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An Integrated Approach for the Production and Isolation of 5-Hydroxymethylfurfural from Carbohydrates

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In the near future, the world will need to gradually replace the use of fossil resources for energy consumption and platform chemicals with other resources.[1] For the energy issue, the ongoing approach is based mainly on a diversity of resources, such as nuclear, coal, hydraulic and wind power, photovoltaics, and biofuels. In the case of chemical platforms, probably the major resource will be based on a bioplatform either by intensive biotransformation processes or by functional transformation of existing biorenewable resources, for example, wood-derived materials such as cellulose, lignin, and other polysaccharides.

Among several building blocks derived from renewable resources (e.g., ethanol, glycerol, lactic acid, furfural,[2]) 5-hydroxymethylfurfural (HMF) has been identified as a very promising building block, being the starting point for different applications such as biofuels (dimethylfuran), polymer monomers (2,5-diformylfuran and 2,5-furandicarboxyllic acid), levulinic acid, and many other specific molecules,[3] for example, a shorter synthesis of the active pharmaceutical ingredient ranitidine (Zantac) reported recently.[4]

The most desirable route for the production of HMF involves widely available biorenewable resources such as cellulose and inulin. However, an efficient direct transformation of cellulose into HMF appears less feasible, mainly because of (1) the occurrence of side reactions (e.g., humin formation); (2) different reactivity pathways that require complementary catalysts, for example, glucose isomerization is more efficiently catalyzed by a base[2a, 5] whereas fructose dehydration is catalyzed by acids; and (3) experimental conditions that are not compatible with HMF, which is unstable.[3c] The most-often explored synthetic route is based on a multistep approach, comprising hydrolysis of cellulose to glucose, isomerization of glucose to fructose, and dehydration of fructose to HMF. Because the dehydration of fructose to HMF is less demanding, the one-pot transformation of glucose to HMF has also been intensely explored. The catalysts $CrCl_n$ ($n=2,3$) appears to be the best ones at the present stage, requiring temperatures above 100 °C.[3c, 6] For dehydration of fructose to HMF, a broader range of efficient catalysts has been reported. In general, homogeneous and heterogeneous mineral and organic acids are used, at temperatures ranging from RT to above 100 °C.[3c] In addition, the transformation is also possible in the absence of a catalyst. In these cases specific solvents, such as dimethyl sulfoxide (DMSO) and ionic liquids, are used to promote the reaction, although higher temperatures are generally required (up to 120 °C).[3c] Isolation of HMF from the reaction mixture is a very important issue due to the specific properties of HMF, such as (1) its high solubility in aqueous media and polar solvents; (2) its low vapor pressure (114–116 °C/1 mbar); (3) its low melting point (30–34 °C); and (4) its thermal and chemical instability. These factors complicate the large-scale isolation of HMF by solvent extraction, distillation, or crystallization. In fact, the majority of literature reports provide HMF conversion and/or yields based on HPLC, and to a lesser extent GLC, analysis of the reaction mixture, rather than isolated yields.[3c]

In the case of the best traditional organic solvent (i.e., DMSO), isolation requires partial distillation of HMF under vacuum followed by column chromatography.[3c, 7] For reaction media based on imidazolium,[8] choline,[9] and betaine[10] cations extractions with diethyl ether, ethyl acetate, or methyl isobutyl ketone have been reported, with continuous or repeated extraction required.[3c] It appears that currently, there is still no literature report on a combined methodology for the production and isolation of HMF that is applicable to large-scale production.

Because crystallization is one of the best separation processes to use industrially, we explored the possibility of using readily available, easily crystallized, and low-volatility solids as efficient reaction media, promoting the production of HMF under homogeneous conditions by melting of the reaction media and solubilization of carbohydrates at the temperature required for the reaction. Furthermore, after cooling, precipitation could occur at room temperature when using the appropriate organic solvent, allowing isolation of the HMF in the mother liquor just by evaporation of the organic solvent, which can then be reused (Scheme 1).

Considering that DMSO is one of the best solvents for the dehydration of fructose to HMF,[3c, 11] the use of other solid sulfoxides such as *p*-tolyl sulfoxide (m.p. 94–96 °C) in the presence of Amberlyst-15 as catalyst was explored. Under these conditions, 90 % of the *p*-tolyl sulfoxide could be recovered by crystallization. Unfortunately, the isolated yield of HMF was very low (28 %) compared to DMSO (70 %; see Table 1, entries 1 and 2; Supporting Information). Furthermore, purification by chro-

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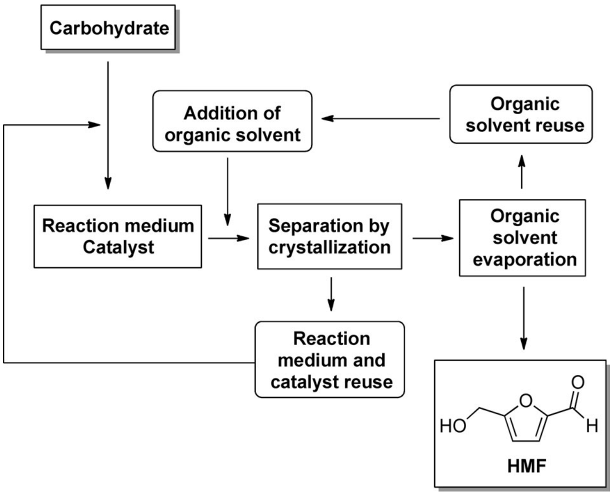

Scheme 1. Integrated approach for the production and isolation of HMF from carbohydrates.

matography was still required to afford HMF in high purity (94%).

Based on literature precedents describing the efficient use of imidazolium-based cations (bearing in mind some concerns about instability) and choline-based eutetic mixtures, we then explored the potential of ammonium salts as reaction media.[7] Interestingly, tetrapropylammonium bromide (TPAB) and tetraethylammonium bromide (TEAB) provided outstanding results (91%) in reactions catalyzed by Amberlyst-15 (10% (*w/w*) at 100 °C (Table 1, entries 6 and 7). In the course of this study, a report on the use of tetraethylammonium chloride (TEAC) as efficient promoter and/or reaction medium for the conversion of fructose and glucose to HMF appeared in the literature.[12]

In the absence of catalyst, the fructose dehydration also occurred, although more slowly and at a higher temperature (110 °C; see Table 1, entries 3–5). Further optimization showed that the use of 10–15% (*w/w*) Amberlyst-15 and the presence of small amounts of water (10–15%) were important to achieve a very clean transformation (entries 6–8).[7] In addition, an initial preheating (10 min, from 80 to 100 °C) proved desirable to achieve higher yields (91% and quantitative) of HMF and outstanding purity (97 and 99%), using TEAB containing 10% water in 1:5 and 1:10 fructose/TEAB (*w/w*), respectively. HMF was isolated by crystallization of the reaction medium, first dissolving the reaction mixture in a minimum amount of hot ethanol (EtOH) followed by the addition of ethyl acetate (EtOAc), filtration, and evaporation of the ethanol–ethyl acetate solvent system (entries 7 and 11). The TEAB salt is more appropriate for the integrated process because crystallization is easier and also because it is commercially available at a moderate price (15 € kg^{-}).[13] This transformation has already been reproduced more than 50 times under different conditions (see the Supporting Information) and in a scale-up to 20 g of fructose (100 g of TEAB) by different researchers, providing an average yield of 93% and outstanding purity (98%, entry 10). In addition, in an experiment using 20 g of fructose, the reaction medium and the catalyst were efficiently reused, providing comparable results (Table 2).

Furthermore, excellent recycling results were obtained when using a 1:10, instead of 1:5, fructose/TEAB ratio (*w/w*, 2 g scale), providing high isolated yields (94% overall yield) and purity (> 96%) over six cycles (Table 2). During the 7th cycle an

Table 1. Reaction media for the preparation of HMF from fructose.

Entry	Fructose [g]	Reaction medium[a]	Water [%] (*w/w*)	Fructose/ medium (*w/w*)	Catalyst [%] (*w/w*)	*T* [°C]	*t* [min]	Isolated yield [%]	Purity[b] [%]
1	6	DMSO	–	1:37	6.7	120	150	70	98
2	1	*p*-tolyl sulfoxide	–	1:3	10	120	120	28	94
3	1	TPAB	–[c]	1:5		110[d]	60	37	99
							90	71	99
4	1	TEAB	14[e]	1:5		110[d]	30	79	–[f]
5	1	TPAB	3[g]	1:5		100	30	77	98
6	2	TPAB^{-}	–[c]	1:5	10	100[h]	15	91	70
7	2	TEAB	10[i]	1:5	5	100[h]	15	71	96
					10			91	97
					15			90	95
8	2	TEAB	5[i]	1:5	10	100[h]	15	80	77
			15[i]					71	98
9	5	TEAB	10[i]	1:20	10	100[h]	15	29	99
					20			57	99
10	20	TEAB	10[i]	1:5	10	100[h]	15	92	98
								94[j]	97[j]
								92[j]	98[j]
11	10	TEAB	10[i]	1:10	10	100[h]	15	97	99
	2							100	99

[a] DMSO: dimethyl sulfoxide, TEAB: tetraethylammonium bromide, TPAB: tetrapropylammonium bromide. [b] Determined by HPLC. [c] Used commercial sample of ammonium salt. [d] With preheating from 80 to 110 °C for 12 min. [e] Old (> 15 years) and wet (average water content of 14% *w/w*) TEAB sample. [f] Pure HMF isolated by TLC. [g] Used commercial sample of ammonium salt followed by addition of water. [h] Preheating from 80 °C to 100 °C for 10 min. [i] Determined by Karl Fisher on the commercial sample followed by addition of water. [j] Repetition of the experiment by another researcher.

Table 2. Catalyst and reaction medium reuse in the preparation of HMF from fructose.[a]

Cycle	Fructose/TEAB (1:5), catalyst (15 %)		Fructose/TEAB (1:10), catalyst (10 %)	
	yield [%][b]	purity [%][c]	yield [%][b]	purity [%][c]
1	92	98	98	99
2	86	97	95	99
3	93	93	94	99
4	64	91	91	99
5			89	99
6			97	96
7			63	95
8[d]			123 (93)[e]	94

[a] All experiments were performed by adding fructose (commercial grade from supermarket) and Amberlyst-15 to TEAB containing 10 % of water (*w/w*) and heated for 10 min from 80 to 100 °C, followed by another 15 min at 100 °C. [b] Isolated yield. [c] Purity of HMF determined by HPLC. [d] The recovered TEAB was purified and fresh Amberlyst-15 (10 %) was added. [e] Combined yield of the 7th and 8th cycles.

erosion on the reaction performance was observed (63 % yield); however, after reloading of the catalyst an isolated yield of 123 % was obtained. This corresponds to an overall yield of 93 % for the combined 7th and 8th cycles, due to transformation in the 8th cycle of fructose accumulated in the previous cycle.

The continuous transformation of fructose to HMF was also explored by passing fructose dissolved in TEAB containing 25 % of water (*w/w*) through Amberlyst-15 (3.5 g) supported in a glass tube reactor (developed in house) at 100 °C. For the different experimental conditions tested so far, yields in the range of 81–90 % and purities of 91–97 % were obtained (Table 3).[7]

Table 3. Continuous preparation of HMF from fructose.[a]

Entry	Fructose/TEAB ratio (*w/w*)	Flow [mL min^{-1}]	Yield[b] [%]	Purity[c] [%]
1	1:20	0.3	90	91
2	1:20	0.9	90	97
3	1:15	0.9	91	93
4	1:10	0.9	85	92

[a] All experiments were performed by continuously passing 1 g of fructose in TEAB containing 25 % (*w/w*) of water, through a glass reactor containing Amberlyst-15 (3.5 g) heated at 100 °C. [b] Isolated yield. [c] Purity of HMF determined by HPLC.

This integrated process was also explored for the direct transformation of glucose, inulin, and sucrose to HMF, using some catalysts already reported for this transformation. All catalysts tested so far under non-optimized conditions showed that the transformation occurred in moderate isolated yields, although in high purity (Table 4).

In conclusion, we describe an integrated, simple, efficient, reusable, and scalable method for the transformation of carbohydrates (mainly fructose) into HMF that overcomes a major obstacle in the large-scale production of HMF: its isolation and purification. Simple crystallization (precipitation) of the reaction medium (TEAB) by using renewable solvents such as ethanol and ethyl acetate followed by solvent evaporation provides HMF in excellent yields and purity without any further purification. The method also provides opportunities for the discovery of more efficient catalytic systems that may allow the direct conversion of glucose, or ultimately cellulose, to HMF under conditions that can be more easily transferred to large-scale production processes.

Table 4. Preparation of HMF in TEAB starting from other carbohydrates.[a]

Entry	Carbohydrate	Catalyst	Catalyst amount [%] (*w/w*)	Yield[b] [%]	Purity[c] [%]
1	sucrose	Amberlyst-15	10	32	90
2	inulin	Amberlyst-15	10	55	98
3	glucose	PMA	10	15	87
4	glucose	boric acid	34	26	85
5	glucose	$CrCl_3 \cdot 6H_2O$	3	35	82

[a] All experiments were performed in a 2.0 g scale of carbohydrate and TEAB containing 10 % of water (*w/w*) and a carbohydrate/TEAB ratio of 1:5 (*w/w*) and catalyst, and heated within 10 min from 80 to 100 °C, followed by another 15 min at 100 °C. For the boric acid reaction, 100 °C was applied for 60 min instead of 15 min. For PMA, the mixture was heated from 80 to 100 °C within 10 min, followed by 100 °C for 15 min and 120 °C for 20 min. [b] Isolated yield. [c] Purity of HMF determined by HPLC. [d] PMA: phosphomolibdic acid.

Experimental Section

Batch experiments were performed by adding fructose (commercial grade, purchased locally) and catalyst (Amberlyst-15, unless stated otherwise) to the reaction medium (TEAB, unless stated otherwise) and heating in an open flask for 10 min, from 80 °C to 100 °C, followed by an additional 15 min at 100 °C. Continuous experiments were performed by continuously passing 1 g of fructose in TEAB containing 25 % (*w/w*) of water through a glass reactor containing Amberlyst-15 (3.5 g) heated at 100 °C. Isolation of HMF was performed by dissolution of the reaction mixture in ethanol followed by precipitation with ethyl acetate, filtration, and removal of ammonium salt traces by filtration with silica. HMF purity was determined by HPLC.

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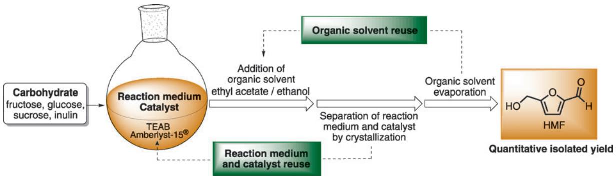

Crystal clear: An integrated, simple, efficient, reusable, and scalable methodology for the dehydration of fructose to HMF offers outstanding yields and high purities. The method uses wet tetraethylammonium bromide as reaction medium, allowing the isolation of HMF by crystallization from the reaction medium. The process is also feasible starting from other carbohydrates, such as glucose, sucrose, or inulin.

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