and the conversion of acids were calculated according to equations (1) and (2):

$$\% \text{ yield} = \frac{2 \times \text{moles of ketone obtained}}{\text{moles of acid A fed} + \text{moles of acid B fed}} \times 100 \quad (1)$$

$$\% \text{ acid conversion} = \frac{\text{moles of acid fed} - \text{moles of unreacted acid}}{\text{moles of acid fed}} \times 100 \quad (2)$$

2.8. The multilevel factorial DOE model

DOE model included three experimental factors, temperature, molar fraction of acid **B**, and liquid hourly space velocity (LHSV), hr^{-1} , with three levels of each factor and two blocks. Conversion of acids, the yield of the cross-product, and the yields of two symmetrical products were measured and used as response variables in the regression analysis. The selected design had 16 runs, using the same portion of the catalyst for all 16 runs and collecting one product sample for each run. Prior to DOE experiments, each catalyst was aged by running ketonization at 375-400 °C for at least 2 hrs. A quadratic model of the process factors with 11 coefficients was used. Insignificant process factors and their interactions were eliminated during regression analysis to achieve the p-value less than 5%. R^2 -Values ranged from 65% to 99%. The selection of factors created a different dependence of the response variables for each catalyst, either a quadratic, or a linear (Supporting Information, Table S2).

2.9. The “inside GC/MS” pulse microreactor

GC/MS pulse microreactor was built and used as previously described [20], [23].

2.10. Calculation of the fraction of path “b” in the mechanism of the cross ketone formation

Reactions with isotopically labeled molecules were run using the “inside GC/MS” pulse microreactor. A sample of catalyst, 40 ± 1 mg, was placed inside the injection port at $400\text{ }^{\circ}\text{C}$ and kept for 10-15 min to allow desorption of water and CO_2 . The inlet temperature was set to the desired value and a mixture of isotopically labeled acetic, $\text{CH}_3^{13}\text{CO}_2\text{H}$, and isobutyric acids, $0.1\text{ }\mu\text{L}$, in molar ratios 1:4, 1:1, 4:1, and 9:1, was injected 20–40 times at each temperature, 200, 250, 300, 350, and $400\text{ }^{\circ}\text{C}$ using the same catalyst. Ten pulses of water were added after each series of acid pulses before switching to higher temperature. The fraction of path “b” was calculated as the ratio of ions 86 and 86+87 abundances in the chromatographic peak of the cross-ketone according to the equation (3)

$$\% \text{ Fraction of path "b"} = \frac{\text{abundance of } m/z \text{ 86}}{\text{abundance of } m/z \text{ 86} + \text{abundance of } m/z \text{ 87}} \times 100\% \quad (3)$$

2.11. Equilibrium concentration of adsorbate on catalyst surface

Adsorption experiments were performed with 40 mg of a fresh catalyst sample at each temperature prepared as described above. A sequence of 5 pulses of water, 30 pulses of isobutyric acid, 10 pulses of water, and 20 pulses of acetic acid was added via automatic injector at each temperature, 200, 250, 300, 350, and $400\text{ }^{\circ}\text{C}$. The injected volume of liquid for each pulse was $0.1\text{ }\mu\text{L}$. Time between pulses was 3 min. The amount of products registered by the GC/MS detector was calculated according to their calibration based on m/z 18 for water, m/z 58 for acetone, m/z 60 for acetic acid, m/z 86 for methyl isopropyl ketone and m/z 114 for di-isopropyl ketone. As the surface was populating, the amount of

adsorbate registered in the gas phase in each pulse was growing until surface was completely saturated. The amount of acid adsorbed on a sample at saturation was calculated as the difference between the sum of the amount added in pulses and of that registered in the gas phase up to the saturation point. The sum of isobutyric acid amount replaced from the catalyst by acetic acid matched that one calculated by its adsorption. At high temperatures when the ketonization reaction took place, the above calculations were based on accounting all molecules with the methyl group for acetic acid adsorption, and all molecules with the isopropyl group for isobutyric acid adsorption. The equilibrium amount of water on surface was determined by switching from H₂O to D₂O [23].

2.12. Characterization of catalyst activity for H/D exchange of alpha hydrogens.

Ten pulses of a mixture of isobutyric acid and D₂O in 1:1 molar ratio were added to a 20 mg sample of ZR, ZK, ZP, and TP catalysts placed inside GC/MS pulse microreactor as described above, at 5 degrees temperature intervals within 120-175 °C range. The same catalyst sample was used at each temperature. The last four pulses at each temperature were used to calculate the H/D exchange rate as the fraction of m/z 72 abundance to the sum of m/z 71 and m/z 72 abundances of the isobutyric acid GC peak.

3. RESULTS AND DISCUSSION

3.1. Yield of the cross-ketone vs. symmetrical ketones as a function of temperature and the molar fraction of acids A and B.

All studied catalysts make ketones with high selectivity compared to other products. A mixture of two acids, acetic **A**, and isobutyric **B** (Scheme 1) generates two symmetrical ketones, acetone **AA**, and diisopropyl ketone **BB**, and one cross-product, methyl isopropyl

ketone **AB**, within the temperature range 250-425 °C. Other products are formed in less than ~2% yield within the specified temperature range. A detectable formation of by-products begins only above 400 °C temperature and increases with the further temperature increase. Among those, short-chain, isomerized, or unsaturated, ketones are identified by GC/MS analysis as the major by-products. The amount of by-products depends on the catalyst and is the highest for the untreated zirconia and the lowest for KOH and K₂HPO₄ treated zirconia. At temperatures above 450 °C the yield of the expected ketones decreases and the amount of by-products increases, up to ~10%, because of the decomposition of products or side reactions taking place. The mass balance in each run after accounting for the theoretical amount of CO₂ is above 85%-92% depending on the catalyst and conditions.

A significant drop of the catalytic activity was observed within ~30 min of being on stream. After the fast initial change, the catalyst activity stabilized and did not change for the duration of the entire experiment, ~48 hrs. All experiments were done with catalysts aged for at least 2 hrs on stream. Some coke deposition was observed on untreated catalysts at temperatures above 425 °C, but almost none was found on the treated catalysts. Lifetime of ZK and TK catalysts exceeds 1000 hrs at 450-475 °C without a substantial change of the catalyst activity.

The purpose of statistically designed experiments with each catalyst was to obtain the dependence of ketones yields and selectivities on temperature and the acid composition in an integral reactor within a wide range of these parameters applicable to industrial conditions. A bench scale integral reactor is often used as a first step for the estimation of a catalyst performance under industrial conditions before measuring intrinsic rates and

building a kinetic model. In addition, the known inhibition effect of water, CO₂, and acids on the ketonization rate [9] was also observed in our study, making it more difficult to use differential rates. Therefore, the integral reactor was chosen in the current study as the most practical and conclusive method to study cross-selectivity.

The obtained regression coefficients are presented in the Appendix A: Supplementary Material, Table A.2. The most rational and convincing way to observe and analyze the above relations is through graphical representations. In this section, we will discuss the obtained 3D graphs.

The reactivity of both acids with all catalysts increases with temperature (Figure 1). Two of the most active catalysts are ZR and ZK, whereas the least active catalyst is TI. An equal reactivity of two carboxylic acids **A** and **B** would be rather an exception and is not observed. Acetic acid is consumed faster than isobutyric acid with all studied catalysts as shown in Figure 1. Under certain conditions this may result in a case when all acetic acid is reacted while the conversion of isobutyric acid is still incomplete. If such a mixture containing unreacted isobutyric acid is allowed to react further, for example, by increasing either the temperature or residence time, it would produce an additional amount of the symmetrical ketone **BB**. From both the practical and theoretical points of view, forcing the conversion of isobutyric acid to completion is not desirable. Practically, this does not help to increase the yield of the cross-ketone. Instead, the unreacted acid **B** could be recycled. For reporting the selectivity trends, it may only create confusion. If the less reactive acid **B** is allowed to react further and to produce an additional amount of ketone **BB**, then the relative selectivities to all ketones achieved at the point of the full conversion of acid **A** will be altered. When one

of the acids is not fully converted, the effective molar ratio of the two acids spent for making ketone products would deviate from their initial ratio. Again, confusion may appear in the analysis of the selectivity trend dependence on the molar ratio of the two acids. Selectivity toward a certain product can be used as a way to characterize and compare catalysts with each other. Two types of selectivities, differential or integral, can be used for evaluating catalysts. The differential selectivity is defined as the ratio of the reaction rate leading to the specific product to the sum of rates of all reactions consuming the starting materials (eq. 4), whereas the integral selectivity is the ratio of the amount of the specific product to the summation of all products amounts obtained from the starting materials (eq. 5). In general, both types of selectivities depend on the extent of conversion.

$$S_i^{dif} = \frac{r_i}{\sum_i r_i} \quad (4)$$

$$S_i^{int} = \frac{P_i}{\sum_i P_i} \quad (5)$$

To avoid any possible confusion, we report the yield of ketones as specific products instead of the general integral selectivity. We define the yield as the ratio of moles of each ketone product produced over the number of moles of two acids fed according to equation (1). It is important to use the sum of the two acids in the denominator for the yield calculation of a bimolecular reaction.

A misleading approach could still be found in literature [21], [22] when the yield is calculated on the basis of just one of the acids, for example, on the basis of the more expensive acid for the calculation of the production cost. A single component analysis for bimolecular reactions could lead to a potential inconsistency because the cross-selectivity

does actually depend on the concentration of the second component which cannot be artificially excluded.

The yield of the cross-ketone **AB** obtained for the mixture of acetic and isobutyric acid depending on their molar composition (expressed as the acid B molar fraction) and temperature with six catalysts is shown in Figures 2a-f. Performance of the most selective catalyst for cross-ketonization, KOH-treated titania (TK), is surprisingly high and significantly exceeds that achieved with the rest of the catalysts. The cross-ketone is formed with TK catalyst in a yield well above the statistically expected binomial value within a broad range of temperatures and acid compositions (Figure 2e). The rest of the studied catalysts produce the cross-ketone in a yield that is lower than expected for a binomial distribution. The fact that one of the catalysts is so different from the rest in providing high selectivity to the cross-ketone is remarkable and deserves a special attention. We aspired to find and explain the reason(s) behind its outstanding performance.

The binomial distribution of products **AA**, **AB**, and **BB** is defined on the basis of the probability of matching two components, **A** and **B**, and therefore on their concentration in the mixture. If the concentration of one of the reagents, e.g., **B**, is x and that of the second one is $(1 - x)$, where $0 < x < 1$, then the probabilities of making two symmetrical ketones are $y_4 = x^2$, and $y_1 = (1 - x)^2$, respectively. The probability of making the unsymmetrical product, cross-ketone, is $y_2 + y_3 = 2 \times x(1 - x)$, with the maximum at $x = 0.5$ (grey mesh surface in Figures 2a-f), i.e. at the 1:1 molar ratio of two acids.

A parabolic shape of the cross-ketone yield dependence on acid concentrations, typical for a bimolecular reaction (Figure 2), is observed. The maximum yield is found near the

equimolar mixture of two acids for ZK, TK, and TP catalysts. An exception is observed for ZR and TI, i.e. untreated catalysts, and ZP catalyst, which might have the expected parabolic shape and a maximum outside of the studied range of the binary mixture composition, 10-90%.

The deviation of the yield for all ketones from the expected binomial values is shown in Figures 3a-f. The highest deviation of the yield of symmetrical ketones from the binomial distribution is observed at a high concentration of either A_c or B_c , i.e., on the edges of the acid concentration range, for all studied catalysts. The region near the equimolar mixture has the most negative deviation of the cross-ketone yield from the binomial distribution, except for TK catalyst (Figure 3e).

In the absence of any side or reverse reactions, the deviation of the observed selectivities from the binomial, statistically expected distribution can be explained by the difference between the reaction rates of four competing reactions leading to the formation of four ketones. Two of these ketones represent the cross-ketone, formed by path “a” or path “b” (Scheme 1, Table 1). The yield dependencies can be modeled by knowing reaction rates for all competing reactions. In the next section we propose a ketonization mechanism and a reaction kinetic model against which the distribution of four ketones can be tested.

3.2. The mechanism of the catalytic decarboxylative ketonization.

The most currently accepted ketonization mechanism through a beta-ketoacid formation [10] was originally proposed by Neunhoeffer and Paschke [24], but it was missing the acid enolization step. We have adopted this mechanism and modified it by focusing on the enolization step (Scheme 2). Compared to the earlier proposed mechanisms via a beta-

ketoacid intermediate summarized in the most recent reviews [9], [10] the new main characteristics of our mechanism are outlined below.

Scheme 2. Catalytic cycle in the decarboxylative ketonization mechanism with ZrO_2 catalysts.

The most important aspect which we propose is that the activation of the enolic component through the enolization of carboxylates on metal oxide surface is a reversible process. This is a reasonable assumption based on the known chemistry of the enolic form of carboxylic acids [25], which is much higher in energy and kinetically easily protonated

back to the carboxylic group in an equilibrium process characterized by a very small equilibrium constant in aqueous solution at room temperature, 10^{-12} - 10^{-16} . The DFT electronic energy of carboxylates' enolization reaction on zirconia surfaces is about 15-20 kcal/mol [19]. The equilibrium constant estimated from the above reaction energy must be on the order of 10^{-6} - 10^{-5} at temperatures ca. 300-400 °C. Thus, equilibrium should be significantly shifted away from the enolized structure **II** toward the initial surface carboxylate **I** (Scheme 2). The consequence for the catalytic reaction rate is that the concentration of the enolic component on the surface determined by the equilibrium constant is very low compared to the concentration of surface carboxylates.

Increasing temperature may promote the enolization step in two ways. First, it can do so by increasing the enolization equilibrium constant. Second, higher temperatures help decrease the concentration of surface water [23] which otherwise might protonate the enolized structure **II** back to the carboxylate **I**. The inhibition of the ketonization reaction rate [9] by the presence of water, CO₂, and even by the excess of carboxylic acids can now be understood as proton donors, and other electrophiles, may readily engage in a chemical reaction with the enolized carboxylate **II**. Protonation of **II** may depend on the concentration of proton donors, such as water or a carboxylic acid, not only located on surface near the reactive sites, but also coming from the gas phase. It proceeds at the rate $r_{-1} = k_{r-1} \times [\text{II}] \times [\text{H}^+]$ shifting the equilibrium back to the surface carboxylate and decreasing the concentration of the enolic component on the surface.

If the enolized structure is used in the ketonization mechanism, a kinetic model must not ignore the fact of its low concentration. Reaction kinetics can be described by equation (6),

where k_{rds} is the rate constant representing the rate-determining step (RDS) among steps 2-4, which is most likely associated with step 4 [26].

Reaction kinetics described by equation (6) fall into a category of saturation models, e.g. the Michaelis-Menten model. The ketonization reaction is observed as a second order process at low partial pressures of carboxylic acids in the gas phase, 0.05 atm with ceria-zirconia catalyst [27] or 0.016 atm with Ru/TiO₂ catalyst [28]. With increasing the partial pressure of the carboxylic acid, approximately above 0.1 atm, the surface becomes saturated by carboxylates and the ketonization reaction order becomes zero with respect to the gas phase acid concentration [27]. In our model, population of the enolized carboxylates on surface is even lower compared to initial carboxylates, because it is controlled by an additional equilibrium, $\text{I} \rightleftharpoons \text{II}$.

Based on the calculated activation energies, the equilibrium between **I** and **II** is likely established in a process which is conceivably faster than the RDS. Once **II** is formed, it has a choice to go back to **I** with the calculated activation energy less than 15 kcal/mol [19], and even 9 kcal/mol [26], or to proceed toward ketonization in a series of steps in which the rate determining step requires a higher activation energy, calculated as 26 kcal/mol [26] and experimentally measured as 28 kcal/mol [20]. All energies are referred to the same case of acetic acid ketonization on zirconia and, thus, are comparable. Based on these data, we propose that the consumption of the enolized carboxylate **II** by protonation, i.e., by the

reverse reaction of enolization, occurs faster than the competing reactions down the ketonization path. As the result, the experimental catalytic reaction rate is lower than would be expected for the non-reversible enolization.

The rate-determining step with the zirconia catalyst has been recently identified in a computational study [26] as decarboxylation of a beta-ketoacid, which is similar to step 4, **IV** $\rightarrow$ **V**, Scheme 2. This conclusion has caused criticism [9], because experimental reaction rates for the decarboxylation of beta-ketoacids are several orders of magnitude higher than the typical ketonization rate. Therefore, nomination of step 4 for being the rate-limiting step has been questioned [9]. If we assume that the enolization step in the ketonization mechanism is severely limited by the equilibrium, this controversy can now be resolved. Because RDS is the function of both the rate constant and the concentration of those species undergoing that step, a low concentration of the enolized species does affect the ketonization rate. We propose that the enolized species are converted back to carboxylates in the reverse enolization reaction and they are also consumed in the forward reaction, thus being under the quazi-equilibrium conditions.

When setting up kinetic equations for this model, we can see that the catalytic reaction rate for the ketonization of a single acid is proportional to the concentration of the enolized carboxylate on the catalyst surface, **II**. For example, if step 4 is rate limiting, the ketonization rate can be calculated as the product of k_{rds} , and the concentration of species **IV**:

$$r = k_{rds} \times [\text{IV}] \quad (7)$$

When omitting dehydration step 3 as nonessential, the rate of the concentration change for **IV** according to equation (6) can be written as

$$-\frac{d[\text{IV}]}{dt} = -k_2 \times [\text{II}] \times [\text{carbonyl component}] + k_{-2} \times [\text{IV}] + k_4 \times [\text{IV}] \quad (8)$$

Applying the steady state approximation, it can be seen that the concentration of **IV** on surface is limited by the concentration of **II** from which it is rapidly replenished:

$$[\text{IV}] = \frac{k_2 \times [\text{II}] \times [\text{carbonyl comp}]}{k_4 + k_{-2}} \quad (9)$$

Thus, the catalytic rate of ketonization can be approximated by equation 10:

$$r = k_4 \times \frac{k_2 \times [\text{II}] \times [\text{carbonyl comp}]}{k_4 + k_{-2}} = k_{eff} \times [\text{II}] \times [\text{carbonyl comp}], \quad (10)$$

wherein the effective rate constant is equal to $k_{eff} = \frac{k_4 \times k_2}{k_4 + k_{-2}}$.

Alternatively, if the RDS in the ketonization mechanism is step 2 instead of 4, as recently proposed by Pham et. al. [28], this does not fundamentally change equation (10). In such case the effective rate constant will be replaced by k_2 , i.e. $k_{eff} = k_2$.

The absolute concentration of the second, i.e., carbonyl component of this bimolecular reaction, coming either from the gas-phase (Eley-Rideal model) or adsorbed on the surface (Langmuir-Hinshelwood model), may not always be known. When calculating selectivities it may be accepted that for both models the relative (dimensionless) concentrations of carbonyl components, **A_c** and **B_c**, are proportional to the fraction of each acid, **A** and **B**, in the gas phase.

For the ketonization of a mixture of *i* carboxylic acids, there is *i* × *i* number of competing reactions between *i* enolic components, **II_i**, and *i* number of carbonyl components, which control the distribution of surface intermediates **IIIa-d**, and **IVa-d**, and ketone products,

Vla-d, according to the equation (4). When calculating relative rates of these competing reactions, relative concentrations of the carbonyl components, **A_c** or **B_c** can be used.

$$r_{B_e A_c} = k_{4a} \times \frac{k_{2a} \times [\text{IIa}] \times [A_c]}{k_{4a} + k_{-2a}} = k_a^{eff} \times [\text{IIa}] \times [A_c] \quad (11a)$$

$$r_{A_e B_c} = k_{4b} \times \frac{k_{2b} \times [\text{IIb}] \times [B_c]}{k_{4b} + k_{-2b}} = k_b^{eff} \times [\text{IIb}] \times [B_c] \quad (11b)$$

$$r_{A_e A_c} = k_{4c} \times \frac{k_{2c} \times [\text{IIc}] \times [A_c]}{k_{4c} + k_{-2c}} = k_c^{eff} \times [\text{IIc}] \times [A_c] \quad (11c)$$

$$r_{B_e B_c} = k_{4d} \times \frac{k_{2d} \times [\text{IId}] \times [B_c]}{k_{4d} + k_{-2d}} = k_d^{eff} \times [\text{IId}] \times [B_c] \quad (11d)$$

Equations (11) are the key to understanding the selectivity of the cross-ketonization versus self-ketonization. They have two critical elements, reactivities of the enolic and carbonyl components, expressed by the concentration of **II_i** and effective rate constant, k_i^{eff} , respectively.

By definition, equilibrium constants for acid enolization are

$$K_e^A = \frac{\text{IIb}}{\text{Ib}} \quad (12a)$$

$$K_e^B = \frac{\text{IIa}}{\text{Ia}} \quad (12b)$$

Parameter **e** can be introduced to describe the relative ability of acid **B** vs. acid **A** to be converted to an enolic component, which we associate with their enolization:

$$e = \frac{K_e^B}{K_e^A} \quad (13)$$

Then, the ratio of concentrations of **A_e** (**IIb** or **IIc** on Scheme 2) vs. **B_e** (**IIa** or **IId** in Scheme 2) can be calculated depending on the ratio of acids **A** and **B** on the catalyst surface, and on their relative ability to enolize, **e**.

$$\frac{\text{IIa}}{\text{IIb}} = e \times \frac{\text{Ia}}{\text{Ib}} \quad (14a)$$

Acetic and isobutyric acids have very close DFT adsorption energies on zirconia [19] and almost equal dynamic concentration on the zirconia catalyst surface, as was found by acid switching experiments [20]. Equal heat of adsorption energy for various carboxylic acids was also observed during a kinetic study of their ketonization on Ru/TiO₂ catalyst [28]. For this reason, the ratio of acids on the surface from equation (14a) can be replaced with the initial molar ratio of these acids in the gas phase:

$$\frac{\Pi_a}{\Pi_b} = e \times \frac{[B]}{[A]} \quad (14b)$$

Therefore, the difference in the concentration of the enolic components on surface should be due to the ratio of two carboxylic acids in the gas phase and to their different ability to enolize, which is characterized by parameter e .

The effective rate constants, k_a^{eff} , k_b^{eff} , k_c^{eff} , and k_d^{eff} , may be used to characterize the relative activity of the carbonyl components, for example, **B_c** forming **IVb** and **IVd**, vs. **A_c** forming **IVa** and **IVc** (Scheme 2), as described by parameter c

$$c = \frac{k_b^{eff}}{k_c^{eff}} \quad (15)$$

A noticeable characteristic of the described kinetic model is that the formation of each individual ketone is a first order reaction with respect to the fraction of each acid representing the carbonyl and enolic components, yielding the overall second order. It is in contrast to the zero order kinetics obtained for a single acid ketonization after the surface saturation using the same model. Thus, cross-ketonization reaction of a mixture of acids creates an opportunity to study the effect of substituents on the reactivity of each component.

3.3. Selectivity in the reaction of a common component with two competing reagents.

The yield of the two isotopologues of the cross-ketone resulting from the two mechanistic paths “a” and “b” can be measured separately by using an isotopic label on one of the carbonyl groups. Using this methodology we have previously reported that the fraction of path “b” in the mechanism of the cross-ketone formation with ZK catalyst is above 95% for the 1:1 molar ratio of acids **A** and **B** at 250 °C and it is decreasing to 65% with the temperature increase up to 350 °C [20]. We have now studied a broad range of molar fractions of the acid **B** in the binary mixture from 10% to 80% and a range of temperatures from 200 °C to 400 °C. A linear dependence of the fraction of each path “a” and “b” on the acid **B** concentration is found with ZR, ZK, TI, and TK catalysts in the pulse microreactor inside GC/MS (Figure 4a-d). Knowing the yield of the combined cross-ketone from the DOE experiments in the continuous mode and the fraction of each of the isotopologues **A_eB_c** and **B_eA_c** composing the cross-ketone under the same conditions in the pulse microreactor “inside GC/MS”, the yield of each part of the cross-ketone, **A_eB_c** and **B_eA_c**, is calculated depending on the temperature and the molar ratio of two acids. Yields of four ketones obtained with ZR, ZK, TI, and TK catalysts at LHSV=7 hr⁻¹ are expressed as the rate of their formation, mmol•hr⁻¹•g-cat.⁻¹, averaged over the course of the reaction (Figures 5-8).

Isotopic labeling provides a possibility to compare the reactivity of a common component with two competing reagents. For example, Figure 5a shows that **A_eA_c** is formed faster than **A_eB_c** with ZR catalyst when acid **A** is used in excess, and somewhat slower under the excess of acid **B**. This graph demonstrates the concentration effect of the two carbonyl components, **A_c** and **B_c**, when they compete with each other in the reaction with the same

enolic component, A_e . It can be also visually detected from Figures 5-8 that, between two carbonyl components, the A_c is more reactive at the equimolar concentration of A and B with all catalysts except for TK. TK catalyst makes B_c become more active than A_c in the reaction with the common A_e (Figure 8a), which explains the high selectivity toward the cross-ketone. This conclusion is based on the location of the A_eB_c and A_eA_c surfaces intersection line being closer to a low concentration of B with TK catalyst (Figure 8a) and, to some extent, with ZK catalyst (Figure 6a).

With all catalysts, the alternative path to the mixed ketone, B_eA_c , via enolization of isobutyric acid provides a lower yield compared to A_eB_c (graphs b in Figures 5-8). It can be explained by a smaller degree of isobutyric acid enolization relative to acetic acid with all catalysts. Thus, a simple visual analysis of the cumulative rates (yields) of the four products suggests that acetic acid is the more reactive enolic component compared to isobutyric acid with all catalysts. Acetic acid is also the more reactive carbonyl component with all catalysts except for TK.

Higher reactivity of the acetic acids as both the enolic and the carbonyl component causes the preferred formation of acetone. Fast consumption of acetic acid at the top section of the catalyst bed leaves no choice for isobutyric acid, but to react with itself near the bottom section. As already discussed in the section 3.1., a substantial difference in the acids reactivity may cause separation of the catalyst bed into two zones, making preferentially the first symmetrical ketone in the first zone, and the second symmetrical ketone in the second zone. The cross-ketone in such case is made in a less than binomial yield.

As a precaution, reactions of the less reactive $\mathbf{B_e}$ as the common enolic component should not be used for a direct comparison of the relative activity of the two carbonyl components. Because of the acids reactivity difference and the reactor zoning effect, some portion of $\mathbf{B_eB_c}$ could form in the absence of acid $\mathbf{A}$, i.e. noncompetitively, in the second zone. For example, Figure 5b for ZR catalyst may illustrate a potential misinterpretation. The intersection of two surfaces, $\mathbf{B_eB_c}$ and $\mathbf{B_eA_c}$, on Figure 5b, is located near 20% of the fraction $\mathbf{B}$. This could mistakenly lead to a conclusion that the $\mathbf{B_c}$ concentration as low as 20% is sufficient to produce the same yield as what $\mathbf{A_c}$ may do when used in an 80% concentration. Thus, it could be mistakenly concluded that $\mathbf{B_c}$ is more reactive than $\mathbf{A_c}$ in the reaction with the common enolic component $\mathbf{B_e}$. In fact, it could be a result of the separation of two acids by their reactivity along the catalyst bed. By the time all acid $\mathbf{A}$ is reacted, a relatively large amount of acid $\mathbf{B}$ is left, which has to react with itself. Separation of acids by reactivity happens with all catalysts, but to the smallest extent with TK catalyst, and to the highest – with ZR catalyst.

To avoid mistakes, the analysis of the relative activity should be done on the basis of all four ketones. Relative rates of acetic vs. isobutyric acid reacting as the enolic and carbonyl components are important to know because they control the cross-selectivity. We have done a theoretical analysis for the proposed ketonization mechanism to identify conditions for having a high selectivity toward the cross-product vs. symmetrical products, which is discussed in the next section.

3.4. Factors controlling the cross-selectivity.

Conditions for the cross-selectivity to exceed binomial values, or to decline below them, are defined by the rate constants for the set of competing reactions. It is clear that the separation of the reaction zones for acids A and B would increase the selectivity to the symmetrical products and decrease the cross-selectivity. In order to maximize the cross-selectivity and minimize formation of symmetrical products, it is not sufficient just to have the equal reactivity of both acids. We will show that two acids must also take opposite roles, one acid being a more active enolic component while the second acid being a more active carbonyl component. This would be similar to any cross-reactions between two reagents with opposite functions. An extreme case of that is exemplified by reactions between acids and bases, oxidants and reducers, donors and acceptors, etc., for which self-reactions are rare if not impossible, and the cross-product is the only one formed. While it is challenging to completely separate roles of two acids in their decarboxylative ketonic condensation, any shift toward acid's specialization increases the cross-selectivity. This criterion is formulated by equations (18) and (19) as described by the theoretical analysis below.

We built a model based on equations (4) and (11) with dimensionless concentrations and length for making **B_eA_c**, **A_eB_c**, **A_eA_c**, and **B_eB_c** ketones.

$$r_3 = b_e \times a_c \times \mathbf{B} \times \mathbf{A} \quad (16a)$$

$$r_2 = a_e \times b_c \times \mathbf{A} \times \mathbf{B} \quad (16b)$$

$$r_1 = a_e \times a_c \times \mathbf{A}^2 \quad (16c)$$

$$r_4 = b_e \times b_c \times \mathbf{B}^2 \quad (16d)$$

The system of differential equations (16) with the boundary conditions, $x > \mathbf{B} > 0$ and $(1 - x) > \mathbf{A} > 0$, for acid fractions $\mathbf{B}$ and $\mathbf{A}$ changing with the conversion, was solved numerically to obtain the product concentrations, P_i depending on coefficients a_e, a_c, b_e , and b_c . The integral selectivities, S_i^{int} , were obtained by P_i normalization:

$$S_i^{int} = \frac{P_i}{\sum_{i=1}^4 P_i} \quad (17)$$

We have mathematically proven², that the sum of the distribution functions S_2^{int} and S_3^{int} , which represent the cross-ketone, deviate positively from the sum of binomial probability functions $y_2 + y_3 = 2 \times x \times (1 - x)$, i.e. $S_2^{int} + S_3^{int} > y_2 + y_3$ in two cases, if

$$\begin{cases} a_e > b_e \\ a_c < b_c \end{cases} \quad (18a)$$

or if

$$\begin{cases} a_e < b_e \\ a_c > b_c \end{cases} \quad (18b)$$

Under all other conditions, a negative deviation was found, i.e. $S_2^{int} + S_3^{int} < y_2 + y_3$. After defining parameters $e = b_e/a_e$ and $c = b_c/a_c$, similar to equations (13) and (15), the criteria for a positive deviation of the cross-selectivity from the statistical binomial distribution can be specified as either

$$\begin{cases} e < 1 \\ c > 1 \end{cases} \quad (19a),$$

or

$$\begin{cases} e > 1 \\ c < 1 \end{cases} \quad (19b)$$

² The complete mathematical proof is provided in Appendix A: Supplementary Material.

Thus, the mathematical condition for having a high cross-selectivity requires one of the acids, for example, isobutyric, to be a more reactive carbonyl component and a less reactive enolic component (19a), or vice versa (19b).

Through regression analysis, by fitting calculated S_i^{int} into the experimental distribution of ketones (yields) with four catalysts depending on temperature, acid ratio, and LHSV, coefficients a_e , a_c , b_e , and b_c , were obtained.

The calculated parameters e and c for the four catalysts are presented in the Table 3 and have the meaning of the relative reactivity of the isobutyric acid vs. acetic acid in their role as the enolic and carbonyl components, respectively. Under a purely kinetic control of experimental runs, coefficients a_e , a_c , b_e , and b_c could signify the intrinsic rate constants. However, while the absence of mass transport limitations is verified³, the reaction has not been tested for the absence of a chemical and thermodynamic equilibrium. Because of that uncertainty, dimensionless parameters e and c are used instead, which may equally well describe apparent relative reactivities, under either a kinetic or a thermodynamic control.

The ability of acetic acid to serve as the preferred enolic component over isobutyric acid with all studied catalysts is characterized quantitatively, as shown in Table 3, $e < 1$. Acetic acid is also the preferred carbonyl component with untreated zirconia and titania, $c < 1$. Catalyst TK is the only catalyst which promotes a higher reactivity of isobutyric acid vs. acetic acid as the carbonyl component, $c > 1$, at all LHSV values, which explains its remarkably high cross-selectivity. The other example is ZK catalyst approaching a high cross-selectivity at a low and medium LHSV (Table 3). Understanding the reason(s) for the KOH

³ See Fig. A.7a-b, Appendix A: Supplementary Material

promotion effect on the isobutyric acid shift toward being the preferred carbonyl component is the subject of our future work.

A special case of the cross-ketonization is presented when one of the acids, for instance acid **B**, is unable to enolize. This is the case for aromatic acids [14], pivalic acid, and other acids missing alpha protons. In some cases, enolization may be severely disfavored, such as for cyclopropylcarboxylic acid and for other acids producing highly strained enolized structures. In all such cases two of the ketone products, **BB**, and **B_eA_c**, are excluded from the formation. The selectivity between one symmetrical **AA** and one cross-product **A_eB_c** will depend on the ratio and the reactivity of the available carbonyl components **A_c** and **B_c**.

The rules for having high selectivity to cross-products can be extended to other types of reactions. Thus, in the earlier mentioned example of the highly selective Tishchenko reaction [4] the reactivity of two aldehydes is discriminated in opposite directions. The alkyl group serves as the donor, and the aryl group as the acceptor. As the result, each of the aldehydes reacts with itself much slower than with the other one. Formation of the symmetrical esters is disfavored and the cross-ester is produced with a high selectivity.

To guide future catalyst development, it should be noted that the ketonization of carboxylic acids involves only the acid-base properties of catalysts. There are no redox steps involved in the proposed mechanism through acids enolization. Therefore, the ability of metal oxides to be reduced or oxidized during the catalytic reaction is not required for serving as an efficient catalyst. This hypothesis was confirmed experimentally in a recent study in which reducibility of the mixed cerium and manganese oxide catalysts did not correlate with their activity as ketonization catalysts [29]. Inadvertently, certain oxidation or

reduction treatments may change the surface structure and affect the catalyst acid-base function. Any change of the selectivity or the activity of the treated catalyst must be attributed to the change in the catalyst ability to activate the enolic or the carbonyl component.

3.5. Catalysts characterization

The essential factors affecting catalyst activity are the number of active sites and their intrinsic activity. The former is directly proportional to the surface area of a catalyst sample and the concentration of active sites on surface. All three important characteristics affecting catalyst activity are discussed below.

3.5.1. Catalysts surface area.

Samples of titania and zirconia support for this study were chosen so as to have comparable surface areas. BET surface area was found 48, 45, and 45 m²/g for ZR, ZK, ZP catalysts, and 37, 42, and 38 m²/g for TI, TK, TP catalysts, respectively (Appendix A: Supplemental Material, Table A.2). Evidently, alkaline treatment did not cause a substantial change of the surface area of zirconia and titania. This conclusion is also supported by the literature data showing that zirconia doped with Na, K, or Cs has almost the same surface area as pure untreated zirconia [30]. Therefore, the surface area factor can be excluded from consideration when analyzing the difference in catalyst behavior.

3.5.1. Concentration of active sites.

Without knowing what constitutes active sites, it is difficult to find their concentration. This problem can be approached from the other side, i.e. the concentration of carboxylic

acids adsorbed on catalyst surface could be used to estimate the concentration of active sites and, possibly, to identify their structure.

It has been reported in literature that doping zirconia with Cs and K had no effect on the concentration and the strength of basic sites on surface [30]. In fact, zirconia doped with Na, indicated a decline in the number of both the strongly basic sites found by adsorption of phenol, and the moderately basic sites found by adsorption of acrylic acid. In contrast, the catalytic activity of the doped zirconia samples in the ketonization reaction is significantly increased by the presence of either Cs, or K, or Na, suggesting no relation to the concentration and the strength of the basic sites.

The absence of the correlation between the catalyst surface basicity and the catalytic activity forced us to search for more relevant methods of catalysts characterization. One such important characteristic is the equilibrium concentration of reactants on surface estimated by pulse chemisorption. In this method relatively small pulses of adsorbate molecules are added to a catalyst sample capable of adsorbing more molecules than contained in one pulse. Under such condition, the surface is gradually saturated, and a thorough accounting for the amount of all molecules which are added in and came out, provides a method for estimating surface adsorption capacity for the specific adsorbate. When the pulse chemisorption method is used at reaction temperatures, an equilibrated, or a steady-state, concentration of carboxylic acids on surface can be found. A variation of this method is a chemical switch, i.e. replacing one type of molecules with another type during catalytic reaction. An example of pulse chemisorption of isobutyric acid followed by the switch to acetic acid is shown in Appendix A: Supplemental Material, Fig. A.8.

We have previously used a pulse microreactor inside GC/MS to find the equilibrium concentration of water on ZR, ZK, TI, and TK catalysts by switching to D₂O [23], and that of acetic and isobutyric acids on ZK catalyst [20]. We have now characterized the same ZR, ZK, TI, and TK catalysts by the equilibrium concentration of acetic and isobutyric acids on surface and compared to that of water at the same range of temperatures (Fig. 9a-d). DFT study shows that carboxylic acids are adsorbed on the same surface sites as water, but with a higher adsorption energy [19]. As expected, higher concentration of carboxylic acids on surface is observed relative to water concentration at temperatures below the catalytic ketonization reaction, i.e. at 200 °C (Fig. 9). As the temperature increases, the ketonization reaction takes place, and the equilibrium concentration of acids decreases. In contrast, water molecules are inert, and their concentration remains almost unchanged as the temperature increases from 200 to 400 °C. Most notably, we have found no large difference between the equilibrium concentrations of isobutyric vs. acetic acid. Also important is that the alkaline treatment does not significantly change the equilibrium concentration of both acids on the KOH treated zirconia compared to the untreated zirconia, and only makes a slight change of that for titania (Fig. 9), which is in full agreement with literature data [30].

The fact that the untreated zirconia is also capable of catalyzing ketonization reaction suggests that the presence of alkaline cations is not an absolute requirement for the creation of active sites. Moreover, the presence of alkaline metals does not change the concentration of basic sites, nor the number of carboxylic acids adsorbed on the surface at the steady state of the catalytic reaction (Fig. 9). At the same time, presence of alkaline metals on catalyst surface increases the rate of the ketonization reaction [30]. The most

likely explanation for all of the combined facts is that alkaline metals may increase the intrinsic activity, as opposed to increasing the concentration of active sites.

3.5.3. Catalyst intrinsic activity.

According to the proposed mechanism, a plausible explanation for the intrinsic activity increase by alkaline metals may consist in a shift of the enolization equilibrium in the direction which can provide a higher concentration of the enolized carboxylates on surface. To test this hypothesis, we have characterized catalysts by testing their activity for the enolization of carboxylic acids. The rate of deuterium incorporation into the alpha position of carboxylates serves as an indicator of the degree of the enolization, because the exchange of the alpha protons for deuterium in carboxylates may only proceed through their enolization.

When a mixture of isobutyric acid and D_2O vapors in 1:1 molar ratio was passed through a catalyst bed at temperatures below ketonization reaction, alpha-deuterated isobutyric acid was produced along with H_2O and DHO . KOH Treated zirconia exhibited the highest conversion of this reaction among the four catalysts tested under identical conditions (Fig. 10). In the reverse reaction protons are replacing deuterium, but the theoretical conversion, near 50%, representing equilibrium for the 1:1 molar ratio mixture, has not been reached at temperatures up to 180 °C, which is significantly below a typical range of the ketonization reaction temperatures, 300-450 °C. Extrapolation of the degree of conversion to the temperatures above 300 °C indicates that enolization of acids occurs at a significantly faster reaction rate than their decarboxylative ketonization.

A similar increase of the H/D exchange rate was also observed for acetic acid with KOH treated zirconia catalyst compared to the untreated catalyst. However, interpretation of the results for acetic acid is more complicated because of the three alpha protons involved in the sequential H/D exchange. Comparative analysis of the enolization of acetic vs. isobutyric acids will be reported in a separate study.

Thus, catalysts characterization data support the proposed mechanism in which enolization plays an important role. The role of metal cations could be simply a reduction of the number of mobile protons on surface, capable of protonating enolized carboxylates, or they could assist in some other possible stabilization of the enolized structures. In this regard it should be noted that K_2HPO_4 treatment does not increase enolization activity (Fig. 10), possibly because the Brønsted acid type phosphate group on surface, $-O_2P=O(OH)$, can serve as a source of protons.

4. CONCLUSIONS

The dependence of two symmetrical and one cross-ketone product distribution on a broad range of the two acids molar ratios as well as on temperature has been obtained through a set of DOE experiments. The idea of analyzing acids reactivity separately in terms of the enolic or the carbonyl component helps to reveal factors controlling the cross-selectivity depending on the catalyst type, acids ratio, temperature, and space velocity. The condition for having a high selectivity to the cross-product is expressed such as one of the coupling acids must be more reactive as the enolic component while the other acid being more reactive as the carbonyl component. If one of the acids is more reactive than the other in both of these roles, it selectively reacts with itself producing the first one out of the

two symmetrical ketones. Because of the shortage of the first acid, the second acid is forced to react with itself in the lower part of the plug-flow reactor and to produce the second symmetrical ketone. Reaction zones for two acids are separated in a plug-flow reactor, and the selectivity to the cross-ketone drops below the binomial statistical distribution.

It is proposed that the critical step for the decarboxylative ketonization mechanism, enolization of surface carboxylates, is a fast and reversible process. In such case, concentration of the enolized carboxylate, i.e., the enolic component, should be severely limited by the enolization equilibrium, which is shifted away from the enolized structure toward the carboxylate. The rate-determining step occurs after the enolization, but the overall reaction rate depends on the enolization equilibrium constant, as in the Michaelis-Menten or similar kinetic models exhibiting saturation by at least one of the reagents.

The cross-selectivity results from the competition between four reactions involving two enolic and two carbonyl components. If the proposed assumption for the enolization equilibrium is correct, the highest reaction rate is determined not only by the competition in the post-enolization rate-limiting step, but also by the concentrations of two enolized carboxylates on the catalyst surface.

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Appendix A. Supplementary Material: Mathematical proof of the criterion for the positive deviation of the cross-selectivity from the binomial distribution.

FIGURE CAPTIONS

Figure 1. Conversion of a mixture of acetic **A** and isobutyric **B** acids with a) zirconia-based and b) titania-based catalysts as a function of temperature and acids composition at LHSV=7 hr⁻¹, c) Individual conversion of each acid **A** and **B** for their 1:1 molar mixture as a function of temperature with six catalysts at LHSV=7 hr⁻¹.

Figure 2. Yield of mixed ketone **AB** as a function of temperature and molar composition of acids **A** and **B** at LHSV=7 hr⁻¹ with a) ZR, b) ZK, c) ZP, d) TI, e) TK, f) TP catalysts. The statistically expected binomial distribution is shown as the grey mesh surface. Deviation of the **AB** yield from the binomial distribution, blue for negative and red for positive, is shown as the color coded projection on the top and the bottom surface.

Figure 3. Deviation of the yield for all ketones from the binomial distribution is shown as the color coded 3D surface for the mixed ketone **AB**, and as the projection on the top and on the bottom surface for the two symmetrical ketones **BB**, and **AA**, respectively, depending on temperature and the molar composition of the mixture of acids **A** and **B** with a) ZR, b) ZK, c) ZP, d) TI, e) TK, f) TP catalysts at LHSV=7 hr⁻¹.

Figure 4. Fraction of path “b”, formation of **A_eB_c**, in the cross-ketone mechanism depending on temperature and molar composition of acids **A** and **B** with four catalysts a) ZR, b) ZK, c) TI, d) TK.

Figure 5. Reaction rates averaged over the course of reaction for the competing formation of ketones from a) acid **A** as the enolic component, b) acid **B** as the enolic component with ZR catalyst at LHSV=7 hr⁻¹.

Figure 6. Reaction rates averaged over the course of reaction for the competing formation of ketones from a) acid **A** as the enolic component, b) acid **B** as the enolic component with ZK catalyst at LHSV=7 hr⁻¹.

Figure 7. Reaction rates averaged over the course of reaction for the competing formation of ketones from a) acid **A** as the enolic component, b) acid **B** as the enolic component with TI catalyst at LHSV=7 hr⁻¹.

Figure 8. Reaction rates averaged over the course of reaction for the competing formation of ketones from a) acid **A** as the enolic component, b) acid **B** as the enolic component with TK catalyst at LHSV=7 hr⁻¹.

Figure 9. Equilibrium concentration of carboxylic acids and water on surface of a) ZR, b) ZK, c) TI, and d) TK catalysts as a function of temperature.

Figure 10. Conversion of the H/D exchange of isobutyric acid alpha hydrogens as a function of temperature for 1:1 molar ratio of isobutyric acid and D₂O with four catalysts, ZR, ZK, ZP, TP.

SCHEME TITLES

Scheme 1. Decarboxylative ketonization of a mixture of acetic (**A**) and isobutyric (**B**) acids yielding the cross-ketone (**AB**) and the two self-condensation products (**AA** and **BB**).

Scheme 2. Catalytic cycle in the decarboxylative ketonization mechanism with ZrO₂ catalyst

TABLES.

Table 1.

Activation energies for the formation of all possible ketones in the cross-ketonization of a mixture of isobutyric **B** and acetic **A** acids in 1:1 molar ratio performed in a pulse microreactor with KOH-treated zirconia catalyst, kcal/mol, cited from ref [20].

(Path "a")	B_eA_c	18.9 ± 0.7	B_eB_c	30.9 ± 0.5	
	A_eA_c	14.0 ± 0.3	A_eB_c	16.9 ± 0.6	(Path "b")

Table 2. Design of experiments.

Run #	Temperature, °C	Molar fraction of isobutyric acid, %	LHSV, hr ⁻¹
1	300	10.0	2
2	450	10.0	2
3	300	90.0	2
4	450	90.0	2
5	375	50.0	7
6	300	10.0	12
7	450	10.0	12
8	300	90.0	12
9	450	90.0	12
10	250	50.0	7
11	500	50.0	7
12	375	1.0	7
13	375	50.0	7
14	375	99.0	7
15	375	50.0	1
16	375	50.0	18

Table 3. Relative reactivity of isobutyric vs. acetic acid in the role of the enolic component, parameter **e**, or the carbonyl component, parameter **c**, at the temperature 400 °C depending on LHSV with four catalysts.

LHSV, hr ⁻¹	ZR		ZK		TI		TK	
	e	c	e	c	e	c	e	c
2	0.84	0.98	0.28	3.67	0.04	1.34	0.14	3.92
7	1.08	1.05	0.27	1.55	0.06	0.54	0.14	3.92
12	1.08	1.04	0.13	0.96	0.04	0.47	0.14	3.92

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CROSS-SELECTIVITY IN THE KETONIZATION OF CARBOXYLIC ACIDS

Alexey V. Ignatchenko, Joseph S. DeRaddo, Vincent J. Marino, and Adam Mercado

a)

b)

Figure 1. Conversion of a mixture of acetic **A** and isobutyric **B** acids with a) zirconia-based and b) titania-based catalysts as a function of temperature and acids composition at LHSV=7 hr⁻¹, c) Individual conversion of each acid **A** and **B** for their 1:1 molar mixture as a function of temperature with six catalysts at LHSV=7 hr⁻¹.

Figure 2. Yield of mixed ketone **AB** as a function of temperature and molar composition of acids **A** and **B** at LHSV=7 hr⁻¹ with a) ZR, b) ZK, c) ZP, d) TI, e) TK, f) TP catalysts. The statistically expected binomial distribution is shown as the grey mesh surface. Deviation of the **AB** yield from the binomial distribution, blue for negative and red for positive, is shown as the color coded projection on the top and the bottom surface.

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a)

b)

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a)

b)

Figure 6. Reaction rates averaged over the course of reaction for the competing formation of ketones from a) acid **A** as the enolic component, b) acid **B** as the enolic component with ZK catalyst at LHSV=7 hr⁻¹.

a)

b)

Figure 7. Reaction rates averaged over the course of reaction for the competing formation of ketones from a) acid **A** as the enolic component, b) acid **B** as the enolic component with TI catalyst at LHSV=7 hr⁻¹.

a)

b)

Figure 8. Reaction rates averaged over the course of reaction for the competing formation of ketones from a) acid **A** as the enolic component, b) acid **B** as the enolic component with TK catalyst at LHSV=7 hr⁻¹.

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CROSS-SELECTIVITY IN THE CATALYTIC KETONIZATION OF CARBOXYLIC ACIDS

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APPENDIX A: SUPPLEMENTAL MATERIAL

Statement. Distribution functions P_2 and P_3 , which represent the cross-ketone, deviate positively from the binomial probability functions y_2 and y_3 , in two cases, if

$$\begin{cases} a_1 > b_1 \\ a_2 < b_2 \end{cases} \quad (\text{A.1a})$$

or if

$$\begin{cases} a_1 < b_1 \\ a_2 > b_2 \end{cases} \quad (\text{A.1b})$$

Analysis and proof by algebra methods.

The probability functions for making $\mathbf{A_eA_c}$, $\mathbf{A_eB_c}$, $\mathbf{B_eA_c}$, and $\mathbf{B_eB_c}$ ketones respectively, on the basis of the binomial statistical approach are

$$y_1 = (1 - x)^2 \quad (\text{A.2a})$$

$$y_2 = x \times (1 - x) \quad (\text{A.2b})$$

$$y_3 = x \times (1 - x) \quad (\text{A.2c})$$

$$y_4 = x^2 \quad (\text{A.2d})$$

where $(1 - x)$ and x represent fractions of acid **A** and **B**, respectively.

Coefficients, a_1 , a_2 , b_1 , and b_2 , are assigned to transform functions y_n into Y_n .

$$Y_1 = a_1 \times a_2 \times (1 - x)^2 \quad (\text{A.3a})$$

$$Y_2 = a_1 \times b_2 \times x \times (1 - x) \quad (\text{A.3b})$$

$$Y_3 = b_1 \times a_2 \times x \times (1 - x) \quad (\text{A.3c})$$

$$Y_4 = b_1 \times b_2 \times x^2 \quad (\text{A.3d})$$

Coefficients a and b represent acids **A** and **B**, respectively. Subindexes $_1$ and $_2$ represent the enolic and the carbonyl components, respectively. Coefficients $c = \frac{b_1}{a_1}$, and $c = \frac{b_2}{a_2}$ have the meaning of the relative activity of acid **B** vs. acid **A** as the enolic or as the carbonyl component, respectively.

The adjusted distribution functions P_n are obtained through Y_n normalization and represent the differential selectivities to the four products.

$$P_n = \frac{Y_n}{\sum_{n=1}^4 Y_n} \quad (\text{A.4})$$

The denominator in eq. (A.4) can be transformed into a shorter form:

$$\begin{aligned} \sum_{n=1}^4 Y_n &= a_1 a_2 (1 - x)^2 + b_1 a_2 x (1 - x) + a_1 b_2 x (1 - x) + b_1 b_2 x^2 = \\ &= a_2 (1 - x) \times (a_1 (1 - x) + b_1 x) + b_2 x \times (a_1 (1 - x) + b_1 x) = \\ &= (a_2 (1 - x) + b_2 x) \times (a_1 (1 - x) + b_1 x) \end{aligned} \quad (\text{A.5})$$

After dividing the numerator and the denominator by $a_1 a_2$ each P_n function is transformed into a new form:

$$\begin{aligned}
P_1 &= \frac{a_1 a_2 (1-x)^2}{(a_2(1-x) + b_2 x) \times (a_1(1-x) + b_1 x)} = \frac{(1-x)^2}{\left(1-x + \frac{b_2}{a_2} x\right) \times \left(1-x + \frac{b_1}{a_1} x\right)} = \\
&= \frac{(1-x)^2}{(1-x + cx) \times (1-x + ex)}
\end{aligned}
\tag{A.6a}$$

$$\begin{aligned}
P_2 &= \frac{a_1 b_2 \times x \times (1-x)}{(a_2(1-x) + b_2 x) \times (a_1(1-x) + b_1 x)} = \frac{\frac{b_2}{a_2} \times x \times (1-x)}{\left(1-x + \frac{b_2}{a_2} x\right) \times \left(1-x + \frac{b_1}{a_1} x\right)} = \\
&= \frac{c \times x \times (1-x)}{(1-x + cx) \times (1-x + ex)}
\end{aligned}
\tag{A.6b}$$

$$\begin{aligned}
P_3 &= \frac{b_1 a_2 \times x \times (1-x)}{(a_2(1-x) + b_2 x) \times (a_1(1-x) + b_1 x)} = \frac{\frac{b_1}{a_1} \times x \times (1-x)}{\left(1-x + \frac{b_2}{a_2} x\right) \times \left(1-x + \frac{b_1}{a_1} x\right)} = \\
&= \frac{e \times x \times (1-x)}{(1-x + cx) \times (1-x + ex)}
\end{aligned}
\tag{A.6c}$$

$$\begin{aligned}
P_4 &= \frac{b_1 b_2 x^2}{(a_2(1-x) + b_2 x) \times (a_1(1-x) + b_1 x)} = \frac{\frac{b_1}{a_1} \frac{b_2}{a_2} x^2}{\left(1-x + \frac{b_2}{a_2} x\right) \times \left(1-x + \frac{b_1}{a_1} x\right)} = \\
&= \frac{ecx^2}{(1-x + cx) \times (1-x + ex)}
\end{aligned}
\tag{A.6d}$$

The relation between functions P_n and y_n is analyzed separately under four different terms.

Results are summarized in Table A.1.

Table A.1. The relation between P_n and y_n functions under four terms.

Terms		AA	BB	AB
1)	$e < 1,$ $c < 1.$	$P_1 > (1 - x)^2$	$P_4 < x^2$	$P_2 + P_3 < 2x(1 - x)$
2)	$e > 1,$ $c > 1.$	$P_1 < (1 - x)^2$	$P_4 > x^2$	$P_2 + P_3 < 2x(1 - x)$
3)	$e < 1,$ $c > 1.$	$P_1 < (1 - x)^2$ if $\frac{1}{1-c} + \frac{1}{1-e} < x;$ $P_1 < (1 - x)^2$ for any x	$P_4 < x^2$ when $\frac{c}{1-c} + \frac{1}{1-e} > x$ If $e + c > 2ec,$ $P_4 < x^2$ for any $x.$	$P_2 + P_3 > 2x(1 - x)$ If $\begin{cases} e + c > 2 \\ ce < 1 \end{cases}$
4)	$e > 1,$ $c < 1.$	if $e + c > 2.$ $P_1 > (1 - x)^2$ If $\frac{1}{1-c} + \frac{1}{1-e} > x$ true for any x if $ec < 1$	If $ec > 1,$ then $P_4 > x^2$ for any $x.$	

Function P_1 , term 1) $a_1 > b_1; a_2 > b_2$, or $e < 1; c < 1$. In this case

$$P_1 = \frac{(1 - x)^2}{(1 - x + cx) \times (1 - x + ex)} > (1 - x)^2$$

is true, because if $c < 1$, then $(1 - x + cx) = 1 + x(c - 1) < 1$. Similarly, $(1 - x + ex) = 1 + x(e - 1) < 1$, therefore the denominator is less than 1, but the whole fraction is greater than 1.

$$\frac{1}{(1 - x + cx) \times (1 - x + ex)} > 1$$

i.e. $P_1 > y_1$ under term 1.

Function P_1 , term 2) $a_1 < b_1$; $a_2 < b_2$, or $e > 1$; $c > 1$. Under this term, it can be proven than $P_1 < y_1$ simply by changing the sign in all equations obtained under term 1) above, i.e., because $e > 1$; $c > 1$, therefore, $(1 - x + cx) = 1 + x(c - 1) > 1$, and $(1 - x + ex) = 1 + x(e - 1) > 1$, therefore the denominator is greater than 1, but the whole fraction is less than 1.

$$\frac{1}{(1 - x + cx) \times (1 - x + ex)} < 1$$

Therefore, $P_1 < y_1$ under term 2.

Function P_1 , term 3) $a_1 > b_1$, $a_2 < b_2$, or $e < 1$, $c > 1$; **and term 4)** $a_1 < b_1$; $a_2 > b_2$, or $e > 1$; $c < 1$.

After the next transformation, the criteria for a negative deviation of P_1 from the binomial value is:

$$\frac{1}{(1 - x + cx) \times (1 - x + ex)} = \frac{1}{(1 - x)^2 + (e + c) \times x \times (1 - x) + cex^2} < 1$$

Or, it can be further transformed into the next form with the change of the inequality sign:

$$(1 - x)^2 + (e + c) \times x \times (1 - x) + cex^2 > 1$$

Because $1 = (1 - x)^2 + 2 \times x \times (1 - x) + x^2$, the next form can be obtained:

$$(1 - x)^2 + (e + c) \times x \times (1 - x) + cex^2 > (1 - x)^2 + 2 \times x \times (1 - x) + x^2 ,$$

$$\text{or, } (e + c) \times x \times (1 - x) + cex^2 > 2 \times x \times (1 - x) + x^2$$

Further transformations provide the simplified criteria:

$$(e + c) \times x - (e + c) \times x^2 + cex^2 > x \times (2 - x)$$

$$(e + c) - (e + c) \times x + cex > 2 - x$$

$$(e + c) > 2 - x + x \times (e + c - ce)$$

$$\frac{e + c - 2}{e + c - ce - 1} > x$$

$$\frac{2 - e - c}{(1 - e) \times (c - 1)} > x$$

$$\frac{2 - e - c}{(1 - e) \times (1 - c)} < x$$

$$\frac{(1 - e) + (1 - c)}{(1 - e) \times (1 - c)} < x$$

in the final form:

$$\frac{1}{1 - c} + \frac{1}{1 - e} < x$$

(A.7)

where $0 < x < 1$.

For a positive deviation of P_1 from the binomial value the sign of the inequality (A.7) is reversed:

$$\frac{1}{1 - c} + \frac{1}{1 - e} > x$$

(A.8)

Under the terms 3 and 4, function P_1 can deviate from the binomial value in both a positive and negative way depending on x and parameters e and c . Condition for a region of a negative deviation, independent of x , is

$$\frac{1}{1-c} + \frac{1}{1-e} < 0$$

$$1 - c < e - 1$$

$$e + c > 2$$

Criteria for a positive deviation, $P_1 > y_1$ independent of x can be found from the condition:

$$\frac{1}{1-c} + \frac{1}{1-e} > 1$$

Which can be transformed into

$$\frac{1}{1-c} > 1 + \frac{1}{e-1}$$

$$\frac{1}{1-c} > \frac{e}{e-1}$$

$$e - 1 < e - ec$$

$$ec < 1$$

Function P_4 , term 1) $a_1 > b_1$; $a_2 > b_2$, or $e < 1$; $c < 1$.

$$P_4 = \frac{ecx^2}{(1-x+cx) \times (1-x+ex)} \text{ is compared vs. } x^2, \text{ or}$$

$$\frac{c}{(1-x+cx)} \times \frac{e}{(1-x+ex)} \text{ compared vs. } 1$$

$$\frac{c}{(1-x+cx)} < 1, \text{ because } c < 1-x+cx, \text{ or } c(1-x) < 1-x, \text{ if } c < 1.$$

Similarly,

$$\frac{e}{(1-x+ex)} < 1, \text{ because } e < 1-x+ex, \text{ or } e(1-x) < 1-x, \text{ if } e < 1.$$

If each multiplier is less than one, then the product is also less than one, i.e. $P_4 < 1$.

Function P_4 , term 2) $a_1 < b_1$; $a_2 < b_2$, or $e > 1$; $c > 1$. Changing the sign in all equations

under term 1 proves that $P_4 > 1$ under term 2.

Function P_4 , term 3) $a_1 > b_1$, $a_2 < b_2$, or $e < 1$, $c > 1$; **and term 4)** $a_1 < b_1$; $a_2 > b_2$, or $e > 1$; $c < 1$.

A quick solution for the negative deviation of P_4 from the binomial value can be obtained by switching acids **A** and **B** in equation SI-7. Parameters e and c are replaced by their reciprocal values, and x is replaced with $1 - x$.

$$\frac{1}{1 - \frac{1}{c}} + \frac{1}{1 - \frac{1}{e}} < 1 - x$$

The last equation can be modified to:

$$\frac{c}{1 - c} + \frac{1}{1 - e} > x \quad (\text{S} - 9\text{a})$$

$$\frac{1 - ec}{(1 - c) \times (1 - e)} > x \quad (\text{S} - 9\text{b})$$

To find when the negative deviation does not depend on x , it is set to $x = 1$ and equation (A.9b) is transformed into $1 - ec > (1 - c) \times (1 - e)$, or

$$e + c > 2ec \quad (\text{A.10})$$

Equation (A.10) is the criteria for having a negative deviation of P_4 , i.e. $P_4 < y_4$

For a positive deviation, $P_4 > y_4$, regardless of x , equation (A.9b) is solved for $x = 0$

$$\begin{aligned} \frac{1 - ec}{(1 - c) \times (1 - e)} &< 0 \\ \frac{1}{(1 - c) \times (1 - e)} &< \frac{ec}{(1 - c) \times (1 - e)} \\ 1 &< ec \end{aligned}$$

Functions $P_2 + P_3$, general remarks for a positive deviation. To preserve the unity of

$\sum_{n=1}^4 P_n$ a negative deviation of P_1 and P_4 automatically means a positive deviation of $P_2 + P_3$.

Condition for having positive deviation of functions $P_2 + P_3 > y_2 + y_3$ from the binomial value can be obtained by combining equations SI-3b, SI-3c, SI-6b, and SI-6c

$$\frac{(e + c) \times x \times (1 - x)}{(1 - x + cx) \times (1 - x + ex)} > 2 \times x \times (1 - x)$$

which gives after transformation

$$\begin{aligned} \frac{e + c}{(1 - x + cx) \times (1 - x + ex)} &> 2 \\ e + c &> 2 \times (1 - x)^2 + (e + c) \times 2x(1 - x) + 2cex^2 \\ (e + c) \times (1 - 2x(1 - x)) &> 2 \times (1 - 2x + 2x^2 + 2cex^2) \\ \frac{e + c}{2} \times \frac{2x^2 - 2x + 1}{(1 + ce)x^2 - 2x + 1} &> 1 \end{aligned} \tag{A.11}$$

A sufficient, but not necessary condition for the solution of eq. (A.11) is given when each multiplicand is greater than one:

$$\left\{ \begin{array}{l} \frac{e + c}{2} > 1 \\ \frac{2x^2 - 2x + 1}{(1 + ce)x^2 - 2x + 1} > 1 \end{array} \right.$$

or

$$\left\{ \begin{array}{l} \frac{e + c}{2} > 1 \\ 1 + ce < 2 \end{array} \right.$$

or

$$\left\{ \begin{array}{l} e + c > 2 \\ ce < 1 \end{array} \right.$$

(A.12)

A more broad solution for eq. (A.11) depending on x is graphically illustrated in Fig. A.1.

Fig. A.1. Graphical illustration for the positive deviation of the cross-selectivity, $P_2 + P_3$ from binomial functions $y_2 + y_3$ for $x = 0.3, 0.4, 0.5, 0.6, 0.7$, represented by values above 1.0 in eq. (A.11) as **a)** a multi-colored 3D-graph (other than blue), and **b)** a projection in (e,c) coordinates (red colored area).

Functions $P_2 + P_3$, term 1) $a_1 > b_1$; $a_2 > b_2$, or $e < 1$; $c < 1$. Because $e < 1$; $c < 1$, the first condition in (A.12), $e + c > 2$, is not true.

Functions $P_2 + P_3$, term 2) $a_1 < b_1$; $a_2 < b_2$, or $e > 1$; $c > 1$. Because $e > 1$; $c > 1$, the second condition in (A.12), $ce < 1$, is not satisfied.

Functions $P_2 + P_3$, terms 3) and 4). Under these terms eq. (A.11) can be satisfied by eq. (A.12), which is sufficient, but not necessary.

The behavior of functions P_n under terms 1-4 is illustrated by graphs in Figures A.2-A.5.

Parameters e and c for graphs in Figures A.2 and A.3 are chosen so as to demonstrate the

symmetry of graphs with respect to the choice of acid, **A** and **B**, i.e., $e_1 = \frac{1}{e_2}$ and $c_1 = \frac{1}{c_2}$.

Parameters under term 3 are those found for TK catalyst (Fig. A.4). An example of parameters e and c in Fig. A.5 demonstrates the case when cross-selectivity can change from positive to negative deviation depending on the composition of acids' mixture.

Fig. A.2. Comparison of functions P_n to y_n under term 1, $e < 1$, $c < 1$

Fig. A.3. Comparison of functions P_n to y_n under term 2, $e > 1$, $c > 1$

Fig. A.4. Comparison of functions P_n to y_n under term 3, $e=0.14 < 1$, $c=3.92 > 1$

Fig. A.5. Comparison of functions P_n to y_n under term 4, $e=1.9 > 1$, $c=0.9 < 1$

Everything discussed above applies for the differential selectivities. In order to get the integral selectivities, a law for the reactants concentration change along the length of the flow reactor has to be known. However, for any specific ratio of the two acids changing along the reactor length, the specified criteria (Table A.1) are still valid for calculating the differential selectivities. Reactor model for TK catalyst (Fig. A.6) shows selectivity graphs for all products closely matching those theoretically calculated for the same parameters e and c (Fig. A.4).

Fig. A.6. Integral selectivities for the reactor model with TK catalyst at temperature of 425 °C.

Conclusion. In summary, it has been shown that when

$ec < 1$, then $P_4 < y_4$, but $P_1 > y_1$. On the other hand, if

$e + c > 2$, then $P_4 > y_4$, but $P_1 < y_1$. If both conditions $\begin{cases} ec < 1 \\ e + c > 2 \end{cases}$ are satisfied, then

$\begin{cases} P_4 < y_4 \\ P_1 < y_1 \\ P_2 + P_3 > y_2 + y_3 \end{cases}$. This allows P_2 and P_3 to exceed binomial functions $y_2 + y_3$. The

combined condition, $\begin{cases} ec < 1 \\ e + c > 2 \end{cases}$, requires either $\begin{cases} e > 1 \\ c < 1 \end{cases}$, or $\begin{cases} e < 1 \\ c > 1 \end{cases}$

Table A.2. Catalysts and empirical formulas obtained from the regression analysis for ketones yield depending on temperature T, °C, molar fraction of isobutyric acid [B], %, and LHSV, hr⁻¹.

catalyst	Type	BET surface area, m ² /g	acetone yield, %	MIPK yield, %	DIPK yield, %
ZR	untreated monoclinic zirconia	48	[AA] = 48.20 + 6.58×10 ⁻² ×T - 1.29×[B] + 6.26×10 ⁻³ ×[B] ²	[AB] = -147.20 + 0.84×T + 0.11×[B] + 1.85×(LHSV) - 1.05×10 ⁻³ ×T ²	[BB] = 17.75 - 8.09×10 ⁻² ×T - 0.32×[B] + 4.19×10 ⁻³ ×T×[B] - 1.01×10 ⁻² ×[B] ²
ZK	KOH-treated monoclinic zirconia	45	[AA] = -89.48 + 0.68×T - 1.14×[B] + 6.83×(LHSV) - 8.20×10 ⁻⁴ ×T ² - 1.40×10 ⁻³ ×T×[B] + 1.28×10 ⁻² ×[B] ² - 4.43×10 ⁻² ×[B]×(LHSV) - 0.21×(LHSV) ²	[AB] = -0.28 + 7.40×10 ⁻² ×T + 1.08×[B] - 2.19×(LHSV) - 1.27×10 ⁻² ×[B] ² + 2.72×10 ⁻² ×[B]×(LHSV)	[BB] = 36.26 - 9.33×10 ⁻² ×T - 1.17×[B] - 0.91×(LHSV) + 4.29×10 ⁻³ ×T×[B]
ZP	K ₂ HPO ₄ -treated monoclinic zirconia	45	[AA] = -53.92 + 0.26×T + 1.11×[B] + 1.42×(LHSV) - 3.93×10 ⁻³ ×T×[B] - 2.84×10 ⁻² ×[B]×(LHSV)	[AB] = -44.2024 + 0.12×T + 1.13×[B] + 1.98×(LHSV) - 8.51×10 ⁻³ ×[B] ² - 3.96×10 ⁻² ×[B]×(LHSV)	[BB] = 89.22 - 0.41×T - 1.62×[B] + 4.16×10 ⁻⁴ ×T ² + 5.19×10 ⁻³ ×T×[B]
TI	untreated anatase titania	37	[AA] = -119.80 + 0.40×T + 0.94×[B] + 4.07×(LHSV) - 3.69×10 ⁻³ ×T×[B] - 1.46×10 ⁻² ×T×(LHSV) + 2.82×10 ⁻² ×[B]×(LHSV)	[AB] = 102.79 - 0.75×T + 0.20×[B] + 3.42×(LHSV) + 1.30×10 ⁻³ ×T ² - 6.29×10 ⁻⁴ ×T×[B] - 9.50×10 ⁻³ ×T×(LHSV)	[BB] = 0.62 - 5.00×10 ⁻³ ×T - 9.65×10 ⁻³ ×[B] + 9.12×10 ⁻² ×(LHSV) + 7.81×10 ⁻⁶ ×T ² + 3.96×10 ⁻⁵ ×T×[B] - 2.10×10 ⁻⁴ ×T×(LHSV) - 4.19×10 ⁻⁴ ×[B]×(LHSV)

TK	KOH-treated anatase titania	42	$[AA] = 6.04 + 0.32 \times T$ $- 1.48 \times [B] - 3.01 \times 10^{-4} \times T^2$ $- 1.07 \times 10^{-3} \times T \times [B]$ $+ 1.06 \times 10^{-2} \times [B]^2$	$[AB] = -280.51$ $+ 1.51 \times T + 2.10 \times [B]$ $- 1.90 \times 10^{-3} \times T^2$ $- 2.25 \times 10^{-2} \times [B]^2$	$[BB] = 44.48$ $- 0.13 \times T$ $- 1.86 \times [B]$ $+ 5.92 \times 10^{-3} \times T \times [B]$
TP	K ₂ HPO ₄ - treated anatase titania	38	$[AA] = -202.64 + 1.04 \times T$ $+ 0.53 \times [B] - 8.16 \times 10^{-4} \times T^2$ $- 5.17 \times 10^{-3} \times T \times [B]$ $+ 8.14 \times 10^{-3} \times [B]^2$	$[AB] = -51.4347 + 0.15 \times T +$ $1.14 \times [B]$ $- 1.14 \times 10^{-2} \times [B]^2$	$[BB] = 25.19$ $- 7.53 \times 10^{-2} \times T$ $- 1.21 \times [B]$ $+ 3.79 \times 10^{-3} \times T \times [B]$

To check for a possible presence of an external diffusion control, we have made a standard verification test by changing linear velocity and the catalyst volume at a constant space velocity (Fig. A.7a-b). Increase of the reaction rate with the velocity usually indicates a possible external diffusion limitation. For the 3 ml catalyst bed size used in DOE experiments, the flow rate, 3.6 g/hr, is sufficiently high to stop increasing the rate even at LHSV = 1.2 hr⁻¹. Therefore, diffusion limitations are not likely for the DOE studied range of LHSVs from 2 hr⁻¹ to 12 hr⁻¹.

Fig. A.7. Dependence of the reaction rates for the formation of acetone (AA), and MIPK (AB) on the flow rate with TK catalyst at 375 °C, at a) LHSV = 1.2 hr⁻¹, and b) LHSV = 7 hr⁻¹

Fig. A.8. Composition of a mixture coming from a catalyst in pulse chemisorption experiments on 40 mg of Zirconia at 200 °C.

An example of chemisorption experiments on 40 mg of Zirconia catalyst is shown of Fig. A.8. Sequence of 5 pulses of water, followed by 30 pulses of isobutyric acid, and again 10 pulses of water, 20 pulses of acetic acid and 7 pulses of water was performed. Each pulse is adding 0.1 mkl of liquid. Isobutyric acid is gradually replacing water from surface (pulses 1-13). Water is able to replace only a small portion of isobutyric acid (pulses 31-33) or acetic acid (pulses 61-63). The rest of isobutyric acid and water is replaced by acetic acid (pulses 31-60).