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2,4,5-Trihydroxy-3-methylacetophenone: A Cellulosic Chromophore as a Case Study of Aromaticity

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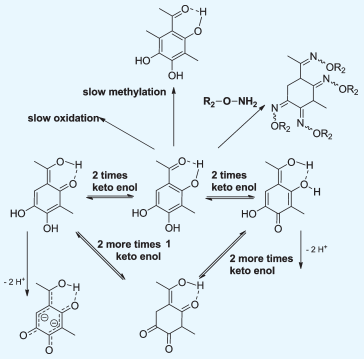
Supporting Information

ABSTRACT: The title compound (2,4,5-trihydroxy-3-methylacetophenone, **1**) was isolated as chromophore from aged cellulosic pulps. The peculiar feature of the compound is its weak aromatic system that can be converted into nonaromatic (quinoid or cyclic aliphatic) tautomers, depending on the conditions and reaction partners. In alkaline media, the participation of quinoid canonic forms weakens aromaticity, whereas in neutral and acidic media, the strong hydrogen bond between the 2-hydroxyl group and the acetyl moiety plays an important role in favoring quinoid tautomers. As a result, compound **1**, with quinoid contributions being already "preset", is relatively stable toward oxidation and hardly undergoes alkylation or nitration at CH-6, whereas the 2,4,5-trimethoxyderivative, being "properly" aromatic and even more sterically hindered, is readily alkylated or nitrated. The lability of the aromatic system is best demonstrated by the unusual reaction of **1** with hydroxylamine, producing a tetroxime that is derived from its 2,4,5-triketo tautomer. The high oxidative stability and low reactivity of the compound hinder oxidative bleaching of this chromophore in cellulosic pulps and detection reactions for analytical purposes.



INTRODUCTION

The past several years have seen considerable progress in the identification of chromophores—literally "color carriers" in ancient Greek—from cellulosic matrices, such as pulps, papers, bacterial cellulose, cotton, and others. Analysis of these compounds has been hampered by their very low concentration in the ppb range and the diversity of colored compounds, all of which combine to produce the observed overall yellowing effect. With the "chromophore release and identification" procedure for isolation of cellulosic chromophores,[1−3] such compounds became accessible and their structure, which until then could only be approximated and guessed at based on spectroscopic methods, could now be directly determined. Chromophore isolation has been performed for different cellulosic matrices,[4−6] and the products of the procedure have been shown to belong to three key classes: hydroxy-[1,4]-benzoquinones, hydroxy-[1,4]-naphthoquinones, and 2-hydroxyacetophenones.[7] These compounds are generated according to the complex condensation pathways from oxidized, "aged" carbohydrate moieties and ubiquitous for cellulosic matrices.

One of the substances thus found[6] was the title compound, 2,4,5-trihydroxy-3-methylacetophenone (THMA, **1**), a highly substituted acetophenone that can also be thought of as a derivative of 1,2,4-trihydroxybenzene (**3**, hydroxyhydroquinone). As for all of the cellulosic chromophores, the chemistry of the compound was of great interest, particularly with regard to oxidation and bleaching chemistry, under conditions that are mild enough to leave the cellulose unharmed. For comparison, we also used the nonmethylated parent compound 2,4,5-trihydroxyacetophenone (THA, **2**) in parallel experiments. The studies of the chemical behavior held some surprises and led to some unexpected but interesting detours into questions of aromaticity, which we would like to communicate within the present account.

RESULTS AND DISCUSSION

A prominent feature of THMA and THA, present both in neutral and acidic solution media, is the exceptionally strong hydrogen bond between the 2-OH group and the carbonyl oxygen, as illustrated by the ^{1}H NMR resonance of about 12 ppm (see Experimental Section). This strong H-bonding causes a partial blocking of the 2-OH group, which shows a decreased reactivity. Acetylation under standard conditions (Ac_2O/pyridine), for instance, produces the 4,5-diacetate after 30 min. This outcome did not change even after prolonged reaction times of 24 h. Treatment of **1** with BF_3/acetic acid

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complex, afforded the 4,5-diacetate as well. The 2-OH group was apparently not acetylated due to its involvement in strong H-bonding. A similar reaction behavior with a largely unreactive ortho-hydroxy group has been observed for a structurally similar 2-hydroxy-acetophenone related to α-tocopherol.[8,9]

Hydroxyhydroquinone (**3**), having an OH pattern similar to TH(M)A, is highly prone to oxidation. Exposure of its solutions, in particular alkaline ones, to air causes fast oxidation, accompanied by progressing discoloration. This oxidative instability is even more pronounced, and almost notorious, for pyrogallol (**4**, 1,2,3-trihydroxybenzene), which can even be used to effectively remove oxygen from gas streams that are passed through its alkaline solution. It was surprising to see that THMA was much less susceptible to oxidation than one would expect in general from polyhydroxybenzenes, or based on the highly oxidizable hydroquinone structure. THMA was completely stable against air over a period of days in the solid state. 1 M solutions in distilled water, acetone, or ethanol were stable against air over 24 h with compound losses smaller than 3%, whereas similar solutions of pyrogallol or hydroxyhydroquinone showed no more remaining starting material after that time. After 96 h in air (replacing evaporated solvents every 24 h), only 8% of the THMA in 1 M solutions was oxidized. Even in 3 M aqueous sodium hydroxide, 1 M THMA was relatively slowly consumed, 24% after 5 h and 63% after 12 h. By contrast, under similar conditions, pyrogallol (**4**) was completely converted after 30 min and hydroxyhydroquinone (**3**) after 75 min.

When the three hydroxyl groups of TMHA were methylated, the resulting 2,4,5-trimethoxy-3-methylacetophenone (**5**) reacted faster than the parent compound with its free hydroxyl groups: a 1 M solution of **5** in 3 M NaOH in aqueous methanol (water/methanol, v/v = 1:1) showed 32% conversion after 5 h and 66% after 12 h. This was, at least at a first glance, a quite counterintuitive result: an O-protected polyphenol being oxidatively less stable than the nonprotected parent compound. The deoxo-derivative **7**, in which the acetyl motif in THMA was replaced by an ethyl group, showed a high lability toward oxygen, the reaction rate being in the same order of magnitude as that of pyrogallol and hydroxyhydroquinone. The apparent oxidative stability of T(H)MA allows the technically important conclusion that bleaching with molecular oxygen (in an O stage) will have little effect on this cellulosic chromophore, and likely also on similarly substituted polyhydroxybenzenes, such as some hydroxylated guaiacyl structures in technical lignins.

Methylation at the benzene core, a special case of Friedel–Crafts alkylations, is a typical reaction of aromatic systems. As an electrophilic aromatic substitution (S_E^{Ar}), the reaction occurs more easily with more electron-rich aromatic systems. Obviously, also the steric accessibility of the free aromatic position will influence the methylation rate, although neighboring (ortho) hydroxyl and methyl substituents do not have any significant steric shielding. If those steric effects are neglected in a first approximation, the methylating action of a suitable system can well be used to qualitatively assess the relative aromaticity and reactivity of a probe compound. We used a 0.5 M solution of the probe compounds in tetrahydrofuran, reacting with 5 M methyl iodide in the presence of 2% BF_3 etherate at room temperature for 15 min. Longer reaction times of 90 min helped to more effectively differentiate between less reactive compounds. The consumption of the starting materials reflects its reactivity (neglecting a small error introduced by double methylation in some cases). Evidently, activating (electron-donating) groups, such as hydroxy and methoxy moieties, increased the reactivity of the remaining free aromatic positions, whereas deactivating (electron-withdrawing) groups, such as acetyl, lowered the reactivity. "Activating" and "deactivating" refers to the sum of inductive and mesomeric effects that a substituent exerts on the aromatic system to which it is attached. These effects of substituents as well as the resulting directing action with regard to further substituents are well-known concepts from organic chemistry.[10] They have become widely applied as linear free energy (LFE) relationships, the Hammett and the Kamlet–Taft equations being the most common ones.[11]

Expectedly, the reactivity, i.e., the rate at which the compound is methylated, increases with the number of activating substituents. The positive and negative effects were additive, as expected according to the LFE concept, with the effect of methoxy groups being stronger than that of hydroxyl groups. In general, compounds with one hydroxyl/methoxy group reacted slower than the ones with two, and these, in turn, reacted slower than aromatic systems with three activating OH/OMe groups.

Hydroxyhydroquinone (**3**) and pyrogallol (**4**) were among the fastest reacting compounds in the test system, being consumed with conversions above 80% after 10 min. The yield of trimethylhydroquinone (**9**), although having only two hydroxyl groups, was similarly high, proving that steric hindrance did not play any significant role, so that the last remaining free aromatic position was readily methylated. Acetophenones with three hydroxyl groups in patterns different from TH(M)A, such as the 2,3,4-trihydroxyacetophenone (**10**) and 3,4,5-trihydroxyacetophenone (**11**), which can be considered to be acetyl derivatives of hydroxyhydroquinone and pyrogallol, behaved similarly: the acetyl group had only a minor deactivating effect. The corresponding methoxy derivatives reacted even faster (formulae and data not shown). To our surprise, THMA (**1**) and its methyl-less parent compound THA (**2**) were extremely slowly consumed, only 3% (5%, respectively) after 90 min. Their rate was thus slower than that of chlorobenzene (7% after 90 min), which is usually considered a rather deactivated aromatic system. The 2,4,5-trimethoxy counterparts of TH(M)A, compounds **5** and **6**, by contrast, reacted very fast and in the same order as hydroxyhydroquinone (**3**), pyrogallol (**4**), and the other trihydroxyacetophenones (**10**, **11**). As in the above oxidation case (see Figure 1, Schemes 1 and 2), TH(M)A behaved rather unexpectedly, in both instances not showing the typical chemical behavior of a polyhydroxybenzene as a highly activated aromatic system.

It was not unlikely that the strong hydrogen bond between the acetyl group and the ortho-hydroxy group, which, as has been mentioned, causes differential reactivity among the hydroxyls, could have some general influences on the overall reactivity of the molecule. To understand such putative effects better, we used the TH(M)A-derivative in which the keto oxygen was reduced, i.e., the compound carrying an ethyl instead of the ethanone moiety. The effect on the chemical behavior was quite drastic as portrayed above: both oxidative stability and electrophilic substitution (ring methylation) behavior became almost identical to that of hydroxyhydroquinone (**3**), and the former difference of TH(M)A from structurally similar hydroxybenzenes was completely eliminated.

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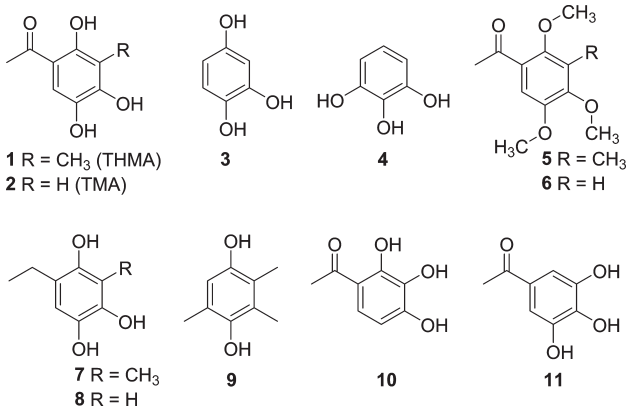
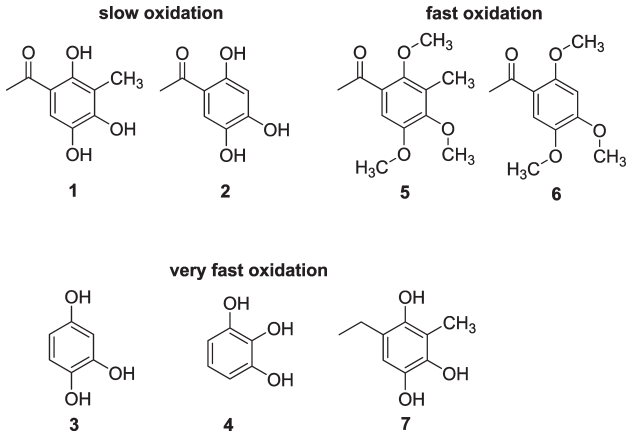


Figure 1. THMA (**1**), TMA (**2**), and derivatives.

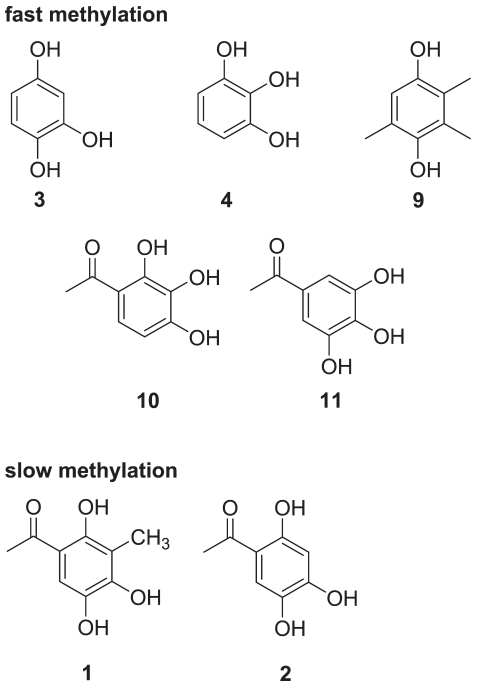
Scheme 1. Oxidative Stability of Trihydroxyacetophenones and Derivatives



The peculiar reactivity of TH(M)A was evidently not a consequence of the hydroxyl substitution or the substitution pattern alone because hydroxyhydroquinone, with the same hydroxyl pattern, was oxidatively highly unstable and easily underwent ring methylation, both in stark contrast to the THMA behavior. Similarly, the presence of an additional acetyl group per se could not be the reason: as mentioned, 2,3,4-trihydroxyacetophenone (**10**) and 3,4,5-trihydroxyacetophenone (**11**) reacted very similarly to hydroxyhydroquinone or pyrogallol, but very differently from THMA. Also, the *ortho*-hydroxyacetophenone motif on its own could not be the sole trigger of the reactivity differences—simply from comparison to *ortho*-hydroxyacetophenone itself and all of the other "well-behaving" *ortho*-hydroxyacetophenones. Thus, we speculated that the combination of one *ortho*-hydroxyacetyl motif, three hydroxyl groups in total, and a 2,4,5-trihydroxy substitution pattern might be the reason for the reactivity peculiarity observed.

An interesting point in this regard came from cellulose chromophore chemistry—which was not only the reason why we stumbled upon THMA, but then also set us on the right track to better understand its—at first admittedly rather puzzling—chemical behavior. 2,5-Dihydroxy-[1,4]-benzoquinone (DHBQ, **12**), a key chromophore in cellulosics, is an especially stable compound.[12−14] Its dianion is strongly resonance-stabilized, with two delocalized negative charges and four chemically and magnetically equivalent C−O moieties

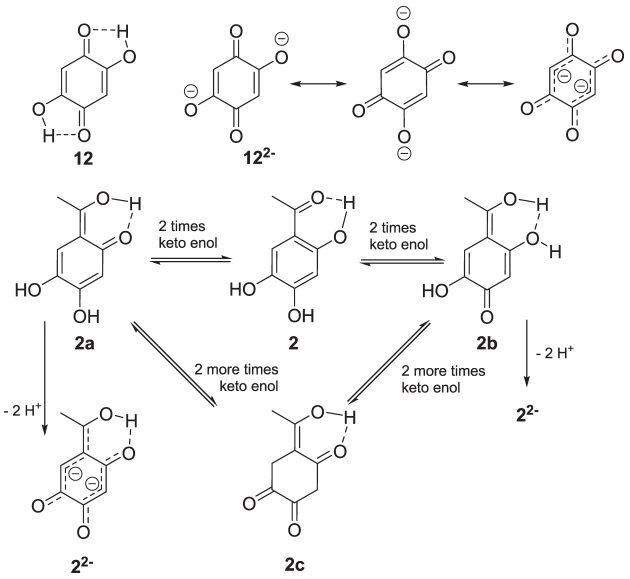
Scheme 2. Reactivity toward Methylation (Friedel−Crafts Alkylation)[a]



[a]High reactivity—hydroxyhydroquinone (**3**), pyrogallol (**4**), trimethylhydroquinone (**9**), and trihydroxyacetophenones **10** and **11**; low reactivity—2,4,5-trihydroxy-3-methylacetophenone (THMA, **1**) and 2,4,5-trihydroxyacetophenone (THA, **2**).

(Scheme 3). The dianion is highly symmetric and has four C−O motifs of equal bond lengths. In an acidic medium and solid state, the bond lengths between the bridging hydrogen and the two neighboring oxygens are equidistant, so that the stabilized dianion structure is still maintained. DHBQ (**12**) and THA (**2**) are similar with regard to the strongly H-bonded ortho-OH

Scheme 3. Analogy between THA (2) and DHBQ (12) and Their Dianions, Respectively



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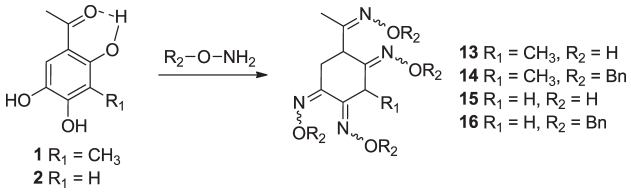
groups and the hydroxyl substitution patterns, with the difference that one OH in DHBQ is replaced by the acetyl group in THA.

If we hypothesize that THA's acetyl moiety can easily assume its enol form, facilitated by the "prebound" hydrogen from the ortho-OH, the result is an *ortho*-quinoid structure, actually an *ortho*-quinone methide derivative (**2a** in Scheme 3). The acetyl's keto−enol tautomerism is obviously coupled with the formation of a keto group from the ortho-OH, and in this way the two interlinked tautomerisms would go hand in hand with an aromatic-to-quinone conversion. A similar tautomerism leads to *para*-quinone methide **2b**, this time involving the 4-hydroxyl group instead of the 2-OH.

This alone cannot yet account for the special reactivity of THMA because *ortho*-hydroxyacetophenone, for instance, should then react in a similar fashion, which it obviously does not. Assuming that the formation of the *ortho*-quinoid structure and the loss of aromaticity enables the two remaining hydroxyl groups also to undergo keto−enol tautomerism, finally resulting in a cyclohexane system (**2c** in Schemes 3 and 4), it would

Scheme 4. Neat Conversion of TH(M)A into the Corresponding Tetroximes



explain the observed inertness toward oxygen and electrophilic substitution (methylation). Analogously, double deprotonation of either **2a** or **2b** leads to a dianionic structure ($\mathbf{2}^{2-}$) for which a resonance stabilization similar to that of the DHBQ dianion ($\mathbf{12}^{2-}$) can be assumed. In these processes, the hydrogen bridge between the acetyl group and the vicinal OH group quasi allows for a keto−enol tautomerism, actually a [1,3]-sigmatropic proton shift, without the actual "movement" of the hydrogen. The bond order changes are not accompanied by a significant rearrangement of the atomic positions. This way, THA/THMA, and their dianions in particular, would possess inherent quinoid canonic contributions that weaken the aromatic system. Due to the possibility of undergoing tautomerism and the stabilization of the resulting quinoid structures, THA/THMA possess a "pseudoquinoid" character that accompanies or superimposes on its aromatic one, explaining the peculiar reaction behavior.

If this hypothesis is true, the keto counterparts of the ring hydroxyl groups should be trappable by appropriate derivatizations, anchoring the trihydroxybenzene ring system in its cyclohexanetrione form. Intriguingly (but in a way hoped for), THA/THMA reacted with hydroxylamine, producing a tetroxime, involving the three keto tautomers of the ring hydroxyls and the acetyl carbonyl group in addition. Whereas the reaction with hydroxylamine gave yields of approximately 60% and the product was unstable when stored in air, the corresponding *O*-benzyloxime derivative, obtained by reaction between THMA and *O*-benzyl hydroxylamine, gave superb yields of 98% and produced a crystalline, air-stable tetra-*O*-benzyl-tetroxime. In other words, treatment of THMA with hydroxylamine (derivatives) cancels its aromaticity and converts it into a cyclohexa-1,3,4-trione derivative, and the same applies to THA analogously. Because this does not happen with either hydroxyhydroquinone (**3**) or the ethyl derivatives (**7**, **8**), the acetyl group must be a crucial factor in this process: the preformed *ortho*-quinoid (*ortho*-quinone methide) canonic form weakens the overall aromaticity and at the same time enables and facilitates enol-to-keto conversions of the involved hydroxyl groups. A recent study has addressed electron localization in 1,2-benzoquinones.[15]

Calculations have been applied to support the experimental results indicating the pseudoquinoid character of **1** and **2** that is superimposed on the aromaticity in the two molecules. An analysis of the aromaticity of the molecules **1** to **11** can explain their differences in reactivity in the "classical" phenol/aromatic reactions of oxidation and Friedel−Crafts type methylation as well as the formation of oximes in reaction with hydroxyl amines in the case of **1** and **2**. Aromaticity cannot be measured or calculated directly, as it is not a defined physical observable.[16] Because there is no fixed formula or method of describing or comparing aromaticity, alternative methods have to be found. One approach is certainly the experimental observation of a molecule's behavior in reactions that are typical for aromatic systems, such as benzene or phenols and aromatic polyols, i.e., compounds **3**, **4**, and **7**. Alternatively, computational methods have been proposed to describe and quantify aromaticity.[17−20] A concept that is simple and well established is the calculation of harmonic oscillator model of aromaticity (HOMA) values.[21,22] The HOMA model is based on the first geometrical aromaticity index *A*, introduced by Julg and François in 1967.[23] This index *A* is based in the observation that in the fully aromatic benzene all of the C−C bonds are equidistant, but cyclohexane also has equal bond lengths, such that *A* was not able to recognize the aliphatic (i.e., nonaromatic) character of cyclohexane and could not be used to compare aromaticity among molecules. This drawback of *A* was overcome by the introduction of the HOMA concept,[21] in which a fully aromatic compound would result in a HOMA value of 1 and a nonaromatic compound would have a value of 0. Other concepts aiming at assessing aromaticity are nucleus-independent chemical shifts (NICS)[20] and the calculation of the anisotropy of the magnetically induced current density (ACID) concept.[24,25] When we calculated the HOMA values of the compounds **1**−**11** according to Ostrowski et al.,[22] we found them matching the experimental behavior astoundingly well. HOMA values were then compared with the NICS results of the compounds **1**−**11**. NICS(0) and NICS(1) were calculated for each compound. NICS(0) represents the absolute chemical shielding of a virtual nucleus in the ring plane, whereas NICS(1) for a virtual nucleus 1 Å perpendicular to the center of the ring plane. NICS values are given with a negative sign, in analogy with the experimental NMR chemical shifts. Consequently, the lowest NICS values represent the highest aromaticity, which is reverse for HOMA. NICS(1) is the recommended as the best measure for π-electron delocalization[20] and shown in Table 1.

The compounds hydroxyhydroquinone (**3**) and pyrogallol (**4**) had the highest HOMA values, 0.994 and 0.998, respectively. Thus, they can be considered as the systems with the highest aromaticity among the compounds tested, a fact that is well supported by their very fast oxidation and Friedel−Crafts type ring methylation. HOMA values of compounds **7**−**11** were still quite high, ranging between 0.993 and 0.969. The compounds that behaved the least like

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Table 1. HOMA and NICS(1) Values of 1−11 Optimized at the M06-2X/6-311++G(d,p) Level of Theory

compound	HOMA value	NICS(1)
1	0.927	−9.72
2	0.929	−9.62
3	0.994	−10.46
4	0.998	−10.76
5	0.953	−10.26
6	0.957	−10.05
7	0.990	−10.31
8	0.993	−10.32
9	0.981	−9.97
10	0.960	−10.34
11	0.991	−10.71

aromatic compounds in oxidation and methylation reactions, 2,4,5-trihydroxy-3-methylacetophenone (THMA, **1**) and 2,4,5-trihydroxyacetophenone (THA, **2**), indeed had the lowest HOMA values of 0.927 and 0.929, respectively. Finally, 2,4,5-trimethoxy-3-methylacetophenone (**5**), with its experimental behavior located between the "pure" aromatics **4**, **3**, and **7**−**11** and the pseudoquinoid compounds **1** and **2**, had a corresponding HOMA value of 0.953, which is lower than the values of **4**, **3**, **7**−**11** but higher than those of **1** and **2**. The HOMA calculation was thus found to be an excellent tool for describing the observed experimental differences of THMA (**1**) and TMA (**2**) compared to structurally similar compounds (**3**−**11**). The influence of strong H-bonding, the *ortho*-hydroxyacetyl motif found in **1** and **2**, and the presence of three hydroxyl groups in combination with a 2,4,5-trihydroxy substitution pattern certainly cannot be neglected. HOMA, however, clearly confirmed the weakening of aromaticity by the *ortho*-quinone motif of **1** and **2**, as predicted by the formation of oximes when THMA and TMA were reacted with hydroxylamine and its derivatives. The NICS(1) values resulted in a similar pattern as the HOMA calculations: the compounds **1** and **2**, the least aromatic compounds according to experimental behavior and HOMA results, also gave the highest NICS(1) values of −9.72 and −9.62, respectively. Furthermore, **3** and **4**, compounds of high aromaticity, ranked high in HOMA and low in NICS(1) calculations: in HOMA calculations, they had the highest values; indeed, 4 gives also the lowest NICS(1) value of all compounds (−10.76) and the structure **3** is the third lowest with −10.46. The result of structures **10** and **11** for NICS(1) indicates a very high aromaticity, with −10.34 and −10.71, respectively, in the range of **3** and **4**. These values are lower (i.e., indicating higher aromaticity) than the results of **5** and **6**, that—according to experimental and HOMA—were less typical aromatic structures than **10**. Similarly, for the other compounds **7**, **8**, and **9**, the NICS(1) results point in the same direction as the HOMA values obtained.

CONCLUSIONS

The compound 2,4,5-trihydroxy-3-methylacetophenone (THMA, **1**) and its derivative 2,4,5-trihydroxyacetophenone (THA, **2**) were subjected to a series of investigations regarding their reactivity. Their behavior in classical reactions of aromatic hydrocarbons was remarkable in that they resist oxidation remarkably well, and the methylation on their benzene core is equally slow. The low reactivity is especially striking when compared with structurally similar compounds. Hydroxyhydroquinone (**3**) and pyrogallol (**4**), both benzenetriols, readily undergo methylation and are well-known for their easy oxidation. The compounds 3,4,5-trihydroxyacetophenone (**10**) and 2,3,4-trihydroxyacetophenone (**11**), structurally related even closer to **1** and **2** by the acetyl and the three hydroxyl groups present, reacted considerably faster in Friedel−Crafts methylation and oxidation reactions. The strong H-bonding between the hydroxyl hydrogen and the acetyl motif in hydroxyl acetophenones is an obvious reason for decreased reactivity of these compounds. Keto−enol tautomerisms taking place in T(H)MA result in *ortho*-quinoid structures, representing an aromatic-to-quinone conversion. Subsequent tautomerisms involving the two remaining hydroxyl groups result in a cyclohexane system and explain the observed lack of reactivity toward oxygen and electrophilic substitution (methylation). Analogously, double deprotonation at alkaline pH leads to a resonance stabilization similar to that of the DHBQ dianion. Thus, T(H)MA possesses a pseudoquinoid character that could be confirmed by derivatizations, with the trihydroxybenzene ring system fixed in its cyclohexanetrione form. Calculated HOMA values were indeed representative for the quinoid character of T(H)MA, with their aromaticity values that were lower than those for "fully" aromatic molecules such as pyrogallol and hydroxyhydroquinone. NICS(1) calculations were in good accordance with HOMA and experimental results, although HOMA matched the experimental behavior slightly better than NICS(1).

EXPERIMENTAL SECTION

General. NMR spectra of dry samples were recorded on a Bruker Avance II 400 instrument (Rheinstetten, Germany) with a resonance frequency of 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C. The samples were dissolved in perdeuterated solvents chloroform, dimethyl sulfoxide (DMSO) or pyridine (99.8% D, Euriso-top, Saint-Aubin, France). Raw data processing was carried out with ACD/NMR Processor Academic Edition. Signal assignment was accomplished using attached proton test and two-dimensional NMR techniques (correlation spectroscopy, heteronuclear single-quantum correlation spectroscopy, and heteronuclear multiple-bond correlation spectroscopy). The chemical shift values are given in δ ppm values relative to tetramethylsilane, and respective coupling constants are given in Hertz. Fourier transform infrared experiments were performed on a Perkin-Elmer Frontier infrared Single-Range spectrometer (Waltham, MA) in attenuated total reflection mode (diamond/ZnSe crystal, $LiTaO_3$ detector, KBr windows). Elemental analyses were done on a EURO EA 3000 CHNS-O instrument from HEKAtech (Wegberg, Germany) at the Microanalytical Laboratory of Vienna University. Halide contents (Cl) were determined by argentometry.

Thin-layer chromatography was performed on Silica gel 60 F254 precoated glass plates (Merck). Flash column chromatography was performed on Silica gel 60 from Merck (Darmstadt, Germany). Solvents were purchased in synthesis grade from Roth, Sigma-Aldrich, and VWR and used as received. Reagents were obtained from Sigma-Aldrich, TCI, and Fluka. Melting points were determined on a Kofler hot stage microscope and are uncorrected.

Compounds 1−4. The starting compounds were obtained from commercial sources. After recrystallization from glacial acetic acid, the compounds were kept in a desiccator under vacuum over silica gel. NMR and analytical data of the

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compounds were in agreement with literature references. In the following, the data are listed for reasons of comparison and completeness.

*2,4,5-Trihydroxy-3-methylacetophenone (THMA, **1**).* ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 3H, Me), 2.58 (s, 3H, CH_3CO), 6.86 (s, 1H), 6.90 (s, b, 4-OH, 5-OH), 12.34 (s, 1H, 2-OH). ^{13}C NMR: δ 8.9 (Me), 27.1 (CH_3CO), 110.2 (6-CH), 114.8 (3-C), 116.4 (1-C), 139.1 (5-C-OH), 148.2 (4-C-OH), 152.6 (2-C-OH), 201.1 (CO). MS (ESI, -), *m*/*z* (%): 138.2 (15), 181.4 (100, [M − H$^+$]). Mp = 87−92 °C (decomp). Microanalysis calcd for $C_9H_{10}O_4$ (182.18): C 59.34, H 5.53; found C 59.22, H 5.72. Analytical data are consistent with literature.[6]

*2,4,5-Trimethoxy-3-methylacetophenone (**5**).* ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H, Me), 2.49 (s, 3H, CH_3CO), 3.62, 3.63, 3.68 (OMe), 7.01 (s, 1H). ^{13}C NMR: δ 8.9 (Me), 27.1 (CH_3CO), 56.4, 59.3, 60.0 (OMe), 110.0 (6-CH), 120.2 (3-C), 123.9 (1-C), 144.5 (5-C-OMe), 147.9 (2-C-OMe), 150.0 (4-C-OMe), 195.2 (C═O). Mp = 134−136 °C. Microanalysis calcd for $C_{12}H_{16}O_4$ (224.25): C 64.27, H 7.19; found C 64.12, H 7.44. Analytical data are consistent with literature.[26]

*1,2,4-Trihydroxy-3-methyl-5-ethylbenzene (**7**).* ^{1}H NMR (DMSO-d_6): δ 1.33 (t, 3H, $CH_2C\underline{H}_3$), 2.22 (s, 3H, Me), 2.54 (q, 2H, $C\underline{H}_2$−CH_3), 6.26 (s, 1H), 6.90 (s, b, 4-OH, 5-OH), 12.34 (s, 1H, 2-OH). ^{13}C NMR: δ 8.4 (Me), 14.5 ($\underline{C}H_3CH_2$), 22.1 ($CH_3\underline{C}H_2$), 109.1 (3-C), 114.8 (6-CH), 121.5 (1-C), 139.3 (5-C-OH), 142.2 (4-C-OH), 146.6 (2-C-OH). Mp = 182−185 °C (decomp). Microanalysis calcd for $C_9H_{12}O_3$ (168.19): C 64.27, H 7.19; found C 64.02, H 7.42.

*Tetroxime of 2,4,5-Trihydroxy-3-methylacetophenone (**13**).* ^{1}H NMR (CD_3OD): δ 1.21 (d, 3H, ^3J = 7.9 Hz, $CH(C\underline{H}_3)$), 2.12 (s, 3H, $C\underline{H}_3C$═N), 2.55 (dd, 1H, ^2J = 12.4 Hz, ^3J = 4.4 Hz, $C\underline{H}_AH_B$), 2.86 (dd, 1H, ^2J = 12.4 Hz, ^3J = 1.1 Hz, $CH_A\underline{H}_B$), 4.14 (dd, 1H, ^3J = 4.4 Hz, ^3J = 1.1 Hz, $C\underline{H}$−CH_AH_B), 3.68 (q, 1H, ^3J = 7.9 Hz, $C\underline{H}(CH_3)$). ^{13}C NMR: δ 8.3 ($\underline{C}H_3$−C═N), 16.4 (CH−$\underline{C}H_3$), 21.4 (CH_2), 33.1 ($\underline{C}H$−CH_3), 43.7 ($\underline{C}H$−CH_2), 160.3, 161.7, 162.3 (C═N), 165.8 (CH_3−$\underline{C}$═N). Mp = 52 °C (decomp). Microanalysis calcd for $C_9H_{14}O_4N_4$ (242.24): C 44.63, H 5.83, N 23.13; found C 44.40, H 6.05, N 23.08. Analytical data are consistent with literature.[6]

*Tetrakis-(O-benzyloxime) of 2,4,5-Trihydroxy-3-methylacetophenone (**14**).* ^{1}H NMR (toluene-d_8): δ 1.20 (d, 3H, ^3J = 6.4 Hz, $CH(C\underline{H}_3)$), 2.26 (s, 3H, $C\underline{H}_3C$═N), 2.52 (dd, 1H, ^2J = 10.8 Hz, ^3J = 5.0 Hz, $C\underline{H}_AH_B$), 3.02 (dd, 1H, ^2J = 10.8 Hz, ^3J = 1.1 Hz, $CH_A\underline{H}_B$), 3.92 (q, 1H, ^3J = 6.4 Hz, $C\underline{H}(CH_3)$), 4.16 (dd, 1H, ^3J = 5.0 Hz, ^3J = 1.1 Hz, $C\underline{H}$−CH_AH_B), 4.82 (m (4 × s), 8H, O−CH_2), 7.28 (m, 4H, 4 × H-4′), 7.30−7.32 (m, 16H, 4 × H-2′, 4 × H-3′, 4 × H-5′, 4 × H-6′). ^{13}C NMR: δ 10.1 ($\underline{C}H_3$−C═N), 17.7 (CH−$\underline{C}H_3$), 23.9 (CH_2), 29.9 ($\underline{C}H$−CH_3), 43.0 ($\underline{C}H$−CH_2), 74.1−74.2 (O−CH_2), 127.8−128.6 (CH^{Ar}), 134.2 (C^{Ar}), 151.4, 158.2, 162.8 (C═N), 164.9 (CH_3−$\underline{C}$═N). Mp = 76−79 °C. Microanalysis calcd for $C_{37}H_{38}O_4N_4$ (602.74): C 73.73, H 6.35, N 9.30; found C 73.86, H 6.28, N 9.42. Analytical data are consistent with literature.[6]

*2,4,5-Trihydroxy-acetophenone (THA, **2**).* ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3CO), 6.64 (s, 1H, H-3), 7.03 (s, 1H, H-6), 7.4 (s, b, 4-OH, 5-OH), 12.16 (s, 1H, 2-OH). ^{13}C NMR: δ 26.0 (CH_3CO), 104.4 (CH-3), 115.2 (1-C), 116.9 (6-CH), 140.2 (5-C-OH), 148.8 (4-C-OH), 150.6 (2-C-OH), 201.4 (CO). MS (ESI, -), *m*/*z* (%): 124.1 (10), 167.10 (100, [M − H$^+$]). Mp = 64−65 °C (decomp). Microanalysis calcd for $C_8H_8O_4$ (168.04): C 57.14, H 4.80; found C 57.06, H 5.08. Analytical data are consistent with literature.[27]

*2,4,5-Trimethoxy-acetophenone (**6**).* ^{1}H NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3CO), 3.64, 3.66, 3.70 (OMe), 6.60 (s, 1H, H-3), 7.22 (s, 1H, H-6). ^{13}C NMR: δ 27.4 (CH_3CO), 52.3, 53.9, 56.1 (OMe), 101.8 (3-CH), 111.8 (6-CH), 125.0 (1-C), 142.9 (5-C-OH), 148.3 (2-C-OH), 153.5 (4-C-OH), 195.0 (CO). Mp = 144−145 °C. Microanalysis calcd for $C_{11}H_{14}O_4$ (2010.10): C 62.85, H 6.71; found C 62.96, H 6.92. Analytical data are consistent with literature.[26]

*1,2,4-Trihydroxy-5-ethylbenzene (**8**).* ^{1}H NMR (DMSO-d_6): δ 1.31 (t, 3H, $CH_2C\underline{H}_3$), 2.45 (q, 2H, $C\underline{H}_2$−CH_3), 6.28 (s, 1H, 3H), 6.42 (s, 1H, 6-H), 6.45 (s, b, 4-OH, 5-OH), 11.82 (s, 1H, 2-OH). ^{13}C NMR: δ 14.8 ($\underline{C}H_3CH_2$), 19.8 ($CH_3\underline{C}H_2$), 101.4 (3-CH), 115.4 (6-CH), 121.9 (1-C), 140.0 (5-C-OH), 143.4 (4-C-OH), 146.9 (2-C-OH). Mp = 160−163 °C. Microanalysis calcd for $C_8H_{10}O_3$ (154.06): C 62.33, H 6.54; found C 62.40, H 6.42.

*Tetroxime of 2,4,5-Trihydroxy-acetophenone (**15**).* ^{1}H NMR (CD_3OD): δ 2.18 (s, 3H, $C\underline{H}_3C$═N), 2.47 (dd, 1H, ^2J = 12.0 Hz, ^3J = 4.4 Hz, CH−$C\underline{H}_AH_B$), 2.56 (dd, 1H, ^2J = 12.0 Hz, ^3J = 2.6 Hz, CH−$CH_A\underline{H}_B$), 3.28 (m, 1H, $C\underline{H}_AH_B$), 3.42 (m, 1H, $CH_A\underline{H}_B$), 4.02 (dd, 1H, ^3J = 4.4 Hz, ^3J = 2.6 Hz, $C\underline{H}$−CH_AH_B). ^{13}C NMR: δ 8.5 ($\underline{C}H_3$−C═N), 18.1 ($\underline{C}H_2$), 24.8 (CH−$\underline{C}H_2$), 42.9 ($\underline{C}H$−CH_2), 158.3, 160.4, 161.3 (C═N), 159.8 (CH_3−$\underline{C}$═N). Waxy solid, mp = 43 °C (decomp). Microanalysis calcd for $C_8H_{12}O_4N_4$ (228.10): C 42.11, H 5.30, N 24.55; found C 421.98, H 5.44, N 24.32. Analytical data are consistent with literature.[6]

*Tetrakis-(O-benzyloxime) of 2,4,5-Trihydroxy-acetophenone (**16**).* ^{1}H NMR (toluene-d_8): δ 2.22 (s, 3H, $C\underline{H}_3C$═N), 2.89 (dd, 1H, ^2J = 10.4 Hz, ^3J = 3.8 Hz, C═N−$C\underline{H}_AH_B$), 3.08 (dd, 1H, ^2J = 10.4 Hz, ^3J = 2.0 Hz, C═N−$CH_A\underline{H}_B$), 3.38 (d, 1H, $C\underline{H}_AH_B$), 3.55 (d, 1H, $CH_A\underline{H}_B$), 4.01 (dd, 1H, ^3J = 3.6 Hz, ^3J = 2.0 Hz, $C\underline{H}$−CH_AH_B), 4.82−4.83 (m (4 × s), b, 8H, O−CH_2), 7.28 (m, 4H, 4 × H-4′), 7.30−7.32 (m, 16H, 4 × H-2′, 4 × H-3′, 4 × H-5′, 4 × H-6′). ^{13}C NMR: δ 12.8 ($\underline{C}H_3$−C═N), 17.5 (CH_2), 24.3 (CH−$\underline{C}H_2$), 40.4 ($\underline{C}H$−CH_2), 74.1−74.2 (4 × O−CH_2), 127.8−128.6 (20 × CH^{Ar}), 134.0 (4 × C^{Ar}), 154.4, 155.3, 156.8 (C═N), 155.3 (CH_3−$\underline{C}$═N). Mp = 93−95 °C. Microanalysis calcd for $C_{36}H_{36}O_4N_4$ (688.27): C 73.45, H 6.16, N 9.52; found C 73.30, H 6.45, N 9.38. Analytical data are consistent with literature.[6]

COMPUTATIONAL DETAILS

The substances **1**−**11** were optimized and frequency calculations ensured the absence of imaginary frequencies. Computations were carried out at the M06-2X/6-311++G(d,p) level of theory, as implemented by the Gaussian 09 program package (Wallingford, CT).[28] The integration grid was set to ultrafine and Grimme's D3 dispersion correction applied. HOMA values were calculated according to the formulae given in ref 22. NICS values were calculated according to ref 20.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00874.

Computational data of the compounds **1**−**11** and NICS(0) and NICS (1) values thereof (PDF)

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Notes

The authors declare no competing financial interest.

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