

1 *Editorial*

2 **Newintensification strategies for the direct** 3 **conversion of real biomass into platform and fine** 4 **chemicals: What are the main improvable key** 5 **aspects?**

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14 **Nowadays, the solvothermal conversion of biomass has reached a good level of development,**
15 **and now it is necessary to improve the process intensification, in order to boost its further growth on**
16 **the industrial scale. Otherwise, most of these processes would be limited to the pilot-scale or, even**
17 **worse, to exclusive academic investigations, intended as isolated applications for the development**
18 **of new catalysts. For this purpose, it is necessary to improve the work-up technologies, combining,**
19 **where possible, reaction/purification unit operations, and enhancing the feedstock/liquid ratio, thus**
20 **improving the final concentration of the target product and reducing the work-up costs.**
21 **Furthermore, it becomes decisive to reconsider more critically the choice of biomass, solvent(s), and**
22 **catalysts, pursuing the biomass fractionation in its components and promoting one-pot cascade**
23 **conversion routes. Screening and process optimization activities on a laboratory scale must be**
24 **fast and functional to the flexibility of these processes, exploiting efficient reaction systems such as**
25 **microwaves and/or ultrasounds, and using multivariate analysis for an integrated evaluation of the**
26 **data. These upstream choices, which are mainly of the chemist's responsibility, are fundamental and**
27 **deeply interconnected with downstream engineering, economic, and legislative aspects, which are**
28 **decisive for the real development of the process. In this Editorial, all these key issues will be**
29 **discussed, in particular those aimed at the intensification of solvothermal processes, taking into**
30 **account some real case studies, already developed on the industrial scale.**

31 **1. Importance of the solvothermal processes for the synthesis of platform and fine chemicals**

32 The use of biomass for the production of platform and fine chemicals is strongly imposing as a
33 valid alternative to the employment of the traditional fossil sources [1]. However, despite the
34 progress achieved in the optimization and development of many carbohydrate-based processes, it is
35 still necessary to invest resources in the **research & development**, to overcome the significant gap
36 between the academic and the industrial world, and this is possible only by improving the process
37 intensification [2]. Process intensification favors the equipment size reduction, leading to
38 enhancement in chemical reaction kinetics, energy efficiency, process safety, minimization of waste
39 generation, and reduction of the capital costs. Maximum atom-economy and minimum energy
40 requirements are fundamental features for the development of more sustainable and greener
41 processes. For example, in the hydrothermal processes, which fall into the broader solvothermal
42 processes, the use of sub- and supercritical water, as the reaction medium, provides a valuable and
43 sustainable path for reducing the use of organic solvents. This technology can be integrated for the
44 development of safer, more flexible, economical and ecological biomass conversion processes, in

45 particular, carbonization, liquefaction, and gasification, which differ mainly in the adopted pressure,
46 temperature, and residence time [3]. Moreover, hydrothermal technology offers the advantage of
47 directly converting raw biomasses, also those with relatively high-moisture content, without any
48 energy-intensive pretreatment [4]. In the last years, increasing research has been devoted to the
49 optimization of the hydrothermal processes, in particular under sub-critical conditions, in the
50 absence or presence of a suitable acid catalyst, for the selective production of reducing sugars or
51 platform chemicals. Some noteworthy examples are the furanic intermediates, such as furfural and
52 5-hydroxymethylfurfural, deriving from the dehydration of C5 and C6 carbohydrates, respectively
53 [5], and organic acids (levulinic plus formic acids), resulting from the rehydration of C6 furanic
54 intermediates [6]. **Most recent advances in the production of these valuable platform chemicals will
55 be described in the following paragraph.**
56

57 **2. Some relevant examples of C5 and C6 derivatives of industrial interest**

58 Nowadays, furfural is exclusively produced from acid-catalyzed hydrolysis of pentosan
59 fraction of lignocellulosic biomasses to xylose and its subsequent dehydration. Its industrial process
60 provides one or two separate steps, carried out in batch or continuous reactors, and in the presence
61 of a mineral acid as the reaction catalyst [7]. Due to the quick degradation of furfural occurring in the
62 liquid phase, it must be readily removed once synthesized and, for this purpose, traditional
63 separation techniques can be adopted, such as steam or nitrogen stripping, supercritical carbon
64 dioxide extraction, mono/biphasic solvent extraction and adsorption on resins. Moreover, on an
65 industrial scale, significant technological improvements have been achieved, always aimed at
66 minimizing its residence time in the liquid phase, enhancing its concentration in the vapor
67 products, and effectively reusing the acid catalyst [7]. Going towards a more intensified process
68 development, also reactive distillation has been proposed, adopting zeolite H-mordenite as the solid
69 catalyst and xylose as the starting feedstock [8]. In this way, the immediate separation of furfural
70 from the reaction system can be advantageously achieved, minimizing the formation of undesired
71 condensation products and leading to significant heat integration benefits. The furfural market size
72 is projected to grow from EUR 500 million in 2019 to EUR 630 million by 2024, with Austria,
73 Belgium, China, Dominican Republic, India, Italy, Slovenia, South Africa, and US being the key
74 market players, and with furfuryl alcohol, tetrahydrofuran, maleic anhydride,
75 2-methyltetrahydrofuran, and 1,5-pentanediol, as the main derivatives, already manufactured on a
76 commercial scale [5]. Also in the case of 5-hydroxymethylfurfural (5-HMF) production, the formation
77 of by-products, separation, and purification issues, as well as catalyst regeneration, have been
78 identified as major challenges [9]. To solve these drawbacks, many efficient solutions have been
79 continuously proposed, such as that of Yan *et al.* [10], who have performed the continuous
80 production of 5-HMF in a flow-reactor, achieving high yields, starting from fructose or glucose, using
81 HCl and AlCl₃ as the catalysts and water as the reaction medium. Also in this case, high yields can be
82 reached thanks to a very efficient extraction step, which allows the continuous removal of
83 this reactive furan from the reaction environment: the produced 5-HMF is extracted into the organic
84 phase in real-time, thus avoiding its further degradation, while the unreacted carbohydrates re-enter
85 spontaneously into the reaction phase for another reaction cycle. Moreover, the authors have
86 performed a techno-economic analysis, demonstrating that 5-HMF could be produced at a minimum
87 selling price of \$1716/ton and \$1215/ton from fructose and glucose, respectively, which brings
88 motivation and a real chance for its further commercial production on greater volumes. The
89 industrial production of 5-HMF is already available and carried out by AVA Biochem [11], with a
90 monophasic water-based hydrothermal process, which has been optimized and acknowledged as
91 sustainable, efficient and robust and certainly economically advantageous. In recent studies of
92 environmental sustainability assessment, the concrete feasibility of the 5-HMF oxidation to
93 2,5-furandicarboxylic acid has been also demonstrated [12,13]. The latter is one of the 12 uppermost
94 chemical building blocks, which can be used for the production of polymers and resins, such as
95 polyethylene furanoate, which is a promising substitute for polyethylene-terephthalate [14].

96 Acid-catalyzed hydrolysis of 5-HMF leads to levulinic acid, another valuable platform chemical of
97 great interest, and also an assessment of this hydrothermal process has been recently evaluated and
98 discussed, demonstrating its environmentally friendly and neutral safety performances [15]. The
99 interest in the scale-up of these hydrothermal processes on an industrial scale is further strengthened
100 by the continuous development of new conversion strategies of the above platform chemicals into
101 more added-value fine-chemicals, which are industrially more attractive, due to their ready-to-use
102 applications [16,17]. However, considerable improvement opportunities are possible, in particular
103 finding more environmentally friendly solvents for performing the reactions and the recovery of the
104 desired product(s) and developing new catalysts, aimed at improving the process efficiency and
105 reducing the energy consumption. Besides water medium, involved in the hydrothermal approach,
106 solvothermal processes can be also performed with other green and sustainable solvents, such as
107 alcohols, in some cases attaining remarkable advantages. Taking into account the hydrothermal
108 process for levulinic acid production as the reference example, the main advantages of the
109 alcoholysis route consist on *i*) the development of more value-added products, the alkyl levulinates,
110 now exploitable as oxygenated-additives for gasoline and diesel fuels; *ii*) easier work-up procedures,
111 generally by distillation, thanks to the lower boiling points of the esters; *iii*) reduced number of
112 process units and enhanced performances of new technological solutions, such as reactive
113 distillation, conducive to the process intensification [18]. In this way, it is possible to combine
114 reaction and separation unit operations, allowing simpler, more efficient, economical and cleaner
115 production processes. Also in this case, worldwide techno-economic and environmental assessment of alkyl
116 levulinates production has been recently proposed, highlighting a promising economic outlook of
117 these bio-products [19].

118 Although solvothermal biomass processing has been recognized as a really promising
119 technology for converting lignocellulosic and waste biomasses into valuable bio-chemicals and
120 bio-fuels, some key aspects should be still considered, for improving the development of their
121 industrial applications, in particular in the perspective of the intensification process development.
122 Some common drawbacks of these processes are already well-known, in particular the corrosion of
123 the equipment, due to the use of concentrated mineral acids for the catalysis, the precipitation of
124 inorganic salts of biomass source in the presence of sulfuric acid as acid catalyst, char/coke
125 formation, associated with the presence of unconverted biomass and thermal decomposition of the
126 bio-oil [20]. However, most of these problems can be solved after an appropriate optimization study,
127 preferring the use of heterogeneous catalysts in the presence of a soluble substrate (for instance,
128 when beverage or sugar industry wastes are converted) and, if this is not possible, adopting very
129 dilute mineral acids, which must be properly recovered. **In the next paragraphs**, we discuss more in
130 detail about some **additional** choices, which should be carefully done upstream of the process
131 development, to significantly improve the next intensification phase **for the production of C5 and C6**
132 **derivatives on a larger scale.**

134 **3. Choose strategic reaction components**

135 **3.1. About the starting biomass**

136 First of all, the efficiency of the hydrothermal-solvothermal processes can be improved
137 upstream, choosing a starting biomass feedstock with a suitable chemical composition, depending
138 on the chemical process to develop. Given the importance of the catalytic upgrading of C5 and C6
139 sugars, a promising biomass feedstock for the production of biofuels and bioproducts should have a
140 good content of carbohydrates and low recalcitrance to their conversion, which is favored by a low
141 lignin content [21-23]. Besides, biomasses of low-cost, low-input cultivation and wide availability on
142 the territory, should be preferred, even at laboratory investigation [24]. Lignocellulosic biomass
143 comprising of agricultural and forest residues (such as wheat straw, rice straw, rice husk, corn
144 stover, sugarcane bagasse) and energy crops, are extremely attractive for these purposes. Even more
145 so, at an advanced stage of process intensification, an economic analysis of biomass supply chains,
146 including collection, processing, and transport, is necessary for identifying the best plant locations

147 that balance economic, environmental, and social criteria, making all actors (farmers, investors,
148 industrial entrepreneurs, government) aware that success relies on agreement advances [25,26].
149 Flexible hydrothermal processes are advisable, allowing the use of different kinds of biomass, an
150 aspect of paramount importance taking into account their certain seasonality. Even waste biomasses,
151 such as food and cooked food wastes, can be effectively exploited to platform chemicals,
152 compensating for seasonality issues of the lignocellulosic biomasses [27]. Cellulosic waste materials
153 from the papermaking processes, which cannot be re-used for the production of the new paper, are
154 valuable feedstocks for the synthesis of bio-products, such as levulinic acid, thus saving the costs
155 deriving from their traditional disposal in landfills or from their use in waste-to-energy plants [28].
156 Hydrothermal treatment of sewage sludge is a promising strategy for sustainable management,
157 allowing its conversion into useful products, and simultaneously mitigating the environmental risks
158 [29]. In this case, besides the catalyst recovery issue, the recirculation of the liquid effluent within the
159 process could overcome the legal thresholds, such as COD and heavy metals [30,31]. These possible
160 drawbacks suggest that European and/or national legislation improvements are still necessary for
161 allowing the development of this process intensification [30,31].
162

163 *3.2. About the reaction medium*

164 The hydrothermal technology involves the use of water as the preferred green reaction solvent,
165 promoting the process sustainability, and shifting the attention towards the development of more
166 efficient and economical work-up strategies, such as solvent extraction, distillation and/or
167 membrane separations. Process intensification provides the combination of multiple process tasks or
168 equipment into a single unit and the development of material/energy integration, as occurs for the
169 production of furans, such as furfural [32] and 5-HMF [9] and organic acids [33], such as the
170 previously mentioned levulinic acid [34,35]. Subcritical water represents a promising reaction
171 medium for the successful biomass exploitation, due to its interesting physicochemical properties, at
172 the typical reaction conditions [36]. However, the replacement of water with an alcoholic solvent
173 should lead to bio-products of higher added-value, such as alkyl-glucosides/xylosides [37,38],
174 alkoxymethyl furfural [39], or the previously mentioned alkyllevulinates [40]. To improve the poor
175 solubility of biomass in water and organic solvents, ionic liquids, and deep eutectic solvents can be
176 effectively used, exploiting their high solvation capacity towards the dissolution of carbohydrates,
177 lignin, even in the case of the raw biomass [41,42]. However, ionic liquids still suffer from several
178 disadvantages, having environmentally unfriendly aspects and requiring cost-intensive preparation
179 procedures, whilst deep eutectic solvents solve many of these disadvantages, in many cases being
180 green, environmental-friendly, and highly tunable. In particular, deep eutectic solvents have been
181 recently proposed not only for the pretreatment of biomass, mainly aimed at the delignification and
182 solubilization of the cellulose and the decrease of its crystallinity degree, but also for their further
183 conversion to added-value bio-chemicals [43]. Some noteworthy examples are cellulose modification
184 by acetylation [44], cationic [45], and anionic functionalization [46], the dehydration of C5 and C6
185 carbohydrates to furfural and 5-HMF, respectively [47], and cellulose oxidation to gluconic acid
186 [48]. However, despite the exciting performances, further research in this field is necessary, in
187 particular for improving the separation and the purification of these deep eutectic solvents, further
188 lowering their cost, and justifying their use on a larger-scale.
189

190 *3.3. About the catalyst*

191 Regarding the appropriate choice of the catalyst, it should be made after that of the biomass, and
192 properly tuned, based on the reaction of interest. For example, the acidity of the high-pressure
193 CO₂ can be advantageously exploited for biomass pre-treatment purposes, for improving the
194 biomass digestibility before enzymatic hydrolysis, or performing the hemicellulose fractionation by
195 mild autohydrolysis [49]. In both cases, cellulose and lignin components remain almost unaltered in
196 the solid phase, which could be further fractionated and up-graded [49]. The use of CO₂ as an acid
197 catalyst for biomass pre-treatments is certainly attractive, thanks to its non-toxicity, low-cost, and
198 ready availability, but its acidity is generally insufficient to perform harsher acid conversion routes,

199 which require the use of stronger acid catalysts. From a practical and environmental perspective, it is
200 imperative to develop heterogeneous catalysts that are hydrothermally stable at the process
201 conditions. In this context, much work has been done, testing synthesized metal-based catalysts on
202 many transformations of C5 and C6 carbohydrates involving the breakage of the C-O bonds for the
203 synthesis of biofuels and bio-products, such as isomerization, dehydration, aldol condensation,
204 ketonization and hydrogenation [50,51]. Based on our experience, Nb-based catalysts are particularly
205 promising for many of these purposes, showing excellent water-tolerance, low-cost, easy synthesis,
206 tunable compositions, good acid properties (acid types, amount and strength), and promising
207 surface properties (specific surface areas, pore size, and volume) [52]. However, despite the
208 numerous advances in the development of efficient heterogeneous catalysts, these often suffer from
209 uninspiring performances due to mass transfer issues, deactivation due to coking and water
210 corrosion at the reaction conditions, clogging of the active pores, poisoning and recycling issues.
211 Consequently, even if new efficient catalysts are hourly synthesized and deeply characterized, their
212 use for the synthesis of base chemicals has been mostly limited to academic investigations. On the
213 other hand, the use of commercial catalysts, which are widely available and cheap, should be
214 preferred for faster development of the bio-product applications, focusing rather on the
215 improvement of other parameters related to the intensification process. The use of homogenous
216 catalysts generally greatly improves biomass accessibility, giving back a better product
217 yield/selectivity. For acid-catalyzed biomass conversion processes, the reactivity of a mineral
218 catalyst is related to several prominent factors, such as its strength and concentration, type/loading
219 of the biomass, and reaction conditions, in particular temperature and reaction time [36], and all
220 these parameters should be properly considered and tuned, preferably by multivariate optimization.
221 In the case of the levulinic acid production, the safety assessment due to the use of mineral acids
222 does not present significant risks [15], whilst the catalyst recovery, together with the
223 isolation/purification of the product(s), both with minimum energy input, still represent a
224 challenging topic [6,20]. For example, the recovery of the acid catalyst within the levulinic acid
225 process can be carried out by flash separation, if volatile hydrochloric acid is the chosen catalyst,
226 whilst organic solvent extraction is still preferred to separate the product from the high-boiling
227 sulfuric acid, which remains in the water solution, ready to be reprocessed [53]. Instead, regarding
228 product isolation/purification, atmospheric/vacuum distillation and steam stripping are adopted for
229 the separation of LA, which can be obtained with a final purity of about 95–97% [17]. However, the
230 high boiling point of levulinic acid is not energetically favorable for the distillation, and solvent
231 extraction could be a viable alternative, but the high amounts of solvent which need to be
232 evaporated make also this operation energy-intensive and costly [54]. Significant improvements are
233 still possible in the work-up procedures, which are decisive for further lowering the production
234 costs of these bio-products.

235

236 **4. Fractionate and exploit each biomass component**

237 *4.1 Selective biomass fractionation*

238 Another aspect to be improved for achieving the best process intensification is the selective
239 fractionation of the biomass in its components, by optimizing each step, in agreement with the
240 biorefinery concept [55]. For example, reactive furanic compounds, such as furfural, must be
241 produced and recovered upstream of integrated processes, through very mild pre-treatments, and
242 possibly applying the key concepts of the process intensification. In this context, Zangé *et al.* [56] have
243 proposed the biorefinery of the switchgrass biomass for the integrated production of furfural, lignin,
244 and ethanol. The chosen reaction system is composed of a biphasic solvent [choline chloride/methyl
245 isobutyl ketone], with the deep eutectic solvent which enables the fast hemicellulose
246 solubilization/conversion to furfural, which is simultaneously extracted by methyl isobutyl ketone.
247 Regarding the fate of the remaining fractions, cellulose is subsequently converted into ethanol by
248 enzymatic hydrolysis, whilst lignin is properly precipitated and recovered, for further added-value
249 applications. Despite the use of a biphasic system and the improvable extraction/purification of the

250 lignin fraction, the developed techno-economic analysis clarifies that the proposed biorefinery is still
251 cost-competitive and has a low-economic risk, with the reaction temperature and the solid loading
252 having the largest impacts on the minimum furfural selling price (estimated at 625 \$/t, in the best
253 case of study). Another interesting approach has been proposed by Rivas *et al.* [57], who studied the
254 hydrothermal conversion of eucalyptus (*Eucalyptus globulus*) to levulinic acid, the latter being further
255 upgraded to γ -valerolactone. In the perspective of developing an integrated approach, a mild
256 hydrothermal pretreatment was optimized upstream, which allowed the almost quantitative
257 solubilization of thermolabile extractives and hemicelluloses, recovering a cellulose-rich solid,
258 which was subjected to harsher hydrolysis to the desired levulinic acid.

259 4.2 Recovery/exploitation of by-products: new trends

261 About the lignin component, many biomass integrated biorefineries underestimate its
262 importance, considering it as a not particularly valuable by-product, more similar to a waste, rather
263 than a resource. In the hydrothermal process for levulinic acid production, lignin is recovered as the
264 main waste stream at the end of the process, being a carbonaceous solid residue, or hydrochar,
265 whilst simple phenols are solubilized in the liquid phase. Regarding the solid hydrochar, it can be
266 immediately used for energy recovery, which is generally impactful for these processes.
267 Alternatively, this hydrochar, which is rich in hydroxylic and carboxylic functionalities [58,59], can
268 be advantageously used to replace traditional fossil-based polyols, for example for the formulation
269 of flexible polyurethane foams [60], but also for applications as adsorbents, precursors of catalysts,
270 soil amendment, anaerobic digestion and composting, and energy storage materials [61]. On the
271 other hand, the solubilized phenols can be advantageously used as efficient antioxidants, as already
272 demonstrated in the case of the hydrothermal treatment of the *Arundo Donax* L. [62], and their
273 separation from the other compounds can be well-integrated with the available process
274 technologies. The new lignin exploitation strategies are generally carried out on the lignin solid
275 residue recovered from the hydrothermal process of levulinic acid, significantly improving the
276 overall process economy, which is already rewarded by the levulinic acid production, at the same
277 time minimizing the waste disposal.

278 On the other hand, the lignin recovery could be even more advantageous if carried out
279 upstream of the integrated biorefinery, as provided by the available organosolv pretreatments,
280 where an organic solvent is used to extract lignin in its native form [63]. High-purity
281 cellulose selectively remains in the solid phase, but it is more prone to the following step of
282 enzymatic/chemical hydrolysis, due to the increased contribution of its amorphous phase. Instead,
283 the extracted lignin can be precipitated from the liquid phase by water dilution and recovered as a
284 solid, while the hemicellulose fraction remains in the liquid stream, thus achieving an efficient
285 fractionation of the biomass in its components. Focusing on the lignin fate, this component is less
286 degraded, if compared with its downstream recovery, and therefore the “upstream” lignin is more
287 useful for the development of higher-value applications, such as the production of carbon materials,
288 vanillin and other oxidized compounds, phenolic antioxidants, bio-oil, BTX hydrocarbons,
289 urethanes, epoxy resins, fire retardants, sequestering agents, nanomaterials, energy storage device,
290 and many more [64]. The choice of “upstream” or “downstream” recovery of the different fractions
291 depends on the value of the primary target product, which should pay off the whole process, and the
292 possibility of obtaining economic surplus from secondary streams must be down-to-earth and
293 supported by feasibility studies.

294 Although hydrothermal/solvothermal reactions can be improved and optimized by choosing
295 appropriate reaction conditions and catalysts, some reaction by-products are inevitably formed. An
296 example of great interest is given by the furanic humins, which are condensation products of C5 and
297 C6 sources [65]. Their formation is particularly favored in the aqueous acid environment and under
298 harsh reaction conditions, like those which typically occur for the levulinic acid production, but also
299 for that of reactive furanic compounds from simple C5 and C6 sugars, e.g. furfural and 5-HMF,
300 respectively [66]. Instead, alcoholic solvents generally stabilize these soluble furans in the liquid
301 phase, minimizing the next humin formation, growth, and precipitation [67], and therefore

302 alcoholysis results more advantageous for improving the selectivity to the target product and the
303 final carbon balance. As a further complication, if real lignocellulosic biomass is chosen as the
304 starting feedstock for developing the conversion of interest, the resulting final solid hydrochar
305 should include both the degraded lignin (as “pseudo-lignin”) of biomass source and humins, the
306 latter being less important in the milder HTC processes [68]. All these by-products must be
307 considered as a resource rather than wastes of the process, and new exploitation strategies must be
308 developed, to lower further the minimum selling price of the main bio-product(s) of interest,
309 smartly completing the biomass biorefinery [69]. Up to now, the best-known applications of
310 carbonaceous hydrochar/humins include energy production [70] and environmental remediation
311 [71]. Besides, new possibilities have been recently proposed for the exploitation of humins, such as
312 the synthesis of new biomaterials [72-74], syngas [75] and carboxylic acids [76,77]. Most of these
313 applications have been developed by the Avantium Company [78], which produces 5-HMF on a
314 pilot scale and a new class of furanic building blocks, called YXY, to use as bioplastics and biofuels,
315 starting from first- and second-generation feedstocks [79]. Therefore, it is clear that the efficient and
316 diversified exploitation of the humins should improve the overall economy of their process. In our
317 opinion, particular attention should be given to the catalytic conversion of humins by
318 hydrotreatment, aimed at their liquefaction, depolymerization, and conversion into more valuable
319 liquid chemicals, such as furanics, aromatics, and phenolics. For this purpose, Wang *et al.* [80]
320 worked at 400 °C, using Ru/C as hydrotreatment catalyst, and formic acid in isopropanol as
321 hydrogen donor, aimed at the selective production of substituted alkyl phenolics and higher
322 oligomers, together with naphthalenes, and cyclic alkanes. Now, Sun *et al.* [81] have synthesized a
323 Ru/W-P-Si-O bifunctional catalyst, testing it for the hydrotreatment of humins to give cyclic and
324 aromatic hydrocarbons. The authors declare a high yield to cyclic hydrocarbons (up to 88.3%),
325 working at 340–380 °C, and exploiting the cooperative catalysis between the nano-Ru particles and
326 the strong Lewis acidity of the solid W-P-Si-O, the latter catalyzing the Diels–Alder reaction on the
327 furan rings.

328 In the context of the developable applications of hydrochar/humins, the synthesis of furanic
329 and carboxylic acid derivatives with catalysts directly developed from wastes and by-products of
330 the same hydrothermal/solvothermal processes represents a very hot topic, which should allow the
331 improvement of the process intensification, also applying the biorefinery concept and the zero waste
332 policies. Besides, the heterogenization of the catalyst should be certainly advantageous for these
333 processes, if the synthesized catalysts result performing, their precursors have a low-cost or, even
334 better, a negative value, and the related synthetic procedures are simple. Sulfonation of bio- and
335 hydro-chars deriving from thermal (e.g. pyrolysis) and hydrothermal processes fully meet these
336 requirements [82]. Their use for some intensified biomass conversion processes has been recently
337 proposed, including the synthesis of 5-HMF [83], furfural [84], levulinic acid [85], alkyl levulinates
338 [86] and other esters [87]. The available data for most of these mild reactions are promising and
339 certainly deserve further **research & development**.

340

341 **5. Prefer efficient heating systems**

342 In order to study and optimize these hydrothermal reactions, microwave heating is
343 certainly one of the best choices, being more rapid, energy-saving, and cleaner than the traditional
344 ones, thus suggesting that such new heating systems could lead to more compact factories in the
345 future [21]. In comparison with conventional heating, microwave irradiation has
346 remarkable advantages, such as fast heat-transfer and short reaction time, selective and uniform
347 volumetric heating performance, easy operation, high energy-efficiency, and reduced formation of
348 by-products, especially in the presence of highly reactive intermediates [88]. In addition to
349 microwaves, also ultrasound have been proposed for the development of more sustainable and
350 intensified biomass conversion strategies, advantageously exploiting their cavitation effects on
351 many reaction systems. Up to now, this heating technology has been mainly applied for performing
352 mild biomass pretreatments, aimed at the intensified recovery of reducing sugars [89-90], lipids [91],

353 lignin [92], also in combination with deep eutectic solvents [93], or ionic liquids [94], thus achieving a
354 more effective fractionation of the starting biomass in its components. The efficient utilization of both
355 microwave and ultrasound energy is expected to improve significantly the product yield, efficiency,
356 and environmental friendliness of biomass fractionation processes.
357

358 **6. Enhance the concentration of the target product**

359 Generally, hydrothermal processes benefit from the dilution of reagents, intermediates, and
360 products, achieving better control of the cross-reactions of the involved species, e.g. a higher
361 selectivity towards the target product. However, a low concentration of the target product would
362 cause too high separation costs in the work-up procedures and, for this reason, it is highly desirable
363 to enhance its final concentration in the reaction mixture, developing the *high-gravity* concept [95].
364 This goal can be partially achieved by increasing the loading of the starting feedstock, as the
365 solid/liquid ratio, which positively impacts on the environmental performances of the process [31].
366 However, this choice is not unconditionally beneficial beyond a certain biomass loading, favoring
367 the excessive occurrence of unwanted cross-reactions. For example, in the hydrothermal process for
368 the production of levulinic acid, the biomass loading is limited to 10–20 wt% [96], whilst a higher one
369 should give practical problems of liquid recovery and promote the excessive formation of undesired
370 solid humins [69]. On the other hand, lower biomass loadings should make the hydrothermal
371 processing economically unviable, due to the high capital investment, power consumption, and heat
372 loss. Therefore, achieving operational status with high solids loading is still a cumbersome task [97],
373 despite some practical solutions have been proposed, such as using the pre-hydrolyzed feedstock
374 and starch gels with cement pumps [98].

375 On this basis, it is crucial to tune properly both the catalytic performances (yield and selectivity)
376 and the final concentration of the target product, preferring the improvement of the latter. A smart
377 improvement of the product concentration could be achieved by performing sequential treatments of
378 recovered reaction mixtures with a new batch of feedstock. In the case of levulinic acid production,
379 this choice should allow achieving higher concentrations of this bio-product (~100 g/L) than those
380 obtained with only one batch experiment (<30 g/L) [96]. Also in this case, it is necessary to balance the
381 product concentration and yield, the latter worsening excessively at very high concentrations of
382 levulinic acid. As previously stated for the reactive furans, another smart solution provides the use of
383 a [water-organic solvent] biphasic system, which stabilizes the reactive intermediates in the liquid
384 phase, improving the next LA production [99] and, if the organic solvent results immiscible with
385 water, also allowing the LA simultaneous extraction [100]. Alternatively, also the use of an
386 uncommon biphasic system [water-paraffin oil] has been recently proposed, where the latter is used
387 as a non-solvent for the compound of interest. This approach allows the increase of the levulinic acid
388 concentration in the water phase, also in this case with concentrations higher than 100 g/L, leaving
389 enough liquid phase to sustain the processability of a high loading slurry but reducing the water
390 volume to be processed downstream. Therefore, the target product can be easily recovered from the
391 aqueous phase, whilst the organic non-solvent can be advantageously recycled and reused, given its
392 good thermochemical stability [101].
393

394 **7. Prefer cascade over stepwise reactions**

395 The synthesis of bio-products often involves multistep reactions, which can be carried out i) in a
396 stepwise manner, e.g. separating and purifying the product from the reaction mixture before
397 performing the subsequent reaction or, more advantageously, ii) in cascade, thus directly using the
398 intermediates deriving from the previous step to give subsequent reactions, without their further
399 isolation. The stepwise approach is widely used due to incompatible reaction conditions between
400 steps and poor catalytic specificity and selectivity of the catalysts. Instead, cascade reactions occur
401 directly, avoiding the isolation and purification of synthetic intermediates, and greatly simplifying
402 the operational procedure. One-pot cascade approach is advantageous related to atom economy,

403 process time, labor and resource management, and waste generation [102], but requires careful
404 tuning of the catalyst properties. Such an approach is particularly attractive when a high selectivity
405 to the target product is desired and, for this purpose, the development of multifunctional catalytic
406 systems, with well-tuned chemical properties, is essential. Moreover, a worsening of the final target
407 product yield may occur, depending on the number and complexity of the involved steps,
408 making this choice extremely attractive, especially when easy conversion steps are required. In this
409 context, a wide and very hot topic is the improvement of mild biomass conversion processes, by
410 developing new catalysts with bifunctional Brønsted/Lewis acid-base properties, which should be
411 tunable in character and strength [103]. Many noteworthy examples are available from the literature,
412 including the 5-HMF production through glucose to fructose isomerization, occurring over a solid
413 base/Lewis acid, and the subsequent fructose dehydration over Brønsted acid sites [104]; the
414 following levulinic acid production by harsher Brønsted acid-catalyzed hydrolysis of 5-HMF, but
415 preferably carried out in cascade approach, starting from carbohydrate precursors [105]; the
416 production of polyols or alkanes via hydrogenation of glucose to sorbitol over metal catalysts and
417 the subsequent hydrogenolysis over metal-acid bifunctional catalysts [106]; the production of
418 isosorbide from C6 carbohydrates via hydrogenation and dehydration, catalyzed by metal-promoted
419 solid acids [107]; the γ -valerolactone production from xylose via Brønsted acid catalysis coupled
420 with Lewis acid- or base-catalyzed Meerwein–Ponndorf–Verley hydrogen transfer, in the presence of
421 isopropanol as the hydrogen donor [108]; the synthesis of 2-methyltetrahydrofuran by
422 bimetallic-catalyzed hydrogenation of γ -valerolactone or, even better, levulinic acid [109]; the
423 condensation/oligomerization of C5/C6-derived bio-products to longer carbon-chain chemicals and
424 their oxygen removal to give liquid alkanes, by hydrogenation [110]. Considering the multiple
425 processes involved, issues of catalyst stability and economic feasibility remain essential priorities for
426 the next development of the process intensification.

427 8. Conclusions

428 Process intensification is a tool that can be very helpful for the development of low-cost
429 processes, with better use of physical spaces and low energy requirements. Chemical, technological,
430 economic, environmental, and regulatory questions have to be considered for improving the
431 solvothermal process intensification. Complete process integration is necessary to get significant cost
432 advantages, preferring the use of cheap and waste biomasses, direct conversion strategies,
433 preferably in cascade, improving the final concentration of the target product, rather than its yield
434 (however maintaining an appreciable yield), in the case of waste starting materials, and exploiting
435 more efficient heating systems, such as microwaves and/or sonication. The development of efficient
436 and cheap heterogeneous catalysts starting from low-cost or negative value precursors, preferably
437 wastes produced within the same biomass biorefinery, still requires further **research & development**,
438 whilst significant progress has been done on the design of multifunctional catalysts for performing
439 cascade reactions. Technological limitations due to the purification of the product/recovery of the
440 acid catalyst have been partially overcome and do not seem to limit the development of the
441 intensification of these processes shortly. On the other hand, environmental problems due to
442 wastewater treatments and legal restrictions of certain types of waste biomasses may slow down
443 their development. Besides, simultaneously with the optimization of the catalysis issue, other
444 strategic business drivers should be taken into account for evaluating the real feasibility of the
445 biomass conversion process, such as biomass transportation cost, agronomic parameters
446 (productivity on a dry basis, input degree), and plant production capacity, thus highlighting that an
447 interdisciplinary Life Cycle Sustainability Assessment should be carefully performed at an advanced
448 stage of process development. An accurate evaluation of project feasibility, capital and operating
449 costs, revenues, and profitability measures is imperative, thus helping to bridge the uncertainty
450 associated with a lack of data on investments on larger-scale plants.



451

452 **Figure 1.** Author Information (*DCCI: Department of Chemistry and Industrial Chemistry).453 **References**

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