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How Do Face-to-Face Stacked Aromatic Rings Activate Each Other to Electrophilic Aromatic Substitution?

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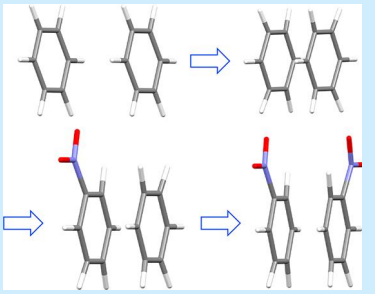
ABSTRACT: We have found that face-to-face π-stacked aromatic rings show the propensity to activate one another toward electrophilic aromatic substitution through direct influence of the probe aromatic ring by the adjacent stacked ring, rather than through the formation of relay or "sandwich complexes." This activation remains in force even when one of the rings is deactivated through nitration. The resulting dinitrated products are shown to crystallize in an extended parallel offset stacked form, in stark contrast to the substrate.



The π-stacking of aromatic rings has proven to be a durable field of interest because of its undeniable importance to chemistry and biology.[1] Generally speaking, edge-to-face and parallel offset are the most common motifs; face-to-face is rather more rare because of electron repulsion between the π-electron clouds.[2,3] The question of how π-stacking affects chemical reactivity has been relatively less explored, although some interesting examples have been reported in the literature.[4,5] From our point of view, a signal reaction that could be so influenced is electrophilic aromatic nitration (Figure 1),[6] which could occur directly or be templated by

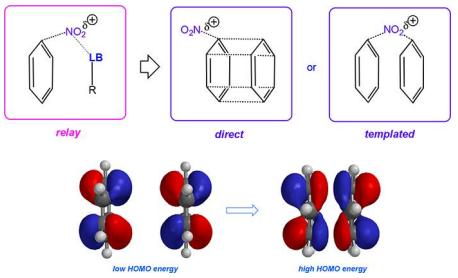
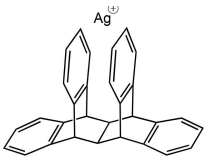


Figure 1. Paradigms of "stacked" electrophilic aromatic substitution (EAS) and change in HOMO energy with stacking distance.

both rings. We recently found that a Lewis base positioned over an aromatic ring can activate the ring toward electrophilic substitution in a type of "relay effect"[10c] and we considered whether the same may be operating here.

As the aromatic rings approach one another face-to-face, HOMO energy increases, which theoretically makes the array more reactive to an electrophile. The literature reveals some indication that face-to-face stacked aromatic rings can influence each other in select EAS reactions.[7] For example, the molecule janusene[7d] (Scheme 1) was shown to undergo

Scheme 1. Silver(I) Coordination in a Stacked Aromatic



preferential nitration at the stacked ring, although very precise structural assignments were lacking at the time of publication. More recently, an intriguing computational study appeared that showed the ability of janusene to stabilize Ag^+ ions through sandwich complexes.[7f] Cram et al. established that EAS in Lewis-base-substituted paracyclophanes often occurred with a preference for the cross-ring pseudogem isomer.[8] Other researchers interpreted this result as arising from a Lewis base deprotonation of a Wheland-type intermediate.[9]

We have had a long-standing interest in through-space activation of electrophilic aromatic substitution[10] and sought an unequivocal test of the fundamental question of how stacked EAS activation would occur. In this note, we confirm the hypothesis in a polyaromatic model probe that was chosen

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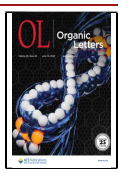

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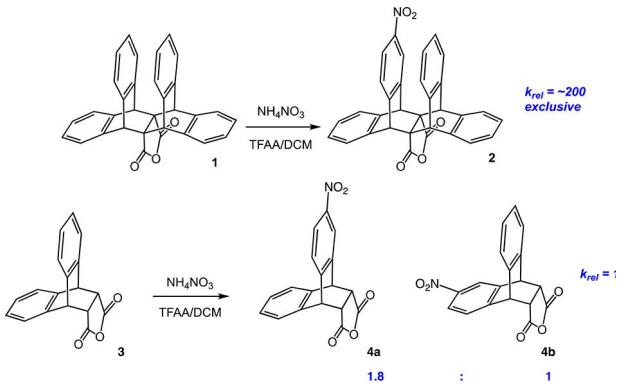
for its ease of synthesis and its tendency toward clean, fairly unequivocal reactions. It possesses a face-to-face stacked system that is ungirded by strained bridges (to the extent that if destabilization occurred, it would be due to electron repulsion of the π-clouds) and possesses internal control aromatic rings whose steric hindrance is approximately the same (if not less). Known tetraaromatic anhydride **1** (Scheme 2) proved to be an ideal candidate, as the probe and control rings contain identical substitution patterns.[4]

Scheme 2. Mononitration of 1 and 3

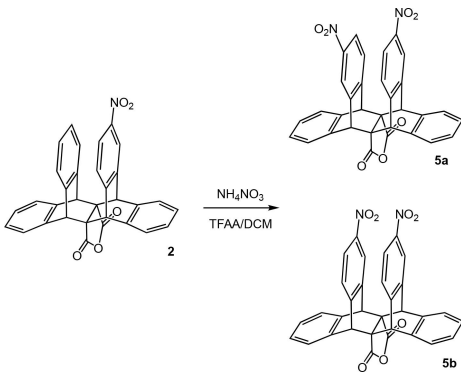


Geometrically, **1** shows a pair of face-to-face stacked aromatic rings that possess a slight splay. The substituted carbons on the stacked rings are each 3.04 Å away from their corresponding partners on the opposite side and presumably contribute most to the hypothesized ground-state destabilization of the system. The para−meta positions on the tops of the rings are 3.97 Å apart. In any case, the distances are short enough to influence reactivity. The contrast between this enforced face-to-face structure and the dominant motif (edge-to-face) occurring in the bulk crystal data of the Cambridge Structural Database (CSD) (Figure S4) should be noted. In the event, **1** underwent rapid and exclusive nitration in 85% yield (1 equiv of NH_4NO_3, trifluoroacetic anhydride, CH_2Cl_2, 12 h) on one of the axial rings, which is consistent with stacked activation (Scheme 2). The assignment was confirmed by an X-ray crystal structure of isolated product **2**; this partially disordered structure showed no evidently interesting extended packing.

Two control experiments established the activated nature of **1**'s axial rings. First, diarene **3**, bereft of a stacked motif yet electronically identical to **1** in every other way, underwent nonselective nitration. Second, a mixture of **1** and **3** was subjected to 0.75 equiv of nitrating agent; only **2** was observed as a product, thereby demonstrating intermolecular activation (consistent with a rate difference in nitration of >200). Resubmission of mononitrated **2** to the same reaction conditions (1 equiv, 12 h) led to additional nitration exclusively on the *adjacent stacked ring* in 72% yield (Scheme 3). Both dinitrated molecules **5a** and **5b**, formed in equal quantities, are symmetrical, as confirmed by their ^{1}H NMR splitting patterns and their X-ray crystal structures.

Product **5a** provides a particularly illuminating contrast to **1** in the solid state (Figure 2). For example, the stacked aromatic rings position themselves more closely (d_1 shrinks 0.8 Å, and the somewhat inflexible d_2 shrinks less at 0.08 Å). This result contrasts and complements the theoretical studies of Wheeler et al. on the origins of substituent effects in π-stacked

Scheme 3. Nitration of 2



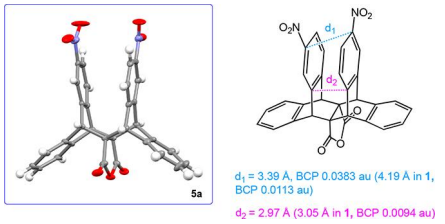


Figure 2. X-ray crystal structure of **5a** (50% probability ellipsoids) and the C−C distances d_1 and d_2.

aromatics,[11] wherein it is shown that key interactions originate primarily from the substituents themselves, not the delocalized rings.

Reduced electron density on the stacked rings would also contribute to a closer interaction, as reflected in AIM calculations,[12] wherein bond critical points (BCPs) between stacked rings increase in magnitude for the nitrated products. For instance, a weak BCP in **1** between substituted carbons on adjacent rings (0.0094 au) is replaced by a significant BCP between nitro-substituted carbons in **5a** (0.0383 au, Figure 2).

We also noted a significant difference in the way these mono- and dinitrated tetraaromatic molecules crystallize. Both dinitrated molecules show networks of parallel offset π-stacked aromatic rings that extend throughout the crystal lattice (Figure 3). In each case, the two nitrated axial rings form a π-

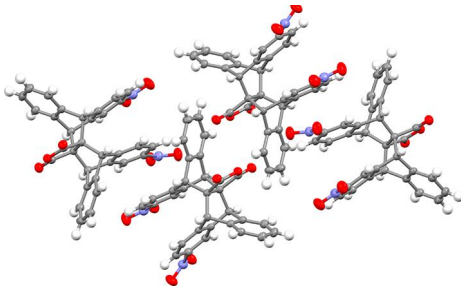


Figure 3. Packing diagram of **5a** showing extended stacking form (top, 50% thermal ellipsoids).

stacked network, whereas no such network is observed in the crystal structure of the mononitrated analogue **2** or non-nitrated starting material **1**.[4] Both reduced splaying of the rings, and the effect of the nitro groups appeared to be determinative in dictating packing. As a point of contrast, related molecules such as nitro- and dinitro[2,2]-paracyclophane[13] pack in an edge-to-face style.

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In terms of DFT calculations,[14] the potential energy surface for initial mononitration strongly indicates an outside approach of nitronium ion to **1** (M06-2*X*/6-311G(d), DCM, Figure 4).

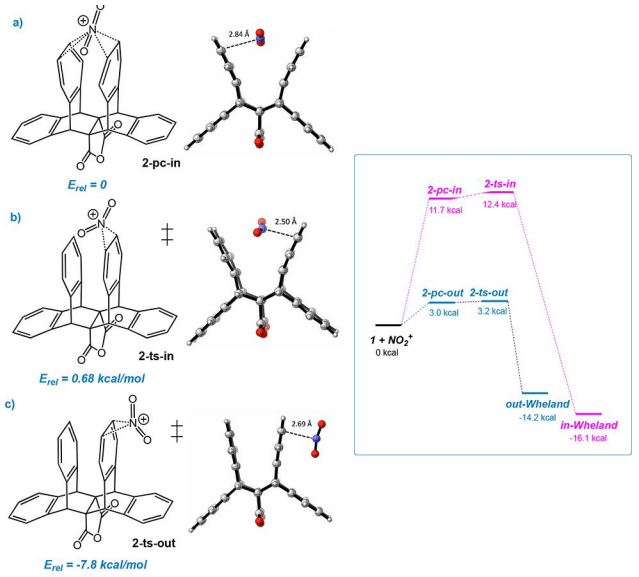

Figure 4. Precomplexation (**2-pc-in**) and transition states (**2-ts-in** and **2-ts-out**) for nitration in π-stacked tetraaromatic moiety **2** optimized at Integral Equation Formalism Polarizable Continuum Model (solvent = DCM) M062*X*/6-311G(d).

However, an inside approach possesses some interesting features. For example, we found a symmetrical precomplex (**2-pc-in**) wherein both aromatic rings are sandwiching the nitronium ion (Figure 4a). This precomplex evolves to the corresponding Wheland intermediate (σ-complex) through transition structure **2-ts-in**, which is located a scant ∼0.68 kcal/mol above the precomplex **2-pc-in** in terms of free energy. In contrast, the outside approach of NO_2^+ results in a transition structure (**2-ts-out**) that is predicted to be ∼9.2 kcal/mol *lower* in free energy than **2-ts-in**. The TS for nitration of the control ring is significantly higher in free energy, vis-à-vis **2-ts-in**, as expected.

To probe the remote effect of the adjacent arene ring upon nitration, truncated ethylene model systems **6** and **7** were investigated. They both reveal slightly higher activation barriers, presumably because of a lack of $\pi-\pi$ through-space activation. Further, a 4.8 kcal/mol ground-state destabilization energy was found from the homodesmotic relationship in Figure 5a, which is indicative of repulsive electrostatic effects. Subsequently, to probe this aspect, we applied a model system comprising two π-stacked benzene rings without an anhydride platform and energy decomposition analysis (EDA). From this truncated model, an optimal "slipped" π-stacking distance of 3.8 Å was found for nitration wherein stabilizing cation$-\pi$ interactions aided by $\pi-\pi$-stacking were present (Figure 5b). Further, this analysis revealed unfavorable Pauli repulsion as the main contributor to the interaction energy (ΔE_{int}) below 3.0 Å, whereas with increasing distance between the ring systems, favorable electrostatic and orbital interactions were the major contributors to ΔE_{int} (Figure 5c). Notably, this optimized distance of 3.8 A is comparable with the crystal structure of **1** with a $\pi-\pi$-stacked distance of 3.9 Å.

Next, we probed how substitution on the adjacent ring engaging in π-stacking and not undergoing nitration would

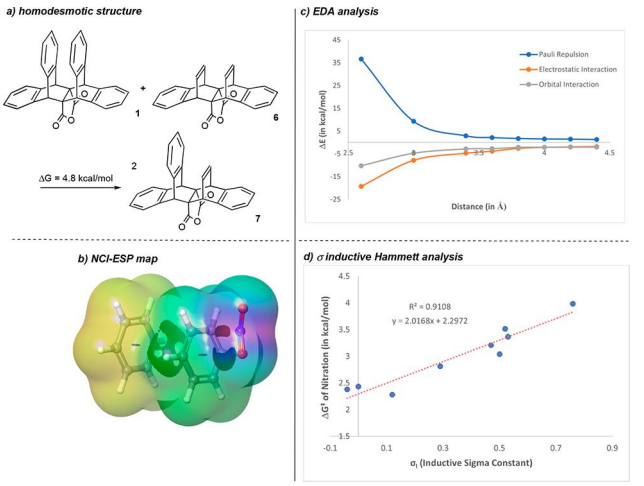

Figure 5. (a) Homodesmotic calculation. (b) Noncovalent interactions and electrostatic potential of aryl−aryl−nitronium interactions. (c) EDA analysis of "slipped" aryl−aryl π-stacked interactions. (d) $\Delta G^{\ddagger}$ of nitration vs σ-induction Hammett analysis for substituents: NH_2, OH, CH_3, H, Br, Cl, F, CN, and NO_2.

impact the activation barriers. This resulted in linear free energy relationship (LFER), derived from the plot of the activation barrier ($\Delta G^{\ddagger}$) vs Hammett inductive sigma constant (σ_I) for a series of nitration transition states, correlated with stabilizing cation-π interaction in the presence of electron-donating groups and destabilization by electron-withdrawing groups (R^2 = 0.91, Figure 5d).

In extrapolating from these findings, we conjectured that bromination would also be a viable mode of reactivity for the tetraaromatic system. We found, for example, that **1** undergoes preferential bromination on the top rings, which results in an inseparable mixture of *ortho*- and *meta*-brominated products (Figure 6).

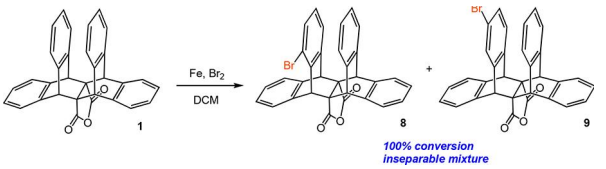

Figure 6. Monobromination of **1**.

The case of stacked aromatic rings in EAS would seem to involve the adjacent aromatic moiety as a through-space *stabilizer* as opposed to a *coordinator*, as precomplexation in this case would involve a very tight squeeze in between stacked aromatic rings, which is in stark contrast to what we found for through-space activation of lone-pair-containing functional groups.[10a−c] The results confirm that a source of π-electron density, including aromatic rings, can activate adjacent rings when properly positioned. Most remarkably, even an $-NO_2$-substituted deactivated aromatic ring can provide the necessary π-density to activate a proximate probe ring. Further studies on other through-space-promoted EAS reactions by stacked aromatic rings are underway and will be reported in due course.

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■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01401.

Compound coordinate data (ZIP)

Experimental procedures, crystallographic data, NMR spectra, and computational information (PDF)

Accession Codes

CCDC 2209581−2209583 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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