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MULTISCALE APPROACH FOR THE OPTIMIZATION OF KETONES PRODUCTION FROM CARBOXYLIC ACIDS BY THE DECARBOXYLATIVE KETONIZATION REACTION

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DECARBOXYLATIVE KETONIZATION

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ABSTRACT. A historical perspective on the advancement of the decarboxylative ketonization catalysis research and development in industry and in academia is given with the focus on the past twenty years. Reviewed topics cover results of the most recent computational modeling and isotopic labeling studies, fine details of the reaction mechanism, experimental evidence for

the existence of hidden degenerate reactions, explanation of the reaction rate inhibition, and reversibility of the reaction course. For this reaction, characterized strictly as acid-base catalysis, the origin of the misconception about the requirement for metal oxide catalysts being reducible and oxidizable is explained. Technology solutions for the selectivity improvement, as well as factors affecting catalyst stability are discussed. The review is prepared with the goal to help with the scaling up decarboxylative ketonization reaction for existing production of industrial ketones and for any bio fuels upgrading processes in the future.

KEYWORDS: Decarboxylative ketonization; monoclinic zirconia; anatase titania; renewable fuels; biomass conversion

1. INTRODUCTION

Decarboxylative ketonization reaction converts carboxylic acids into ketones releasing at the same time carbon dioxide and water [1,2] (Scheme 1). Historically, this reaction, also known as ketonic decarboxylation, has been used for the industrial preparation of acetone since as early as the year of 1888 [3]. Preparation of unsymmetrical ketones, such as methyl nonyl ketone [4], methyl cyclopropyl ketone [5], methyl iso-propyl ketone [6,7], etc., from a mixture of carboxylic acids has been continuously expanding since the middle of the last century. An explosion of research activities in the renewable fuels area taking place during the past decade has spawned additional interest to the catalytic decarboxylative ketonization, and to its mechanism [8–16]. Both versions of this reaction, catalytic and pyrolytic, can be used in the laboratory synthesis of ketones[17]. However, due to a high temperature requirement, laboratory synthesis of ketones is not so convenient and it is less widely used in comparison to the industrial production. Being uncommon and often forgotten in the collection of organic syntheses this method of making ketones has been rediscovered several times in its history [18].

Successful application of the decarboxylative ketonization reaction for commercial purposes implies optimal choices of catalysts, reagents, and process conditions, all of which, ideally, have to be based on understanding the catalytic mechanism at a molecular level. Because a common view on the reaction mechanism through beta keto acids formation (Scheme 1) has undergone through considerable changes in the past five years and the research focus has shifted toward elucidation of fine details of each step, enolization, condensation, and decarboxylation [8–12,16], it is impelling to review recent developments in this area of catalysis.

Scheme 1. Preparation of ketones by decarboxylative ketonization of carboxylic acids.

Recent efforts in the optimization and understanding ketonic decarboxylation catalysis are summarized in the current mini-review according to various levels of scale. At a common one, benchtop testing is used to run kinetic tests, to screen catalysts, to optimize process parameters and feed composition, and to study catalysts lifetime. However, a goal of a catalyst improvement in future necessitates a deep understanding of the reaction mechanism, in particular, the rate-limiting step, and possible reasons for catalysts deactivation. Therefore, at a much smaller scale, isotopic labeling studies of the reaction mechanism have been done in a pulse microreactor inside a GC/MS. Aliphatic acids with a variable degree of branching have been used to test a steric effect on the rate limiting step - condensation, by identifying the preferred source of the ketones carbonyl group during cross-ketonization in a mixture with isotopically labeled acetic acid, $\text{CH}_3^{13}\text{CO}_2\text{H}$ [13]. Additional experiments with isotopically labeled acids and ketones in a mini-autoclave have been recently used to discover the reversibility of the whole catalytic mechanism [14].

The identity of the most abundant surface species being bidentate bridged carboxylates on zirconia and monodentate carboxylates on anatase titania has been confirmed by in situ IR spectroscopy studies, surface characterizations [11] and by a number of DFT computational studies [19–24]. The rank of surface carboxylates stability on various surfaces is important to understand regarding their ability to enter the chain of steps of the catalytic mechanism leading

to the formation of ketones. The currently most accepted mechanism via beta keto acid intermediates has been tested by several in silico studies [8–11,15,16,25] and agreed upon with some minor differences.

Large amount of data from an exponentially growing number of literature publications on decarboxylative ketonization can be helpful for the operation of existing industrial reactors on a scale measured by millions of pounds of ketones in annual production and for the future renewable fuels industry of a potentially larger scale. However, the amount of information flowing back from the industry to academia and guiding future research has been limited. The goal of this review is to restore a balance between both sides by sharing the author's personal industrial experience and underlining problems associated with the scale up of the decarboxylative ketonization reaction.

2. CHOICE OF CATALYSTS

A large number of metal oxides in the periodic system have been tested and proved catalytically active for the decarboxylative ketonization. Relative activity of thirty two metal oxides: Ag, Bi, Cd, Cu, In, Pb, Re, Cr, Mg, Zn, Ca, Ga, Sr, Ba, Al, Eu, Gd, V, Co, Fe, La, Mn, Zr, Ce, Th and U, is described in one publication [26]. The catalytic activity of 14 rare earth oxides: La_2O_3 , CeO_2 , Pr_6O_{11} , Nd_2O_3 , Sm_2O_3 , Eu_2O_3 , Gd_2O_3 , Tb_4O_7 , Dy_2O_3 , Ho_2O_3 , Er_2O_3 , Tm_2O_3 , Yb_2O_3 , and Lu_2O_3 , is tested in another study [27]. In addition, decarboxylative ketonization proceeds by pyrolysis of many metal carboxylates, suggesting that its mechanism is not structure or site specific, but it is rather dependent on a condition universally provided by all catalysts. Because of the wide variation in catalysts activity and stability, the selection of the right catalyst, still, represents an important task. Among many metal oxide catalysts studied in the literature [26–

28], the most often cited are oxides of cerium, zirconium, and titanium. Each one of them is often referred to as the best catalyst for the decarboxylative ketonization without showing the difference in the performance relative to the other two. A comparative performance study under identical conditions has yet to be done in the future to identify strengths and weaknesses of each catalyst in relation to their activity, selectivity, mechanical strength, and a lifetime in industrial applications.

One of the points widely missing in academic research is the effect of catalyst doping by alkaline metals which helps to increase catalyst lifetime and selectivity [7,29–31]. Results of several years of catalysts screening and selection by the author of this review conducted in an industrial lab setting using a bench scale reactor, have been disclosed in several patents [7,30,31]. After an extensive testing, monoclinic zirconia catalysts in pure form and in mixtures with alumina and anatase titania, treated with alkali salts, such as NaOH, or KOH, have been identified as the most selective, robust, and stable to fouling in the production of unsymmetrical methyl ketones. The selection has been done from a wide pool of oxides of Zr, Ti, Ce, Y, Al, Fe, Cr, Mn, Nd, Nb, Ru, Pr, Sm, Mg, and zeolites, silica, aluminosilicates, diatomaceous earth, to name a few. Without alkaline treatment, none of the metal oxides performed well enough to be selected for a long-term production.

Alkaline doping of metal oxides for ketones production has been known and patented since about five decades ago. Examples include patents on alkali treated anatase titania in 1990 [32] and on zirconia in unspecified crystallographic form in 1976 [33]. Prior to that, lithium oxide catalyst supported on alumina has been suggested for the production of mixed ketones from aldehydes and carboxylic acids in 1969 [34]. More recent patents suggest alkaline treated

zirconia, titania, and ceria catalysts for the industrial production of fatty ketones by decarboxylative ketonization of fatty acids or triacylglycerides [35]. However, only a limited number of research studies have focused on the difference in catalysts activity caused by alkaline doping [14,29,36]. Consequently, there is a critical knowledge gap about the effect of doping by alkaline atoms on catalyst performance and the steps of the catalytic mechanism.

Parida and Mishra have found that doping zirconia by alkaline metals does not increase the concentration of basic sites, nor their strength [29]. Moreover, Na doped ZrO_2 shows 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. Concentration of acetic and isobutyric acids on surface of monoclinic zirconia and anatase titania in the equilibrium with the vapor phase is also not affected by KOH treatment, while the rate of H/D exchange of alpha protons in isobutyric acid in the presence of D_2O is increased [36]. Because H/D exchange proceeds through the enolization of carboxylic acids, we may conclude that alkaline doping affects at least one of the steps of the reaction mechanism – the enolization.

Treatment by alkaline metals extends catalyst lifetime beyond one thousand hours, while untreated ceria, alumina, zirconia and titania catalysts cannot last more than a day in a continuous reactor before carbon deposition begins to develop. Moreover, catalyst activity of alkaline treated catalysts at the end of their life can be easily restored to the original level by treatment with air or oxygen in a low concentration at temperatures 400-500 °C [37] or even by steam [38,39].

The activity of untreated zirconia catalyst compared to alkali-metal treated one is changing in the following order: $\text{Na} > \text{K} > \text{Cs} > \text{untreated } \text{ZrO}_2 > \text{Li}$ in the temperature range 523-673 K

(Figure 1) [29]. Both rutile and anatase forms of titania have a very low catalytic activity without alkaline metal doping and they could not be seriously considered for industrial applications. Activity of anatase can be increased by doping with group I, II, or VIIIb metal cations, in which metals from group I are the most efficient. In contrast, activity and selectivity of the rutile form of titania is less sensitive to alkaline doping and remains low even after the treatment. A synergy between metal oxide support and alkali oxide phase on top of it may exist, but no studies have been carried out to find whether the active sites remain on metal oxide or move to the dopant in part or completely. Therefore, an important task for DFT computations, kinetic and spectroscopic studies in the future is to understand the structure of active sites and the decarboxylative ketonization mechanism on alkali-doped surfaces.

Recently, doping by Ru has been suggested for anatase titania as a way of increasing catalyst activity [40]. However, activity of anatase surfaces may very likely be increased by doping with many other metals. Unfortunately, the magnitude of the effect caused by Ru remains unclear, since it has not been directly compared to that produced by doping with the group I or other less expensive metals [32]. Catalysts screening by the “inside GC/MS microreactor”[41] showed that the selectivity to ketones with pure RuO_2 catalyst is low due to side reactions produced mostly by oxidation¹.

A chain of literature citations inaccurately calling the untreated zirconia and titania as the most active [2], efficient [10,15,42] and stable [11] catalysts seems to be triggered by the first appearance of ZrO_2 in DFT modeling publications[25]. Initially, untreated monoclinic zirconia has been selected for DFT modeling of the first steps of the catalytic mechanism, adsorption

¹ Unpublished data of the author.

and enolization, to represent, in a simplified way, a more complex structure of the KOH treated ZrO_2 surface, which is a more active and much more robust catalyst. In the subsequent DFT study by Pulido et al., untreated zirconia has been chosen again for modeling of the complete reaction mechanism, because of its higher activity relative to CeO_2 , ZrCeO_4 , SiO_2 , and Al_2O_3 starting at relatively low temperatures [8,9]. These pioneering studies have attracted subsequent theoretical interest to the untreated zirconia catalyst [11,15,42]. The problem, however, is a low stability of ZrO_2 toward deactivation and fouling, similar to many other metal oxide catalysts when used without doping by alkaline metals. The selectivity to ketones with untreated zirconia is reaching maximum at the temperature 375 °C and decreasing above it, while with ceria catalyst it constantly grows up to 425 °C exceeding the performance of zirconia [8]. In contrast, the activity and selectivity to ketones with KOH treated zirconia is higher and it continues to grow until temperatures 450-475 °C [37].

The stability of catalysts exposed to mixtures of iso-butyric acid with ketones in the vapor phase at temperatures 300-500 °C for 80 hours is ranked in the following order: KOH treated TiO_2 > KOH treated ZrO_2 > untreated ZrO_2 based on the catalyst color change and weight gain (Figure 2) [43].

Another important observation coming from industrial operations is that the use of catalysts with higher surface area does not practically help to increase production rates. This conclusion is also confirmed in a research study by Snell and Shanks [44]. Because the overall reaction is endothermic due to the decarboxylation step, a heat transfer becomes a limiting factor for the reaction rate in large size reactors. Catalysts having surface area in the mid-range, 40-60 m^2/g , maintain production rate practically equal to the one obtained with high surface area catalysts,

above 90 m²/g [30,31]. At the same time, the amount of side reactions is minimized with lower surface area catalysts making them as the preferred choice in the industry. The problem of heat transfer limitations is purposely avoided in kinetic studies in academia, which usually target conditions as close as possible to being isothermal often by using a small amount of catalyst and a high dilution by inert gases. Temperature gradient in a reactor is a common source of discrepancies between results of activity and selectivity tests encountered upon scaling up.

3. CATALYTIC MECHANISM

The reaction mechanism via formation of beta-keto acid intermediate has been modeled by DFT computations on idealized surfaces such as tetragonal (101) [15], monoclinic ($\bar{1}11$) [8,11,42], and monoclinic (111) [16] surfaces of zirconia, anatase (101) and rutile (110) surfaces of titania [10]. Commonly shared by all DFT studies, the initial steps of the reaction mechanism are acid adsorption and enolization as the result of the alpha hydrogen abstraction by lattice oxygen atoms (Scheme 2).

The differences are in the type of the adsorption from which the acid molecule goes into the enolization and condensation steps. The strongest type of adsorption on monoclinic ($\bar{1}11$) [8,11,25,42], and (111) [16] surfaces of zirconia proceeds with the dissociation of O-H bond, proton binding to a lattice oxygen atom, and a bidentate bridging chelation of carboxylate oxygen atoms to Zr metal centers on surface (Figures 3a and 4a, respectively). The same bidentate bridging adsorption with O-H dissociation takes place on anatase (001) [22], and on rutile (011) [10] and (110) [19,21,23,24] surfaces (Figure 5f).

Scheme 2. Decarboxylative cross-ketonization mechanism via beta-keto acid formation proposed on the (111) monoclinic zirconia surface. Catalytic cycle for a pair of two acids is shown with four possible combinations of acids leading to four (three unique) ketone products

through enolization, condensation, dehydration, decarboxylation, and product desorption – acid re-adsorption steps.[36]

Anatase (101) surface of titania is rather an exception on which a monodentate mode of adsorption is preferred without dissociation but still with hydrogen bonding between carboxylic group and lattice oxygen (Figure 5b,c) [10]. Because of the large distance between two Ti

surface atoms, the structure of carboxylates adsorbed on anatase (101) surface in the bidentate bridging mode (Figure 5d) would be distorted by stretching and such adsorption mode is less likely to occur.

Upon dissociative adsorption, carboxylic acids are converted to their conjugate bases, carboxylates. The strength of carboxylic acids adsorption in such case is determined by the strength of the Zr-O and O-H bonds formed. The strength of the created bonds is often explained by the acidity of the metal center and by the basicity of the lattice oxygen [10]. However, another important factor contributing to the difference in adsorption energies on surfaces is the difference in the structure of surface layers. Upon adsorption, atoms from the topmost layer of a pristine surface come back from a relaxed state closer to their original bulk lattice positions lowering the surface energy. Surface atoms with a higher degree of the coordinative unsaturation benefit more from binding to adsorbates. It may happen because of not only the higher basicity or acidity of those atoms. The degree of structural changes is another factor contributing to the strength of adsorption, but these two factors may be difficult to separate one from another. Consequently, acidity or basicity of surface atoms may not be an accurate descriptor for the adsorption strength.

The next step, enolization by alpha hydrogen abstraction is an endothermic and endergonic process. Based on the proximity of alpha hydrogen to a lattice oxygen atom, it is relatively easy to have deprotonation done on corrugated surfaces, such as all studied surfaces of monoclinic and tetragonal zirconia. Examples are shown for ($\bar{1}11$) and (111) surfaces of monoclinic (Figures 3 and 4, respectively) and (101) surface of tetragonal zirconia (Figure 6). The similar effect is also expected for all major surfaces of ceria, which are also not flat. For carboxylates adsorbed

in bidentate bridging mode on flat surfaces of titania (Figures 5d,f), alpha hydrogen abstraction (Figure 8b) requires slightly higher free energy of activation, 28.7, and 31.8 kcal/mol, vs. that on (111) surface of monoclinic zirconia, 22.6 kcal/mol (Table 1). For anatase (101) and (110) surfaces, Wang and Iglesia have proposed the enolization step taking place by an acid adsorbed in a monodentate form (Figures 7a and 8a, respectively), which has the free energy of activation at the temperature 523 K, 28.7 kcal/mol, about 6.5 kcal/mol lower compared to that for the enolization of the bidentate bridged carboxylate, 35.1 kcal/mol (Figure 8b, Table 1) [10]. In contrast, enolization of carboxylates in the most abandoned bidentate mode of adsorption is used for preparing for the condensation step on monoclinic and tetragonal zirconia surfaces in all other DFT studies.

A critical argument has been suggested that the equilibrium of the enolization process may be negatively affected by the presence of proton donors, such as water and excess of carboxylic acids adsorbed nearby on surface or coming from the gas phase [16]. Because the rate of the limiting step, condensation, depends on the concentration of enolized species, factors affecting the enolization equilibrium do have a control over the global rate of the decarboxylative ketonization.

For the rate-limiting step, condensation, DFT computations have tested a variety of nucleophiles and electrophiles. In the order of appearance in the literature, condensation has been considered between enolized bidentate carboxylate and acyl cation by Pulido et al. on monoclinic ($\bar{1}11$) surface (Scheme 3) [8] and by Tosoni and Pacchioni on tetragonal (101) [15] surfaces of zirconia with oxygen vacancies (Figures 9ab). Condensation has been also suggested between monodentate 1-hydroxy enolate (non-dissociated enolized acid) and non-dissociated

carboxylic acid on anatase (101) (Figures 7b,e) and rutile (110) (Figure 8c) surfaces of titania by Wang and Iglesia [10], or between two bidentate carboxylate species, one of which is enolized on (111) surface of monoclinic zirconia, by Ignatchenko et al. (Figure 10) [16]. A model of condensation between 1-hydroxy enolate in a monodentate adsorption mode and non-dissociated carboxylic acid used for titania has been extended by Wang and Iglesia to ($\bar{1}11$) surface of monoclinic zirconia (Figure 11) [11]. According to the DFT results, condensation between bidentate carboxylate does not look viable on this surface because of a less favorable free energy of the enolization step (30.4 kcal/mol, Table 1). However, other options for the enolization step exist on ($\bar{1}11$) m-ZrO₂ surface, such as the one explored by Ignatchenko [16] (Figure 3) and by Pulido et al. [8]. DFT electronic energies of activation for the enolization of bidentate acetate ion on ($\bar{1}11$) m-ZrO₂ surface, 25.0 [25], and 17.9 kcal/mol [8], are even lower compared to that for the bidentate acetate on (111) surface, 29.4 [25], and 25.9 kcal/mol [16], making the pathway via bidentate carboxylates competitive compared to the one via monodentate species on both zirconia surfaces.

Scheme 3. Mechanism of decarboxylative ketonization of acetic acid on m-ZrO₂ proposed by Pulido et al., which includes dissociative adsorption of acid in bidentate bridging mode, enolization, condensation with acyl cation to a beta-keto acid salt and decarboxylation steps [8].

DFT model of the condensation between enolized bidentate carboxylate and acyl cation on monoclinic ($\bar{1}11$) zirconia has been adopted for the ketonization study in aqueous phase by Cai et al. [42].

Despite looking energetically attractive, condensation of monodentate species might be impossible because of the much faster reaction of enols and enolates with acidic proton of the monodentate species instead of the carbonyl group (Figures 7b,e and 8c). Likewise, condensation between enolized bidentate carboxylates on (111) m-ZrO₂ surface and a second acid molecule coming from the gas phase has to be rejected for the same reason regardless of being energetically favorable [16]. Reaction with protons is the same reason for which enolized carboxylates do not condense with free carboxylic acids in a solution. Therefore, the most important role of a heterogeneous catalyst can be seen in trapping protons released upon carboxylic acids adsorption and enolization on surface, which makes condensation step possible. The positive effect of KOH treatment on the enolization step described in Section 2 may consists in trapping protons and shifting the enolization equilibrium.

As it can be seen, the suggested variations of the reaction mechanism do not overlap by the surface studied or by the computational method used, except for ($\bar{1}11$) monoclinic zirconia. For that reason, the preference for one or another species cannot be determined yet. While acyl cation is used in earlier studies, it has a high energy and requires an extra step for its formation. Therefore, alternative forms of the electrophilic reagent for the condensation step such as bidentate carboxylates [16] or non-dissociated carboxylic acids [10,11] have been considered.

Subsequent steps, dehydration and decarboxylation have variations as well, although, they are considered as kinetically irrelevant. An exception may exist for the decarboxylation of a beta keto carboxylate derived from bulky acids [16]. It has been shown experimentally through isotopic labeling that all steps of the decarboxylative ketonization mechanism are reversible [14].

An important recent addition to the catalytic mechanism is the enolization of methyl ketone products followed by their condensation with a surface carboxylate and dehydration to a beta diketone intermediate similar to the formation of beta keto acid intermediates (Scheme 4) [43]. Formation of unsymmetrical beta diketones and their decomposition in the opposite direction can lead to the formation of the second pair of a carboxylic acid and ketone. Experiments in the reaction of acetone with isotopically labeled isobutyric acid by ^{13}C on its carboxyl group have shown that it serves as an exclusive source of the carbonyl group in the resulting methyl isopropyl ketone (MIPK) on Scheme 4.

Re-ketonization is the term suggested to describe reconstruction of ketones due to the reversibility in the formation of beta diketone intermediates [43]. This process is used in the industry for the preparation of methyl ketones from acetone [32,45]. The direction of the equilibrium on Scheme 4 is shifted toward such acid that is more reactive in the self-condensation reaction, because that is how it is taken out of the equilibrium. Thus, acetic acid on the right hand side of the Scheme 4 is more reactive compared to iso-butyric acid on the left hand side. Because acetic acid is self-condensing back to acetone, the equilibrium is shifted to the right, toward formation of MIPK.

of beta diketones.

are not isolated in the decarboxylative ketonization reaction.

a much stronger adsorption of carboxylic acids compared to acetone.

4. DO CATALYSTS HAVE TO BE REDUCIBLE AND OXIDIZABLE?

Further to the previous section discussion, it should be noted that all steps of the reaction mechanism are described as acid-base catalysis. Because there are no oxidation-reduction steps involved, the requirement for ketonization catalysts to be oxidizable-reducible looks surprising and unnecessary. Nevertheless, there is a belief and supporting data that pre-reduction of a reducible metal oxide helps to increase decarboxylative ketonization catalytic activity [40]. Such view has gradually evolved beginning from the 1994 review by Rajadurai in which all of the alternative mechanisms, including the concerted one and the one through beta keto acid formation, show adsorption of two carboxylic acids on the same metal cation (Scheme 5).

Scheme 5. Proposed requirement for two acids adsorption on the same metal cation in the concerted mechanism by Kwart and King reviewed by Rajadurai [46].

Barteau, in his 1996 review, has declared presence of double coordinatively-unsaturated metal cations as the absolute requirement for the decarboxylative ketonization between two acid molecules [47]. Hasan et al. studied surface reduction with hydrogen by infrared spectroscopy in 2003 and suggested it as a way to increase coordinative unsaturation [48]. The requirement for metal oxides to be reducible has been proposed at that time and replicated by several studies later [2].

After DFT computations have shown that two carboxylic acids cannot adsorb on the same metal center due to a large steric repulsion [8,25], the foundation for the above theory has been removed. All DFT models of the reaction mechanism are now using adsorption of two acid

molecules on more than one metal center [8,10,11,15,16]. Coordinative mono unsaturation is always present on metal oxide surfaces and does not have to be a double one for the reaction to proceed. In the long history of the decarboxylative ketonization many metal oxides have been used without reduction [26–28] and a more recent data show no benefit of having hydrogen pretreatment [10,11] for the catalytic activity and no correlation with the reducibility of metal oxides [44].

In DFT computational study Tosoni and Pacchioni showed benefit of removing oxygen atom from (101) surface of tetragonal zirconia [15] which lowers barrier for the rate limiting condensation step. However, these results have a very simple explanation. Removing oxygen atom from stoichiometric surface increases the energy enormously by 6 eV (138 kcal/mol), so the rate limiting condensation step changes from being endothermic to exothermic. Reaction barrier is lowered in agreement with the Evans–Polanyi rule [49], which will also happen every time when the starting energy level is increased by any other means in addition to removing oxygen and increasing coordinative unsaturation.

5. REACTANTS AND FEED COMPOSITION

A small amount of water is always added to a feed composition in continuous reactors operated in industry to provide a continuous cleanup of the catalyst surface and as a diluent to assist with a heat transfer [32,34,37,38]. A complex role of water is addressed in computational [16,42] and experimental [43] studies. Water participation in the reaction mechanism becomes an important question because of a need to utilize aqueous solutions of carboxylic acids from a biomass for the decarboxylative ketonization [42]. Future experimental studies could address

reaction rates dependence on dilution by water for a wider range of concentrations, which may not necessarily change in a uniform way when going from a low to high concentration.

Another example of a discrepancy between academic and industrial goals is the application of water in commercial reactors and the way experiments are set up in a number of kinetic studies. Because water is found to inhibit decarboxylative ketonization, kinetic studies designed to find intrinsic rates are done without adding extra water to the amount produced by the reaction.

While carboxylic acids are the most common feed for the production of ketones from carboxylic acids by decarboxylative ketonization, molecules with other functional groups, such as alcohols, aldehydes, anhydrides and esters can be converted to carboxylic acids in situ and used for the same purpose. An extensive review has been published on the application of a biomass derived feed containing various precursors of carboxylic acids [50].

Ketones, however, are not on the above list because they have not been widely known for their condensation reaction with carboxylic acids under typical conditions of the decarboxylative ketonization up until recently [43]. Application of acetone instead of acetic acid for the preparation of unsymmetrical methyl ketones by the decarboxylative cross-ketonization has been practiced in the industry [32,45] but may look new and surprising to some of the open literature audience.

6. REACTION KINETICS

Decarboxylative ketonization is a bimolecular reaction, rates of which follow second order kinetics at low partial pressure of acids in the gas phase, approximately below 0.1 atm. At higher pressures, the surface becomes saturated by carboxylic acids and a zero order kinetics

are observed [51]. Among many studies, dealing with reaction rates only few of those, which relate their kinetic model to the elementary steps of the reaction mechanism, will be discussed below.

Describing kinetics of hexanoic acid decarboxylative ketonization on mixed ceria-zirconia catalysts, Gaertner et al. consider two kinds of surface sites, one for acids, and the other one for water and carbon dioxide adsorption, and a negligible adsorption of the ketone product (equation 1) [51].

$$r = \frac{\vec{k}_{acid} \times P_{acid}^2}{(1 + K_{acid}P_{acid})^2 (1 + K_{water}P_{water} + K_{CO_2}P_{CO_2})^2} \quad (1)$$

The rate constant for the rate-limiting step is used without specifying which step is it.

Wang and Iglesia use equation (2) to describe acetic acid ketonization on titania and zirconia when condensation is the rate limiting step and all products and reagents share the same surface sites for adsorption [10,11]:

$$r = \frac{\vec{k}_{condens.} K_{enoliz.} K_{ads.}^2 P_{acid}^2}{(1 + K_{ads}P_{acid})^2} \quad (2)$$

The following steps are considered in the kinetic model: adsorption, enolization, and the rate limiting step – condensation (Scheme 6) [11]. The highest point on the energy profile is the TS of the condensation step (TS 3, Figure 12).

Scheme 6. Proposed elementary steps for carboxylic acid ketonization on ZrO_2 (m) surfaces with asymmetric acid-base Zr-O site pairs. Reprinted with permission from ref. [11]

1. Dissociation of ethanoic acid on a Zr_I-O_I pair to form AcO^*

2. Molecular adsorption of ethanoic acid on a $Zr_{II}-O_{II}$ pair to form $AcOH^*$

3. α -C-H cleavage from AcO^* to form 1-hydroxyl enolate on the Zr_I-O_I pair

4. C-C coupling between 1-hydroxyl enolate and co-adsorbed $AcOH^*$ to form α -hydroxy γ -carboxy alkoxide

5. Intramolecular dehydration of α -hydroxy γ -carboxy alkoxide to form β -keto carboxylate

6. H_2O desorption

7. Decarboxylation to form propen-2-olate

8. CO_2 desorption

9. Protonation of propen-2-olate to acetone

10. Acetone desorption

11. Dissociation of ethanoic acid on two vicinal Zr-O pairs to form $^*\text{AcO}^*$

Ignatchenko et al., have developed a DFT based kinetic model for the cross-ketonization selectivity in a mixture of two acids (Scheme 2) depending on the concentration of acids on surface assuming their approximately equal adsorption energy from the gas phase [16]

$$r = \frac{\bar{k}_{\text{enol}} \bar{k}_{\text{condens}} \bar{k}_{\text{dehydr}} \bar{k}_{\text{decarbox}}}{\bar{k}_{\text{decarbox}} (\bar{k}_{\text{enol}} \bar{k}_{\text{condens}} + \bar{k}_{\text{condens}} \bar{k}_{\text{dehydr}} + \bar{k}_{\text{enol}} \bar{k}_{\text{dehydr}}) + \bar{k}_{\text{enol}} \bar{k}_{\text{condens}} \bar{k}_{\text{dehydr}}} \times [\text{Acid}_{\text{surf}}] \quad (3)$$

where $[Acid_{surf.}]$ represents surface concentration of a pair of two acid molecules out of four possible combinations. Enolization, condensation and decarboxylation steps are used in the kinetic model. The selectivity to cross-products vs. symmetrical products matches experimental results [36]. The energy profiles for the mechanistic paths derived from four combinations are shown on Figure 13. There is no single highest point on the energy profile except for the decarboxylation step on the path to the most bulky ketone. However, decarboxylation step for that path only may take place through desorption of the beta keto acid intermediate or via its hydration and departure of hydrocarbonate. The highest free energy of activation and the slowest rate constant are found for the condensation step.

None of the above kinetic models have accounted for the degenerate reaction between acetone and acetic acid or for the acetone condensation with other carboxylic acid leading to the re-ketonization. Rates of those side reactions can be significant, up to one-third the magnitude of the decarboxylative ketonization rate, and have to be included into future kinetic models.

7. EFFECT OF REACTOR SIZE AND OTHER PARAMETERS IN PROCESS OPTIMIZATION

Most important parameters for process optimization include temperature, space-time velocity, feed composition, and catalyst type and position in the reactor, but the results may also depend on the size of the reactor. The main reason for a possible difference in the performance of integral reactors is the radial and axial temperature gradient affecting heat transfer in tubular reactors.

Heat transfer is very important for this endothermic reaction showing a strong dependence of the reaction rates on temperature. Heat transfer problem is of a less concern when the feed

is diluted. Dilution by nitrogen is often used in differential reactors for kinetic studies. Dilution by water takes place for a vapor and aqueous phase ketonization of a bio-derived solution of carboxylic acids in water. In kinetic studies, a differential reactor operating at a low conversion can use the unreacted feed as the heat source to maintain isothermal conditions.

For a large scale industrial reactors dilution is not economical. Usually, a significant temperature drop occurs in the middle of a tubular reactor lowering conversion of less reactive carboxylic acids in the mixture. A typical temperature profile depending on the normalized length in a commercial reactor of an undisclosed size is shown on Figure 14. If a full conversion of carboxylic acids is desired, a special care has to be taken not to overheat the outlet section of the catalyst bed and to avoid thermal decomposition of products at high temperatures. This temperature drop represents a challenging problem when scaling up the decarboxylative ketonization reaction in industry.

8. CONCLUSIONS

As it has been pointed out, application of the large amount of data on the ketonization of carboxylic acids available in the literature to the real world industrial processes requires a careful approach. In the attempt to line up future research goals in academia with the industry needs, the catalytic decarboxylative ketonization process has been reviewed in practical terms such as the choice of the catalyst, use of water, recycle of ketones products for their re-ketonization with acids, and the existence of hidden side reactions to be included in the improved kinetic model. Catalytic transformation of carboxylic acids into ketones with the decarboxylation is a more complicated process compared to how it has been described in the

existing literature. My goal was to bring attention to the problems discussed in this review and to help with the scale up of this process.

In the near future, it is desirable to understand the role which alkali doping plays in the reaction mechanism, in the construction of active sites, and in the catalyst stability enhancement. Recognizing that the core of the reaction mechanism is a base catalyzed condensation step can help with a better proton management in the future catalyst development studies. It is expected that additional computational, spectroscopic, isotopic, and kinetic studies will provide more evidence for the nature of the most reactive species, such as bidentate or monodentate carboxylates. Perhaps, geometrical parameters of the catalyst surface structure can be examined as descriptors for the catalyst activity in addition to the strength of acid-base pairs.

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Table 1. DFT derived Gibbs free energy, kcal/mol, of activation, $\Delta G^\ddagger$, and of reaction, ΔG , for enolization, condensation, and decarboxylation steps of the reaction mechanism.

Surface	m-ZrO ₂ (111) [16]		a-TiO ₂ (101) [10]		r-TiO ₂ (110) [10]		r-TiO ₂ (110) [10]	m-ZrO ₂ ($\bar{1}\bar{1}1$) [11] ^a		m-ZrO ₂ ($\bar{1}\bar{1}1$) [11] ^a	
Adsorption mode	bidentate		monodentate		monodentate		bidentate	monodentate		bidentate	
Temperature	660 K		523 K		523 K		523 K	523 K		523 K	
Energy	$\Delta G^\ddagger$ ^b	ΔG ^b	$\Delta G^\ddagger$ ^c	ΔG ^c	$\Delta G^\ddagger$ ^c	ΔG ^c	$\Delta G^\ddagger$ ^c	$\Delta G^\ddagger$ ^c	ΔG ^c	$\Delta G^\ddagger$ ^c	ΔG ^c
Enolization	22.6	15.6	31.8	26.5	28.7	9.3	35.1	24.7	19.7	34.9	30.4
Condensation	20.7	11.5	11.7	0.5	26.5	17.0		15.9	7.1	25.0	8.9
Decarboxylation	15.9	1.6	17.7	0.5	18.6	-6.0		19.2	15.9	12.5	9.8
Highest energy point	36.3		38.2		35.9			35.6		55.4	

^a estimated from graphs since exact values are not reported.

^b GGA, PBE

^c PBE + D3BJ, PAW

Figure 1. Catalytic activity of alkali metal-doped zirconia catalysts in the decarboxylative ketonization of acetic acid; GHSV = 160 ml g⁻¹ min⁻¹. Reprinted from ref. [29]

Figure 2. Relative order of catalyst stability TK>ZK>ZR based on color change and up to 2% weight gain, after being exposed to mixtures of isobutyric acid and methyl iso-propyl ketone or acetone for the same amount of time, 80 hrs at temperatures 300-500 °C. Reprinted with permission from [43]. Copyright 2011 American Chemical Society.

Figure 3. Electronic energy profile for the enolization of acetate on the $(\bar{1}11)$ surface of monoclinic zirconia. (a) Acetate adsorption in bidentate bridging mode; the dissociated H is attached to the 2-fc lattice oxygen. (b) Optimized transition state. (c) Enolized acetate. Reprinted with permission from [25]. Copyright 2011 American Chemical Society.

Figure 4. Electronic energy profiles for the enolization of acetate on the (111) surface of monoclinic zirconia. (a) Acetate adsorption in the bidentate bridging mode, (b) TS of the enolization by the 2-fc lattice oxygen. (c) Product of the enolization by the 2-fc lattice oxygen. (d) TS of the enolization by the 3-fc lattice oxygen. (e) Product of the enolization by the 3-fc lattice oxygen. Reprinted with permission from [25]. Copyright 2011 American Chemical Society.

(a) AcOH* on a $\text{Ti}_{5c}\text{-O}_{3c}$ pair

(c) AcO* on a unbounded $\text{Ti}_{5c}\text{-O}_{2c}$ pair

(e) AcOH* on a $\text{Ti}_{5c}\text{-O}_{2c}$ pair

(b) AcO* on a bonded $\text{Ti}_{5c}\text{-O}_{2c}$ pair

(d) *AcO* on two $\text{Ti}_{5c}\text{-O}_{2c}$ pairs

(f) *AcO* on two $\text{Ti}_{5c}\text{-O}_{2c}$ pairs

Figure 5. DFT-derived (PBE + D3BJ, PAW) adsorption modes for acetic acid on anatase TiO_2 (101) and rutile TiO_2 (110) surfaces. Distances are given in nm. [10]

Figure 6. Electronic energy profile of acetic acid adsorption and enolization reaction on stoichiometric (101) surface of t-ZrO₂. Blue: Zr; red: O; yellow: C; white H. Energies in eV (computed with respect to a gas-phase acetic acid molecule). [15]

(a) Enolization of AcO^* (1 ML AcO^*)

(b) C-C coupling with AcO^* (1 ML AcO^*)

(c) H-transfer to lattice O-atom (1 ML AcO^*)

(d) Decarboxylation to enolate (1 ML AcO^*)

(e) C-C coupling with AcO^* (1/3 ML AcO^*)

(f) Intramolecular dehydration (1/3 ML AcO^*)

Figure 7. DFT-derived (PBE + D3BJ, PAW) transition state structures involved in ethanoic acid ketonization on $\text{TiO}_2(\text{a})$ (101) surfaces. Distances are given in nm. [10]

(a) Enolization of AcOH*

(b) Enolization of *AcO*

(c) C-C coupling with coadsorbed AcOH*

(d) Intramolecular dehydration

Ti; O; C; H

Figure 8. DFT-derived (PBE + D3BJ, PAW) transition state structures involved in ethanoic acid ketonization on TiO₂(r) (110) surfaces. Distances are given in nm. [10]

a)

Figure 9. Condensation of the enolized acetate with acyl cation on a) hydrogenated t-ZrO₂, b) t-ZrO₂ in the presence of a surface oxygen vacancy. Blue: Zr; red: O; yellow: C; white H. Electronic energies are given in eV (computed with respect to two gas-phase acetic acid molecules). [15]

Figure 10. Side and top views on the enolization (TS 2c) and condensation (TS 4c) steps of the catalytic cycle involving two bidentate bridged acetate molecules (1c) on (111) surface of monoclinic zirconia. Distances are given in Å. [16]

Figure 11. DFT-derived (PBE+D3BJ, PAW) structures for adsorbed acid reactants and transition states involved in ketonization of monodentate acetate (AcO^*) and non-dissociated acetic acid (AcOH^*) on ($\bar{1}\bar{1}1$) surface of $\text{ZrO}_2(\text{m})$. Reprinted with permission from [11]. Copyright 2011 American Chemical Society.

Figure 12. DFT-derived (PBE+D3BJ, PAW) free energy reaction coordinate diagram for ketonization of monodentate acetate, AcO^* , and non-dissociated acetic acid, AcOH^* , on $\text{ZrO}_2(\text{m})$ ($\bar{1}11$) surfaces, at the temperature 523 K, and 1 bar pressure of ethanoic acid, at 2/3 ML acid coverage. All energy values are referenced to an AcO^* - AcOH^* reactant. Reprinted with permission from [11]. Copyright 2011 American Chemical Society.

Figure 13. DFT-derived (GGA, PBE) free energy reaction coordinate diagram for the cross-ketonization of acetic and isobutyric acids according to the four mechanistic paths "a–d" of the catalytic cycle on Scheme 2 at 327 °C (600 K) temperature shown relative to the energy of empty surface with two acid molecules in the gas phase. [16]

Figure 14. Temperature profile depending on the normalized length in the reactor with zirconia catalyst doped by KOH during ketones production from a mixture of carboxylic acids with a top-down flow.²

² Unpublished data of the author.