Synthesis of Rigid Polycyclic Secondary Diamines: Bis-(2,3:6,7-Iminodimethylene)anthracene and Bis-(2,3:6,7-Iminodimethylene)-9,10-dicarboxyethenoanthracene

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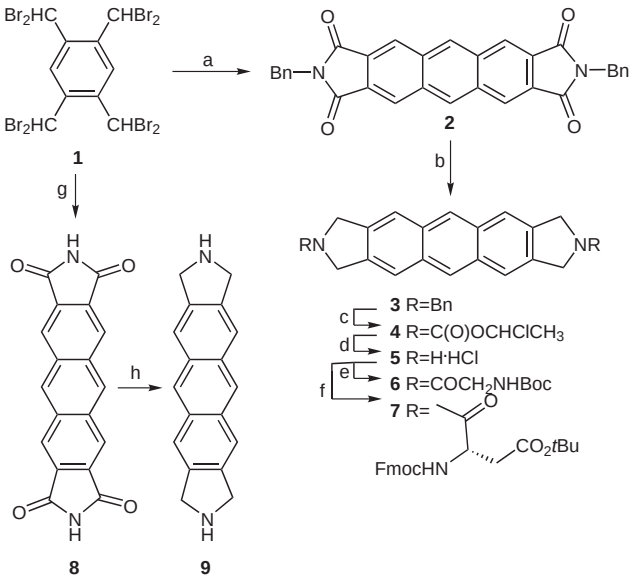
Abstract: The synthesis of two rigid polycyclic secondary diamines, bis-(2,3:6,7-iminodimethylene)anthracene and bis-(2,3:6,7-iminodimethylene)-9,10-dicarboxyethenoanthracene, by means of Diels–Alder reaction between 1,2,4,5-tetra(dibromomethyl)benzene and maleimides followed by imide reduction, is described. Furthermore, these two cyclic secondary diamines undergo acylation with N-protected amino acids, thus providing functionalized, amphiphilic, and chiral building blocks for incorporation into supramolecular systems.

Key words: arenes, amino acids, Diels–Alder reactions, polycycles

Conformationally well-defined and rigid diamino compounds are ideal building blocks possessing reactivity suitable for high-yielding construction of artificial receptors[1–7] and molecular capsules[8] via e.g. amide, urea, sulfonamide bond forming reactions. Furthermore, it is desirable that such diamines possess physical properties (e.g. fluorescence, strong UV-absorption etc.) that allow for simple monitoring of various molecular events (e.g. molecular associations). Within this context, rigid polycyclic aromatic molecules carrying cyclic secondary amino groups appear attractive. Herein we report the synthesis of two novel rigid and fluorescent aromatic secondary diamines; bis-(2,3:6,7-iminodimethylene)anthracene and bis-(2,3:6,7-iminodimethylene)-9,10-dicarboxyethenoanthracene, as well as their acylations with amino acids. These molecules are particularly well suited for incorporation into supramolecular systems, because they present a large hydrophobic surface and can be conjugated with for example amino acids to obtain biomimetic amphiphilic properties.

The synthesis of *N*,*N*′-diphenyl-2,3:6,7-anthracene described by McLaughlin et al.[9] provided a starting point for the present project. The octabromide **1**[9] was subjected to Diels–Alder aromatisation with *N*-benzyl maleimide in the presence of sodium iodide in dimethylacetamide to give **2** in an acceptable 46% yield. The diimide **2** was completely insoluble in all solvents available in our laboratory and NMR spectra could not be recorded. The structure of **2** was finally confirmed by mass spectrometry and by conversion into the known corresponding anthracene tetracarboxylic acid[9] by reflux in 2 M NaOH for 2 hours. The reduction of **2** was achieved with lithium aluminium hydride in the presence of aluminium chloride in THF to give the *N*,*N*′-dibenzyl-derivative **3** in 62% yield. The improved solubility of **3** as compared to **2**, allowed characterization with NMR and MS. Removal of the benzyl groups in **3** was accomplished via 1-chloroethyl carbamate formation[10] to give **4**, followed by immediate hydrolysis of the crude carbamate **4** in refluxing methanol to afford the diamine hydrochloride **5**. The diamine **5** could alternatively be obtained via a shorter reaction sequence, albeit in lower overall yield; BH_3·THF/BF_3·THF-mediated reduction of the Diels–Alder aromatisation product **8** between **1** and unsubstituted maleimide gave the free base **9** in 25% yield. With the diamine **5** at hand, its nucleophilicity was confirmed by acylation with N^{α}-Boc-glycine and N^{α}-Fmoc-L-Asp(*t*-BuO)-OH, which proceeded smoothly to give **6** (65%) and **7** (75%, Scheme 1).



Scheme 1 a) *N*,*N*-Dimethylacetamide, NaI, 80 °C, *N*-benzylmaleimide, 46%; b) $LiAlH_4$, $AlCl_3$, THF, reflux, 62%; c) 1-chloroethyl chloroformate, PhH, $(CH_2Cl)_2$; d) MeOH, reflux, 55% over 2 steps; e) *N*,*N*-diisopropylcarbodiimide, 1-hydroxybenzotriazole, THF, H_2O, $NaHCO_3$, N^{α}-Boc-Gly-OH, 65%; f) *N*,*N*-diisopropylcarbodiimide, 1-hydroxybenzotriazole, THF, H_2O, $NaHCO_3$, N^{α}-Fmoc-L-Asp-(O-*t*-BU)OH, 75%; g) *N*,*N*-dimethylacetamide, NaI, 80 °C, maleimide, 30%; h) THF, BH_3·THF, BF_3·THF, 25%.

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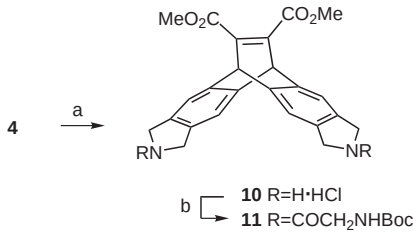
Dibenzobarrelene frameworks obtained by Diels–Alder reactions between anthracene derivatives and acetylenes have proven to be particularly useful building blocks for the synthesis of water-soluble host molecules.[11–15] A dibenzobarrelene framework could be synthesized from the crude bis-carbamate anthracene **4** by Diels–Alder reaction with dimethyl acetylene dicarboxylate, followed by immediate carbamate hydrolysis, to give the diamine **10** (Scheme 2). As for the corresponding anthracene derivative **5**, acylation of **10** with N^{α}-Boc-protected glycine was straightforward to give **11** in 69%.



Scheme 2 a) (i) Dimethyl acetylene dicarboxylate, $PhCH_3$, 120 °C, (ii) MeOH, reflux, 72%; b) *N*,*N*-diisopropylcarbodiimide, 1-hydroxybenzotriazole, THF, N^{α}-Boc-Gly-OH, 69%.

In summary, short syntheses towards novel rigid polycyclic aromatic secondary diamines, have been developed. Furthermore, acylation of these amines, i.e. with amino acids, provided molecules possessing amphiphilic and chiral properties, which are interesting within the context of constructing novel biomimetic host molecules. We envision these diamines to be useful as building blocks for the construction of various supramolecular systems.

***N*,*N*′-Dibenzyl-2,3:6,7-anthracenedicarboximide (2)**: To a solution of **1** (40 g, 52.3 mmol) and *N*-benzylmaleimide (20 g, 105 mmol) in *N*,*N*-dimethylacetamide (500 mL) was added NaI (80 g) and the mixture was heated at 80 °C for 48 h. The dark solution was then filtered and washed with H_2O and hot dioxane to give **2** as a bright yellow solid (12 g, 47%), which was stable up to 230 °C and insoluble in organic solvents. MALDI-TOF-MS; *m*/*z* calcd for $C_{32}H_{20}N_2O_4Na$ [M + Na]: 519.1. Found: 519.4.

***N*,*N*′-Dibenzyl-bis-(2,3:6,7-iminodimethylene)anthracene (3)**: THF (15 mL, dried over $LiAlH_4$) was added to a three-necked round bottom flask equipped with a reflux condenser. $AlCl_3$ (663 mg, 5 mmol) was added slowly at 0 °C under N_2, followed by $LiAlH_4$ (570 mg, 14.2 mmol). To the resulting suspension was added diimide **2** (1.0 g, 2 mmol). The mixture was stirred at r.t. for 1 h, refluxed for 3.5 h, then cooled to r.t., and finally poured onto ice (40 g) in 2 M NaOH. The THF was evaporated and compound **3** was extracted repeatedly into CH_2Cl_2, dried (Na_2SO_4) and concentrated. Column chromatography (SiO_2, CH_2Cl_2/MeOH/Et_3N 60:4:1) afforded **4** in 62% yield as a solid that was stable up to 230 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 2 H, H-9, H-10), 7.74 (s, 4 H, H-1, H-4, H-5, H-8), 7.37–7.50 (m, 10 H, Ph), 4.06 (s, 8 H, C*H*$_2$NCH$_2$Ph), 3.98 (s, 4 H, PhCH$_2$). FAB-HRMS: *m*/*z* calcd for $C_{32}H_{29}N_2$ [M + H]: 441.2331. Found: 441.2350.

bis-(2,3:6,7-Iminodimethylene)anthracene hydrochloride (5): To a solution of compound **3** (500 mg, 1.13 mmol) in 1,2-dichloroethane/benzene (16 mL, 1:1) was added 1-chloroethyl chloroformate (2.2 mL, 20 mmol) at 0 °C under N_2. The reaction mixture was stirred at r.t. and then refluxed for 24 h. The solvent was evaporated to give the crude carbamate **4**, which was sufficiently pure for the next step. The crude **4** was refluxed in MeOH (50 mL) for 24 h. The diamine hydrochloride **5** precipitated, was filtered, washed with MeOH, and dried under vacuum (183 mg, 55% from **3**). Mp 223–226 °C. ^1H NMR (400 MHz, D_2O): δ = 8.40 (s, 2 H, H-9, H-10); 7.92 (s, 4 H, H-1, H-4, H-5, H-8); 4.70 (s, 8 H, 4 CH_2). FAB-HRMS: *m*/*z* calcd for $C_{18}H_{16}N_2$ [M + H]: 260.1313. Found: 260.1353.

bis-[2,3:6,7-(*N*-Boc-glycyl)iminodimethylene]anthracene (6): To a solution of 1-hydroxybenzotriazole (101 mg, 0.75 mmol) and N^{α}-Boc-Gly-OH (128 mg, 0.75 mmol) in dry THF (10 mL), was added *N*,*N*′-diisopropylcarbodiimide (114 μL, 0.75 mmol). The solution was stirred for 45 min then poured into a solution of **5** (100 mg, 0.30 mmol) in H_2O (20 mL), immediately followed by addition of $NaHCO_3$ (63 mg, 0.75 mmol). After 12 h, the product was extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, and flash chromatographed (SiO_2, CH_2Cl_2/MeOH/Et_3N 100:2:1) to give **6** (112 mg, 65%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 2 H, H-9, H-10), 7.85,7.83 (2 s, 4 H, H-1, H-4, H-5, H-8), 5.47 (br s, 2 H, NH), 4.95, 4.89 (2 s, 8 H, $ArCH_2$), 4.02 (bs, 4 H, CH_2), 1.41 (s, 18 H, CH_3). FAB-HRMS: *m*/*z* calcd for $C_{32}H_{39}N_4O_6$ [M + H] 575.2870. Found 575.2880.

bis-{2,3:6,7-[*N*-Fmoc-aspartyl(*t*-BuO)]iminodimethylene}anthracene (7) was prepared in 75% yield in a manner similar to that for **6**. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.38 (s, 2 H, H-9, H-10), 7.89 (s, 4 H, H-1,H-4, H-5, H-8), 7.77 (d, 4 H, *J* = 7.4 Hz, FmocH), 7.62 (t, 4 H, *J* = 6.5 Hz, FmocH), 7.18–7.45 (m, 8 H, FmocH), 5.89 (br d, 2 H, *J* = 9.5 Hz, NH), 5.07 (br q, 2 H, *J* = 6.2 Hz, CHCO), 5.02 (s, 8 H, CH_2N), 4.42 (m, 4 H, CH_2O), 4.24 (br t, 2 H, *J* = 7.2Hz, OCH_2CH), 2.96 (dd, 2 H, *J* = 8.1, 16.0 Hz, CH_2CO), 2.71 (dd, 2 H, *J* = 5.7, 16.0 Hz, CH_2CO), 1.46 (s, 18 H, CH_3). FAB-HRMS: *m*/*z* calcd for $C_{64}H_{62}N_4O_{10}Na$ [M + Na]: 1069.4364. Found: 1069.4397.

2,3:6,7-Anthracenedicarboximide (8) was prepared in 30% yield in a manner similar to that of **2**. Compound **8** was insoluble in organic solvents. FAB-HRMS: *m*/*z* calcd for $C_{18}H_8N_2O_4$ [M]: 316.0484. Found: 316.0487.

bis-(2,3:6,7-Iminodimethylene)anthracene (9): Compound **8** (1 g, 3.2 mmol) was suspended in dry THF (40 mL) under N_2 atmosphere, followed by drop wise addition of BF_3·THF (1.7 mL) over 15 min. The mixture was heated to reflux for 2 h. The suspension was cooled to r.t. and BH_3·THF (50 mL, 1 M in THF) was added over 25 min. The mixture was refluxed for 48 h, cooled to 0 °C, quenched with HCl (6 M, 15 mL), and refluxed for another 24 h. The yellow solid was filtered, washed with THF, and then stirred with water for 2 h. Upon neutralization with aq KOH (6 M), the diamine **9** precipitated (395 mg, 25%). ^1H NMR (300 MHz, CD_3OD): δ = 8.40 (s, 2 H, H-9, H-10), 7.85 (s, 4 H, H-1, H-4, H-5, H-8), 4.75 (s, 8 H, CH_2). FAB-HRMS: *m*/*z* calcd for $C_{18}H_{16}N_2$ [M]: 260.1313. Found: 260.1353.

bis-(2,3:6,7-Iminodimethylene)-9,10-dicarboxyethenoanthracene (10): To a solution of crude **4** (150 mg, 0.32 mmol) in toluene (4 mL) was added dimethyl acetylenedicarboxylate (900 μL, 20 equiv) under N_2 and the solution was then heated to 110 °C in a sealed tube for 36 h. The excess dimethyl acetylenedicarboxylate was distilled off and the residue was refluxed in MeOH (30 mL) for 24 h. The mixture was concentrated and flash chromatography (SiO_2, CH_2Cl_2/MeOH/Et_3N 30:4:1→20:4:1 gradient) of the residue gave **10** (108 mg, 72%). ^1H NMR (300 MHz, CD_3OD): δ = 7.48 (s, 4 H, H-1, H-4, H-5, H-8), 5.63 (s, 2 H, H-9, H-10), 4.54 (s, 8 H, CH_2), 3.76 (s, 6 H, CH_3). MALDI-TOF-MS: *m*/*z* calcd for $C_{24}H_{23}N_2O_4$ [M + H]: 403.2. Found 403.2.

bis-[2,3:6,7-(*N*-Boc-glycyl)iminodimethylene]-9,10-dicarboxyethenoanthracene (11): To a solution of 1-hydroxybenzotriazole (7.0 mg, 52 μmol), **10** (10.0 mg, 21 μmol) and N^{α}-Boc-Gly-OH (8.9 mg, 52 μmol) in dry THF (10 mL), was added *N*,*N*′-diisopropylcarbodiimide (7.9 μL, 52 μmol). After 12 h, the mixture was concen-

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trated and flash chromatographed (SiO_2, CH_2Cl_2/MeOH/Et_3N 100:2:1) to give **11** in (10.4 mg, 69%). ^1H NMR (400 MHz, CD_3OD): δ = 7.21 (2 br s, 4 H, H-1, H-4, H-5, H-8), 5.41 (s, 2 H, H-9, H-10), 4.60, 4.51 (2 br s, 8 H, CH_2), 1.30 (s, 18 H, CH_3). MALDI-TOF-MS: *m*/*z* calcd for $C_{38}H_{44}N_4O_{10}Na$ [M + Na]: 739.3. Found: 739.3.

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