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Bis(hydroxy-isoindolinone)s: Synthesis, Stereochemistry, Polymer Chemistry, and Supramolecular Assembly

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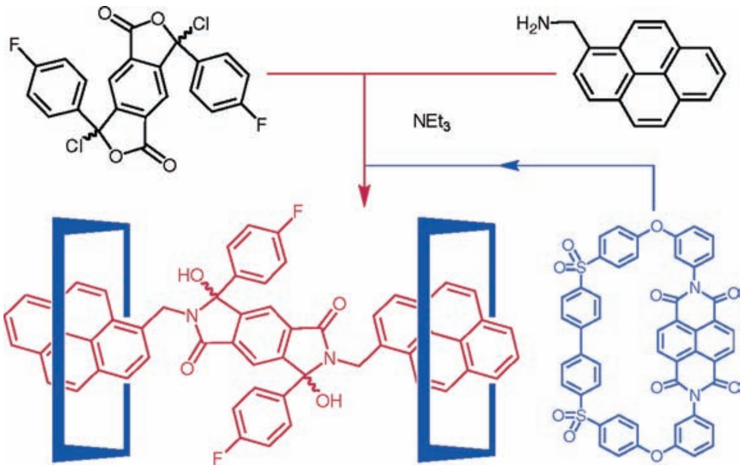
ABSTRACT



Pseudoacid chlorides of 2,5-bis(4-fluorobenzoyl) terephthalic acid and 4,6-bis(4-fluorobenzoyl) isophthalic acid condense with primary amines to afford diastereomeric bis(hydroxyindolinone)s in good isolated yields and with diamines to give high molecular weight poly(hydroxyindolinone)s. Bis-*N*-pyrenemethyl bis(hydroxyindolinone)s assemble, even in dipolar solvents such as DMSO, with macrocyclic diimide-sulfones to give [3]pseudorotaxanes stabilized by electronically complementary aromatic $\pi-\pi$-stacking and shape-complementary van der Waals interactions.

Among the various noncovalent binding interactions, aromatic $\pi-\pi$-stacking has played a very significant role in the development of supramolecular chemistry,[1] with π-donor$-\pi$-acceptor interactions being widely exploited for the construction of complex supramolecules[2] and novel types of co-crystals.[3] For example, the development of π-electron-accepting, tetracationic cyclophanes has enabled the synthesis of entire families of charged catenanes, rotaxanes, redox-driven switches, and molecular logic gates[4] via templated self-assembly with molecules containing π-electron-donor

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aromatic units.[5] A second important group of π-electron-accepting macrocycles, based on aromatic diimides such as naphthalene-tetracarboxylic diimide, has also afforded neutral catenanes and rotaxanes by templated reactions of aromatic diimides with 1,5-dialkoxynaphthalene derivatives.[6]

Prompted by the extreme thermochemical stability of aromatic polyimides and polysulfones, we have recently developed receptor molecules comprising macrocyclic homologues of such polymers.[7] Macrocycles such as **1**, containing π-electron-accepting aromatic diimide residues and biphenylene units with electron-withdrawing arenesulfonyl substituents, are found to bind strongly to electron-rich polycyclic arenes such as pyrene and perylene by electronically complementary $\pi-\pi$ stacking.[7] Computational modeling has also indicated that such binding might be reinforced by O−H···O═C hydrogen bonding in complexes of **1**, through the introduction of hydroxylic substituents on the guest molecule,[7] and in this context we have now explored the previously unknown *N*-pyrenemethyl hydroxy-isoindolinones (e.g., **2**) as potential components for assembly with macrocyclic imide-sulfone receptors such as **1**.

Routes to hydroxy-isoindolinones generally involve either addition of Grignard reagents to phthalimides or reactions of pseudo-2-benzoyl benzoyl chlorides with primary amines.[8] Here we chose to work with pseudo-2-(4-fluorobenzoyl) benzoyl chloride (**3**) since the presence of the fluoro substituent generates a characteristic set of multiplets in the ^{1}H NMR spectrum which enables more straightforward assignment of resonances. Thus, hydroxy-isoindolinone **2a** was obtained in 83% yield by condensation of **3** with 1-pyrenemethylamine in the presence of a tertiary amine. Complexation of **2a** with macrocycle **1** (1:2 molar ratio, 4 mM in **2a**) in $CDCl_3$/hexafluoropropan-2-ol (6:1, v/v) led to large upfield shifts of the macrocycle resonances assigned to H_a and H_b (0.68 and 0.97 ppm, respectively; see Figure S3, Supporting Information), and a 1:1 binding constant of 8×10^2 M^{-1} (±10%)[8] was determined for complex [**1**+**2a**] in this solvent mixture.

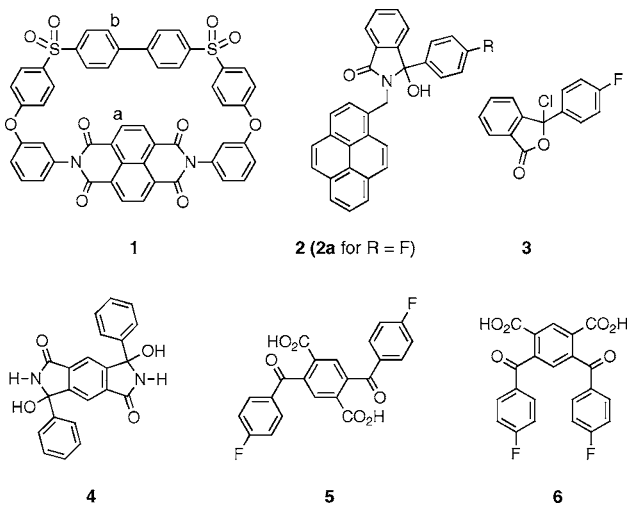

Figure 1. Macrocyclic receptor **1**, guest compounds **2** and **2a**, and intermediate **3**. Compounds **5** and **6** are key intermediates in the present work, and **4** represents the only previous example of a bis(hydroxy-isoindolinone).

Dipolar aprotic solvents such as DMF and DMSO generally inhibit molecular associations involving hydrogen bonding and complementary $\pi-\pi$-stacking, through powerful solvation of the interacting components.[7,9] In this work, however, significant binding between **2a** and **1** (1:2 molar ratio, 4 mM in **2a**) was observed in DMSO, with the pink color arising from intermolecular charge transfer still being visually detectable and resonances assigned to H_a and H_b still showing significant upfield shifts, $\Delta\delta$, of 0.19 and 0.31 ppm, respectively (Figure S4, Supporting Information).

Attempts to obtain single crystals for X-ray analysis of the complex formed between **1** and **2a** were unsuccessful, but as centrosymmetric molecules often crystallize more readily than noncentric structures, we next turned to analogous bis(*N*-pyrenemethyl) bis(hydroxy-isoindolinone)s, as potential components of supramolecular assemblies. Only a single bis(hydroxy-isoindolinone) (**4**) has been reported previously, produced by condensation of ammonia with the pseudoacid chloride of 2-benzoyl benzoic acid.[10] Interestingly, **4** was originally formulated as 2,5-dibenzoyl terephthalamide,[10a] and the actual bis(hydroxy-isoindolinone) structure was only recently identified by single-crystal X-ray analysis.[10b]

In the present work, a mixture of the isomeric dicarboxylic acids **5** and **6** was obtained by reaction of excess fluorobenzene with pyromellitic dianhydride in the presence of aluminum chloride. Fractional crystallization gave pure **5** and **6** in 32% and 37% yields, respectively. Thionyl chloride converted **5** and **6** to the pseudoacid chlorides **7** and **8**, respectively, and reactions of these pseudoacid chlorides with pyrenemethylamine afforded the *N*-pyrenemethyl bis(hydroxy-isoindolinone)s **9** and **10** in 97% and 86% yields (Scheme 1). The identities of compounds **7**, **9**, and **10** were fully confirmed by spectroscopic and single-crystal X-ray analyses (see Supporting Information).

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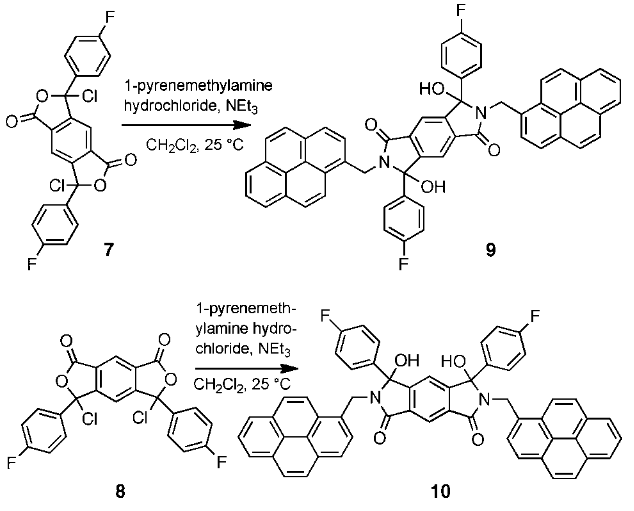
Scheme 1. Synthesis of Bis-*N*-pyrenemethyl Hydroxy-isoindolinones **9** and **10**



Both **9** and **10** are potentially diastereomeric, and although the single crystals isolated in both cases were pure [*R*,*S*/*S*,*R*] (*anti*) enantiomers, there is no obvious reason why the *R*,*R*/*S*,*S* (*syn*) diastereomers should not also be formed. Indeed, the ^{1}H NMR spectrum of **9** showed two singlet hydroxyl resonances and two triplet resonances arising from the protons *ortho* to fluorine, in both cases with relative integrals of ca. 5.5:1 (Figures S5 and S6, Supporting Information). Analogous pairs of resonances were also observed in the spectrum of **10**, though with relative integrals of ca. 3.0:1 reflecting the presence of diastereomers in the same molar ratio.

Complexation of pale yellow macrocycle **1** with colorless **9** in chloroform/hexafluoropropan-2-ol (6:1 v/v) produced an intense red color, indicating formation of a $\pi-\pi$-stacked complex, and ^{1}H NMR studies in this same solvent showed upfield shifts for the macrocycle resonances assigned to H_a and H_b (Figure 1) of 0.87 and 1.00 ppm, respectively, at a 1:1 mol ratio of the two components (Figure S7, Supporting Information). As with **2a**, complexation of **9** with macrocycle **1** was noticeably weaker in DMSO than in chloroform/hexafluoropropan-2-ol as judged by ^{1}H NMR complexation shifts (Figure S9, Supporting Information). Nevertheless, deep red single crystals suitable for X-ray analysis were obtained by vapor diffusion of methanol into a solution of **1** and **9** (2:1 molar ratio) in DMSO. The crystal structure confirmed formation of a centrosymmetric [3]pseudorotaxane (**11**), with each pyrene unit of **9** being fully encapsulated by a molecule of **1** (Figure 2).

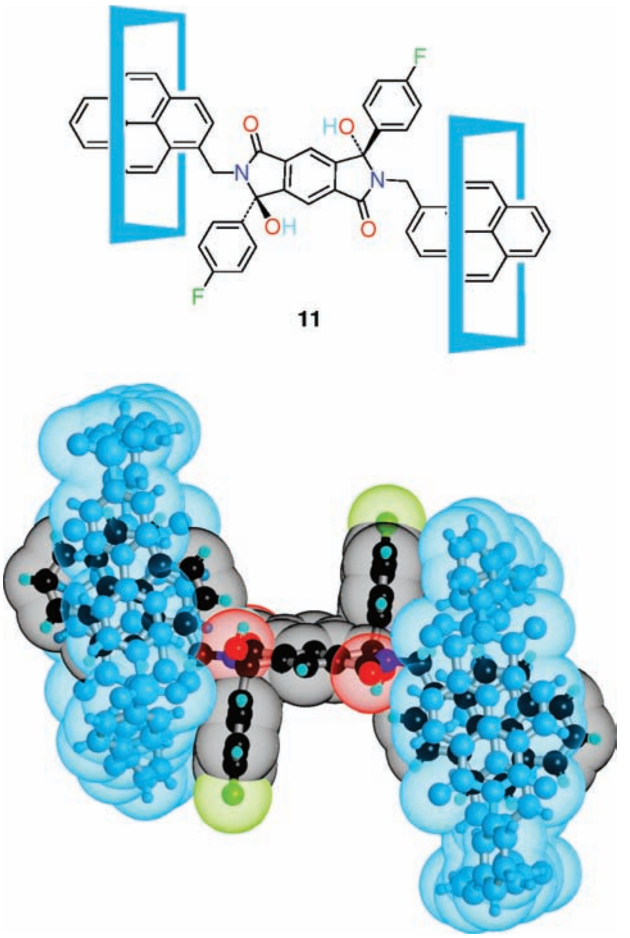


Figure 2. X-ray structure of the [3]pseudorotaxane **11**, formed by assembly of macrocycle **1** (two molecules, in blue) with compound **9** (1 molecule, *anti* isomer). The shape complementarity of the assembled components is evident in the matching of van der Waals surfaces. The hydroxylic hydrogens of **9** do not interact with the macrocycle in the crystal but may form hydrogen bonds to disordered DMSO.

The principal contribution to binding clearly arises from multiple donor−acceptor $\pi-\pi$-stacking between the electron-rich pyrene and electron-deficient diimide and biphenylene-disulfone units. The transannular distances between the centroid of the pyrene unit and the centroids of the biphenylene unit and diimide ring system are 3.81 and 3.68 Å, respectively. The diameter of macrocycle **1** (from the centroid of the biphenylene linkage to the centroid of the diimide residue) contracts from 8.19 Å, in its unbound state,[7] to 7.40 Å on binding to compound **9**. There are close contacts between the fluorophenyl ring of **9** and the 4-sulfonylphenoxy ring of **1**, in the form of shape-complementary C−H···π and a range of other van der Waals interactions (see Figures 2 and S14, Supporting Information). In view of the unexpected absence of hydrogen bonding between components **1** and **9**, we conclude that it is these shape-complementary interactions which provide the additional stabilization needed for assembly of the [3]pseudorotaxane in dipolar solvents such as DMSO.

The pseudoacid chlorides **7** and **8** also react cleanly with primary aromatic amines, specifically 1,4-toluidine, affording compound **12** in 68% isolated yield (Scheme 2). The X-ray structure of the *anti* diastereomer of **12** is shown in Figure 3, again confirming that hydroxy-isoindolinones (not amides) are formed in this type of reaction. This result strongly

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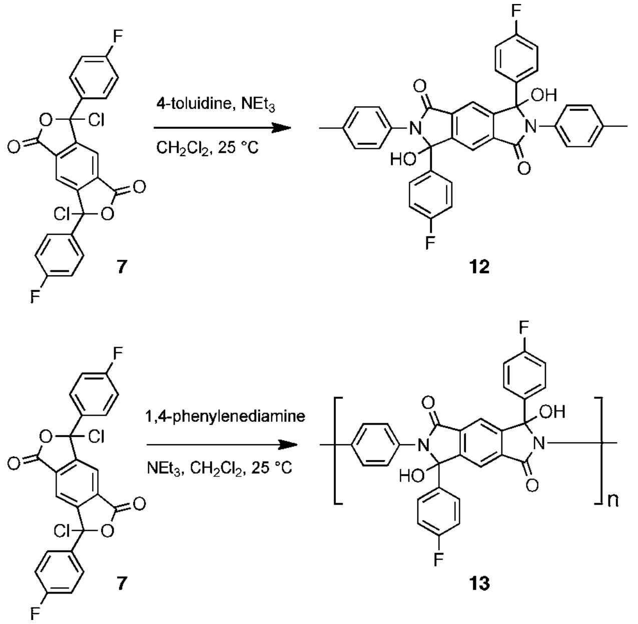
Scheme 2. Synthesis of the Di-*p*-tolyl Bis(hydroxy-isoindolinone) **12** and the Analogous Polymer **13**



suggested that high molecular weight poly(hydroxy-isoindolinone)s might be accessible by condensation of **7** and **8** with aromatic diamines, and indeed condensation of **7** with 1,4-phenylenediamine (1:1 mol ratio, Scheme 2) in *N*-methylpyrrolidone (NMP) afforded polymer **13** in 98% yield, with an inherent viscosity (in NMP) of 0.70 dL g^{-1}.

Gel permeation chromatography (GPC) of **13** gave values of $M_n = 78$ kDa and $M_w = 95$ kDa, relative to polystyrene standards, confirming the formation of high molecular weight polymeric material, and ^{1}H NMR data—though broadened considerably—were consistent with the proposed structure (Scheme 2). This new type of polymer, containing a rigid aromatic backbone and a high density of hydrophilic hydroxyl groups on the main chain, could have potential applications in areas such as nonfouling and highly functional materials for pharmaceutical or biomedical applications. In passing, it should be noted that reactions of the pseudoacid chlorides of 2,5-dibenzoyl terephthalic acid and 4,6-dibenzoyl isphthalic acid with *aliphatic* primary diamines have previously been reported to yield conventional polyamides,[11] but in view of the results described here, it seems almost certain that these "polyamides" must be poly(hydroxy-isoindolinone)s, analogous to **13**.

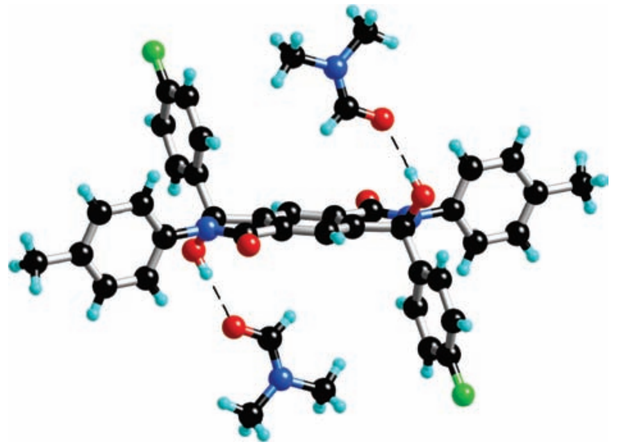


Figure 3. X-ray structure of the bis(hydroxy-indolinone) **12** (*anti*-isomer). The molecule has a crystallographic center of symmetry, and each hydroxy group forms a strong hydrogen bond (OH···O=C = 1.89 Å, O···H···O = 173°) to a molecule of solvating dimethylformamide.

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Supporting Information Available: Methods and materials. Detailed experimental procedures and full characterization data for **2a**, **5**, **6**, **7**, **8**, **9**, **10**, **12**, and **13**. Crystal data and full crystallographic information for **7**, **9**, **10**, **11**, and **12** (CCDC 780120, 780121, 761447, 780122, and 780123, respectively) in CIF format. Proton NMR spectra of macrocycle **1** showing complexation with **2a**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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