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Direct Diels–Alder reactions of furfural derivatives with maleimides†

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The Diels–Alder (DA) reaction of furans is a versatile tool in synthetic organic chemistry and in the production of sustainable building blocks and smart materials. Numerous experimental and theoretical investigations suggest that the diene scope is effectively limited to electron-rich furans, which excludes the most abundant and readily accessible renewable derivatives: furfural and its 5-hydroxymethyl homologue. Herein we show for the first time that electron-poor 2-formylfurans can also directly engage in Diels–Alder couplings. The key to success is the use of aqueous medium, which supplies an additional thermodynamic driving force by coupling the unfavorable DA equilibrium to the exergonic hydration of the carbonyl functionality in the adducts to form geminal diols. This finding enables the direct access to various novel DA adducts derived from renewable furfurals and maleimides, *via* a mild, simple and environmentally-friendly synthetic protocol.

Introduction

The Diels–Alder (DA) reaction of furan dienes towards 7-oxanorbornenes is an old yet powerful tool in organic chemistry, with applications ranging from natural product synthesis and renewable chemical commodities production to drug discovery and materials science.[1] The reaction generally proceeds chemoselectively under mild conditions, often without the need for a catalyst. Depending on the furan/dienophile combination, yields may be low, however, as reactions may be kinetically slow or suffer from thermodynamic equilibrium limitations; moreover, the DA adduct is often quite labile, leading to facile cyclo-reversion back to the addends.

As far as kinetics is concerned, it is well known that the substitution pattern of the furan diene strongly modulates reactivity. In line with the general Frontier Molecular Orbital (FMO) theory of [4 + 2] cycloadditions, numerous studies have shown that furans bearing electron-donating groups (*e.g.* H, Me, OMe, CH_2OH, *etc.*) display good kinetics, while electron-poor furans (*e.g.* with CH=O or COOR) are too sluggish, inactive substrates.[2]

Predicting the thermodynamics of such furan DA cycloadditions is much less straightforward. Being typically moderately exothermic and entropically disfavored, the Gibbs free energy of these reactions is generally in the order of only a few kJ mol^{-1}. Thus, small changes in operating parameters (pressure, temperature, concentration, solvent) have a profound impact on the position of the DA equilibrium. Various strategies have been employed to overcome unfavorable thermodynamics (neat conditions, excess reactants, selective crystallization, elevated pressures, coupling with secondary reactions, *etc.*).

The solutions offered are generally quite case-specific, however, and small changes made in operating conditions to improve thermodynamics can adversely affect kinetics, and *vice versa*. For instance, in case of sluggish conversions, heating may improve kinetics but will negatively impact thermodynamics, since $\Delta S^\circ < 0$. In addition, small changes in the addends structure often impact the DA equilibrium in an intricate manner as well. For example, furan reacts faster with maleic anhydride than with maleimide, but the reaction with the latter is more exergonic.[3] Similarly, methylated furans react more readily with itaconic anhydride than furan itself, but the equilibrium conversion is highest with the latter.[4] Thus, the interplay between kinetics and thermodynamics in furan DA reactions is often rather subtle, making it challenging to understand, control and optimize them.

Currently, synthetic applications of furan DA chemistry are dominated by electron-rich dienes such as furan itself, furfuryl

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alcohol and 2,5-dimethyl furan. To the best of our knowledge, no examples of direct DA reactions involving furfural (2-furan carboxaldehyde) or its homologue 5-hydroxymethylfurfural (5-HMF) have yet been reported; moreover, indirect strategies relying on redox-neutral chemical activation (acetalization,[5] hydrazone formation[6]) are also scarce. That these substrates are not part of the current furan DA toolbox is unfortunate, as these are in fact the most readily accessible furans (and precursors to most other derivatives).[7] Furthermore, having a reactive formyl handle on the DA product offers many opportunities for further synthetic upgrading. The current mismatch between furan diene availability, synthetic potential and reactivity in DA reactions is particularly pressing in the context of the production of biobased chemicals, *e.g.* high-value oxygenates such as phthalic anhydride and terephthalic acid.[8] This field would greatly benefit from expansion of the furan diene scope beyond the ubiquitous methylated derivatives that give high yields for the DA reaction itself, but nevertheless show a low atom-, step- and redox-economy and thus poor sustainability for the overall process starting from the biomass resource (Scheme 1).[9]

Acknowledging this major limitation in scope, we decided to take a closer look at the feasibility of employing furfural as diene. Using prototypical, reactive maleimide dienophiles, we chose to study the DA reaction in water as reaction medium, as water is well-known to improve both the kinetics and thermodynamics of other DA reactions[10] *via* the hydrophobic effect.[11] Furfural has a fairly high solubility in water, which would not only make an 'in-water'-type activation mechanism feasible,[10c] but also allows for concentrated solutions, anticipated to be favorable for both the reaction rate and the equilibrium.

Results and discussion

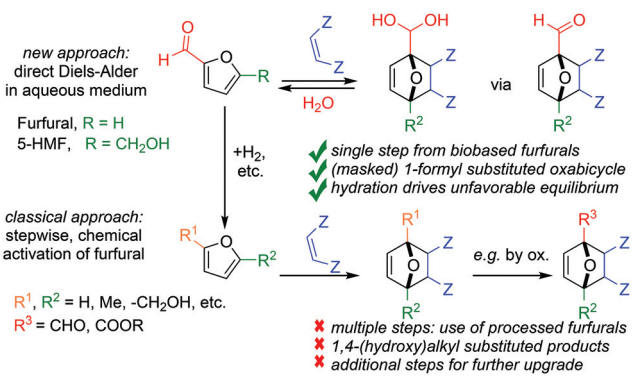
Reaction optimization

The first experiments between furfural **1a** and *N*-methyl maleimide **2a** in concentrated aqueous solution demonstrated the clean formation of DA adducts **3a** (with a modest *exo* : *endo* selectivity of approx. 2 : 1). Intriguingly, the ^{1}H-NMR spectrum of the crude reaction indicated that the adducts were exclusively present in the geminal diol form. This peculiar structural feature proved highly advantageous in downstream processing, as unreacted starting materials could be easily washed away with organic solvents leaving the DA adduct in the aqueous phase in essentially pure form (Fig. 1). Subsequent optimization experiments (see ESI for details†) showed that the highest yields (60–65%) could be obtained in concentrated aqueous solution (2 M), at 60 °C, and in the absence of catalysts or additives. 5-HMF (**1b**) could also be cleanly reacted to its DA adducts, again giving only the geminal diol product and allowing product purification by simple extraction.

The typical kinetic profiles of a reversible DA reaction were obtained, with stereoselectivity for the thermodynamically-preferred *exo*-isomer gradually increasing in time (Fig. 2).[12] Conversion of **1a** reached equilibrium within 60 h, at which point the *exo*-**3a** : *endo*-**3a** ratio was approx. 5 : 1. The nearly identical profiles of total adduct yield and furfural conversion highlight the reaction's high chemoselectivity. For dienophile **2a**, hydrolysis to maleic acid occurred to a very limited extent (typically 1–2% in 16 h). The chemoselectivity for 5-HMF **1b** was similarly high, but the *endo* isomer was still the major product after 60 h.[13,14]

Reaction scope

With the optimal conditions in hand, the substrate scope was further explored (Table 1). The title reaction between furfural **1a** and *N*-methyl maleimide **2a** afforded 58% total yield of



Scheme 1 A new approach to direct Diels–Alder reaction of biobased formyl-functionalized furans.

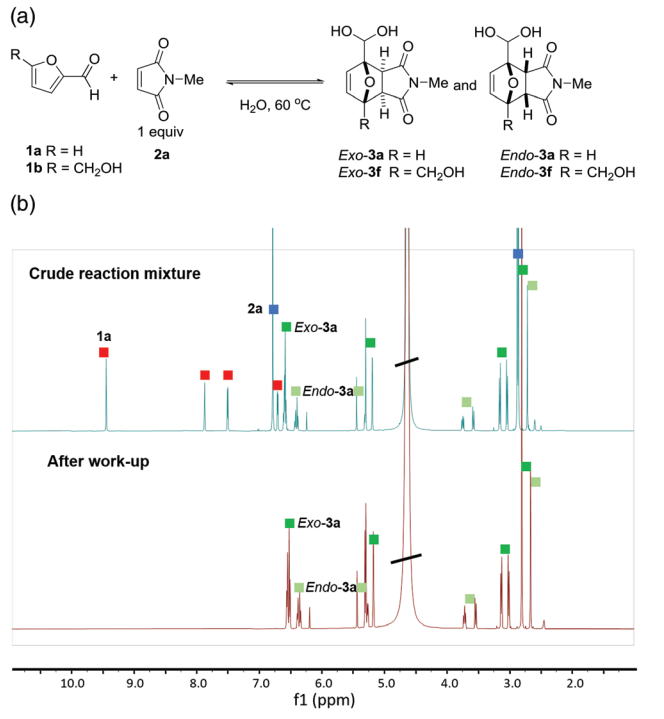


Fig. 1 (a) First examples of the direct DA cycloaddition of formyl-substituted furans furfural **1a** and 5-HMF **1b** (with maleimide **2a**). (b) The DA adducts can be readily purified by extractive work-up, as exemplified by **3a**. ^{1}H-NMR spectrum: crude reaction mixture (above); purified adducts **3a** (below).

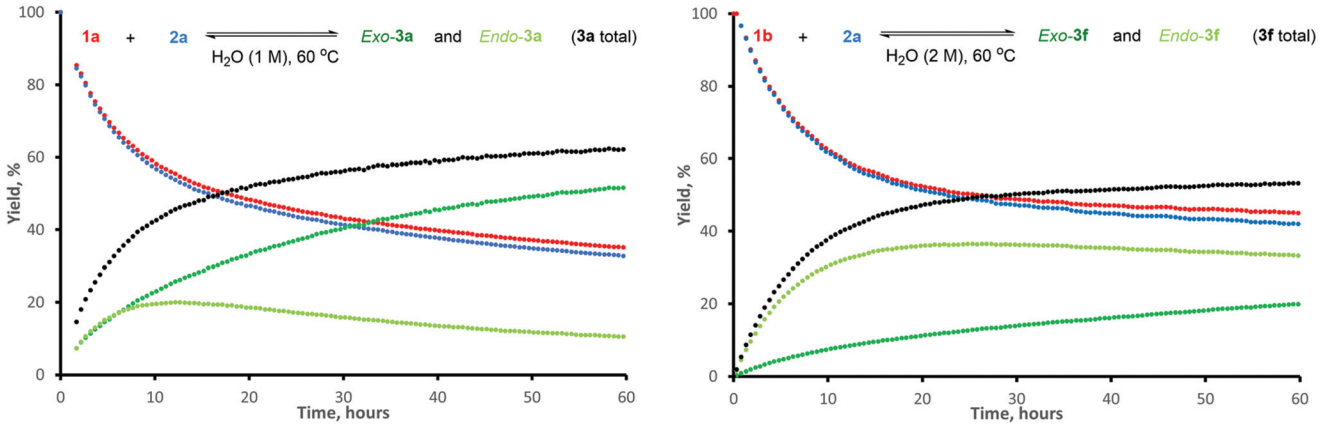
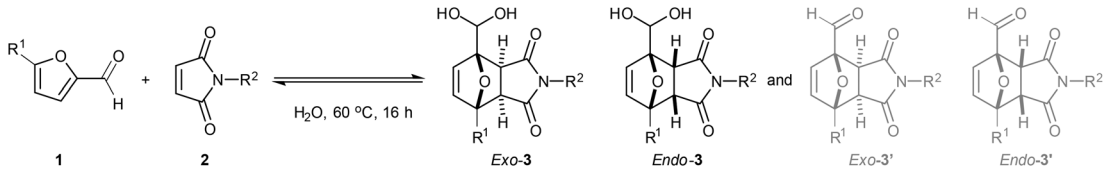


Fig. 2 Kinetic traces for the reaction between: furfural (**1a**) and *N*-methyl maleimide (**2a**), left; 5-HMF (**1b**) and *N*-methyl maleimide (**2a**), right.

Table 1 Influence of furan and maleimide structural features on the Diels–Alder reaction



No	Product	Furan	R^1	Maleimide	R^2	Recovery **1**[a], %	*exo*-**3**, %	*endo*-**3**, %	Total aqueous, %	*exo*-**3′**, %	*endo*-**3′**, %	Total organic, %
1	**3a**	**1a**	H	**2a**	Me	37	40	18	58	3	1	4
2[b]	**3a**	**1a**	H	**2a**	Me	38	35	16	51	5	1	6
3[c]	**3a**	**1a**	H	**2a**	Me	38	34	18	52	4	2	6
4[d]	**3b**	**1a**	H	**2b**	H	53	30	8	38	0	0	0
5	**3c**	**1a**	H	**2c**	Et	48	28	8	36	6	1	7
6[e]	**3d**	**1a**	H	**2d**	*n*Pr	70	7	1	8	11	1	12
7[e,f]	**3e**	**1a**	H	**2e**	Ph	81	1	0	1	5	1	6
8	**3f**	**1b**	CH_2OH	**2a**	Me	51	13	37	50	0	0	0
9[f]	**3g**	**1c**	CH_2OMe	**2a**	Me	67	5	7	12	3	3	6
10[f]	**3h**	**1d**	Me	**2a**	Me	80	8	3	11	3	0	3
11[e]	**3i**	**1e**	Br	**2a**	Me	70	5	12	17	1	9[g]	10
12[f]	**3j**	**1f**	CHO	**2a**	Me	97	2[h]	5[h]	7	0	0	0
13[f]	**3k**	**1g**	COOH	**2a**	Me	94	4	1	5	0	0	0
14[e]	**3l**	**1h**	H[i]	**2a**	Me	61	0	0	0	32[j]	Trace	0

[a] Recovery of **1** and yields of **3** and **3′** were determined by ^{1}H-NMR analysis of the crude reaction mixture with external standard, after extractive work-up. [b] 70 mmol scale. [c] 10 mmol scale with recycled **1** and **2**. [d] Minor amount of unidentified side products observed. [e] Biphasic reaction mixture. [f] DMSO used as cosolvent; reaction mixtures were biphasic in the absence of cosolvent. [g] Mainly present in the hydrated form **3i**. [h] Products were bis-geminal diols. [i] 2-Acetylfuran was used as diene. [j] Isolated yield (silicagel chromatography) and crude yield were identical.

adducts on a 4 mmol scale; promisingly, scaling-up to 70 mmol proved successful (entry 2) as well as the recycling of recovered unreacted starting materials (entry 3). Free maleimide **2b** also worked, giving only a slightly lower conversion and chemoselectivity (entry 4). The reaction still performed well with *N*-ethyl maleimide, but higher homologues (*N*-Pr, *N*-Ph) showed reduced conversion and yields, as a result of their lower aqueous solubility. Noteworthy, these more lipophilic adducts showed an increased preference for dehydration of the geminal diol back to the aldehyde **3′** and partitioning to the organic phase (entry 4 *vs.* 1, 5 and 6).

Next, we studied the performance of 5-substituted furfurals as dienes. 5-HMF **1b** afforded a 50% yield of cycloadducts **3f** (mainly *endo*, entry 8), considerably higher than the methylated derivative **1c** (18% total yield). 5-Methylfurfural **1d** showed a lower conversion, possibly due to less favorable thermodynamics[4] or lower aqueous miscibility (entry 10), as did the bromo derivative **1e** (entry 11). Remarkably, the presence of a second electron withdrawing-substituent (CH═O, entry 12 and COOH, entry 13) still allowed for DA adduct formation, albeit in a very small amount; notably, the adducts of 2,5-diformylfuran **1f** were found to be symmetric bis-geminal diols. Finally, 2-acetylfuran **1h** also proved a suitable diene, giving 32% of *exo*-**3′l**. Interestingly, the geminal diol was not formed in this case.

Illustrative of the sensitivity of the DA reaction to small structural changes, no DA adducts could be detected upon variation

of the dienophile, as neither acrylonitrile, maleic acid, fumaric acid, acetylenedicarboxylic acid or 4-cyclopentene-1,3-dione were found to react with furfural under these conditions. Presumably, in the case of the first three dienophiles, the HOMO–LUMO gap is too large for the reaction to occur with a noticeable rate at 60 °C.[15] For the latter two, dienophile stability was an issue, given the tarry, insoluble product observed after reaction.

Follow-up chemistry

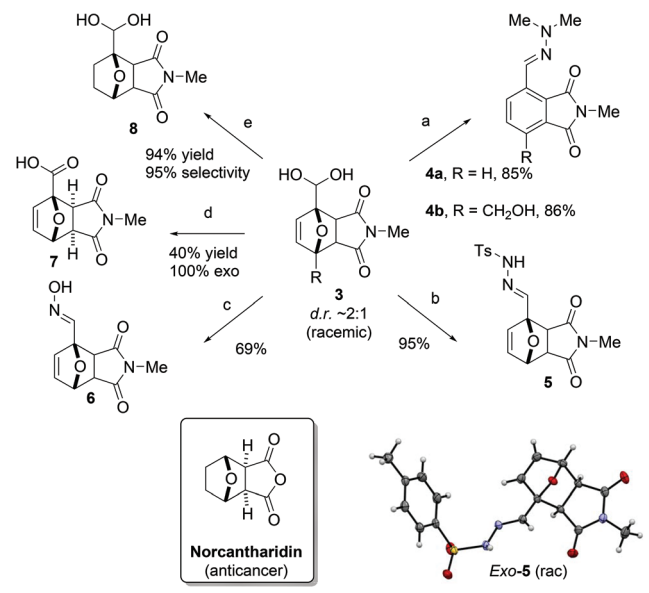
The geminal diol in adduct **3** is an unusual,[16] but versatile functional group for further conversion towards value-added molecules (Scheme 2). Additions of *N*-based nucleophiles to the (masked) carbonyl proceeded readily and the insoluble products were conveniently isolated by filtration. Notably, with *N*,*N*-dimethylhydrazine, spontaneous dehydration resulted in aromatization, as reported in related chemistry.[6] Varying the hydrazine allowed for the tosyl hydrazone to be prepared in excellent yield and a single crystal X-ray diffraction analysis of (racemic) *exo*-**5** provided unambiguous diastereochemistry assignment. The oxime of adduct **3a** was isolated in 69% yield. Next, the geminal diol **3a** could be subjected to a Pinnick-type oxidation,[17] leading to the selective precipitation of the major *exo*-**7** isomer. Finally, careful hydrogenation of the alkene moiety in **3**, a strategy previously developed to stabilize DA adducts,[18] gave **8** with minimal overreduction of the diol to the primary alcohol.

These results demonstrate some of the many downstream chemical diversification options offered by the now more highly substituted 7-oxabicyclo[2.2.1]heptane motif. This scaffold is encountered in natural products[1f,i] and bioactive molecules (*e.g.* norcantharidin and its amide/imide derivatives)[19] and can be readily upgraded into complex synthetic targets.[20] Thus, our novel DA coupling between furfurals and maleimides provides a valuable expansion of the organic chemist's toolbox. In addition, the approach may inspire the development of novel DA-based routes towards renewable building blocks, *e.g.* high-value biobased aromatics, directly from the most readily accessible oxygenated furanics.

Noteworthy, all furfural-derived DA adducts synthesized herein are novel compounds. Our two-stage aqueous protocol is simple, environmentally-friendly and allows for the facile recycling of unreacted starting materials; moreover, high-purity products can be easily obtained without the need for chromatography. Importantly, the aqueous cycloaddition route is superior to alternative reaction sequences: control experiments showed that other furfural derivatives such as the tosyl hydrazone and the oxime are poor dienes in coupling with **2a**.

Mechanistic studies

In these unexpectedly efficient DA reactions, water plays a critical role both as a solvent and as a reactant in geminal diol formation. Two different pathways may account for the formation of the geminal diol adducts **3**, depending on whether aldehyde hydration occurs prior or subsequent to DA coupling. Density functional theory (DFT) calculations at the PBE0-D3(SMD (water))/6-311+G(d) level of theory suggests that the two pathways have similar overall activation barriers and are thus kinetically indistinguishable (see Fig. 3 and ESI for details†). Hydration of furfural significantly increases its reactivity as



Scheme 2 Follow-up chemistry starting with adduct **3a**. Reagents and conditions: a. Me_2N-NH_2, rt; b. TsNH-NH_2, rt; c. $(NH_3OH)Cl$, NaOH, rt; d. $NaClO_2$, H_2O_2, KH_2PO_4, rt. e. H_2, Pd/C, rt.

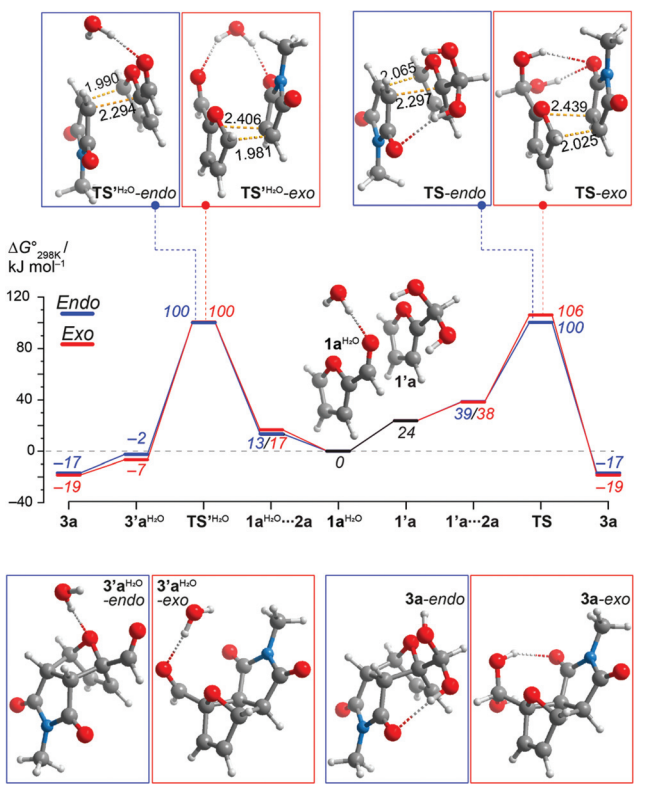


Fig. 3 DFT-computed Gibbs free energy diagram for the reaction between furfural **1a** and maleimide **2a** in water, with hydration prior to (right hand side) or after (left) DA addition.

diene (>20 kJ mol^{-1} reduction in the $\Delta G^{\ddagger}$ for cycloaddition), as the strongly electron-withdrawing formyl substituent is converted into a weakly electron-donating bis-hydroxyalkyl group. This effect can be compared to acetalization, which is known to enhance furfural reactivity towards dienophiles.[5] On the other hand, hydrated furfural (**1′a**) is a high-energy intermediate and is thus formed only to a very small extent in aqueous solution (indeed, we could not detect this species by ^{1}H-NMR). Most likely, less than 1% of furfural is hydrated at equilibrium; for comparison, the p$K_{hydration}$ of benzaldehyde is 2.[21] The enhanced reactivity of **1′a** is thus canceled out by its low concentration. The overall kinetic barrier for this pathway (approx. 100 kJ mol^{-1}) is very similar to the $\Delta G^{\ddagger}$ of the direct Diels–Alder cycloaddition (**1a** + **2a** to form **3′a**) and in good accordance with prior DFT data for related systems.[2d,14] While the calculations did not show a discernable kinetic effect, they do showcase the impact of hydration on the thermodynamics of the overall process. The reaction **3′a** + H_2O to form **3a** provides a substantial thermodynamic drive (−12 to −15 kJ mol^{-1}) to an otherwise barely exergonic cycloaddition (ΔG° is −2 to −7 kJ mol^{-1}). These results suggest that it is not, as typically assumed, kinetics that hampers the desired DA reaction, but thermodynamics. This outcome is rather unusual, as reactivity (and the lack thereof) in furan cycloadditions is generally explained in terms of FMO theory-derived kinetic arguments.[22]

To the best of our knowledge, in nearly a century of DA chemistry, we here present the first direct observation and spectroscopic characterization of cycloadducts of furfural.[22] The crucial role of water is highlighted by the experimentally determined endergonic nature (K = 0.02 M^{-1} for *exo*-**3′a** formation at 60 °C) of the reaction between **1a** and **2a** when run neat or in organic solvents (see ESI†). Intriguingly, attempts to isolate the free aldehyde **3′a** by column chromatography afforded the hydrated form **3a** instead. In aqueous solution, the extent of hydration of **3a** is >99% (by ^{1}H-NMR). Obviously, the adjacent electron-withdrawing ether group greatly enhances the electrophilicity of the carbonyl (*cf.*, degrees of hydration for 2-chloroisobutanal and isobutanal are 83% and 28%).[21,23] Thus, the fairly exergonic hydration of the primary Diels–Alder adducts **3′** in aqueous media provides the critical thermodynamic drive to shift the equilibrium to the product side. On the other hand, hydration seems not to be relevant in the case of 2-acetylfuran **1h** as substrate (for comparison, acetone is <1% hydrated in aqueous solution[21]): both in aqueous media and under neat conditions, adduct **3′l** is formed exclusively in the carbonyl form (at comparable conversion). This observation indicates that physical interactions involving water (hydrogen bonding, hydrophobic effect) are of secondary importance in this system and the major role of water is to pull the equilibrium to the product side by chemically trapping the adducts **3′**.

Conclusions

This work demonstrates the successful use of unfunctionalized furfural derivatives as dienes in Diels–Alder cycloadditions. Thus, a variety of novel DA adducts could be readily obtained following an aqueous protocol in line with the principles of green chemistry. In addition, our mechanistic investigation implies that the well-known limitations of Diels–Alder chemistry with furfural and other related electron-poor furans are of thermodynamic rather than kinetic nature and can be circumvented. The new insights provided can guide further efforts in the development of new chemistry for these oxygenated, electron-poor furans, *e.g.* to allow the more sustainable valorization of the key biobased platform molecules furfural and 5-HMF. Studies on the expansion of the scope of this method in terms of substrates, nucleophilic solvent use (see ESI for preliminary results†) and downstream conversion are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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