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Synthesis of Acetylenic Cyclophanes via Intramolecular Self-Assembly: Evidence of Perfluorophenyl–Phenyl Quadrupole Interactions in the Solution State

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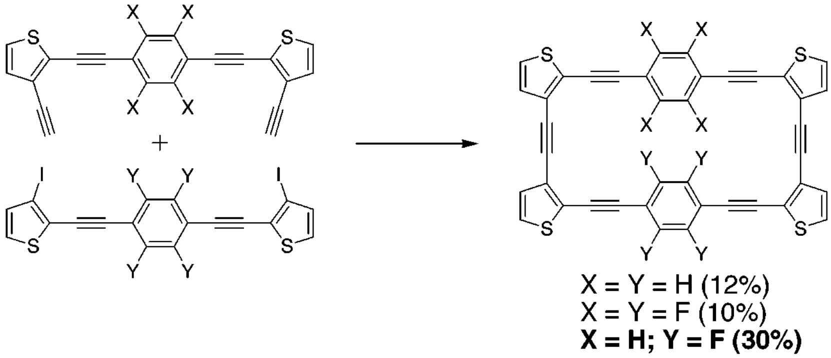
ABSTRACT



Reported herein is an example of a solution-state cross-coupling cyclization with an outcome mediated by perfluorophenyl–phenyl electrostatic interactions.

The alternate coplanar stacking of benzene and hexafluorobenzene in the solid state is a well-known phenomenon attributed to the nearly equal yet opposite quadrupole moments of the two species.[1] Indeed, the prevalence of the aryl−perfluoroaryl (Ar_H-Ar_F) solid-state packing motif has established this couple as a reliable supramolecular synthon for use in crystal engineering, as exemplified by the elegant studies of Coates and co-workers.[2,3] Despite proven utility in the solid state, such electrostatic interactions have not established themselves as viable components of template-directed synthesis in the *solution* state. The paucity of examples illustrating solution-state self-assembly of conformationally flexible molecules via Ar_H-Ar_F stacking interactions is not surprising considering that quadrupole−quadrupole attractive forces are weak and diminish at a rate of r^{-5} (where r is the distance between the two quadrupoles). Indeed, Ar_H-Ar_F interactions in the solution state are typically observed in organic solvents only when Ar_H and Ar_F species are present in high concentrations or held in close proximity by an appropriate scaffold.[4−6] Despite this fact, electrostatic interactions remain a critical component in

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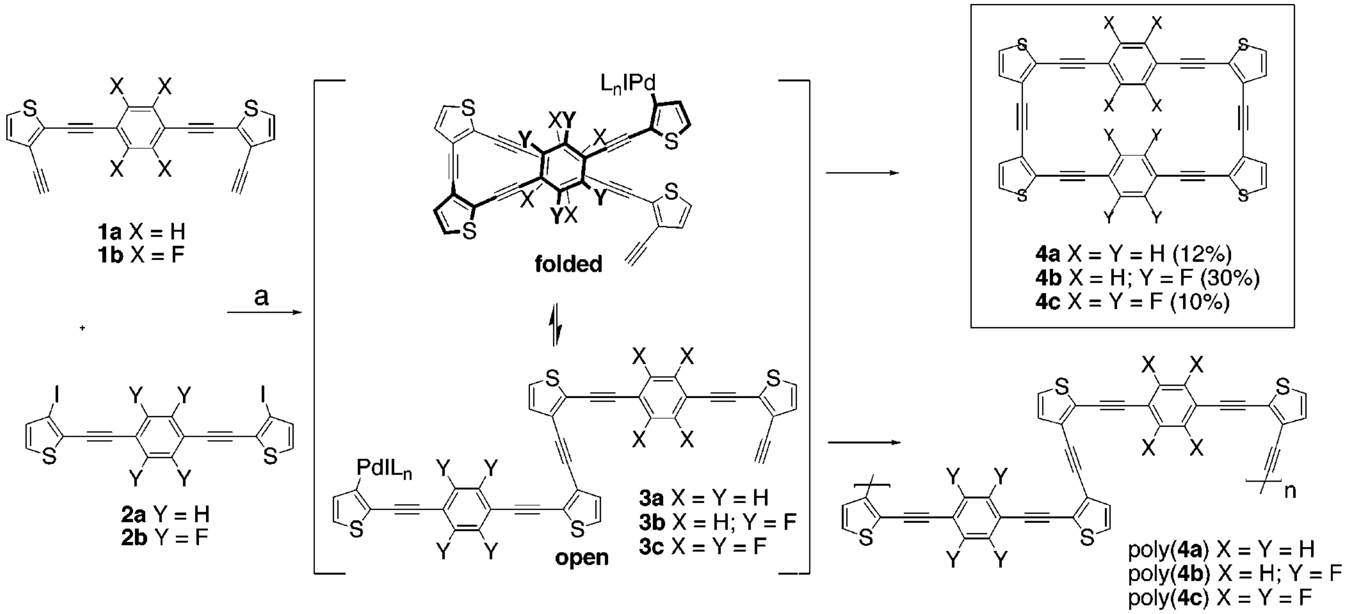
Scheme 1[a]



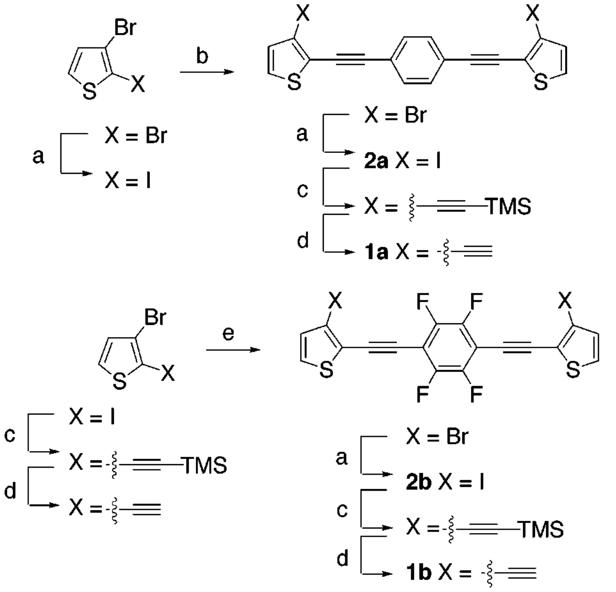
[a] (a) $PdCl_2(PPh_3)_2$; CuI; NH(*i*-Pr)$_2$; THF; 80 °C.

supramolecular chemistry,[2,3,7−9] as re-emphasized by recent studies involving catenane formation.[10] Herein we report an example of a solution-state reaction cyclization with an outcome influenced by $\mathrm{Ar_H}$−$\mathrm{Ar_F}$ electrostatic interactions.

During the course of unrelated studies directed at designing helical conjugated molecular architectures,[11] we serendipitously discovered a model system exhibiting evidence of quadrupole-enhanced self-assembly in the solution state. Specifically, this reaction involved the Sonogashira cross-coupling of **1** and **2** to yield compound **4**, an acetylenic cyclophane analogous to the type recently reported by Fallis and co-workers.[12] Presuming that the formation of cyclophane **4** proceeds via a stepwise cross-coupling, the favored conformation of linear intermediate **3** plays a decisive role in the production of cyclophane **4** or the corresponding poly(**4**) (Scheme 1). As such, favorable interactions between the aryl diad in the folded conformer of intermediate **3** should promote the formation of cyclophane **4**. In this case, intermediate **3** would serve as both substrate and template. In theory, the attractive (or repulsive) interactions between the phenyl moieties of intermediates **3a**−**c** can be qualitatively assessed by comparing the yields of cyclophanes **4a**−**c** versus their corresponding polymers. The syntheses of compounds **1** and **2** are shown in Scheme 2.

For our purposes, the synthesis of macrocycle **4** required subtle modifications to typical Sonogashira coupling conditions.[13] First, to minimize *intermolecular* $\mathrm{Ar_H}$−$\mathrm{Ar_F}$ interactions with solvent, THF was used in place of toluene (a potential $\mathrm{Ar_H}$ source) for the Sonogashira coupling.[14] Second, the reaction was performed under pseudo-high-dilution

Scheme 2[a]



[a] (a) *n*-BuLi; I_2, diethyl ether, −78 °C. (b) 1,4-diethynylbenzene, $PdCl_2(PPh_3)_2$, CuI, NH(*i*-Pr)$_2$, toluene, 80 °C. (c) TMSA, $PdCl_2(PPh_3)_2$, CuI, NH(*i*-Pr)$_2$, toluene, 80 °C. (d) K_2CO_3, MeOH/CH_2Cl_2. (e) 1,4-diethynyl-2,3,5,6-tetrafluorobenzene, $PdCl_2(PPh_3)_2$, CuI, NH(*i*-Pr)$_2$, toluene, 80 °C.

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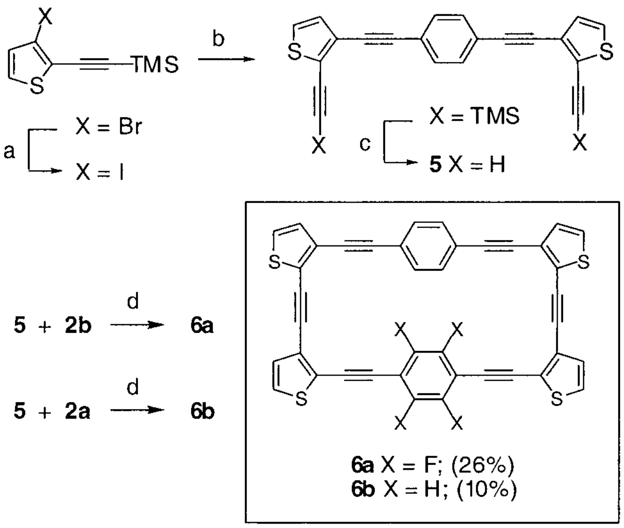
conditions to minimize polymer formation.[15] The yields of the three cross-coupling reactions (**1a** + **2a** → **4a**; **1a** + **2b** → **4b**; **1b** + **2b** → **4c**) are given in Scheme 1.

As would be predicted from electrostatic arguments, cyclophane **4b** (X = H; Y = F) is obtained in highest yield (30% versus 12% and 10% for **4b**, **4a**, and **4c**, respectively). These results were completely reproducible over several attempts despite minor changes to reaction conditions. As a result of the fact that no starting materials were recovered, we have tentatively ruled out inherent reactivity differences among substrates as the source of our observations. These results implicate Ar_H-Ar_F quadrupole interactions as a decisive force in determining the outcome of the reaction. In an effort to test the generality of this observation, Sonogashira cross-coupling of components **2** and **5** to yield macrocycle **6**, a regioisomer of compound **4**, was also performed (Scheme 3). As anticipated, the outcome of this cyclization was similar to that observed for **4**. Specifically, the yield of **6a** (Ar_H-Ar_F; 26%) exceeded that of **6b** (Ar_H-Ar_H; 10%).

Scheme 3[a]



[a] (a) *n*-BuLi, I_2, diethyl ether, −78 °C. (b) 1,4-diethynylbenzene, $PdCl_2(PPh_3)_2$, CuI, $NH(i\text{-}Pr)_2$, toluene, 80 °C. (c) K_2CO_3, MeOH/CH_2Cl_2. (d) $PdCl_2(PPh_3)_2$, CuI, $NH(i\text{-}Pr)_2$, THF, 80 °C.

On the basis of the aforementioned results, we propose that the folded (productive) conformer of **3b** is stabilized relative to that of **3a** and **3c** as a result of attractive Ar_H-Ar_F electrostatic interactions (Scheme 1). An analogous argument holds true for differences observed in compounds **6a** versus **6b**. Calculations[16] on the diethynylbenzene moiety diads of compounds **4a** and **4b** at the PM3 level of theory estimate an energy difference of 0.35 kcal/mol in favor of compound **4b**, thus qualitatively supporting our aforementioned presupposition. These effects may further be amplified if reversible intramolecular coordination to the Pd catalyst in folded intermediate **3** requires an even more intimate contact between the aryl diad. Although entropic effects would typically overwhelm such a small energy difference in solution, the conformationally restricted and rigid nature of intermediate **3** allows this weak interaction to have relatively profound consequences on the outcome of the reaction.

By extension of the results presented herein, electrostatic tuning of cofacial aryl moieties (via perfluorination or its equivalent) should provide a valid mechanism to alter both yield and effective ring strain in conformationally restricted macrocycles such as cyclophanes.

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Supporting Information Available: Experimental procedures and characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Calculations were performed using Titan software. Schrödinger, Inc., 1500 SW First Avenue, Suite 1180, Portland, OR 97201.