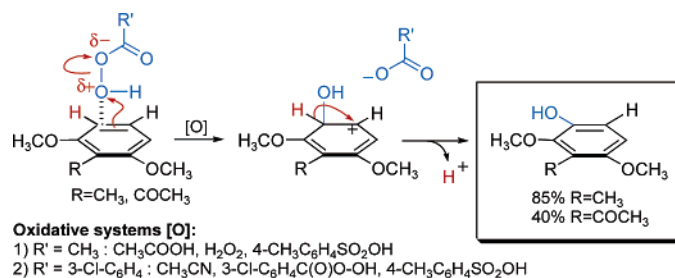# JOC*Article*

Synthesis of Methoxy-Substituted Phenols by Peracid Oxidation of the Aromatic Ring

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Oxidative systems [O]:
1) R' = CH$_3$: CH$_3$COOH, H$_2$O$_2$, 4-CH$_3$C$_6$H$_4$SO$_2$OH
2) R' = 3-Cl-C$_6$H$_4$: CH$_3$CN, 3-Cl-C$_6$H$_4$C(O)O-OH, 4-CH$_3$C$_6$H$_4$SO$_2$OH

A novel benign protocol for the preparation of hydroxy-methoxybenzene derivatives is disclosed. By utilizing this protocol, activated aromatic compounds such as 1,3-dimethoxy-2-methyl-benzene and 1-(2,6-dimethoxyphenyl)ethanone are smoothly converted to the corresponding monohydroxylated compound. The reaction can be considered to be a normal aromatic electrophilic substitution reaction, and the regioselectivity for the reaction thus follows the similar rules as for electrophilic substitutions. The protocol is composed by benign reagents, namely, hydogenperoxide, acetic acid, and *p*-toluene sulfonic acid, which lead to the production of ethaneperoxoic acid in situ. The ethaneperoxoic acid operates as the hydroxylating reagent. The hydroxylation reaction is completed within a short period and requires moreover only mild experimental conditions, which make this novel protocol a green, cheap, and rapid process leading to hydroxy-methoxybenzene derivatives. The proposed reaction mechanism is supported by density functional theory and NMR spectroscopy experiments. The mechanism is constituted by two discrete steps: (a) addition of OH$^+$ to the most nucleophilic carbon atom of the aromatic ring, which is the rate-determining step, and (b) the loss of the proton from the aromatic ring.

Introduction

Hydroxylation of aromatic compounds has for decades been a research topic of extensive interest from an academic as well as an industrial standpoint. Direct hydroxylation of simple aromatic and polycyclic aromatic hydrocarbons can be performed by means of a plethora of methods. Free-radical processes utilizing molecular oxygen or metal-catalyzed hydrogen peroxide oxidation known as Fenton-type oxidation reactions are examples that generate the •OH radical as the reactive species.[1] The Udenfriend[2] and the Hamilton[3] protocols are two more methods based on the generation of the •OH radical

as the reacting species for the direct oxidation of the aromatic ring. Peroxydisulfate[4] or peroxydiphosphate[5] operate successfully as oxidants for the aromatic ring in the presence of another oxidant such as Cu(II). Typical for all of these radical methods is that they operate with a varying degree of selectivity. Various metal complexes containing Fe,[6] Pt,[7] or V[8] have been studied for the oxidation of benzene to phenol as an alternative to the

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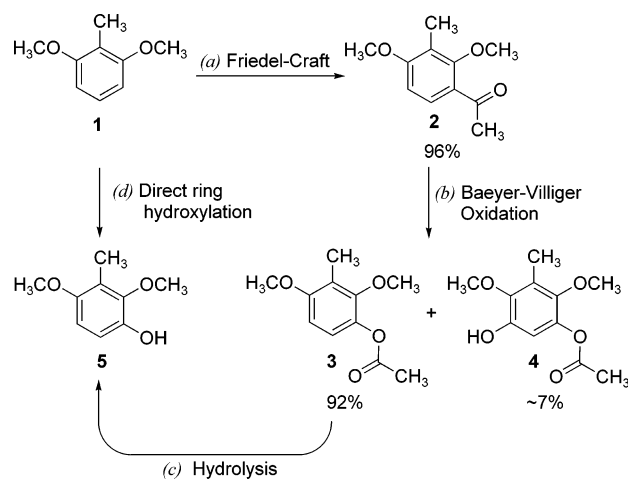(7) Sakai, K.; Matsumoto, K. *J. Mol. Catal.* **1991**, *67*, 7−18.
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autoxidation process of cumene.[9] Some heterogeneous systems with hydrogen peroxide as the terminal oxidant have also been established, though one of the more successful ones utilizes titanium silicalite together with hydrogen peroxide.[10] Electrophilic monohydroxylation of aromatic compounds was demonstrated using a series of peroxide reagents,[11] although a common characteristic for these protocols was that they provided rather low yields of the target phenols. Olah and co-workers have demonstrated in a series of reports[12] how electrophilic hydroxylation of the aromatic ring can be performed using hydrogen peroxide and superacid. These protocols provide good to high yield, although under rather harsh and cryogenic conditions. In these systems it is supposed that the $H_3O_2^+$ ion operates as the reacting species. Cytochrome P450 catalyzed oxidation of polyaromatic compounds, a reaction that involves the NIH shift, was disclosed by Jerina and co-workers.[13]

A system that attracted our interest was the Lewis acid promoted electrophilic hydroxylation with peracids as disclosed by Hart and Buehler[14] and in the communications of Griffin and co-workers.[15,16] A similar oxidation seems to have taken place as a side reaction in a current project in our laboratory, although with the presence of a Brønsted rather than a Lewis acid. Our project involves investigation of new strategies and protocols leading toward the synthesis of the carbazole framework in general and of Carbazomycines (A–H)[17] in particular. For this purpose we required access to 2,4-dimethoxy-3-methylphenol **5** (Scheme 1) and derivatives thereof. In addition to the preparation of the required compound, we wanted to perform a "green chemistry improvement" of existing syntheses,[18,19] especially the B–V oxidation step. Instead of performing B–V oxidation with mCPBA, we designed a protocol involving hydrogen peroxide,

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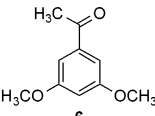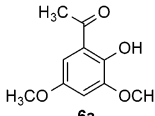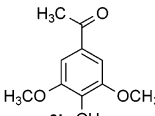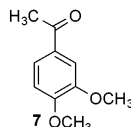
SCHEME 1

2

96%

5

3

92%

4

~7%

(a) Friedel-Craft

(d) Direct ring hydroxylation

(b) Baeyer-Villiger Oxidation

(c) Hydrolysis

acetic acid, and *p*-toluene sulfonic acid (pTSA) as the oxidizing system. This reagent substitution was foreseen (1) to improve the atom economy and thus reduce the quantity of effluents, (2) to avoid handling of chloroorganics, and (3) to utilize benign, cheap, large-scale industrial chemicals that are easy to handle.

Similar to prior disclosures,[18,19] we utilized a synthetic pathway as outlined in Scheme 1, steps *a–c*. The commercially available 2,6-dimethoxy-3-methylbenzene **1** was submitted to Friedel–Craft acylation by treatment with acetyl chloride and aluminum trichloride using nitroethane as solvent.[20] The reaction proceeded with high yield (96%) to give the acetophenone **2**. The next step was the Baeyer–Villiger oxidation utilizing our new protocol to successfully achieve the acetate **3** in high yields (92%) and with the side product (~7%) acetic acid 5-hydroxy-2,4-dimethoxy-3-methylphenyl ester **4**. The phenol **5** was obtained under hydrolytic conditions, pathway *c*, in nearly quantitative yields.

At this stage, our original task was satisfactorily accomplished. However, the observed results raised three questions, namely, (1) is the novel B–V oxidation protocol a general procedure for the transformation of acetophenones to the corresponding phenylacetates, (2) what is the mechanism that provided the byproduct **4**, and (3) can the observed direct hydroxylation reaction be developed into a novel route to phenols? The observation of the phenol **4** turned out to be of special interest, since compound **4** apparently was produced by direct hydroxylation of the aromatic ring by the action of the peracid or by protonated hydrogen peroxide.[21]

Methods and Results

Reaction and Spectroscopic Experiments. A series of methoxy-substituted acetophenones were submitted to the Baeyer–Villiger protocol composed of H_2O_2, CH_3COOH, and pTSA. Moreover, for comparison purposes,

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TABLE 1.   Experimental Results from Two Various Oxidation Systems: (1) mCPBA/pTSA in CH₃CN/80 °C^a and (2) H₂O₂/pTSA/CH₃COOH/80 °C^b

Substrates %-conv. methods a, b	Oxidation products %-yield methods a, b				
6 Conv 14%, 5%	**6a** 11%, 5%	**6b** 3%, -			
7 Conv 88%, 100%	**7a** 88%, 100%				
8 Conv 60%, 88%	**8a** 22%, 15%	**8b** 19%, 9%	**8c** 18%, 48%	**8d** 1%, 15%	**8e** <1%, <1%
9 Conv 58%, 85%	**9a** 39%, 12%	**9b** 16%, 67%	**9c** 4%, 6%		
10 Conv 15%, 6%	**10a** 9%, 3%	**10b** 4%, 2%	**10c** 2%, 1%		
11 Conv 100%, 100%	**11a** >99%, >99%				
12 Conv 93%, 100%	**12a** 89%, 89%	**12b** 4%, 11%			

^{a} Acetophenone (1.0 mmol) was dissolved in CH₃CN (5.0 mL) followed by addition of *p*-toluene sulfonic acid monohydrate (0.20 mmol) and mCPBA (1.0 mmol). The reaction mixture was then leaved under stirring for 1 h at 80 °C (reflux)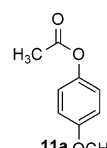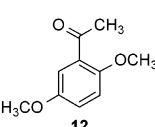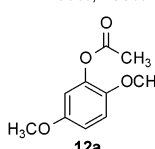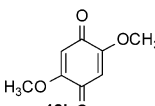. Another portion (1.0 mmol) of the oxidant mCPBA was then added and the reaction mixture was then left 1 h under stirring at reflux. ^{b} Acetophenone (1.0 mmol) was dissolved in CH₃COOH (5.0 mL) followed by adding *p*-toluene sulfonic acid monohydrate (0.20 mmol) and hydrogen peroxide (5.0 mmol). The reaction mixture was then left under stirring and heating at 80 °C for 1 h.

the acetophenones were also submitted to the B−V protocol that utilizes mCPBA as oxidant. Details concerning the experimental conditions and results obtained are provided in Table 1.

All of the acetophenones **7**−**12** were oxidized to afford the expected phenyl acetates. 3,5-Dimethoxyacetophenone **6** was, however, oxidized to only a small extent, only 14% conversion. The expected phenyl acetate was not observed among the oxidized products from this compound. Only two of the acetophenones, namely, 3,4-

dimethoxyacetophenone **7** and 4-methoxy acetophenone **11** provided the corresponding phenyl acetates (**7a** and **11a**) with a selectivity of ~100%.

Some of the products obtained form the oxidation of the acetopheneones **6**, **8**, **9**, and **10** were, however, unexpected, since these were shown to be oxidized directly on the aromatic ring to provide the corresponding hydroxy acetophenone or hydroxyphenyl acetate as oxidation products. The experimental result achieved suggests that the hydroxylation proceeds with a preference

SCHEME 2
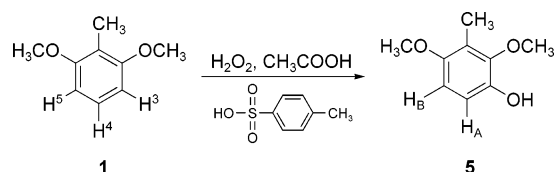
for the para position to the methoxy group. In cases where this position was blocked by another group, hydroxylation did not take place on the aromatic ring.

The results attained spurred us on to subject compound **1** to the oxidation conditions in an attempt to produce the original target 2,4-dimethoxy-3-methylphenol **5** via direct oxidation. To the best of our knowledge, such a reaction has not been previously described.

1,3-Dimethoxy-2-methylbenzene **1** was thus submitted to oxidative conditions constituted by hydrogenperoxide, acetic acid, and pTSA (Scheme 2). An oxidation experiment was monitored by means of ^{1}H NMR spectroscopy with the two-fold goal of identifying the structure of the reaction product and of searching for transient chemical entities present during the course of the reaction, information that subsequently could be used as pieces of the reaction mechanistic puzzle.

Figure 1 shows details from the regions δ 7.2–6.5, 3.8–3.2, and 2.4–1.9 ppm of the ^{1}H NMR spectra recorded during the course of the reaction. The spectrum shown in Figure 1a was recorded at 298 K after a reaction time of 10 min. The only visible signals are the aromatic ones belonging to compound **1**, namely, at 7.12 ppm (proton H,[4] triplet) and 6.59 ppm (the protons H[3] and H,[5] doublet), respectively.

The reaction mixture was then heated to 318 K and left for 1 h after which a spectrum was recorded (Figure 1b). A new chemical entity was now present in the solution since a new resonance was discerned at δ 6.76 ppm (doublet). The spectrum shown in Figure 1c was recorded after a reaction time of 2 h, still at a temperature of 318 K. The new entity was at this time much more clearly seen in two aromatic signals, one doublet at δ 6.76 ppm, which was already present after 1 h (Figure 1b) and a second doublet at δ 6.58 ppm that was undetectable in the spectrum of Figure 1b because it was buried under the starting compound signal. At this stage of the reaction, about 45% of the substrate 1,3-dimethoxy-2-methylbenzene **1** was converted into the new entity.

The reaction mixture was cooled to 306 K, and a spectrum was recorded after an additional 1 h of reaction time (3 h); see Figure 1d. The new entity was now more abundant than the starting material **1** (65% conversion).

The new oxidation product showed two aromatic protons that gave rise to an AB system in which J_{AB} is 8.8 Hz (A, δ 6.74 ppm; B, δ 6.59 ppm). This is typical of vicinal protons. Together with these signals, two new *O*-methyl resonances (δ 3.67 ppm and δ 3.66 ppm) and a *C*-methyl (δ 2.06 ppm) emerged. The presence of only two aromatic protons (on adjacent carbons) and the two distinct methoxy signals indicate that the oxidation product is 2,4-dimethoxy-3-methylphenol **5**. Moreover, a singlet integrating for one proton at δ 3.32 ppm accounts for the OH group of the phenol **5**.

In addition to the structure elucidation of the oxidizing product, we looked for intermediates of this reaction. One of our initial, mechanistic proposals embraces an arene
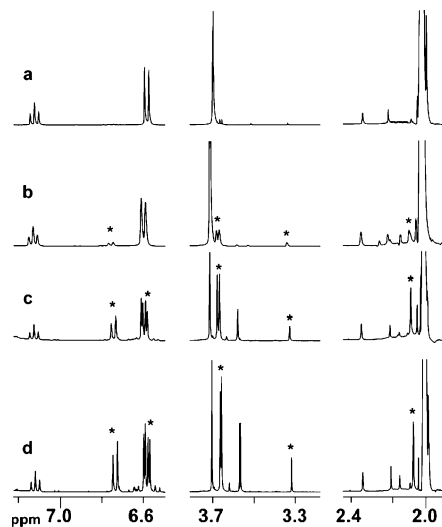

FIGURE 1. ^{1}H NMR monitoring of the oxidation carried out by means of hydrogen peroxide, acetic acid, and *p*-toluene sulfonic acid of 1,3-dimethoxy-2-methylbenzene **1** to 2,4-dimethoxy-3-methylphenol **5**. Chemical shifts are referred to the CD$_2$HCN peak at δ 1.98 ppm. Spectrum **a** reveals only 1,3-dimethoxy-2-methylbenzene **1**. The labeled peaks (∗) of spectrum **d** shows 2,4-dimethoxy-3-methylphenol **5** as the major component of the mixture, while the spectra **c** and **d** shows how those signals steadily are strengthened during the course of the reaction.

SCHEME 3
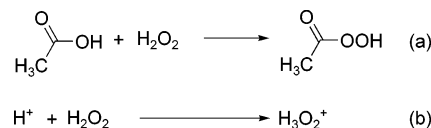
oxide species similar to the mechanism for the arene oxidation catalyzed by cytochrome P450 (involving the NIH shift).[13] Signal peaks of the vicinal protons of such an arene oxide were expected to be found in the region of δ 3.25 ppm. However, such a signal was absent in all of the recorded spectra.

It is known that $H_3O_2^+$ can act as a source of $HO.^{+}$[22] The hydroxylation conditions we utilized here, that is, with the presence of the strong acid pTSA, provide conditions for the formation of the $H_3O_2^+$ ion. This species may thus be the source of the cation acting in place of or in mutual action with the ethaneperoxoic acid formed in situ. An experiment was thus designed for the resolution of this problem: acetonitrile was used as reaction medium in place of acetic acid. A large quantity of pTSA (0.3 equiv) and the oxidant hydrogen peroxide (6 equiv) was mixed, and the substrate 1,3-dimethoxy-2-methylbenzene **1** (3 equiv) was added and heated at 75 °C for 1 h. Samples were analyzed on GC−MS, but only traces of the expected phenol were detected. In contrast, when acetic acid was used as the solvent under otherwise similar conditions, a yield of 85% of the phenol was achieved. From these experiments we can conclude that the $H_3O_2^+$ ion eventually formed in the reaction mixture (pathway b of Scheme 3) acts only to a very small extent as the hydroxylation reagent and that the ethaneperoxoic acid formed in situ operates as the hydroxylation reagent (pathway a of Scheme 3).

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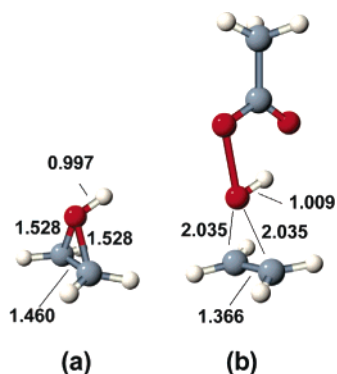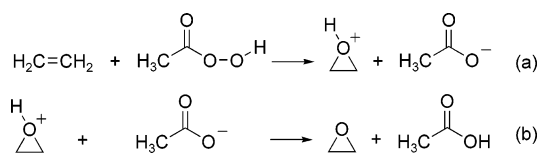
FIGURE 2. (a) Structure of protonated ethene epoxide. (b) Transition state for epoxidation of ethene by etheneperoxoic acid.
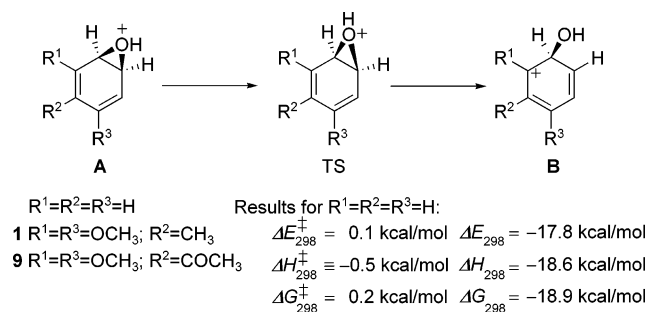
SCHEME 4

To unravel the importance of the presence of the strong acid (pTSA), an experiment was conducted in acetic acid without the presence of the pTSA, heating at 75−80 °C for 6 h to obtain a yield of 65%. Prolonging the reaction time to 8 h resulted in a higher conversion, but a minor decomposition of the phenol was also observed as well. This experiment demonstrates that the hydroxylation rate is promoted by the presence of a Brønsted acid, but the excess of the Brønsted acid is not required to operate the reaction.

DFT Calculations. Density functional theory calculations were performed in our endeavor to establish further mechanistic information for the direct oxidation of the aromatic ring of the methoxybenzene derivatives shown in Table 1. The calculations were performed on three different reactant pairs: (1) 1,3-dimethoxy-2-methylbenzene **1** and ethaneperoxoic acid, (2) 1-(2,6-dimethoxyphenyl)ethanone **9** and ethaneperoxoic acid, and for comparison purposes (3) benzene and ethaneperoxoic acid.

It is known that peracids can act as electrophiles in the epoxidation of alkenes,[23−25] a reaction that proceeds through a concerted transition state to provide directly the epoxide with the corresponding carboxylic acid as a side product. The transition state for the epoxidation of ethene with ethaneperoxoic acid (see Figure 2b) shows a H−O bond length (∼1 Å) similar to those of the corresponding protonated epoxide (see Figure 2a), which indicates that the deprotonation has not yet been initiated in the transition state and hence may suggest that the epoxidation proceeds over two consecutive steps. The first step is OH⁺ transfer from the peracid to the double bond [step a, Scheme 4], producing the protonated epoxide as an intermediate (strong acid). A straightforward deprotonation by means of the carboxylate ion [step b, Scheme 4] concludes the epoxidation.

SCHEME 5

R¹=R²=R³=H

1 R¹=R³=OCH₃; R²=CH₃
9 R¹=R³=OCH₃; R²=COCH₃

Results for R¹=R²=R³=H:

$\Delta E^{\ddagger}_{298} = 0.1$ kcal/mol $\quad \Delta E_{298} = -17.8$ kcal/mol
$\Delta H^{\ddagger}_{298} = -0.5$ kcal/mol $\quad \Delta H_{298} = -18.6$ kcal/mol
$\Delta G^{\ddagger}_{298} = 0.2$ kcal/mol $\quad \Delta G_{298} = -18.9$ kcal/mol

This interpretation suggests considering the peracid as a soft electrophile,[26−28] which is capable of transferring OH⁺ to soft nucleophiles, such as alkenes. Aromatic compounds, for example, benzene, are able to react with several relatively strong electrophiles in order to undergo electrophilic substitution.

Our experimental data (Table 1) reveal that activated aromatic compounds such as 1-(2,6-dimethoxyphenyl)ethanone **9** and 1,3-dimethoxy-2-methylbenzene **1** react with the peracid to produce the corresponding phenols in high yields. In both cases, the OH group is introduced in the para position to a methoxy group. It is reasonable to believe that the course of the reaction can proceed in a similar way as in the case of alkenes, namely through an OH⁺ transfer to two vicinal nucleophilic carbons, namely, C³ and C,⁴ and to possess a similar transition state as well. Although another workable mechanism is that the HO⁺ transfer proceeds only to the most nucleophilic and thus the most electron-rich carbon, which is C³ for the two studied compounds **1** and **9**.

Scheme 5 outlines a reaction pathway for the hydroxylation of the aromatic ring, here exemplified by benzene. Geometry optimization of protonated benzene oxide **A** (7-oxonia-bicyclo[4.1.0]hepta-2,4-diene) results in a very shallow minimum with a barrier to formation of the hydroxylation that vanishes upon inclusion of thermal corrections. Rearrangement to the much more stable hydroxyl cation **B** can thus be expected to be rapid. Obviously, this also suggests that the hydroxylation of benzene proceeds via a transition state involving the cation (Figure 3b) and not an intermediate or a transition state involving protonated benzene oxide (TS) (Figure 3a).

All of our attempts to obtain a transition state involving a symmetric protonated oxide (structure **A**, Scheme 5) for each of the two derivatives 1,3-dimethoxy-2-methylbenzene **1** and 1-(2,6-dimethoxyphenyl)ethanone **9** failed. Similar efforts with benzene led instead to a second-order saddle point (see Figure 3a), with one imaginary frequency (−421 cm⁻¹) due to a mode that leads to the symmetric epoxide, and one imaginary frequency at (−112 cm⁻¹) due to a mode that leads to the asymmetric cation transition state (structure **B**, Scheme 5). The cation transition state is easily obtained and the optimized geometries for benzene, 2,6-dimethoxybenzne, and 1-(2,6-dimethoxyphenyl)ethanone are shown in Figure 3b, c, and d, respectively.

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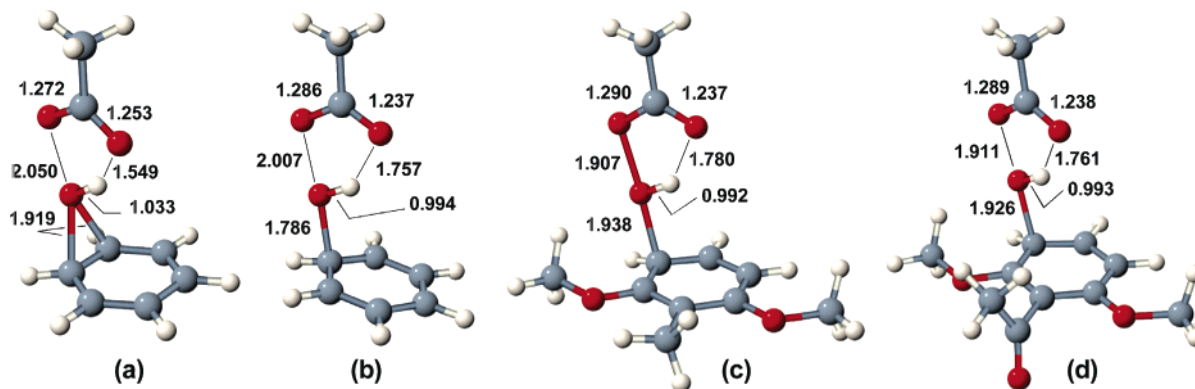(28) Ho, T. *Chem. Rev.* **1975**, *75*, 1−20.

FIGURE 3. (a) Second-order saddle point structure for benzene and *s-cis* ethaneperoxoic acid. (b) Saddle point (transition state, TS) structure for benzene and *s-cis* ethaneperoxoic acid. (c) TS structure for 1,3-dimethoxy-2-methylbenzene and *s-cis* ethaneperoxoic acid. (d) TS structure for 1-(2,6-dimethoxyphenyl)ethanone and *s-cis* ethaneperoxoic acid.

SCHEME 6. Proposal for Mechanism for Hydroxylation of the Aromatic Ring with a Peroxoic Acid
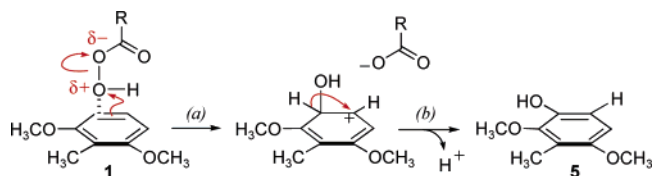
On the basis of the above considerations and spectroscopic and experimental results, our proposal for the reaction mechanism is as follows. The reaction appears to take place over two steps. The first one is the OH$^+$ transfer from the peracid to the aromatic carbon in the para position to a methoxy group. The second step is a concerted process involving the proton loss and rearomatization to yield the corresponding phenols. An outline for the reaction of **1** → **5** is given in Scheme 6. The first step, pathway a, is the rate-limiting step, and analysis of the transition state energies can provide information about the relative rates of different substrates; see Table 2. Our experimental data show that the 1,3-dimethoxy-2-methylbenzene **1** is slightly more reactive than 1-(2,6-dimethoxyphenyl)ethanone **9** and that benzene did not react under these reaction conditions. These experimental results are in agreement with the relative order of the transition state energy, namely, $\Delta G^{\ddagger}_{298K}$ (benzene) > $\Delta G^{\ddagger}_{298K}$ (**9**) > $\Delta G^{\ddagger}_{298K}$ (**1**); for details see Table 2. It is also evident that this trend in barrier heights follows Hammonds postulate.[29] The early TS found for **1** (Figure 3c), as judged from, for example, the length of the O–H bond to be broken, is also associated with the lowest barrier.

The loss of proton from the aromatic ring, step b, can take place following several pathways, but all involve the participation of a base, and a series of DFT calculations of such processes have in all cases given reaction barriers that are substantially lower than those of pathway a. Several entities in the reaction mixture can intervene during this proton loss: the acetate ion, the *p*-toluensulfonate ion, and water. A detailed discussion regarding this deprotonation, however, goes beyond the scope of the present study.

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TABLE 2. Calculated Energies for Direct Oxidation of Aromatics Compounds with Peracid (Calculated for *s-cis* Ethaneperoxoic Acid)

#	Substrate	Energy[a]	TS[b]	Hydroxylated product
1		ΔE	26.0	−62.9
		ΔH_{298K}	25.2	−62.2
		ΔG_{298K}	33.8	−63.1
		ΔS_{298K}	−29.0	3.1
2		ΔE	15.3	−59.7
		ΔH_{298K}	14.6	−58.7
		ΔG_{298K}	25.2	−58.2
		ΔS_{298K}	−35.5	−1.6
3		ΔE	14.6	−60.4
		ΔH_{298K}	15.3	−59.6
		ΔG_{298K}	25.7	−58.8
		ΔS_{298K}	−35.2	−2.9

[a] ΔE, ΔH, and ΔG are in kcal mol^{-1} and $\Delta S^{\ddagger}$ is in cal mol^{-1} K^{-1}. [b] Restricted DFT (RB3LYP) calculations were performed throughout, except for the TS of the oxidation of benzene for which a triplet instability was detected. This TS was therefore optimized using unrestricted formulation (UB3LYP). Details are given in Experimental Section.

Discussion and Conclusion

A novel reaction for the hydroxylation of methoxybenzene derivatives utilizing peracids is presented. The reaction proceeds through electrophilic substitution of the aromatic ring with HO$^+$ provided from a peracid. In electrophilic substitution reactions, the methoxy group operates as strongly activating, which thus leads to electrophilic attack in the ortho or para positions to itself. The two compounds **1** and **9** that have been thoroughly investigated in the present study possess methoxy groups in the 2- and 6-positions that correspond to the meta position relative to the 4-position of the molecule. The consequence is a strong deactivation toward electrophilic attack on the 4-position of the two molecules. Thus, the obtained oxidation products of **1** and **9** utilizing the disclosed protocol provide the corresponding phenols where the hydroxyl group is introduced in the 3-position.

The proposed reaction mechanism is supported by density functional theory and is constituted by two discrete steps: (a) the addition of OH$^+$ to the aromatic

ring, which is also the rate-determining step, and (b) the loss of the proton from the aromatic ring. The transition state of step (a) essentially has a O−H bond distance equal to that of the resulting hydroxyl cation, which shows that this step proceeds as a direct addition of HO⁺ to the most nucleophilic carbon atom of the aromatic ring.

Moreover, a mechanism of oxidation through formation of a peroxide transition state or intermediate is found not to be viable. The reaction can be considered to be a normal aromatic electrophilic substitution reaction, and thus the regioselectivity follows the similar rules as for electrophilic substitutions.

The hydroxylation reaction needs as substrates activated aromatic compounds such as 1,3-dimethoxy-2-methylbenzene **1** and 1-(2,6-dimethoxyphenyl)ethanone **9**. Benign reagents and mild conditions make this novel protocol a green, cheap, and rapid process to hydroxylmethoxybenzene derivatives, which can be utilized in the synthesis of numerous natural compounds, and for example, compound **5** is used in the synthesis of the Carbazomycins G and H.[19]

Experimental Section

Oxidation of 1,3-Dimethoxy-2-methylbenzene (1) with H₂O₂ as Terminal Oxidant. 1,3-Dimethoxy-2-methylbenzene **1** (0.456 g, 3 mmol) was dissolved in glacial acetic acid (15 mL) and thereafter were added *p*-toluene sulfonic acid monohydrate (57 mg, 0.3 mmol) and hydrogenperoxide (30%, 0.68 mL, 6 mmol). The reaction mixture was heated at 70 °C for 1 h under vigorously stirring with a magnetic stirrer bar. The reaction mixture was cooled to room temperature, and the acetic acid was evaporated under vacuum. Water (50 mL) was added and extracted with dichloromethane (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum to achieve the phenol **5** (crude 0.218 g, GC purity >99%, ~1.3 mmol).

Oxidation of 1-(2,4-Dimethoxy-3-methylphenyl)-ethanone (2) with H₂O₂ as Terminal Oxidant. 1-(2,4-Dimethoxy-3-methylphenyl)-ethanone **2** (1.27 g crude product, GC purity 96%, ~6.29 mmol) was dissolved in glacial acetic acid (15 mL) and thereafter were added *p*-toluene sulfonic acid monohydrate (300 mg, 1.6 mmol) and hydrogenperoxide (40%, 2.0 mL, 26 mmol). The reaction mixture was heated at 70 °C for 2 h under high speed stirring with a magnetic stirrer bar. The reaction mixture was cooled to room temperature, and the acetic acid was evaporated under vacuum. Water (50 mL) was added and extracted with dichloromethane (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum to achieve the ester **3** (crude 1.33 g, GC purity 92%, ~5.8 mmol).

Oxidation of 1-(2,4-Dimethoxy-3-methylphenyl)-ethanone (2) with mCPBA as Terminal Oxidant. The acetophenone **2** (1.0 mmol) was dissolved in CH₃CN (5.0 mL) followed by adding *p*-toluene sulfonic acid monohydrate (0.2 mmol) and mCPBA (1.0 mmol). The reaction mixture was then left under stirring for 1 h at 80 °C (reflux). Another portion (1.0 mmol) of the oxidant mCPBA was then added and the reaction mixture was then left for 1 h at reflux. A sample (0.1 mL) was withdrawn from the reaction mixture, dichloromethane (2 mL) was added, and analysis was carried out by GC−MS.

NMR Experiment 1 → 5. 1,3-Dimethoxy-2-methylbenzene **1** (456 mg, 3.0 mmol) was dissolved in glacial acetic acid (3 mL). *p*-Toluene sulfonic acid monohydrate (57 mg, 0.3 mmol), hydrogenperoxide (0.68 mL 30%, 6 mmol), and 25% (v/v) of CD₃CN (1.0 mL) were then added to the reaction mixture under good agitation and heated at a temperature of 25 °C

(298 K) for a period of 10 min. From this mixture, a sample of ca. 1 mL volume was withdrawn and transferred to a NMR tube, whereas a spectrum was immediately recorded. The temperature was then raised to 45 °C (318 K). After reaction times of 1 and 2 h, NMR spectra were recorded. The temperature was then decreased to 33 °C (306 K) and left for 1 h, when a spectrum was recorded. The ¹H NMR spectra were recorded on a Bruker DPX 400 MHz Spectrometer. 1D spectra were acquired accumulating 128 transients into 32 k data points over a spectral width of 8.0 kHz.

Computational Details. Geometry optimizations were performed using the B3LYP hybrid functional,[30] as implemented in the Gaussian 03 set of programs,[31] in conjunction with 6-311+G(d,p) basis sets.[32,33] The latter basis sets imply the contractions [4s,1p] for H atoms and [5s,4p,1d] for carbon and oxygen atoms.

Thermochemical corrections to obtain enthalpies and Gibbs free energies were computed within the harmonic-oscillator, rigid-rotor, and ideal-gas approximations using the same method and basis sets as in the geometry optimizations. A restricted formulation, i.e., RB3LYP, was initially used throughout and all the thus obtained solutions were tested for triplet instabilities. A triplet instability was only detected for the transition state of oxidation of benzene with peracid and thus an unrestricted formulation was used for the optimization of this structure. The spin expectation value before ($\langle \hat{s}^2 \rangle = 0.185$) and after ($\langle \hat{s}^2 \rangle = 0.005$) anhilation of the first (S + 1) spin contaminant showed that the resulting mixed state was only marginally contaminated by higher spin states and almost exclusively by the triplet state.

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