Iron(III) Complexes for Highly Efficient and Sustainable Ketalization of Glycerol: A Combined Experimental and Theoretical Study

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Supporting Information

ABSTRACT: The growing production of biodiesel as a promising alternative and renewable fuel led as the main problem the dramatic increase of its by-product: glycerol. Different strategies for glycerol derivatization have been reported so far, some more efficient or sustainable than others. Herein, we report a very promising and eco-friendly transformation of glycerol in nontoxic solvents and chemicals (i.e., solketal, ketals), proposing three new families of Fe(III) compounds capable of catalysing glycerol acetalization with unpublished turn over frequencies (TOFs), and adhering most of the principles of green chemistry. The comparison between the activity of complexes of formula [FeCl3(1-R)] (1-R = substituted pyridinimine), [FeCl3(2-R,R′)] (2-R,R′ = substituted O,O′-deprotonated salens) and their corresponding simple salts reveals that the former are extremely convenient because they are able to promote solketal formation with excellent TOFs, up to 10^5 h^-1. Satisfactory performances were shown with respect to the entire range of substrates, with results being competitive to those reported in the literature so far. Moreover, the experimental activity was supported by an accurate and complete ab initio study, which disclosed the fundamental role of iron(III) as Lewis acid in promoting the catalytic activity. The unprecedented high activity and the low loading of the catalyst, combined with the great availability and the good eco-toxicological profile of iron, foster future applications of this catalytic process for the sustainable transformation of an abundant by-product in a variety of chemicals.

INTRODUCTION

Biodiesel is a mixture of alkyl esters of fatty acids obtained by transesterification/esterification of vegetable oils or fats with light alcohols (Scheme 1).

The growing interest in renewable resources increases biodiesel production year by year. As a consequence, its by-product glycerol is dramatically invading the market: it is estimated that 41.9 billion liters will be produced in 2020.1,2 Transforming this by-product into a renewable bio-based raw material is, therefore, a priority. Not surprisingly, many new processes have been proposed that use glycerol as a starting material for a wide range of solvents, chemicals, and intermediates.3−7 Due to its unique structure, glycerol is a promising intermediate for the synthesis of acrolein, glycolic acid, ethylene glycol, oxalic acid, syngas, 1,2-propanediol, mono-, di-, and tri-glycerides, epichlorohydrin, polyglycerols, acetalts, ketals, and many others (Scheme 2).

Among these compounds, acetals and ketals are an emerging class of products that can be used as nontoxic solvents,8 fuel additives8−10 and building blocks as glycerol-protected intermediates.11

The formation of glycerol-based acetals/ketals is an equilibrium reaction and is typically acid-catalyzed, following the general Scheme 3.

The reaction appeal is evidenced by the intense search for effective catalytic systems adhering to the conditions prescribed by the principles of green chemistry,12 such as atom economy, absence of auxiliaries, and ease of recovery of the catalyst. Most of the known catalysts are heterogeneous,13−55 and only a few examples refer to homogeneous systems.36−40 Furthermore, although some mechanistic hypothesis have been proposed,26,41 theoretical in-depth studies are very rare.42

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Some of us have long been involved in the development of Lewis acid catalysts for the sustainable transformation of vegetable oils and derivatives. Within this field we recently communicated preliminary results about a set of homogenous catalysts based on iron(III), capable of promoting the synthesis of solketal (five-member ketal in Scheme 2, where $R_1 = R_2 = \text{Me}$). Importantly, the results suggested a high capacity of iron(III) complexes in promoting the functionalization of glycerol.

In this work, we report the synthesis of a broad scope of ketal-based chemicals through several iron(III) catalysts. Satisfactory performances were shown with respect to the entire range of substrates with results competitive to those reported in the literature. The best catalyst showed a turn over frequency (TOF) of $10^5 \text{ h}^{-1}$, which is 3 orders of magnitude greater than those reported in the literature so far for the best homogeneous catalysts. The experimental study has been accompanied for the first time by a detailed investigation of the general mechanism through a sophisticated ab initio calculation, which highlighted the significant role of iron(III) as Lewis acid. The calculated thermodynamic and kinetic parameters are in full agreement with previously presented experimental values.

Overall, the unprecedented high activity of the catalysts, the low loading (up to 10 ppm), the good eco-toxicological profile, along with their generous availability promise to be convincing.
RESULTS AND DISCUSSION

Catalytic Synthesis of Solketal. The synthesis of solketal (P1) is reported in Scheme 4. A review of the literature (Table 1) discloses flourishing articles, which propose new catalytic systems for the promotion of the reaction, and that most of them are heterogeneous (in italic in Table 1).

Substantial amounts of catalyst (≥3–5%) are necessary to achieve conversions higher than 95% (entries 4, 6, 7, and 13), and more often the conversion is incomplete with heterogeneous catalysts, probably due to the establishment of equilibria inside the pores of the solids. In view of these disadvantages, the possibility of recycling the catalyst must be mentioned, which in some cases has been claimed.15,25,26,40 Homogeneous catalysts are much less represented (entries 16–20) and, as expected, are used in lower concentrations, although never negligible.

Table 1. Literature Reports on the Synthesis of Solketal

| entry (ref) | acetone/glycerol | catalyst* (loading) | conditions | conv. (%) |
|------------|-----------------|---------------------|------------|----------|
| 116        | 6:1             | SiO$_2$–SO$_3$H (5% wt)$^a$ | 70 °C, 0.25 h | 80 |
| 214        | 1.2:1           | β-zeolite (19% wt) | 70 °C, 1 h | 90 |
| 314        | 10:1            | HPW (1% mol) | RT, 2 h | 58 |
| 451        | 3:1             | MoPO/SBA-15SiO$_2$ (15% wt) | RT, 3 h | 100 |
| 551        | 1.5:1           | Amberlist-36 (5% wt) | 40 °C, 8 h | 88 |
| 617        | 6:1             | ZrO$_2$/SO$_3$H$^c$ (5% wt) | RT, 1.5 h | 98 |
| 711        | 10:1            | Re/SiO$_2$ (5% wt) | 30 °C, 1 h | 100 |
| 845        | 6:1             | HPW/SiO$_2$ (5% wt) | 30 °C, 4 h | 97 |
| 950        | 1.5:1           | Nb$_2$O$_5$ (5% wt) | 70 °C, 6 h | 80 |
| 1085       | 4:1             | Nb$_2$O$_5$/Al$_2$O$_3$ (3% wt)$^c$ | 50 °C, 2 h | 84 |
| 1185       | 2:1             | Zr,Hf/TUD-1 (3% wt) | 80 °C, 6 h | 65 |
| 1215       | 4:1             | montmorillonite (0.7% wt)$^b$ | 50 °C, 0.5 h | 73 |
| 1315       | 4:1             | carbon–SiO$_2$ (3% wt) | RT, 6 h | 97 |
| 1415       | 1:1             | dealuminated zeolite (5% wt) | 30 °C, 0.5 h | 80 |
| 1515       | 6:1             | C$_{25}$H$_{48}$PW$_{12}$O$_{40}$/SiO$_2$ (5% wt) | RT, 0.25 h | 94 |
| 1615       | 9:1             | [Cp*IrCl$_3$]$_2$ (0.2% mol) | 40 °C, 1 h | 90 |
| 1715       | 6:1             | TsOH (1% mol) | reflux, 12 h | 83 |
| 1815       | 4:1             | SnCl$_4$ (1% mol)$^d$ | 25 °C, 2 h, MeCN | 81 |
| 1915       | 1:1             | FeCl$_3$ (0.03% mol) | reflux, 0.1 h | see text |
| 2015       | 15:1            | Bronsted acid ionic liquid (2.7% mol)$^d$ | RT, 0.25 h | 97 |

$^a$Heterogeneous catalysts in italic. $^b$Three recycles. $^c$Six recycles. $^d$Four recycles.

Figure 1. [FeCl$_3$(1-R)] and [FeCl(2-R,R’)] catalyst families.

features for the sustainable transformation of a renewable by-product in a nontoxic solvent.$^{50–53}$
The first target of our work was the choice of a convenient set of modular iron(III) catalysts for the synthesis of solketal. Three families were chosen: complexes of formula \([\text{FeCl}_3(1-R)]\) containing \(N_N'-\text{pyridinimine ligands 1-R}\), complexes of formula \([\text{FeCl}(2-R,R')\)]\), containing \(N_N',O,O'\) ligands derived from the deprotonation of salen \(2-R, R'-H_2\), and simple Fe(III) salts. The choice was to reveal the effects of (i) the presence of a ligand, (ii) the different geometry of the complexes, and (iii) the stereoelectronic nature of the substituents within the same class (Figure 1).

Initially, the complete set of complexes was screened. All of the runs were performed under reflux with an acetone/glycerol ratio of 4:1 for 1.5 h. The catalyst loading was kept at 0.050% mol/mol with respect to glycerol, such that all of the complexes resulted soluble in the reaction mixture. To efficiently eliminate water and shift the equilibrium towards the product, a dedicated experimental apparatus was set up (Figure 2), in which a small column of 3 Å molecular sieves was introduced on top of the condenser, able to trap the water both in gaseous and condensed liquid phases. It should be noted that a complete conversion using \(\text{FeCl}_3\) has been recently reported under conditions that do not require the use of a water trap (entry 19 of Table 1). This claim is, however, contradicted by the observations of the authors themselves, who report that the system remains biphasic even at the end of the reaction. In our opinion, this instead reflects a limited conversion, overestimated due to a nonappropriate analysis of the reaction mixture.

The initial biphasic reaction mixture gradually became homogeneous because solketal improves the mutual miscibility of the components.

The progress of the reaction was monitored by recording the \(^1\text{H}\) NMR spectrum of a small aliquot of the reaction mixture diluted in 0.6 mL of D\(_2\)O. Conversion and selectivity could be assessed by proper integration of selected regions.

This first set of experiments disclosed that complexes of type 1 are more active than type 2 (Table 2). In fact, the former ones could quantitatively transform glycerol over the course of 1.5 h, whereas the conversion was only partial with the salens species, a sign that substitution of chloride ligands for the more basic alkoxide donor atoms depresses the Lewis acidity of the metal center.

Within this class (entries 9–15), the variation of substituents determined significant effects on the activity: the presence of electron-withdrawing groups enhanced the conversion up to 65% (entries 14 and 15).

Also, the simple salts could effectively promote the reaction (entries 2–4), and, therefore, further refinements were carried out by comparing type \([\text{FeCl}_3(1-R)]\) complexes and simple salts. Only at 0.00050% mol/mol (that is ca. 3 ppm of iron versus glycerol), \(\text{FeCl}_3\) and the nitro derivative \([\text{FeCl}_3(1-\text{NO}_2)]\) proved to be the best catalysts, with TOF values of \(10^5\) h\(^{-1}\), that is few orders of magnitude greater than those reported in the literature so far for the best homogeneous catalysts.\(^{36-40}\) Although iron(III) chloride was slightly more active, \([\text{FeCl}_3(1-\text{NO}_2)]\) was considered the best candidate for subsequent tests, as it is stable to air, easy to handle, and with excellent solubility. These qualities are particularly appreciated because they enhance the versatility of the catalyst and allow its use in convenient conditions. As a proof, a run was performed for isolating solketal.\(^{47}\) The catalyst loading was kept at 0.00020%, and the product was easily obtained by flash distillation of the excess of acetone with an iron content of less than 10 ppm, and therefore already useful for numerous applications.

A conversion vs time plot was also obtained that showed the reaction profile and the high initial TOF. The data was collected monitoring the progress of the reaction both by NMR spectroscopy and by detecting the trend of the boiling point of the mixture with a thermocouple immersed in the reaction media (Figure 3). In fact, the progressive formation of solketal gradually increases the boiling point of the mixture.

**Other Substrates.** The iron-catalyzed ketalization of glycerol was extended to other carbonyl substrates, by using...
catalyst \([\text{FeCl}_3(1\text{-NO}_2)]\). Benzaldehyde or ketones (aliphatic: butanone, cyclohexanone; aromatic: acetophenone; and functionalized: methyl levulinate) were selected as substrates. Also, in these cases, previous literature mainly refers to heterogeneous catalysts (in italic in Table 3), both inorganic and organic in nature.\(^{54-72}\) A first general observation is again that satisfactory conversions are obtained using high catalyst amounts or more sophisticated reaction conditions, such as inert atmosphere or ultrasounds. Less represented are experiments with homogeneous catalysts, of greater interest in this context. Conversion of benzaldehyde, butanone, acetophenone, and cyclohexanone with the ionic liquid \([\text{MeSO}_3\text{bmm}]\text{MeSO}_4\) did not exceed 87%, a result partially weakened by the high cost of the catalyst and the need to use toluene as co-solvent (entries 10, 19, 22, and 34). Better results were achieved with phosphomolybdic acid, used in percentages of 0.5% mol/mol (entries 14, 20, and 23). The catalyst was reused, although considerable quantities of toluene were necessary to extract the product.

Within this frame, we carried out the experiments using \([\text{FeCl}_3(1\text{-NO}_2)]\) (Table 4). Two concentrations were chosen: 0.5% mol/mol, the most convenient for comparisons with similar homogeneous systems, and 0.01%, to verify the permanence of activity even in the case of more challenging substrates. The reactions were conducted at a temperature so as to favor the kinetics without compromising the stability of the catalyst. In the case of high boiling substrates, removal of water was favored by working at low pressure to allow its entrapment in the molecular sieves (Figure 2), as detailed in the table.

Benzaldehyde, butanone, cyclohexanone, acetophenone, and methyl levulinate (entries 1–3 and 5–6) were quantitatively converted at a loading of 0.5% mol/mol, and even at this lower value, this simple catalyst demonstrated its excellent performance (87 and 82%, respectively, with benzaldehyde and butanone). These results are extremely competitive with the previously discussed literature reports. According to literature data, the benzaldehyde ketal consisted of a mixture of the five- and six-membered products,\(^{39}\) as revealed by the NMR spectrum in deuterated methanol. As expected,\(^{69}\) less satisfying were the outcomes of the catalysis with cyclopentanone (entry 4).

**Mechanistic Study.** Density functional theory (DFT) calculations were performed to gain insights into the mechanism of the Fe-catalyzed glycerol ketalization with acetone. \([\text{Fe(H}_2\text{O})_6]^{3+}\) was chosen as model active species because it demonstrated to be active (entry 3, Table 2) and its simple structure avoids complication due to geometrical isomerism.

The proposed catalytic cycle is resumed in Scheme 5.

First, acetone binding to the Lewis acid activates the ketone for the glycerol nucleophilic attack (I \(\rightarrow\) II). Then, proton...
transfer between glycerol hydroxylic groups occurs to yield an acyclic ketal (II → III). The loss of a water molecule from intermediate III is concerted with the intramolecular cyclization to yield the cyclic ketal IV. Finally, displacement of the newly formed solketal with a water molecule completes the catalytic cycle.

The computed mechanism for the glycerol acetalization is reported in Figure 4, whereas the selected geometric parameters for reaction intermediates are shown in Figure 5.

Coordination of acetone to [Fe(H2O)6]3+ is the first step of the catalytic cycle. The exchange of one water molecule with acetone to give [Fe(H2O)5(acetone)]3+ is exergonic ($\Delta G = -4.39$ kcal/mol). The acetone oxygen (Oa in Figure 5) strongly interacts with the iron ion, indeed the Oa−Fe distance is 1.89 Å and the Fe−Oa−Ca angle is 180° (see intermediate I in Figure 5).

Fe−acetone binding polarizes the C=O bond, increasing the electrophilic character of the Ca atom and activating the carbonyl group for the nucleophilic attack by glycerol.

Indeed, the acetone−glycerol adduct dissociates without the binding of acetone with the Fe(III) Lewis acid, and a stable product of the acetone−glycerol nucleophilic addiction cannot be optimized.

A barrier of 13.57 kcal/mol is computed for the nucleophilic addition of glycerol on [Fe(H2O)5(acetone)]3+.

Moreover, the glycerol binding to acetone modifies the acetone coordination to the iron center. Intermediate II is characterized by a Fe−Oa−Ca angle of 144°, whereas the Fe−Oa and Oa−Ca distances are 1.81 and 1.36 Å, respectively (see Figure 5). The observed structural rearrangement results from the change in the hybridization state of the Ca atom. The trigonal, planar sp² hybridized Ca of intermediate I changes to

| Entry | Substrate | Product(s) | $T$ | Yield (%) |
|-------|-----------|------------|-----|-----------|
| 1$^a$ | | | 80°C | 2 : 1 | 18 | >99 | 87 |
| 2 | | | Reflux | 98 : 2 | <1 | >99 | 82 |
| 3$^a$ | | | 110°C | 98 : 2 | <1 | 50 | 24 |
| 4 | | | 110°C | >99 : 1 | 48 | 64 | 56 |
| 5 | | | 110°C | >99 : 1 | 40 | >99 | 68 |
| 6$^a$ | | | 110°C | >99 : 1 | <1 | >99 | 65 |

$^a$Reaction time: 1.5 h. P: 760 mmHg. $^b$P = 36 mmHg. $^c$Reaction time = 4 h.

Table 4. Screening of [FeCl3(1-NO2)] Catalyst$^d$

$^d$Reaction time: 1.5 h. P: 760 mmHg. $^b$P = 36 mmHg. $^c$Reaction time = 4 h.

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a tetrahedral, sp\(^3\) hybridized state in intermediate II, leading to an increase of the C\(_a\)−O\(_a\) distance of about 0.11 Å when going from I to II. The interaction between O\(_a\) and the iron also increases resulting in a decrease of the Fe−O\(_a\) distance of about 0.08 Å when going from intermediate I to II. Another conformation for intermediate II (IIb, see Supporting Information), which can lead to the proton transfer from the glycerol to the acetone oxygen was also examined at the same level of theory. This other conformation resulted to be 6.52 kcal/mol less stable with respect to II (see Supporting Information).

The O\(_b\)−H\(_b\) hydroxyl group in II is strongly hydrogen bonded to O\(_c\) (the O\(_c\)−H\(_b\) distance is 1.74 Å). The proton transfer between O\(_b\) and O\(_c\) is slightly exergonic (\(\Delta G = -1.30\) kcal/mol) with a very low activation barrier (\(\Delta G^\ddagger = 0.81\) kcal/mol).

Once intermediate III is formed, a concerted nucleophilic attack and loss of a water molecule bring the formation of the cyclic ketal coordinated to the iron complex. A barrier of 24.65 kcal/mol is computed for the concerted intramolecular cyclization.

Moreover, the solketal product is weakly bound to the iron complex (Fe−O\(_a\) distance is 1.96 Å in IV). The displacement
of the cyclic ketal with a water molecule is exergonic ($\Delta G = -7.96 \text{ kcal/mol}$), and it completes the cycle allowing the catalyst regeneration.

A $\Delta G$ of 0.04 kcal/mol is computed for the complete reaction of Scheme 5, in perfect agreement with the experimental equilibrium constant of about 1.49.

**CONCLUSIONS**

This paper reports a combined experimental and theoretical study on the synthesis of glycerol-based ketal promoted by iron(III) complexes. The screening of catalysts has shown that the presence of chloride ions enhances the performance of the catalysts compared to those containing alkoxide donors. Very gratifying results were obtained with low catalyst loading, in some cases leading to nearly quantitative conversions with an iron content below 10 ppm. Mechanistic studies have demonstrated the key role played by iron(III) as Lewis acid.

Overall, the ensemble of results returns a clear picture of the "green" features of the process, of actual relevance because a renewable by-product is converted into useful chemicals, and confirms the prominent role played by iron in relevant synthetic processes.

**EXPERIMENTAL SECTION**

**General.** The known products were characterized by comparing their NMR spectra with those reported in the literature, by using a Bruker Avance Ultrashield 400 operating at a proton frequency of 400 MHz. The following abbreviations were used for describing NMR multiplicities: s, singlet; t, triplet; q, quartet; and m, multiplet. Benzaldehyde and the other ketones were commercially available (Sigma-Aldrich) and were used as received. The iron complexes were prepared according to literature methods (see Figure 1).

**Catalytic Runs.** A mixture of glycerol (0.92 g, 10 mmol), the appropriate carbonyl compound (40 mmol), and the iron catalyst was stirred according to the conditions described in Tables 2–4. When appropriate, depressure was applied to the reaction system of Figure 1, and the internal pressure was monitored by connection to a mercury column. The product composition was analyzed through NMR spectroscopy by adding a small aliquot of the homogeneous reaction mixture to 0.6 mL of the appropriate deuterated solvent.

$^1$H NMR (methyl levulinate glycerol ketal, two diastereoisomers, 298 K, CDCl$_3$): 6 4.21 (m, 1H), 4.03 (q, 1H), 3.80 (m, 2H), 3.69 (s, 3H), 3.58 (m, 1H), 2.40 (m, 2H), 2.10 and 2.0 (t, 2H), 1.38 and 1.33 (s, 3H).

**Computational Details.** All DFT calculations were performed using the Gaussian 16 suite of programs. The structures of all intermediates were optimized using the M06 density functional. The 6-31+G(d,p) basis set was adopted for C, H, and O, whereas the Fe atom was described by the LANL2DZ basis set and the associate effective core potential, which was demonstrated to be a suitable choice to describe the reactivity of metal centers.

Frequency calculations were performed to assess the nature of each stationary point (minimum or transition state). Bulk solvent effects (acetone) were accounted for by using the polarizable continuum model in its conductor-like version (C-PCM). Dispersion, repulsion, and cavitation terms were also considered.

The computation of harmonic frequencies was also performed to calculate the free energy of all molecules at $T = 298 \text{ K}$ and $P = 1 \text{ atm}$, assuming an ideal gas behavior.

**ASSOCIATED CONTENT**

* Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02546.

Investigation of another possible reaction path. Figure S1: Structures of two different conformations for Intermediate II; Figure S2: Computed reaction path for the proton transfer from the glycerol hydroxyl group to the acetone oxygen (PDF)

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**Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Figure 5. Structures of I–IV intermediates for Fe-catalyzed glycerol acetalization computed at the M06/LanL2DZ/6-31+G(d,p)/C-PCM ($\varepsilon = 20.49$) level of theory.
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■ ABBREVIATIONS
DFT, density functional theory; NMR, nuclear magnetic resonance

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