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Conformation as a Protecting Group: A Regioselective Aromatic Bromination En Route to Complex π-Electron Systems

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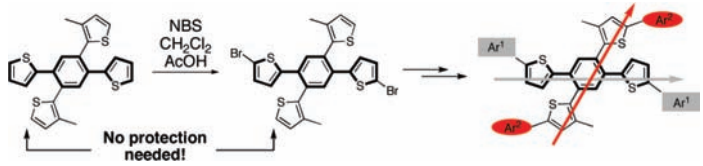
ABSTRACT



A new strategy to achieve regioselective functionalization of a sterically congested aromatic system driven by conformational demands is described. Electrophilic substitution occurs at the more planarizable subunit without undesired chemistry at mutually reactive sites and without the need for protecting or masking groups that must be manipulated later. Model studies are described to understand this selectivity, and possibilities for the construction of orthogonal, differentially substituted π-systems of relevance for molecular electronics are demonstrated.

The conformational dynamics of congested oligoaromatic molecules have been a subject of intense research for several decades.[1] Steric bulk positioned ortho to arene−arene linkages has pronounced effects on the available macromolecular conformational space. In the most extreme of cases, this leads to *atropisomerism* allowing for the separation and isolation of distinct conformations at room temperature. More commonly, conformation has marked impacts on reactivity, such as the dramatic rate differences found during the course of several transformations of cyclohexanes possessing reactive axial or equatorial substituents.[2] We report here our studies of a crowded aromatic system that bears mutually reactive sites yet whose conformation allows for these sites to be addressed selectively and in a stepwise manner rather than reacting simultaneously but at different rates, in effect a conformationally controlled and protecting-group-free regioselective bromination. We present model systems to understand the selectivity and then apply this transformation to the syntheses of conformationally distinct thioacetate-functionalized π-conjugated systems of relevance for organic electronics.

The synthesis of elaborate organic electronic materials poses a frustrating bottleneck in the pursuit of fundamental investigations or commercial exploitations. Palladium-catalyzed cross-coupling chemistry has risen to this challenge as witnessed by π-conjugated cruciform architectures and other types of cross-conjugated systems.[3] In some cases, these molecules are built by joining two complex subunits at a late stage in the synthetic execution; unfortunately, the requisite cross-coupling partners are not routinely available on the scales of their simpler commercial counterparts.

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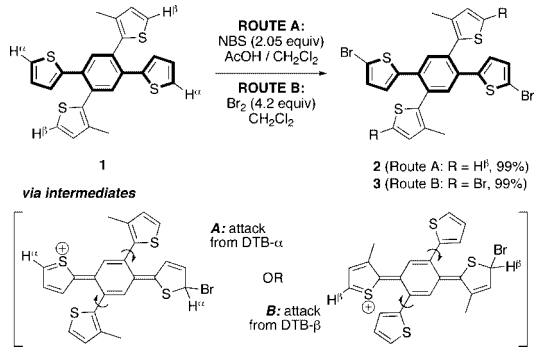
Iterative construction of π-conjugated architectures via selective masking and unveiling of reactive functional groups has yielded many complex structures built from simpler components.[4] Equally important is the development of new chemistry that minimizes reliance on protecting group manipulation to selectively and in a stepwise manner functionalize particular sites of π-conjugated systems in the presence of multiple mutually reactive sites.

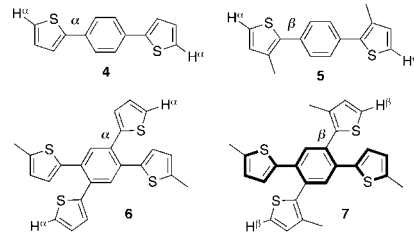
Sterically congested **1** was designed as an electrochemical precursor to porous conducting polymers since the four *o*-thiophenes cannot adopt completely coplanar conformations. It bears two distinct *p*-di-2-thienylbenzene (DTB) subunits with reactive α-thienyl positions indicated by the carbons attached to H^{α} (DTB-α) and H^{β} (DTB-β). We could not determine the prevalent connectivity of electrochemically prepared polymers derived from **1** given the lack of structural detail afforded by cyclic voltammetry (CV). We conjectured that the methyl groups should enforce a more twisted π-system in the DTB-β fragment, thereby biasing polymerization through the more easily planarized DTB-α fragment (boldened in **1**). On the other hand, the slightly electron-donating methyl groups would favor oxidation and subsequent reactivity through the DTB-β fragment with or without the need to engage the entire DTB π-system.

Scheme 1. Regioselective (Route A) and Exhaustive (Route B) Bromination of a Crowded Aromatic (Top) and Possible Reaction Intermediates (Bottom)



As the intermediates formed during electrophilic aromatic substitution resemble those from anodic electropolymerization, we examined the reactivity of **1** with brominating agents (structures **A** and **B** represent possible brominated intermediates). Initial experiments indicated a strong preference (ca. 80−90%) for the dibromide **2** corresponding to bromination at the carbon formerly bearing H^{α}: the optimized conditions (route A) yielded **2** quantitatively and on a gram-scale. Reaction through DTB-β might require higher energy planar intermediates (such as **B**) given the potential for steric clashing between the thienyl methyl groups and the phenylene ring protons if forced into coplanarity. However, treatment of **1** with 4.2 equiv of Br_2 (route B) provided tetrabromide **3** quantitatively. The fact that *both* DTB pathways reacted set the stage for the selective and stepwise construction of differently substituted π-conjugated systems built from the core scaffold **1**. Before proceeding, we sought to understand the origins of this unusual selectivity.

Thiophenes readily brominate at the α-positions, and the slightly electron-donating methyl substituent would suggest enhanced reactivity at the H^{β} carbons of DTB-β in the absence of any directing stereoelectronic effects. We prepared models to dissect or block the DTB pathways present in **1** (Figure 1) using routine Stille coupling to install the



entry	DTB-α / °	DTB-β / °
1	38	61
4	25	-
5	-	43
6	49	-
7	-	61

Figure 1. Model DTB pathways and their calculated (B3LYP/6-31G*, Spartan) thiophene−phenylene dihedral angles determined about the bonds labeled by α or β.

individual thiophenes. Models **4** and **5** eliminated any cofacial influences while maintaining the presumably reactive oligoaromatic DTB π-system. Models **6** and **7** were prepared to examine the reactivity of DTB-α and DTB-β in the presence of cofacial thiophenes that have been rendered unreactive due to the α-methyl groups.

Comparative reactivity studies were conducted with the two sets of model compounds. Both **4** and **5** were separately treated with NBS to provide near-quantitative conversions to their respective α,α′-dibromides ($H^{\alpha}\rightarrow$Br). Competition experiments with equimolar ratios of **4** and **5** led to essentially equimolar consumption when applying either route A or route B. While **6** was consumed over the course of 3 days under route A conditions to converge on what we also assign as the α,α′-dibromide ($H^{\alpha}\rightarrow$Br), **7** provided a complex and undecipherable mixture of products. This is due to apparent reactivity elsewhere within **7** such as along the α-methyl fragment shown in bold. Although interpretation of the competition experiments between **6** and **7** was precluded by the lack of clear NMR handles that could be resolved and assigned to products resulting from bromination at the carbon bearing H^{α} (**6**) or H^{β} (**7**), over the course of 1 week, **6** was consumed in greater amounts when reacted competitively with **7**.

These results at first glance may seem to indicate that both DTB pathways are viable reaction partners during the slow generation of bromine in route A. However, they are consistent with the reactivity found for **1** after inspection of

(4) (a) Zhang, J.; Moore, J. S.; Xu, Z.; Aguirre, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 2273–2274. (b) Schumm, J. S.; Pearson, D. L.; Tour, J. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1360–1363. (c) Liess, P.; Hensel, V.; Schlüter, A.-D. *Liebigs Ann.* **1996**, 1037–1040. (d) Bell, M. L.; Chiechi, R. C.; Johnson, C. A.; Kimball, D. B.; Matzger, A. J.; Wan, W. B.; Weakley, T. J. R.; Haley, M. M. *Tetrahedron* **2001**, *57*, 3507–3520. (e) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717. (f) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758–759.

the relevant dihedral angles existing among neighboring thiophene and benzene units (Figure 1, right). Despite the difference in calculated gas-phase (B3LYP/6-31G*) dihedral angles among the planes of the arenes in **5** (43°) relative to **4** (25°), the thiophene nuclei of both dissected DTB pathways underwent comparable electrophilic aromatic substitution. The calculated dihedral of **6** was 49°, rendering it slowly reactive under the conditions of route A, while the 61° dihedral for **7** shut down a clean reaction at H^{β}. Given that **1** holds dihedral angles within the DTB-α and DTB-β segments at 38° and 61°, respectively, there must exist a transition between 50°−60° at which point the bromination becomes less favorable (vide infra).

Trends in reactivity were mirrored in electronics. The first CV sweep of **4** and **5** revealed essentially identical onsets of oxidation (0.95 V), although the more complex behavior for **5** may reflect inductive perturbations of the methyl groups or differences in diffusion to the working electrode (Figure 2A). The onset for **1** was *more positive* than for **4**, but the

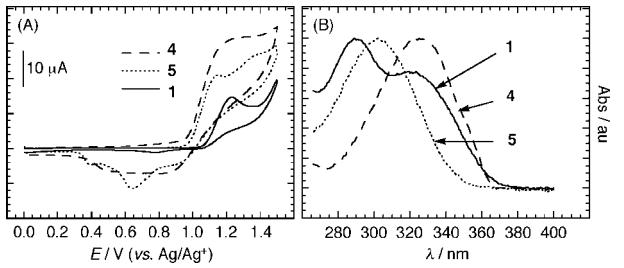


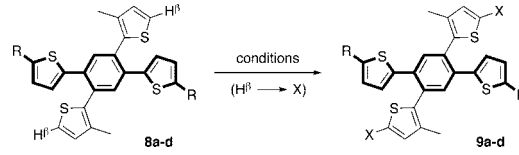
Figure 2. (A) CV and (B) UV−vis for **1** (——), **4** (---) and **5** (▪▪▪). CV conditions: 100 mV/s at a 2 mm^2 Pt button, 0.2 mM monomer in 0.1 M *n*-Bu_4PF_6/CH_2Cl_2. UV−vis conditions: $CHCl_3$.

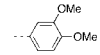
potentials of peak anodic activity ($E_{p,a}$) for **1** and **4** were identical. The UV−vis of **1** revealed a bimodal signature with peak absorptions at 290 and 322 nm, while **4** had a λ_{max} at 324 nm and **5** had a λ_{max} at 305 nm (Figure 2B). The lower energy λ_{max} of **4** (compared to **5**) implies a longer conjugation path as expected for a system that should be easier to planarize given the lack of steric clashing from the methyl groups. The lower energy absorption of **1** closely matched that of **4**.

These data suggest that the methylthiophenes play a *steric* role to dictate solution conformational preferences and subsequent reactivity differences among the two DTB segments, as opposed to an electronic influence stemming from the cofacially disposed *o*-thiophenes of **1**.[5] Oligothiophene ionization potentials increase with the torsion angle between repeat units, even more sharply at angles greater than 40°.[6] This rationalizes the indiscriminate reactivity of **4** and **5** in competition experiments, the lack of clean reactivity for **7** and the selectivity observed in the bromination of the DTB-α pathway in **1**. The 61° dihedral within DTB-β renders its ionization potential high enough to drive reactivity to the more coplanar DTB-α π-system of **1** yet not high enough to shut down reactivity under more aggressive conditions. This subtle energy difference is powerful enough to take advantage of synthetically as further described below.

Palladium cross-coupling efficiently diversified the electronics of the DTB-α pathway of dibromide **2** via arylation (Stille, **8a**; Suzuki, **8d**) and alkynylation (Sonogashira, **8b**,**c**). Subsequently, a diverse scope of reaction chemistries listed in Table 1 was employed for additional manipulation at the

Table 1. Diversification of the DTB-β Pathway[a]



entry	R	conditions	X	yield / %
a	-Ph	A	Br	99
b	-C≡C-Si(*i*-Pr)$_3$	B	I	86
c	-C≡C-Ph	C	I	86
d		D	I	68[b]

[a] Reagents and conditions: (A) NBS, DMF, rt; (B) (i) *n*-BuLi (3 equiv), THF, TMEDA, 0 °C, (ii) I_2, 0 °C to rt; (C) same as (B) but no TMEDA; (D) (i) $Hg(OAc)_2$, CH_2Cl_2/AcOH (95:5), rt; (ii) I_2. [b] Yield from NMR analysis of mixtures with inseparable monohalogenated impurities.

carbon bearing H^{β} such as electrophilic halogenation (**9a**,**d**) and direct α-thienyl lithiation (**9b**,**c**). The conversion of **8a** to **9a** using NBS was more the exception that the rule: most other substrates provided complex reaction mixtures after treatment with NBS or molecular bromine. Indeed, these reaction conditions were not easily generalized for other substrates thereby requiring fine-tuning of specific conditions on a case-by-case basis. Although we focused our efforts on thienyl halides for palladium cross-coupling, the organolithium intermediates prepared in situ could be trapped in principle by a variety of other electrophiles to generate Grignard reagents, silanes, aldehydes, etc.

After installing the reactive handles, we prepared molecules designed to assemble on electronically relevant surfaces (Scheme 2). It is important to recognize that the sequences from **2** utilize fairly routine transformations and smaller cross-coupling partners.[7] From **9b**, a Suzuki, protiodesilylation and Sonogashira sequence yielded **10** while Sonogashira coupling on **9d** yielded **11**. The *conformation* imposed on the π-systems spanning the two distinct thioacetate linkage pathways was a key design element. The more

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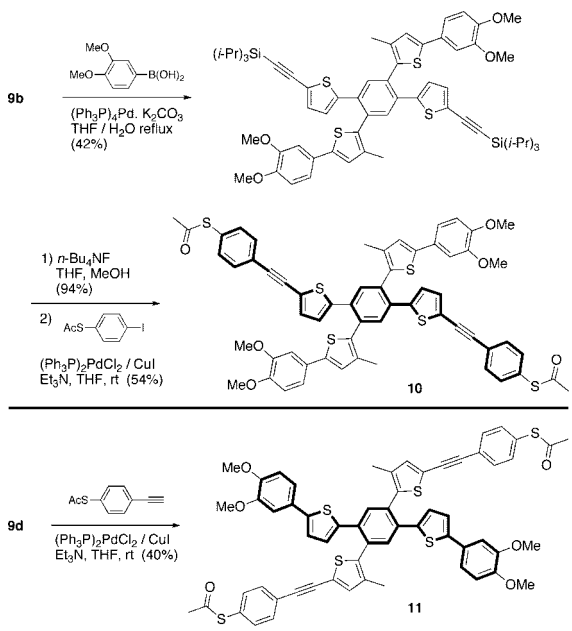
(7) Shi, Z. F.; Wang, L. J.; Wang, H.; Cao, X. P.; Zhang, H. L. *Org. Lett.* **2007**, *9*, 595–598.

Scheme 2. Synthesis of Conformationally Distinct Cruciform Molecules **10** and **11**



planarizable (boldened) pathway spans the two sulfur anchors in **10** while in **11** it does not. The dimethoxyphenyl units were employed only to facilitate chromatography. The separation of minor side products resulting from incomplete conversion on more nonpolar substrates proved problematic, but they could be carried through additional synthetic transformations and removed at a later stage. The calculated HOMO and LUMO orbitals for **10** and **11** show clear differences in spatial distrubution due to the conformational perturbation imposed on the cruciform π-system. These densities should prove easily tunable in practice through the inclusion of different substituents in lieu of the dimethoxybenzene moieties.

Experimentally, this conformational bias perturbed the optical properties and the redox behavior of **10** and **11**. The relative oscillator strengths of the lowest energy transitions were altered, and the relative luminescence quantum yield of **10** was reduced by 55% compared to **11** (Figure 3A). The anodic behavior for **10** was split into two defined redox processes, while **11** displayed a single redox wave of greater intensity (Figure 3B). Orbital density, π-conjugated backbone conformation and through-space interaction also affect charge transport in molecular electronics.[8] The approach described here will enable the rapid preparation and evaluation of a spectrum of complex molecular electronic materials relevant for a more detailed understanding of transport phenomena

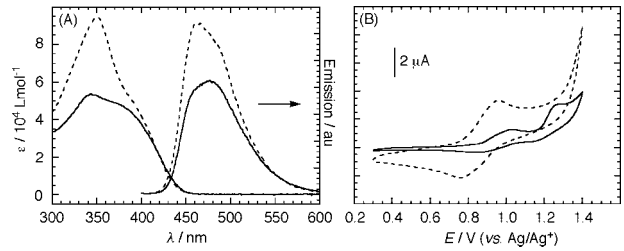


Figure 3. Electronic properties of **10** (——) and **11** (---). Conditions for UV−vis (A) and CV (B) are as detailed in Figure 2. Fluorescence excitation at 390 nm.

at the single molecule level. We are currently exploring the molecular properties of these and related molecules.

In conclusion, we report a highly selective functionalization strategy that relies upon the subtle conformational dynamics of a densely substituted benzene core. Unlike most conformational effects on reactivity that are manifested in rate differences among competing conformers, we see here how conformer energetics effectively protect one site from engaging an electrophile *but do not completely prohibit it*. As both DTB pathways are mutually reactive, this stereoelectronic bias allows us to address the two pathways stepwise without the need for masking or blocking groups that must be unveiled later. Standard manipulations with readily available reagents can rapidly diversify the simple core scaffold to generate electronic structures that otherwise would require synthetically complex cross-coupling partners. This approach offers unusual molecules whose electronic properties may be modulated through both macromolecular conformation and the electronics of their π topologies.

Acknowledgment. We thank Johns Hopkins University and the National Science Foundation (CAREER, DMR-0644727) for generous and continued support.

Supporting Information Available: Monomer synthetic schemes, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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