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Bio-based chemicals: 1,2,4-benzenetriol, selective deuteration and dimerization to bifunctional aromatic compounds

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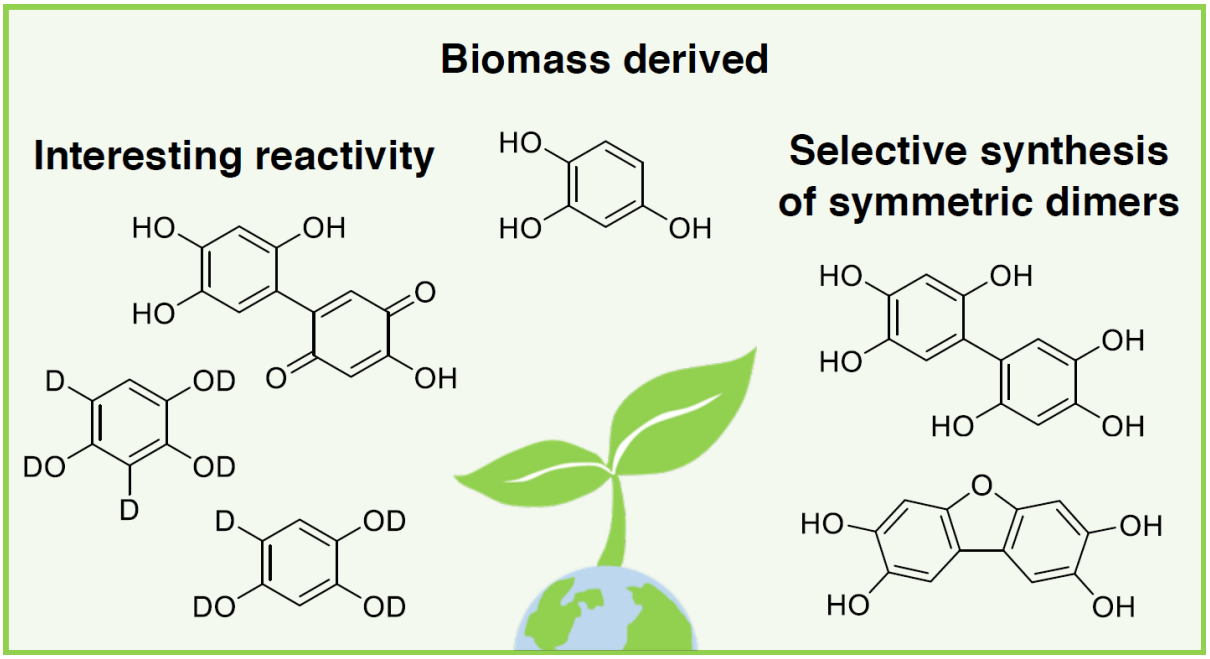
Biomass derived
Interesting reactivity
Selective synthesis of symmetric dimers
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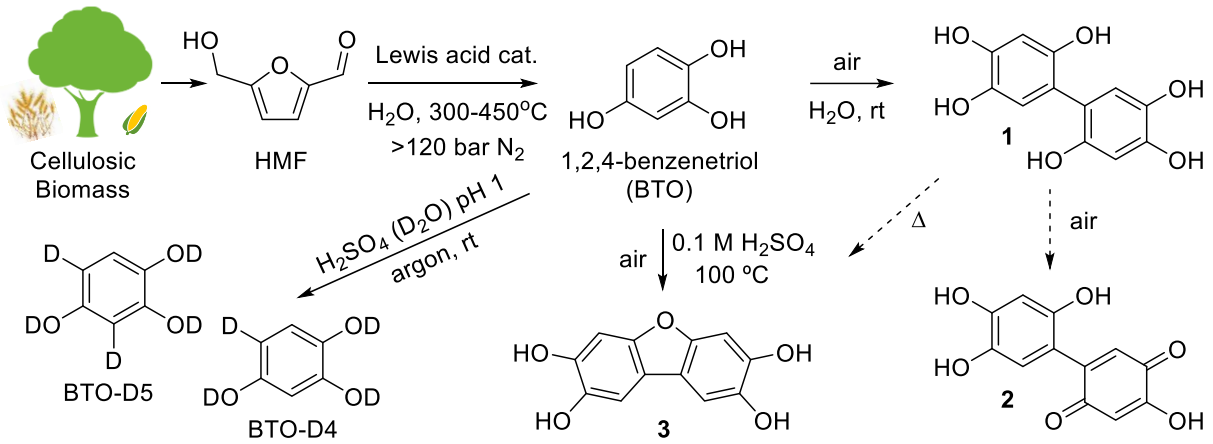
Keywords: Bio-based chemicals, dimerization, hydroxybenzenes, deuteration, hydroxy-quinone

Abstract: 1,2,4-benzenetriol (BTO), sourced from the carbohydrate derived platform chemical 5-hydroxylmethylfurfural (HMF), is an interesting starting point for the synthesis of various bio-based aromatic products. However, BTO readily undergoes dimerization and other reactions at mild conditions, making analysis and isolation challenging. In order to both control and utilize the reactivity of BTO to produce bio-based building blocks, its reactivity needs to be better understood. Here, it was found that specific BTO aromatic C-H bonds are reactive towards deuterium exchange with D_2O, which appears pronounced under acidic conditions at room temperature and can lead to selective formation of BTO with an aromatic ring that contains one or two deuterium atoms, the first at the 5 and the second at the 3 position. By exposure to air it was shown that BTO forms a 5,5'-linked BTO dimer [1,1'-biphenyl]-2,2',4,4',5,5'-hexaol (**1**) and subsequently a hydroxyquinone containing dimeric structure 2',4,4',5'-tetrahydroxy-[1,1'-biphenyl]-2,5-dione (**2**). Additionally, condensed dimer dibenzo[b,d]furan-2,3,7,8-tetraol (**3**) can be relatively easily accessed. The controlled formation of these symmetric and asymmetric multifunctional dimers illustrates diverse possibilities for BTO to be converted to valuable bio-based aromatic compounds. Deuterium exchange was attributed to electrophilic aromatic substitution since this reactivity was found to be independent of oxygen and acid mediated. On the other hand the dimerization was dependent on the presence of oxygen and thus likely involves radical intermediates. Thus, this report overall displays different accessible reaction pathways for BTO that can be exploited for the production of BTO derived compounds.

Introduction

Many valuable chemicals are derived from finite fossil resources and thus useful renewable alternatives are needed to create a sustainable chemical industry. Therefore, the production of renewable chemicals from lignocellulosic biomass such as wood and crop residues is of major interest.[1] A significant role has been allocated to 5-hydroxymethylfurfural (HMF), a renewable platform chemical that can be obtained in good yields from carbohydrates and can be converted into many interesting chemicals, like levulinic acid, adipic acid, 1,6-hexanediol, caprolactam, caprolactone, and a number of furanic compounds.[2] The production of C6-aromatic compounds from HMF is also of high interest.[3] Recently, we have shown that HMF under aqueous (sub)supercritical conditions in the presence of Lewis acidic metal salts can be converted to 1,2,4-benzenetriol (BTO, Scheme 1).[4] Historically, BTO was identified as an undesired side product in many reactions that involve HMF as product or starting material, especially under hydrothermal conditions.[5] However, there are only a limited number of reports that target the production of BTO from HMF.[4,6] This is also partly due to its reported instability, hindering adequate product analysis.[5a,c] Our initial findings showed that the main reaction pathway for BTO is symmetric dimerization to give [1,1'-biphenyl]-2,2',4,4',5,5'-hexaol (**1**) which occurs readily at room temperature when exposed to air (Scheme 1).[4]



Scheme 1. Overview of previously reported formation of BTO[4] and subsequent BTO chemistry discussed in this work.

In addition to the formation of **1,** we here report further oxidation of **1** to a hydroxyquinone containing dimer 2',4,4',5'-tetrahydroxy-[1,1'-biphenyl]-2,5-dione (**2**, Scheme 1). Also discussed is the synthesis of the condensed dibenzo[b,d]furan-2,3,7,8-tetraol dimer (**3**), which is a rigid symmetric dimer of BTO. In particular the symmetric BTO dimers are interesting as these provide a canvas for symmetric modification and di-functionalization to obtain bifunctional molecules with potential use as building blocks for polymeric products. Additionally, during these studies the selective deuteration of the aromatic C-H's of BTO with D_2O at room temperature was explored which was readily achieved under acidic conditions to obtain BTO-D4 and BTO-D5.

Results and Discussion

Dimer **1** forms from BTO under aerobic conditions in water (Scheme 1).[4] A crystal structure was obtained, confirming the C-C bridged structure on the 5 position of both BTO molecules

involved in the reaction, confirming previously suggested structures.[7] Under mild conditions the formation of **1** is relatively slow, but since the product tends to precipitate or crystallize from water, this can hamper accurate analysis of solutions containing BTO.[4,5c] The formation of **1** and other dimers and oligomers is associated with significant darkening of the clear BTO solution as illustrated by the UV-vis spectra of the isolated compounds (Figure S1). For the purpose of controlling the reaction of BTO to **1,** we aimed to study its reactivity under varying conditions in order to either prevent or promote its formation.

Initial studies on the dimerization of BTO were performed in a range of conditions (acid, base, air, light) in D_2O by following the reactions in time using NMR with an internal standard (Figure 1a). From these experiments the effect of temperature, and the addition of acids and base was evident. All of these were found to increase the rate of BTO conversion significantly compared to BTO conversion at room temperature and neutral pH. Analysis by mass spectroscopy (ES^+) showed that under the acidic conditions and increased temperature **1** is the major product, whilst basic conditions promoted the formation of a range of products including **1**, trimers and possibly higher oligomers (Figure S2).

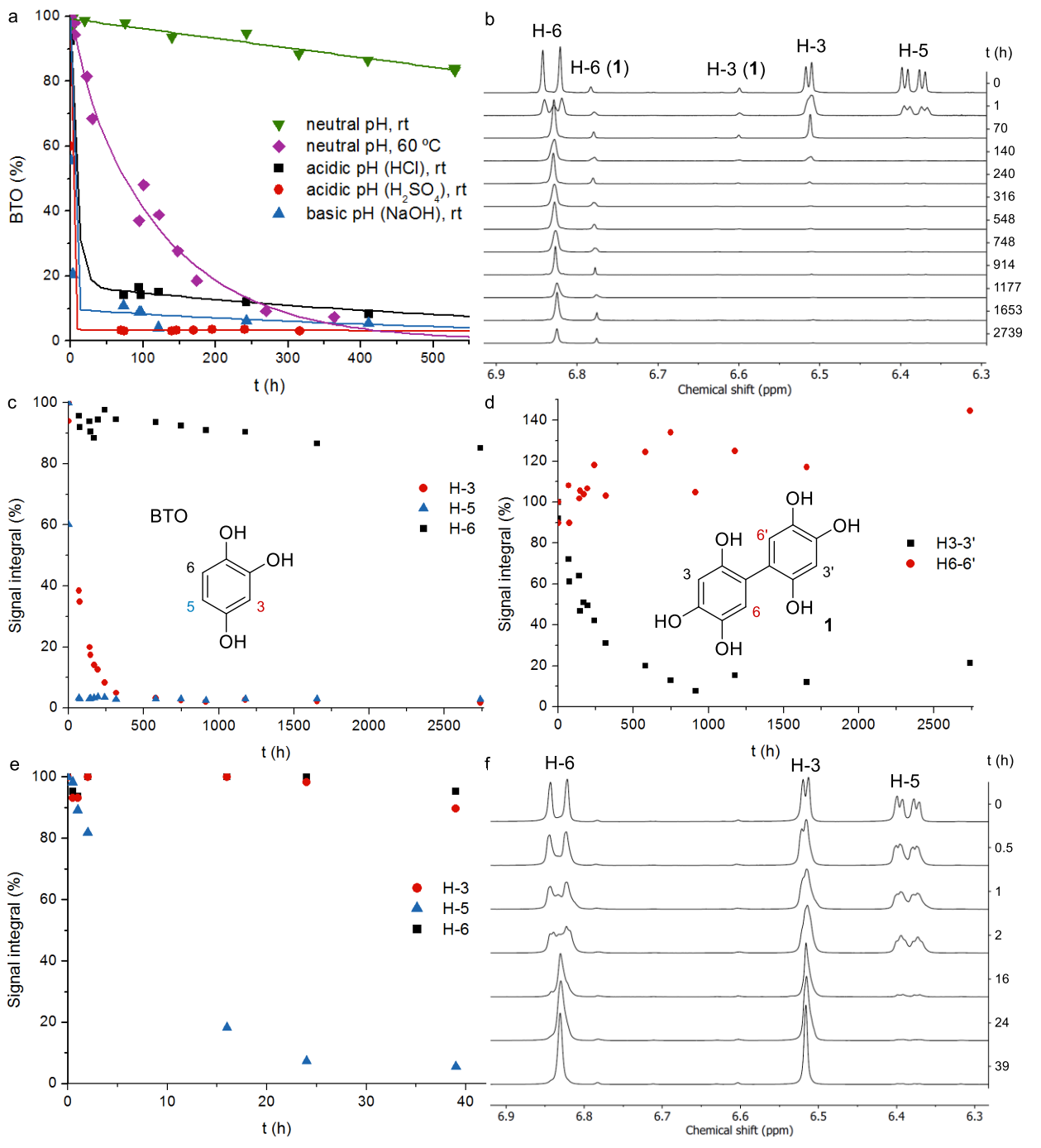
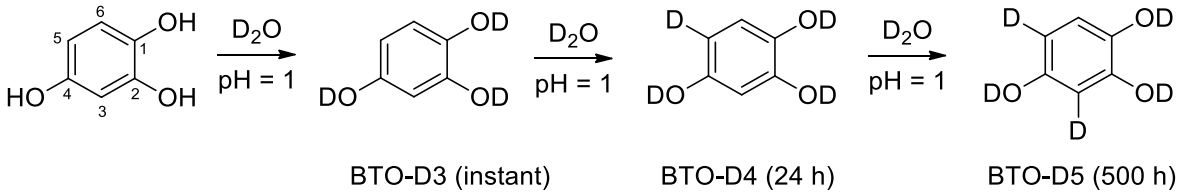


Figure 1. a) Decomposition of BTO (TCI) in D_2O (0.125 M) as a function of time under different conditions (acidic: pH 1, basic: pH 10) monitored by ^{1}H-NMR via the signal of the 5-Ar-H compared to an internal standard (for illustration lines are added obtained through fitting a second order exponential decay). b) Series of ^{1}H-NMR spectra of BTO in acidic (H_2SO_4) D_2O.

c) Relative decrease of different signal integrals compared to integrals at t_0 for different aromatic protons of BTO and d) for **1**. e) Repeat of spectra series of BTO (Aldrich) in acid (H_2SO_4) and D_2O at short time-scale. f) Relative decrease of different signal integrals compared to integrals at t_0 for different aromatic protons of BTO at shorter time-scale.

While following these reactions in D_2O by NMR a unexpected phenomenon was observed which did effect analysis of BTO conversion to its dimer **1**, namely deuterium exchange of BTO's aromatic C-H's to generate BTO-D4 and BTO-D5 (Scheme 2). This is in addition to the expected exchange at the Ar-OH signals which instantly generates BTO-D3. This could clearly be observed by tracking the ratios of the Ar-H signals that started fluctuating in time even before significant formation of the dimer **1**. This is represented in Figure 1b by the change in intensity of the different signals of BTO as shown by NMR monitoring over an extended time period. When the integrals of the Ar-H signals are individually monitored against the internal standard Figure 1c is obtained showing the different rates of signal-loss associated with deuteration for BTO. The signal for the 5-Ar-H (δ 6.40 ppm, dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.8 Hz) decreased relatively rapidly under acidic conditions, already seeing a significant decrease after 1 h. By the time the subsequent sample was taken, after 70 h, the signal 5-Ar-H had already almost completely disappeared, transforming the doublets for the protons at the 6 and 3 positions (δ 6.84 ppm, d, $^3J_{HH}$ = 8.7 Hz and δ 6.53 ppm, $^4J_{HH}$ = 2.8 Hz respectively) to singlets by loss of coupling to the neighboring hydrogen. These singlets were also relatively broad due to H-D coupling. This indicated that at this stage BTO-D4 was nearly exclusively present in solution. The singlet for the 3-Ar-H of BTO decreased compared to the 6-Ar-H over time. After 500 h, this signal had also completely disappeared, showing the selective formation of BTO-D5. The

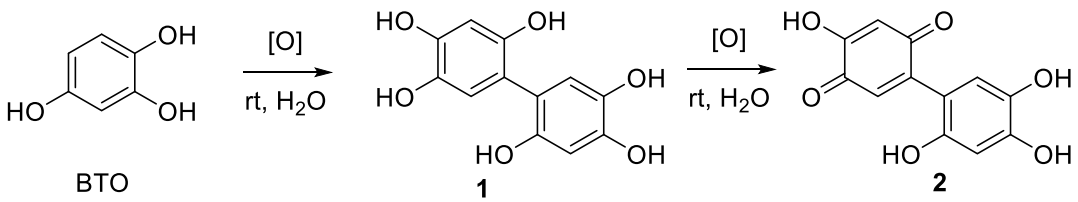
signal of 6-Ar-H also weakened in time compared to the internal standard, however this is more likely associated with the formation of **1**, which could be shown by an increase of the respective signal for H6 and H6' (δ 6.80 ppm, s). The deuterium exchange was also visible for the 3 and 3' position of **1** (δ 6.62 ppm, s), with a clear decrease of this signal in time compared to the H6-6' signal. The deuteration of the 3 and 5 position of BTO could also be observed when a ^{2}H-NMR spectrum was recorded (Figure S3). In a separate experiment it was determined that the deuterium exchange at 5 position is actually completed after 24 h and thus relatively fast (Figure 1e and 1f). This reaction is remarkable as it involves selective deuterium exchange of aromatic C-H's at room temperature in acidic D_2O and was even observed at neutral pH in D_2O. Such reactions are typically only reported under more forcing conditions by for example application of strong bases and acids, elevated temperatures or transition metal catalysts.[8]



Scheme 2. Selective sequential deuteration of BTO.

Further experiments to investigate BTO reactivity were conducted in non-deuterated water to avoid deuterium exchange effects aiming to specifically investigate the formation of dimer **1** (Scheme 3)**.** This compound is clearly identified in the ^{1}H-NMR spectrum in DMSO-d6 by the proton signals of the 3-Ar-H and 6-Ar-H at δ 6.33 and δ 6.51 ppm respectively and is already present in small amounts in most commercial samples of BTO (SI section 1). In order to demonstrate the stability of BTO solutions upon exclusion of oxygen, an experiment was set-up

at 400 mg scale and monitored in time, whilst alongside comparable experiments were performed where the solution was left to stand exposed to air with and without exclusion of light. Samples were taken and subsequently analyzed by NMR over a time period of 5000 h by removal of the solvent from the collected aliquot and solvation of the dried material in DMSO-d6. BTO and **1** were quantified using average integration of all Ar-H signals against dimethyl sulfone, which was used as internal standard (Figure 2). The reaction in the absence of air did indeed show that BTO is completely stable for at least 5 months when stored under exclusion of air (Figure 2a, Figure S5). No further formation of the 5,5-dimer **1** was observed apart from the 5,5'-dimer **1** that already appeared to be present in the commercial sample used in this study (Figure S10). When a solution with the same concentration of BTO was exposed to air and monitored a completely different picture arose (Figure 2b, Figure 3). Complete conversion of BTO is observed after nearly three months. Here BTO is converted into its 5-5'-linked dimer **1**. A similar reactivity pattern was observed for BTO that was excluded from light and left to stand in air (Figure 2c, Figure S6). This demonstrated that exposure to air is the sole requirement for the conversion BTO at room temperature and only protection from light is not effective for longer storage of BTO solutions.



Scheme 3. Formation of the 5-5' linked BTO dimer **1** under exposure to air.

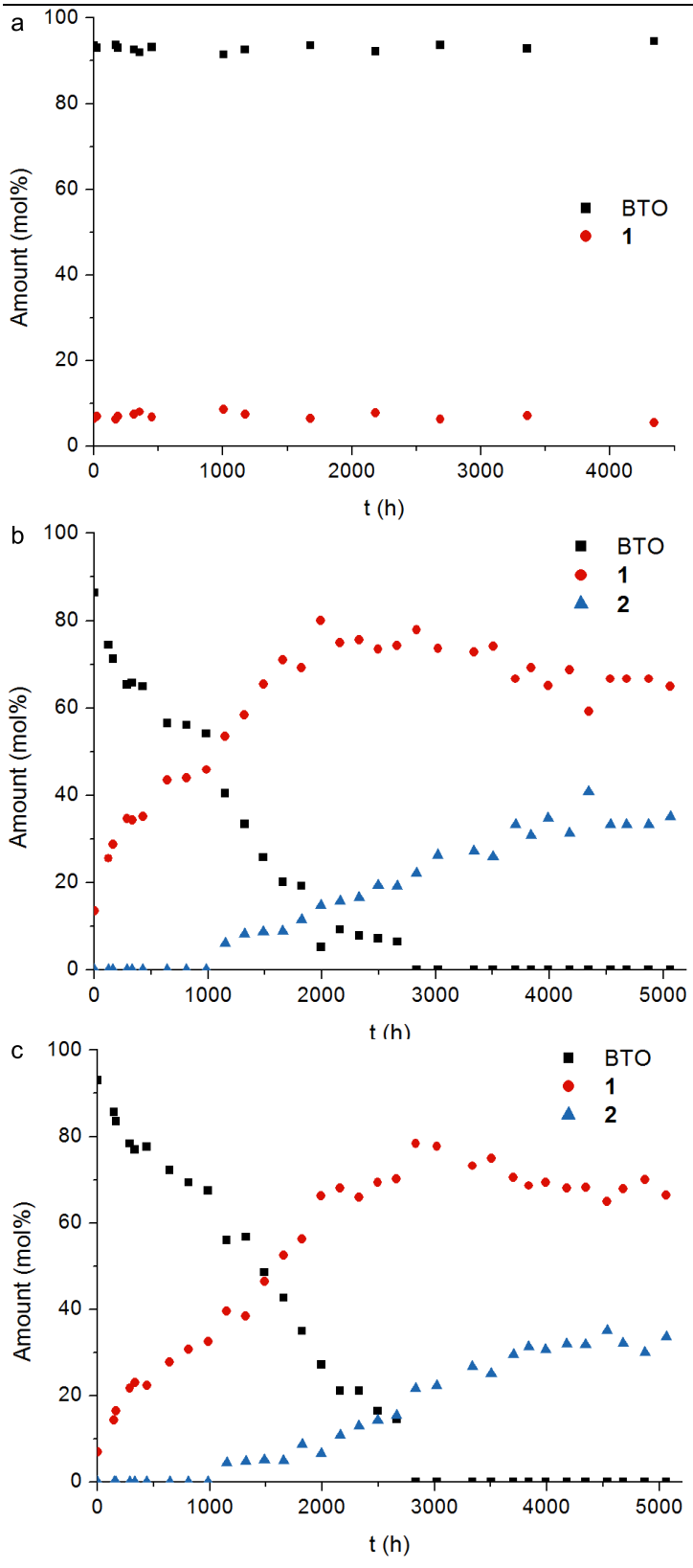


Figure 2. Aqueous BTO stability and dimer formation in time. a) Under exclusion of air. b)

open to air. c) open to air with exclusion of light (160 mM initial BTO concentration, monitored by ^{1}H-NMR by using dimethyl sulfone as internal standard. Note: after the levels of **1** became relatively high (>40%) precipitate could be clearly observed. Before sampling some effort was taken to solubilize this precipitate using sonication, but the formation of some precipitate as well as different efficiency at solubilizing the material could be the reason for the fluctuations sometimes observed in these graphs.

The dimerization of BTO was shown not to be completely selective toward **1**. Interestingly, at long exposure to air (1000+ h) an additional set of signals appeared in the ^{1}H-NMR (signals **C** in Figure 3), which did not correlate to oligomeric BTO structures earlier observed under stronger oxidative or basic conditions.[4] These signals were assigned to a hydroxyquinone containing dimeric structure **2** (scheme 3). Based on the reaction profile, **2** seemed to form from **1** over time. The structural characterization was performed by NMR analysis of **2** in a mixture containing **1** (Figure S16-18). The ^{1}H-NMR showed 4 singlets in and the absence of J-coupling partners, which indicates hydrogens in para-positions. The ^{13}C-NMR displayed 12 carbon signals including two in the region above δ 180 ppm indicating carbonyls. Overall, the number of signals in ^{1}H-NMR and ^{13}C-NMR suggested an asymmetric structural version of **1**. HMBC-NMR (Figure 4) analysis on a sample obtained after 5982 h helped to verify the hydroquinone-dimer structure of **2** by showing that the carbonyls are located on the same ring. The NMR signals of the hydroxyquinone part of **2** were comparable to those reported for other substituted hydroxyquinones found in literature, supporting the proposed structure.[9] The remaining set of signals were similar to those of **1**. The formation of **2** was suggested in literature from the 1960's but never confirmed.[10] Oxidation leading to other (hydroxy)quinones has been reported in

literature for related structures, including BTO.[7,11] Additionally, hydroxyquinones are known intermediates in the biodegradation of phenolic compounds.[12]

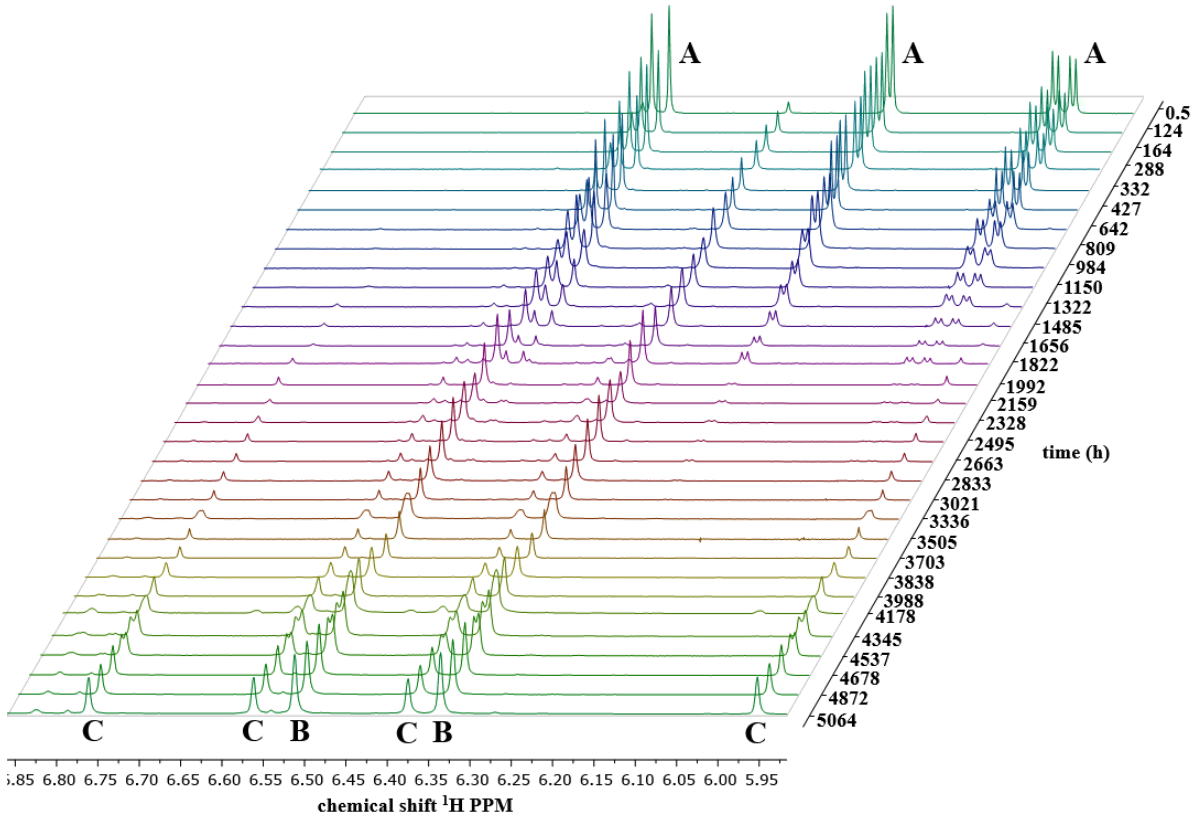


Figure 3. Series of ^{1}H-NMR spectrums in dmso-d6 obtained by sampling an aqueous BTO solution in time. **A**: 1,2,4-benzenetriol (BTO); **B**: dimer **1**; **C**: hydroquinone dimer **2**. This spectrum series was used to generate Figure 2b.

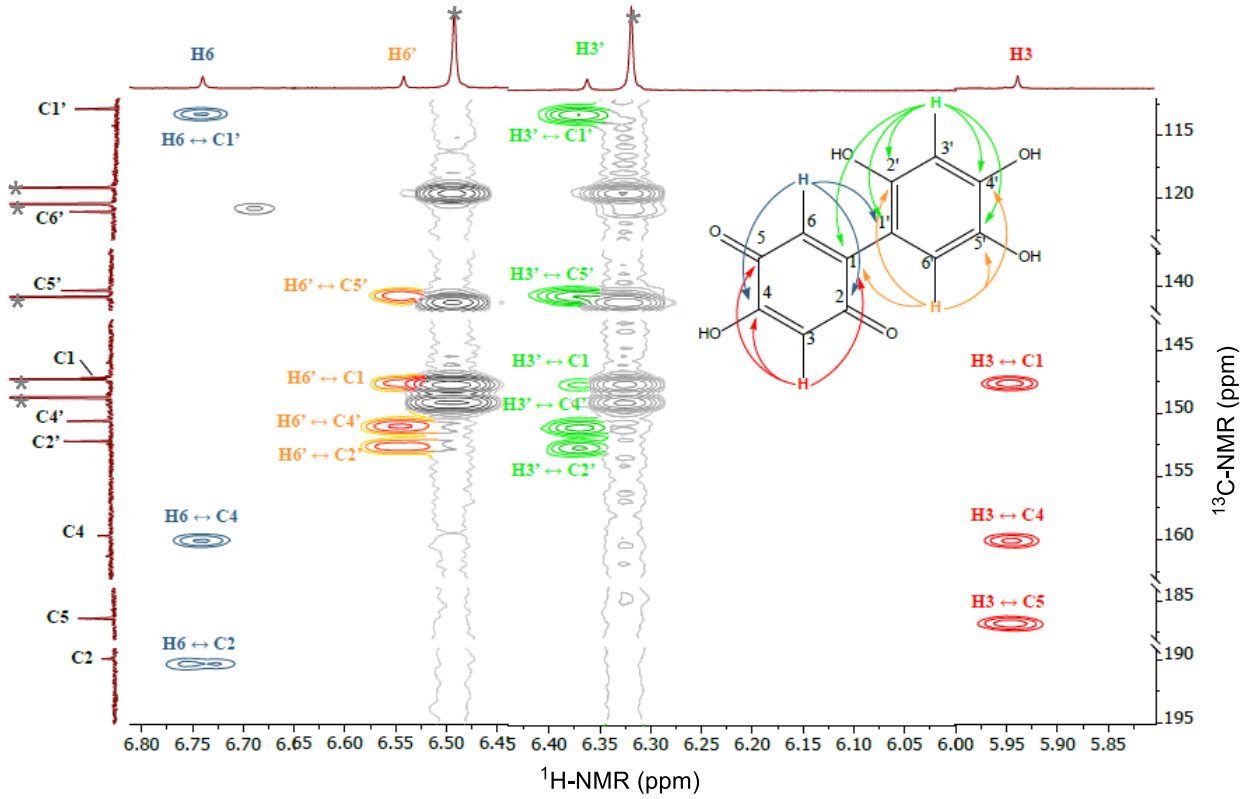
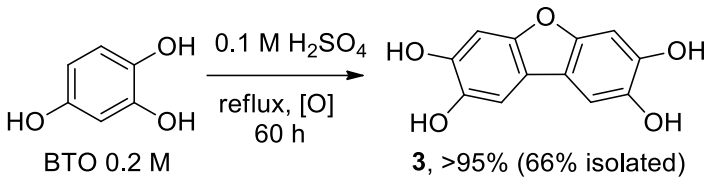


Figure 4: Selected area of the HMBC-NMR spectrum in dmso-d6 of a sample (after 5982 hours) containing the hydroxyquinone motif containing dimer **2** (Grey signals labeled with * belong to the 5,5'-BTO dimer **1**).

The formation of the dimeric structure **1** from BTO by exposure to oxygen was initially identified as a undesired degradation pathway that can hamper accurate analysis. Nevertheless, due to the symmetric functionalized nature of **1**, it can also be viewed as an interesting starting material for polymeric materials and other applications. As previously discussed, the formation of **1** was slow at room temperature, taking 2000+ h under neutral conditions to reach full conversion as evidenced by Figure 3. Therefore, we investigated more convenient conditions for the synthesis of **1**. It was already shown in the first section that increasing the temperature and addition of acid and bases did cause significant BTO conversion, although this was partly

obscured by deuterium exchange. Basic conditions afforded a range of side products, including oligomeric structures, and were thus deemed unsuitable. Different conditions using acids and increased temperature (up to 100 °C) significantly increased BTO conversion up to 70% in 20 h (Table S1). However, these reactions gave inconsistent results due to partial precipitation of products from the solution at different stages of the reaction, causing the formation of undesired side-products. Higher conversion of BTO to **1** could be achieved by performing the reaction without solvent. It was found that by melting BTO (mp = 140.5 ºC)[13] in aerobic conditions resulted in the rapid formation of dimer **1** in short reaction times (2 h). The obtained solid contained **1** in 80% purity with some unreacted BTO, which could readily be removed by subsequent washings with cold water. This fast synthesis technique is detailed in the SI Section 7. In general, it was found that although BTO conversion could be improved by prolonged reactions times or application of harsher conditions, this was at the expense of BTO to dimer **1** selectivity, due to the formation of side products like **2**, **3** (see below) and other oligomers. Low selectivity was highly undesirable, as dimer **1** was difficult to separate from such side products. However, the separation of **1** from BTO was straightforward, and thus running reactions at lower conversion with high selectivity was preferred. A mixture of BTO and **1** could be separated by addition of cold water and centrifugation to settle the dimer. This technique allowed one to obtain pure samples of **1** from mixtures of BTO and **1**. Nevertheless, due to low conversion, only 48% yield could be achieved in water, with 44% isolated yield of **1** (92% purity, NMR). Subsequently, **1** can be crystallized from a solution containing leftover BTO, however yields are low to moderate.

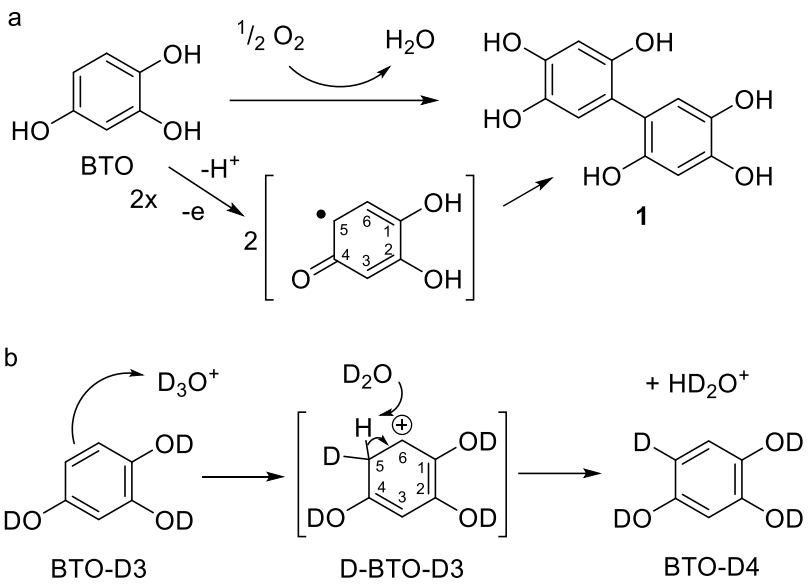
One interesting side product that was encountered from the attempts to form **1** in water was condensed dimer **3** (Scheme 4, Figure S19-22 for NMR spectra). This product was initially identified from an attempt to purify **1** by sublimation under high vacuum, in which small amounts of a pure condensed solid were identified as **3** (Figure S8). Thus, **3** can be formed from **1** by expelling water, as was suggested more than a century ago[14] but never confirmed by more advanced analytical techniques, such as NMR. Like **1**, **3** is obtained as a black solid and has significant absorption in the visible region in aqueous solution (Figure S1). **3** can be directly accessed from BTO by refluxing BTO in an acidic aqueous solution at elongated reactions times. By boiling a solution of BTO (0.2 M) in an aqueous H_2SO_4 solution (0.1 M) for 60 hours while exposed to air, near quantitative yield of **3** was obtained (Scheme 4). **3** could subsequently be obtained as dark brown solid by solvent extraction. Refluxing the solution proved important, as the reaction at 95 ºC showed only 8% yield of **3** after 65 h at 34% conversion of BTO with the remainder being dimer **1** and other unidentified products. Interestingly, HCl was shown to be completely ineffective for the formation of **3,** as only trace amounts were detected when the reaction was performed with this acid instead of H_2SO_4. Summarizing, it was thus demonstrated that both dimers **1** and **3** can be readily obtained from BTO. The synthesis of **3** was found to be more straightforward compared to that of **1,** which is likely due to the high resistance of **3** to further reactions to form trimers and higher oligomers. This set of reactions allows for the development of more effective methods for producing these interesting symmetric polyphenolic compounds.



Scheme 4. Synthesis of **3** from BTO.

Overall, two types of reactivity were found for BTO in this work, oxidation and deuterium exchange. Firstly, the oxidation of BTO by air to form **1**. Subsequently, **1** can be further oxidized to **2** by air. The first oxidation step is likely to proceed via a two-electron oxidation step with radical intermediates that are recombined to form **1** (Scheme 5a). The regioselectivity for the formation of the 5-5' dimer is the result of the relative stability of radicals on the 5 and 3 positions over the 6 position of the aromatic ring due to the superior stabilization of having two phenolic groups in the ortho/para or ortho/ortho positions respectively. This is combined with reduced steric hindrance at the 5 position compared to the 3 position, leading to increased reactivity for the coupling reaction. Indeed, we previously reported that creating more forcing conditions by addition of hydrogen peroxide afforded 3-5 coupling.[4] The oxidation of **1** to **2** seems more favored compared to 3-3 or 3-5 coupling at room temperature upon exposure to air. Also, this reaction likely proceeds by a two-electron oxidation, generating water from oxygen. No formation of hydroxyquinone was observed directly from BTO, indicating that the formation **1** is preferred from BTO, while for **1** hydroxyquinone formation is preferred over further C-C bond formation. Secondly, the observed deuteration of the aromatic CH's is likely to proceed via deuteration of the aromatic ring of BTO-D3 to D-BTO-D3 and subsequent re-aromatization to BTO-D4 (Scheme 5b). Quantum mechanical (QM) calculations revealed pKa values[15] for D-BTO-D3 with conjugate bases BTO-D3 and BTO-D4 of -4.13 and -5.66, respectively. This is in

line with the reported pKa of -3.37 determined for protonated 1,3,5-benzenetriol[16], which is expected to be slightly less acidic due to the positions of the hydroxyl groups compared to 1,3,4-benzenetriol. In this deuteration pathway the reactivity pattern of the aromatic C-H's will be the same as for electrophilic aromatic substitution.[17] The observed selectivity is due to the preferred location of the carbocation. Resonance stabilization is more effective at positions 2, 4 and 6 compared to positions 1, 3 and 5 due to the positioning of the oxygens. Position 5 is more reactive for deuteration compared to position 3 due to steric effects, but after longer reaction times, the latter is also deuterated via the same mechanism. Additionally, the formation of BTO-D4 is energetically preferred over BTO-D3 (Table S2) due to lower zero-point vibrational energy, which, together with the excess D_2O, shifts the equilibrium towards BTO-D4 and BTO-D5. In principle, the deuteration of BTO can also be explained by the radical initiation shown for the formation of **1**. However, deuteration was still observed under exclusion of air with no apparent change in reaction rates or reactivity (Figure S4).



Scheme 5. Proposed mechanism for a) the dimerization and b) deuterium exchange reaction observed for BTO in this work.

Conclusions

Bio-based 1,2,4-benzenetriol, an aromatic product attainable from 5-hydroxymethylfurfural (HMF), can be used as a polyphenolic building block. In this study it is shown that BTO possesses interesting reactivity. Although this reactivity can provide challenges for accurate analysis of BTO in studies where its reactivity is not carefully considered, here it was shown that this reactivity can lead to formation of bio-based compounds that can have potential as chemical intermediates. Firstly, it was shown that previously reported 5-5'-linked BTO dimer [1,1'-biphenyl]-2,2',4,4',5,5'-hexaol (**1)** is formed exclusively under aerobic conditions at room temperature, which likely proceeds via a radical intermediate. Furthermore, **1** can be subsequently oxidized to afford a hydroxyquinone-containing dimeric structure, 2',4,4',5'-tetrahydroxy-[1,1'-biphenyl]-2,5-dione (**2)**, under the same conditions. It was also demonstrated

that dimer **1,** as well as a condensed dimer dibenzo[b,d]furan-2,3,7,8-tetraol **(3),** can be readily produced from BTO. The symmetric nature of these two dimeric products provide a potential platform for bio-based polymeric products, as for example bisphenol A[18] replacements. This is one of the future directions that will be explored in our group. Additionally, it was shown that the specific sequential deuterium exchange of the aromatic C-H's of BTO is readily achieved under acidic conditions at room temperature. Deuterium incorporation first occurs at the 5 position followed by the 3 position to yield BTO with 4 and 5 deuterium atoms respectively, which is likely to proceed through electrophilic aromatic substitution. These studies exemplify two types of reactivity that BTO can be involved in, which should be considered when working with this compound and which can also be exploited for accessing bio-based compounds from BTO.

Experimental

Sequential BTO deuteration in acidic D_2O

A NMR tube was charged with BTO (10 mg, 0.08 mmol) and dmso as internal standard (4 mg, 0.05 mmol). A measured amount of D_2O (0.5 mL) was added as solvent. D_2O was acidified to pH 1 using concentrated H_2SO_4 (non-deuterated). The reaction was kept at the desired temperature. NMR spectra were collected at defined time points, and the signal intensities of the BTO protons were determined by integration relative to the signal of the internal standard. ^{1}H-NMR δ/ppm (400MHz, D_2O); **BTO** - 6.84 (d, 1H, $^3J_{HH}$ = 8.7 Hz, C6-H), 6.53 (d, 1H, $^4J_{HH}$ = 2.8 Hz, C3-H), 6.40 (dd, 1H, $^4J_{HH}$ = 2.8, Hz, $^3J_{HH}$ = 8.7 Hz, C5-H).

BTO stability in H_2O

A clarified polypropylene centrifuge tube (50 mL) was charged with BTO (400 mg, 3.2 mmol) and H_2O (20 mL). For the experiment with exclusion of air, the H_2O was degassed by repeateded freeze-pump-thaws under argon atmosphere and the contents were added under an argon atmosphere. For the experiment with exclusion of light the tube was wrapped in aluminum foil. To sample each solution, an aliquot was abstracted from each reaction vessel , weighed (about 0.2-0.4 g), and placed in a centrifuge tube (1.5 mL). The sample was frozen in liquid nitrogen and freeze-dried to remove all moisture. Dimethyl sulfone of known quaintly was added to each centrifuge tube containing dry substrate as an internal standard, and dmso-d6 was used to solvate all contents. The dmso-d6 solution was transferred to an NMR tube and quantitative ^{1}H-NMR was recorded (32 scans 2s delay). The solution constituents were quantified by integration against internal standard dimethyl sulfone using the average of integration for the signals corresponding to the aromatic C-H's. For the experiment run under exclusion of air, all these steps were performed under an argon atmosphere. Due to the water insolubility of the dimeric products, extensive shaking or sonication was necessary before each sampling. Observed NMR signals for the different quantified species: **BTO** - ^{1}H-NMR δ/ppm (400MHz, dmso-d6); 8.65 (s,1H, C4-O<u>H</u>), 8.47 (s,1H, C2-O<u>H</u>), 8.01 (s,1H, C1-O<u>H</u>), 6.48 (d, 1H, $^3J_{HH}$ = 8.5 Hz, C6-<u>H</u>), 6.20 (d, 1H, $^4J_{HH}$ = 2.8 Hz, C3-<u>H</u>), 6.00 (dd, 1H, $^4J_{HH}$ = 2.8, Hz, $^3J_{HH}$ = 8.5 Hz, C5-<u>H</u>); ^{13}C NMR δ/ppm (100 MHz, dmso-d6); 150.2 (C4), 145.7 (C2), 137.6 (C1), 115.8 (C6), 105.1 (C5), 103.5 (C3); **1** - ^{1}H-NMR δ/ppm (400MHz, dmso-d6); 8.71 (s, 2H, C4,4'-O<u>H</u>), 8.50 (s, 2H, C2,2'-O<u>H</u>), 8.20 (s, 2H, C1,1'-O<u>H</u>), 6.51 (s, 2H, C6,6'-<u>H</u>), 6.33 (s, 2H, C3,3'-<u>H</u>); ^{13}C NMR δ/ppm (100 MHz, dmso-d6); 146.4 (C4,4'), 145.0 (C2,2'), 138.5 (C1,1'), 118.1 (C6,6'), 116.8 (C5,5'), 104.6

(C3,3'); T-FTMS – p ESI *(m/z)*: calculated for $C_{12}H_{10}O_6$ [M – H^+]: 249.0394; found: 249.0398. **2** - ^{1}H-NMR δ/ppm (400MHz, dmso-d6); 11.3 (s, Ar-OH), 9.30 (s, Ar-OH), 9.10 (s, Ar-OH), 8.36 (s, Ar-OH), 6.75 (s, C6-H), 6.56 (s, C6'-H), 6.38 (s, C3'-H), 5.95 (s, C3-H). ^{13}C NMR δ/ppm (100 MHz, dmso-d6); 187.2 (C2), 183.7 (C5), 157.0 (C4), 149.5 (C2'), 148.0 (C4'), 144.8 (C1), 137.7 (C5'), 130.0 (C3), 118.4 (C6'), 110.3 (C1'), 108.9 (C6), 103.8 (C6'). T-FTMS – p ESI *(m/z)*: calculated for $C_{12}H_8O_6$ [M – H^+]: 247.0231; found: 247.0245.

*Typical synthesis and purification of **1** by reflux in H_2O*

BTO (149 mg, 1.18 mmol) and H_2O (6.9 mL) were weighed into 50 mL round bottom flask fitted with a straight tube condenser. BTO appeared as an off-white beige powder, and in aqueous media afforded a golden solution. The solution was stirred and heated to reflux in a sand bath (set to 110 °C) for 20 hours. The solution, which appeared black with black precipitate, and appeared to stain the glass, was left to cool to room temperature and subsequently freeze-dried. The dry material collected was brown in color. This material was sampled for ^{1}H-NMR analysis in dmso-d6. Products were identified and compared via integral analysis to determine product composition. Analysis showed a 52.9% BTO, 43.7% **1**, and 3.4% **3** yield. By washing the solid with cold water, dimer **1** could be isolated with a 92% purity. Further purification could be achieved by crystallization from water described previously[4], but only in low yield. Analysis data see above.

*Typical synthetic procedure for **3***

BTO (521 mg, 4.13 mmol), H_2SO_4 (56.5 mg, 0.58 mmol), and H_2O (21 mL) were mixed into a 50 mL round bottom flask fitted with a straight tube condenser. The solution was stirred and refluxed in a sand bath (set to 110 °C) for 91 hours. The obtained black solution with visible precipitate on the flask surface was left to cool to room temperature (NMR at this stage shows >90% **3**). Tetrahydrofuran (THF) was added to dissolve all dimeric and monomer compounds and phase-separated by addition of NaCl to obtain a saturated aqueous phase. The organic layer was collected and THF removed *in vacuo*. The obtained product was freeze-dried, yielding 317.0 mg (1.36 mmol, 66%) of isolated **3** as a brown powder. Dimer **3**: ^{1}H-NMR δ/ppm (400MHz, dmso-d6); 9.15 (s, 2H, H4,4'), 8.76 (s, 2H, H3,3'), 7.14 (s, 2H, H2,2'), 6.90 (s, 2H, H5,5'). ^{13}C NMR δ/ppm (100 MHz, dmso-d6): 149.6 (C1,1'), 144.6 (C3,3'), 141.9 (C4,4'), 115.4 (C6,6'), 105.0 (C2,2'), 98.4 (C5,5'). T-FTMS – p ESI *(m/z)*: calculated for $C_{12}H_8O_5$ [M – H^+]: 231.0299; found: 231.0298.

ASSOCIATED CONTENT **Supporting Information**. Contains general information on materials and methods, UV-Vis data for BTO, **1** and **3**, mass-spectroscopy data, additional data on the deuterium exchange, all ^{1}H-NMR data for BTO stability in time, dimer **1** synthesis in water and without solvent, decomposition of **1** and formation of **3**, details on the QM calculations to obtain the theoretical pKa's and NMR spectra for BTO from different supplies, **1**, **2** and **3**.

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