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Through-Space Activation Can Override Substituent Effects in Electrophilic Aromatic Substitution

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Supporting Information

ABSTRACT: Electrophilic aromatic substitution (EAS) represents one of the most important classes of reactions in all of chemistry. One of the "iron laws" of EAS is that an electron-rich aromatic ring will react more rapidly than an electron-poor ring with suitable electrophiles. In this report, we present unique examples of electron-deficient arenes instead undergoing preferential substitution in intramolecular competition with more electron-rich rings. These results were made possible by exploiting the heretofore unknown propensity of a hydrogen-bonding OH−arene interaction to switch to the alternative HO−arene interaction in order to provide activation. In an extreme case, this through-space HO−arene activation is demonstrated to overcome the deactivating effect of a trifluoromethyl substituent, making an otherwise highly electron-deficient ring the site of exclusive reactivity in competition experiments. Additionally, the HO−arene activation promotes tetrabromination of an increasingly more electron-deficient arene before the unactivated "control" ring undergoes monobromination. It is our hope that these results will shed light on biological interactions as well as provide new strategies for the electrophilic substitution of aromatic rings.

Electrophilic aromatic substitution (EAS) is one of the most fundamentally important reactions in the science of chemistry.[1,2] In the classroom setting, students are taught at length about how EAS reactions are governed by "substituent effects" in terms of relative reaction rates and selectivity.[3] For instance, imagine that a molecule with two different aromatic rings, separated by a linker, is subjected to an EAS reaction. In principle, substitution will occur at the more electron-rich ring, assuming that other factors be equal. This deactivating effect on EAS reactions by electron-withdrawing groups is well established, and it is a fundamental concept in textbook organic chemistry. On the other hand, what if a traditionally deactivated ring were to experience an external source of activation that would compensate for its inherent unreactivity? This situation is reminiscent of Meisenheimer complexes—anionic σ-adducts formed from the interaction of highly electron-deficient arenes with alkoxide nucleophiles.[4−6] With that in mind, it stands to reason that if an oxygen-based functional group is poised, at very close distance, to an electron-deficient arene ring in space, its lone pair of electrons should stabilize a Meisenheimer-like transition state[7,8] and thus alter its reactivity toward EAS (Figure 1).[9]

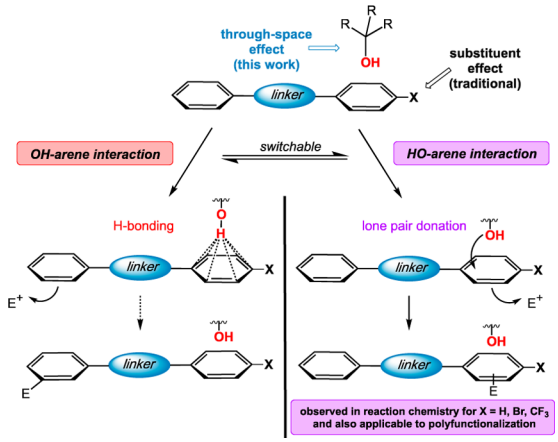

Figure 1. Switchable OH/HO−arene interaction guides nontraditional electrophilic aromatic substitution reactivity/selectivity.

Herein, we present examples of electron-deficient arene rings that undergo preferential substitution in competition with relatively electron-rich rings, whereby through-space interactions override traditional substituent effects. Furthermore, we exploit the heretofore-unknown propensity of a hydrogen-bonding OH−arene interaction to switch to the alternative HO−arene interaction in order to provide the basis for activation. We recently reported an F−arene interaction that achieves through-space EAS activation; we believed the phenomenon would be much stronger with an oxygen atom incorporated in a similar molecular scaffold, thus allowing traditional reactivity patterns to be reversed.[10]

To test our initial hypothesis, we chose target molecule **1**, which contains a hydroxyl group poised directly over an aromatic ring (Scheme 1); we envisioned this could assist with EAS through a Meisenheimer-like interaction. The synthesis of **1** is shown in Scheme 1. First, benzylation of previously reported alcohol **2**,[10] followed by saponification and anhydride ring formation, affords alkene **3** (29% yield over three steps). To establish the "probe" and "control" rings, a Diels−Alder reaction of anthracene with **3** (160 °C, sealed tube), followed by debenzylation (H_2, Pd/C), provides alcohol **4** (43% yield

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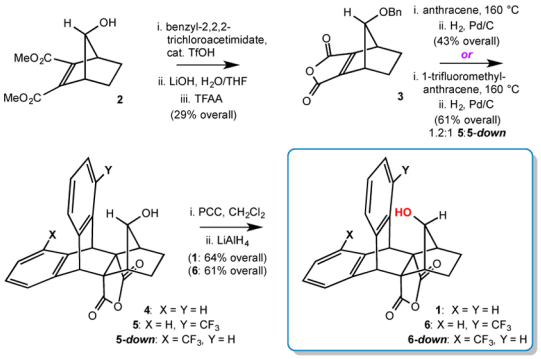
Scheme 1. Synthesis of the Probe Molecules 1 and 6



over two steps). Finally, epimerization of the hydroxyl group in **4** (PCC oxidation, then $LiAlH_4$ reduction) yields the desired alcohol **1** (64% yield over two steps).

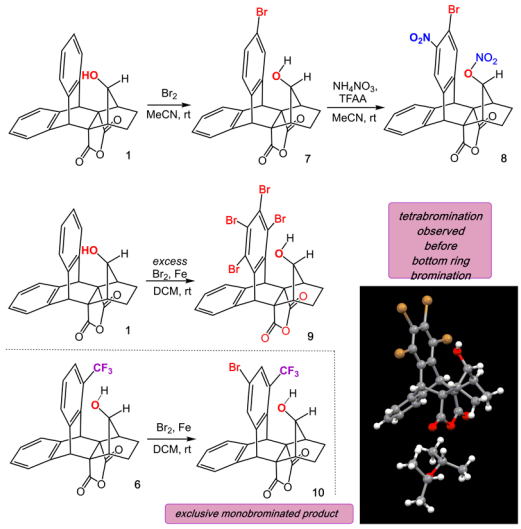
The OH−arene interaction of **1** is revealed by a red-shifted OH stretch (32 cm^{-1}) in the IR spectrum in chloroform when compared to the *out*-diastereomer **4** (Table S1). In the NMR spectrum ($CDCl_3$), the oxygen-bound proton is shielded (−0.21 ppm) and sharp in comparison to the broader resonance of the OH group in **4**, which is comparatively deshielded (1.16 ppm). Thus, it appears that intramolecular hydrogen bonding to the arene dominates in **1**, similar to interactions observed between OH groups and nonconjugated C=C bonds.[11]

The OH−arene hydrogen bond can be categorized as a type of cation−π interaction. It has been observed biologically; for example, the OH group of a threonine residue is positioned above the π-cloud of tyrosine in the enzyme glutathione transferase when complexed with glutathione.[12−15] Additionally, a water−phenylalanine interaction is featured in the complex of the anti-Alzheimer's drug donepezil with its target acetylcholinesterase.[16,17] In the case of small molecules, although a number of well-documented examples exist in the literature,[18−26] many aspects of the interaction remain unexplored. In terms of intermolecular interactions, OH−arene hydrogen bonding plays an important role in the formation of 1,1,2-triphenylethanol dimers in the solid phase.[27]

Upon examining an X-ray crystal structure of **1**, we noticed another interesting feature (Figure S1). The oxygen-bound hydrogen atom is disordered over two orientations: the *in*-form is bound to the arene and the *out*-form is involved in a hydrogen bond with the oxygen of an adjacent molecule. Note that the *out*-form can be described as a dominant HO−arene interaction, between the lone pairs on oxygen and the arene ring, instead of an OH−arene interaction. In order to study this HO−arene interaction in solution, we envisioned that a more electron-deficient arene ring would decrease the favorability of OH−arene hydrogen bonding, so we synthesized **5** and **6** in an analogous fashion to **1** and **4** (Scheme 1), replacing anthracene with 1-trifluoromethylanthracene[28] as the diene. The OH stretching frequencies of **5** and **6** are nearly identical to each other and to that of nonsubstituted *out*−OH **4**, suggesting that, in contrast to **1**, the hydrogen atom of the OH group of **6** is not hydrogen bound to the arene (a statement that is supported by DFT calculations; see Figure S4). In terms of NMR analysis, the OH in **6** is less shielded than **1** by 0.39 ppm. Since the hydrogen atom is facing outward, it is further from the ring and less affected by ring currents.

The OH−arene interaction is expected to be deactivating in an electrophilic aromatic substitution, whereas the HO−arene interaction should be activating. Which effect would dominate in EAS? Monobromination of **1** (Br_2, MeCN, room temperature) forms product **7** exclusively and under mild conditions, confirming that the ring perturbed by the hydroxyl group is activated (Scheme 2).[29,30] Bromine is a moderate electron-

Scheme 2. Reactions of 1, 6, and 7[a]



[a]Bottom right: ball and stick model of **9** from crystallographic coordinates. Note that there is an i-Pr_2O solvent molecule in the asymmetric unit.

withdrawing group that slows the rate of aromatic substitution by about 2 orders of magnitude.[31] Can the HO−arene interaction override bromine's deactivation? We were gratified to find that nitration of **7** also proceeds exclusively on the brominated ring (in addition to nitrate ester formation: Figure S2) (**8**).[32,33] In fact, we found that the nitrate ester forms *prior* to arene nitration (see the SI). It is noteworthy that an electron-deficient oxygen atom, as part of a nitrate ester, can direct EAS. When **1** was subjected to more forceful bromination conditions (excess Br_2, Fe metal, CH_2Cl_2), we monitored the reaction and observed tetrabromination of the top ring **9** before evidence of bottom ring bromination (Scheme 2 and Figure S3 show the crystal structure of **9**).[34,35]

We then sought a stronger electron-withdrawing group that would afford a more dramatic demonstration of the external activating effect of the hydroxyl group. One of the most potent deactivators is the trifluoromethyl group, which reduces the relative reactivity of an arene ring by more than 40000-fold.[36] This significant deceleration also means that any other electron-rich aromatic rings present in a typical synthetic sequence will undergo preferential aromatic substitution under most conditions. When **6** is subjected to standard bromination conditions at room temperature (Scheme 2) product **10** is obtained (57% yield). The mass balance is composed of starting material and a mixture of polybrominated products. No hint of monobromination on the other aromatic ring was observed, thus demonstrating the hydroxyl group's ability to override one of the strongest deactivating substituents. In order to attribute these nontraditional substitution patterns to the HO−arene interaction, several control experiments were conducted (Scheme 3).[37] The simplest comparison is between benzene

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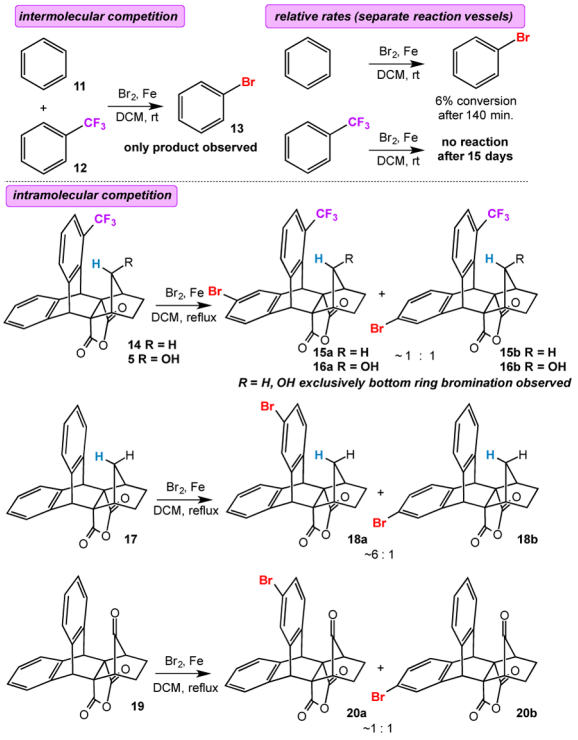
(**11**) and trifluorotoluene (**12**), as no through-space rigid atom−arene interaction would be present.

Scheme 3. Control Reactions Confirming the Role of HO−Arene Interaction in Through-Space Activation



In an intermolecular competitive bromination experiment (with benzene and trifluorotoluene in great excess of other reagents), bromobenzene (**13**) was the only product observed upon complete consumption of Br_2. To illustrate further the relative reaction rates, benzene and trifluorotoluene were subjected to the same bromination conditions in separate vessels. The initial rate of bromobenzene formation was monitored over 140 min to 6% conversion, while no brominated trifluorotoluene isomers were observed after 15 days. However, criticism of these control experiments may come from the rigidity and substitution pattern of our probe molecule—are there unforeseen features of the framework that *prevent* functionalization of the bottom ring (or otherwise activate the top ring)? Thus, we synthesized **14** (see Scheme 3 and S1),[38] with the hydroxyl group replaced by a less (but still slightly activating) hydrogen atom as an intramolecular control experiment. We also employed *out*-OH **5** as another control. At room temperature, no bromination was observed after multiple attempts, thus providing initial support for the necessity of the HO−arene activation. Upon refluxing the mixture, bromination was observed exclusively on the bottom ring at the two distal positions in a ∼1:1 ratio (**15**−**16a**:**15**−**16b**). Therefore, the HO−arene activation is crucial in dictating both reactivity and selectivity with regard to this control.

We employed another control molecule, **17**,[10] where there is equal substitution on the aromatic rings and the hydroxyl group is again replaced with a hydrogen atom (Scheme 3). Bromination of this compound resulted in a mixture of monobromides on the top ring and the bottom ring in a 6:1 ratio. This suggests that the inherent difference in reactivity between the two rings is fairly small on this compound but that the top ring is still slightly activated by the inward facing hydrogen atom. We would expect this theoretically and in analogy to the profusion of "hydrido-bridged" structures in organic chemistry.[39] Additionally, a slight inherent deactivation of the bottom ring may contribute as well, but the effect is evidently small. This result is in rough accord with previous investigations (nitration of this compound gives a 2:1 ratio of top ring to bottom ring substitution).[10] As a final control, we employed ketone **19**, which contains no activating atom (the carbonyl is farther from the arene than the inward hydroxide in **1** or the hydrogen in **17**). Bromination of **19** resulted in a ∼1:1 ratio of top ring to bottom ring products (Scheme 3).

The observed selectivity was further corroborated by DFT calculations. We calculated the relative energies of various σ-complexes leading to potential brominated products of **1**, **6**, and **14** (Table S2). In the case of **1**, the isomer with bromine on the top ring is more stable than that on the bottom ring by 9.0 kcal (ωB97XD/6-311++G**; *exo* bromo slightly more stable than *endo* epimer). This large difference would explain the preferential substitution on the top ring. In the case of **6**, the top ring complex is favored by a lesser amount (3.8 kcal) than in **1**, whereas in the case of **14**, the bottom ring complex is favored by 5.2 kcal.

Is the activation truly "Meisenheimer like"; i.e., is there a developing covalent bond between oxygen and an arene carbon in the transition state? DFT calculations can shed light on this question using **6** as the model. At ωB97XD/6-311+G**, the σ-complex intermediate **6A** for bromination of **6** was optimized with an explicit solvent molecule (dichloromethane). The oxygen atom in the optimized structure is in close proximity (1.57 Å) to the carbon *ortho* to the trifluoromethyl group and *para* to the complexed bromine (Figure 2). There clearly is a

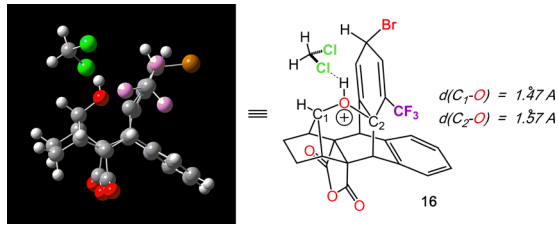


Figure 2. Optimized structure of **6A**, the σ-complex intermediate for endobromination of **6**, at ωB97XD/6-311+G**.

covalent bond between oxygen and the arene carbon atom, which serves to explain the relative stability of this σ-complex compared to those that lead to other products. In addition, an AIM (atoms in molecules) analysis shows the existence of a bond critical point between the oxygen and carbon (Figure S5).[40] Finally, if **6** undergoes exclusive bromination on the top ring (with the trifluoromethyl substituent), is the top ring still considered the more electron-deficient ring in the ground state? Natural bond orbital (NBO) analyses of the carbon atoms on the aromatic rings show more positive charge character on the trifluoromethylated ring regardless of the presence (**6**) or absence (**14**) of the hydroxyl group (Table S3). Thus, the HO−arene activation must be more influential during the formation of the σ-complex.

In conclusion, we demonstrated that the HO−arene interaction dramatically increases an aromatic ring's reactivity with electrophiles such that this phenomenon may override the influence of deactivating substituents. In particular, preferential EAS on a trifluoromethyl-substituted ring over a comparable

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unsubstituted aromatic ring is a testament to the strength of this interaction. Not only does this expand the selectivity "rules" of EAS in chemical synthesis based on substituent effects, but it should also draw attention to interactions in, for instance, enzyme active sites where forced HO−arene interactions are plausible.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09792.

General experimental procedures and characterization data (PDF)
X-ray data for compound **1** (CCDC 1545393) (CIF)
X-ray data for compound **8** (CCDC 1547865) (CIF)
X-ray data for compound **9** (CCDC 1547866) (CIF)

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Notes

The authors declare no competing financial interest.

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