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Amphiphilic Anthracene–Amino Acid Conjugates as Simple Carbohydrate Receptors in Water

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***N*-Alkylation of amino acid methyl esters with 9,10-bis-chloromethylanthracene, followed by methyl ester hydrolysis, yielded water-soluble amphiphilic amino acid–anthracene conjugates. In NMR-titration experiments, a L-arginine–anthracene conjugate was demonstrated to recognize *p*-nitrophenyl glycosides and sialylated oligosaccharides in D_2O in a manner sensitive to the carbohydrate structure.**

Keywords: *N*-alkylation; Glycoconjugate; NMR; Hybrid

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INTRODUCTION

During the last decade, a growing appreciation of the importance of glycoconjugate–protein interactions in life processes, for example in immunology, tumour metastasis, pathogen–host interactions, fertilization, and inflammatory processes, have sparked a rapid development in the research fields of glycobiology and glycochemistry [1,2]. Although it is now clear that the glycoconjugates play roles in life processes equally important as those of other well-studied biopolymers, such as proteins and DNA/RNA, the detailed mechanisms behind recognition and function of glycoconjugates are still largely unclear. Hence, designing novel tools for studying carbohydrate recognition and seeking efficient means of interfering with glycoconjugate–protein interactions are of great relevance. Access to specific artificial carbohydrate receptors would greatly simplify carbohydrate recognition studies and may even lead to novel drugs interfering with glycoconjugate recognition phenomena. Numerous artificial carbohydrate receptors in organic media have been described, as well as a small, but rapidly increasing, number of receptors in the more biologically relevant aqueous environment [3–20]. Furthermore, several receptors exploiting the covalent bond formation between boronates and carbohydrates have been disclosed [21–36].

Glycoconjugate recognition by proteins engages a combination of polar, charge, and hydrophobic interactions [37,38] and an artificial carbohydrate receptor should thus possess structural elements capable of involving in such interactions. *En route* towards receptor molecules possessing such structural elements, we have prepared amino acid–anthracene hybrid molecules (**3a–d**) from 9,10-bis-chloromethylanthracene **1** and studied their recognition of *p*-nitrophenyl glycosides and sialyl oligosaccharides.

RESULTS AND DISCUSSION

The amino acid–anthracene hybrids **2a–d** were prepared by *N*-alkylation of glycine, L-aspartic acid, L-glutamic acid, and L-arginine methyl ester hydrochlorides with bis-9,10-chloromethylanthracene **1** in yields of 54, 31, 39, and 54%, respectively (Scheme 1). Alkaline hydrolysis of the methyl esters **2a–d** afforded the amphiphilic amino acid–anthracene hybrids **3a–d** (88, 88, 60, and 47%, respectively) after reversed solid-phase extraction [39,40].

Initial NMR screening experiments with **3a–d** were performed in D_2O by observing chemical ^1H-shift changes in **3a–d** in the presence of a panel of

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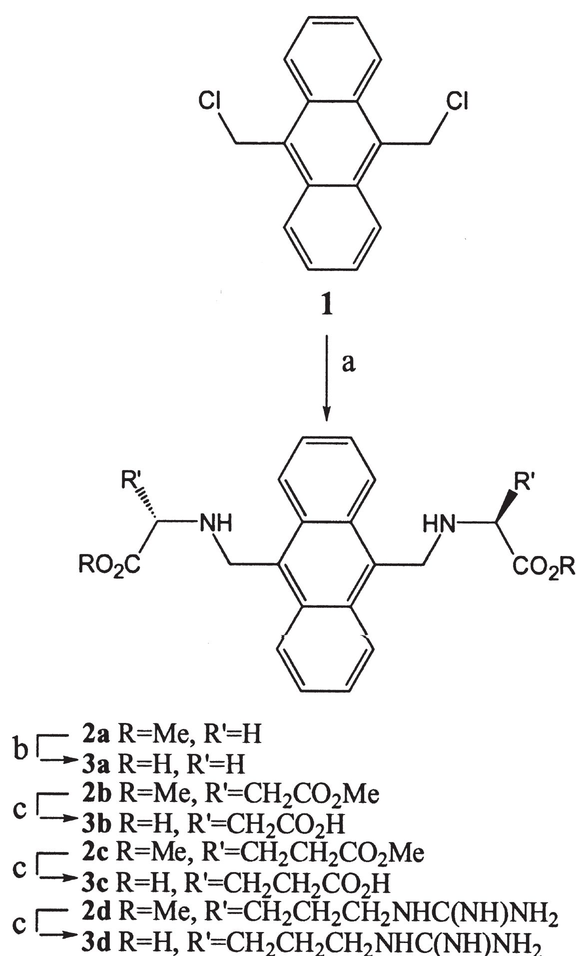

Key to scheme 1: a) Glycine methyl ester hydrochloride, L-aspartic acid dimethyl ester hydrochloride, L-glutamic acid dimethyl ester hydrochloride, or L-arginine methyl ester dihydrochloride, Hünig's base, MeCN, 80°C. b) $NaOH_{aq.}$, acetone. c) $LiOH_{aq.}$, MeOH.

SCHEME 1

p-nitrophenyl glycosides. Compounds **3b–c** displayed only minor shift changes in the presence of the *p*-nitrophenyl glycosides, while the L-arginine-based receptor **3d** displayed significant (up to 0.25 ppm) shift changes. Furthermore, while **3d** was soluble up to 40 mM concentration in D_2O, compound **3a** was practically insoluble and compounds **3b–c** were soluble only at low concentrations. Thus, compound **3d** was selected for further investigations. NMR-titration experiments were performed with increasing concentrations of **3d** and fixed concentrations of the ligands 1-(*p*-nitrophenyl)glycerol **4** (reference ligand) and *p*-nitrophenyl glycosides (α-L-fucopyranoside **5**, β-L-fucopyranoside **6**, β-D-*N*-acetylglucosaminide **7**, α-D-mannopyranoside **8**, β-D-mannopyranoside **9**, β-D-galactopyranoside **10**, β-D-glucuronid **11**, β-D-galacturonid **12**). Complexation induced shifts (CIS) of up to 0.12 ppm were observed for *p*-nitrophenyl protons and up to 0.09 ppm for anomeric protons (Figs. 1 and 2).

The CIS of compounds **4–12** in the presence of **3d** did fit well to a 1:1 binding isoterm ($R = 0.99999–0.98804$), which supports 1:1 complex stoichiometry†. The reference ligand, 1-(*p*-nitrophenyl)glycerol **4**, was bound the least tightly (K_a‡ approximately 70 M^{-1}), while all neutral *p*-nitrophenyl glycosides **5–10** were bound by similar affinities (K_a approximately 75–130 M^{-1}) by **3d**.

The uronides **11** and **12** were bound with the highest affinity by **3d** (K_a approximately 200–300 M^{-1} for **11** and **12**, respectively). This observation was not unexpected, since the carboxyl functionality of **11** and **12** can be expected to form a charge–charge interaction with amino or guanidine groups of **3d**. No CIS in **11** were detected in the presence of L-arginine itself (Fig. 3) or diethylamine, which suggests that the combination of a hydrophobic (i.e. anthracene) and a polar/charged (i.e. L-arginine) moiety is necessary for the interaction to take place. Although the associations between **3d** and *p*-nitrophenyl glycosides **5–12** were rather weak, they showed a dependence on the carbohydrate structure. A major driving force is most likely a solvophobic interaction between the *p*-nitrophenyl and anthracene moieties, while the carbohydrate moiety merely modulates the binding. Nevertheless, the fact that all *p*-nitrophenyl glycosides were bound more strongly than 1-(*p*-nitrophenyl)glycerol clearly suggests the presence of additional interactions between the carbohydrate and **3d**. A higher degree of pre-organization of ligand hydroxyl groups, as in a pyranoside ring, and the presence of a carboxyl group, seem to lead to stronger binding by **3d**.

Encouraged by the results with *p*-nitrophenyl glycosides, we embarked on studying the interaction between **3d** and oligosaccharides GM3 **13** and sialyl $Lewis^X$ **14** (Fig. 4). The oligosaccharides **13** and **14** were chosen because of their biological relevance and because they both carry a carboxy functionality, which in the experiments with *p*-nitrophenyl glycosides seemed to improve binding by **3d**. Indeed, NMR-titration experiments, as for the *p*-nitrophenyl glycosides **4–12**, revealed small CIS (−0.01 to +0.03 ppm) of protons in both **13** and **14**. In particular, the H-3 of the D-galactose residues in **13** and **14** shifted downfield, while H-1 of the L-fucose residue in **14** shifted upfield (Fig. 4). The CIS did fit well to a 1:1 binding isoterm. K_a were estimated to approximately 100 M^{-1} for **13** and **14**. The presence

†Job's plots were distorted due to the self-association of **3d** and could not be used for determination of binding stoichiometries.
‡K_a values should be viewed as approximate, because **3d** did self-associate (K_a 200 M^{-1}). The true K_a values are thus lower. Nevertheless, the relative affinities can still be used for interpretation of intermolecular interactions between **3d** and **4–14**.

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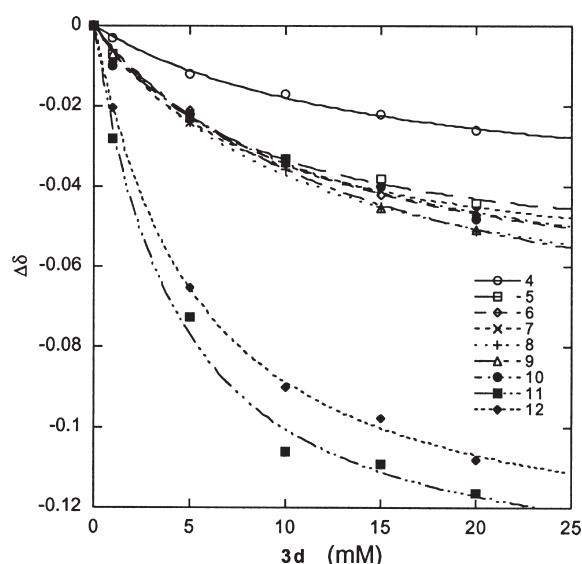

FIGURE 1 Complexation induced shifts of aromatic H-3 of 1-(*p*-nitrophenyl)glycerol **4** and a panel of *p*-nitrophenyl glycosides **5**–**12** in NMR-titration experiments with **3d**.

of acetic acid, diethylamine, or L-arginine did not reveal any CIS in **13** and **14**, which excludes the possibility of acid–base reactions causing the shift changes.

As for the uronides **11** and **12**, the carboxy groups of the sialyl oligosaccharides **13** and **14** are probably interacting with the amino or guanidino groups of **3d**. However, the anthracene moiety of **3d** is probably involved in the interactions with hydrophobic patches of the saccharides **13** and **14**, because L-arginine itself did not induce CIS.

These results show that it is possible to synthesize relatively simple and flexible amphiphilic molecules capable of recognizing carbohydrates in aqueous environment. The high degree of flexibility and the self-association of compound **3d** render it a rather poor receptor molecule, which is difficult to study. Nevertheless, the observed carbohydrate binding by **3d** leads to the conclusion that molecules possessing structural elements allowing a combination of intermolecular interactions (e.g. hydrogen bonding, charge–charge, dipole–charge, hydrophobic, cation-π) to occur, can act as receptors in aqueous environment. However, in order to approach affinities and specificities displayed by Nature's receptor molecules, our artificial receptors need to be conformationally more well-defined than **3d**. Thus, there is an obvious need for synthesis of a second generation of amphiphilic molecules related to **3d**, that are less flexible (but still flexible enough to adapt to geometrical requirements by putative ligands [41,42]) and that possess deeper cavities or clefts for binding.

EXPERIMENTAL

General Methods

NMR spectra were recorded on Bruker ARX-300 or DRX-400 NMR instruments. All chemical shifts are reported relative to Me_4Si and were calculated using the residual solvent peak as a reference. HRMS (FAB) were recorded with a JEOL SX-120 mass spectrometer. Optical rotation measurements were made

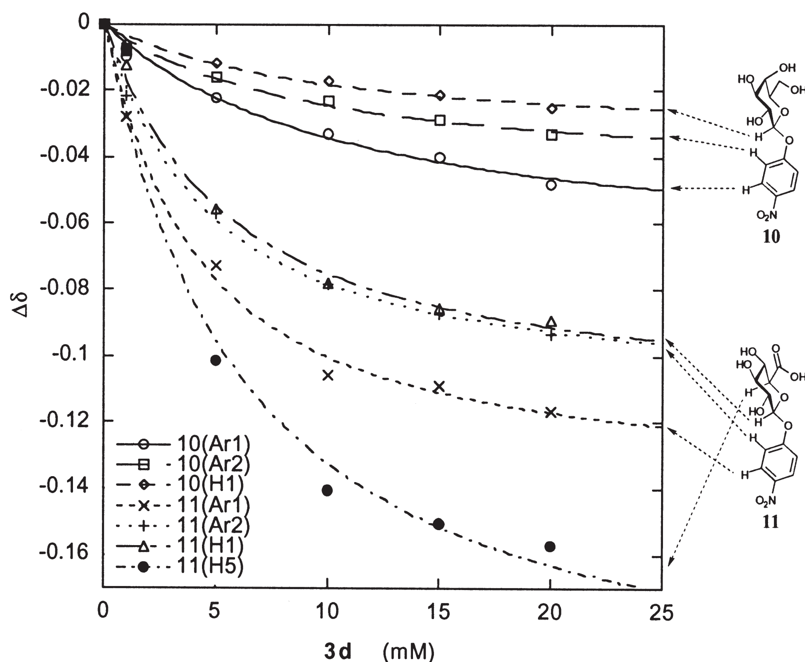

FIGURE 2 Complexation induced shifts in *p*-nitrophenyl β-D-galactopyranoside **10** and *p*-nitrophenyl β-D-glucuronide **11** in NMR-titration experiments with **3d**.

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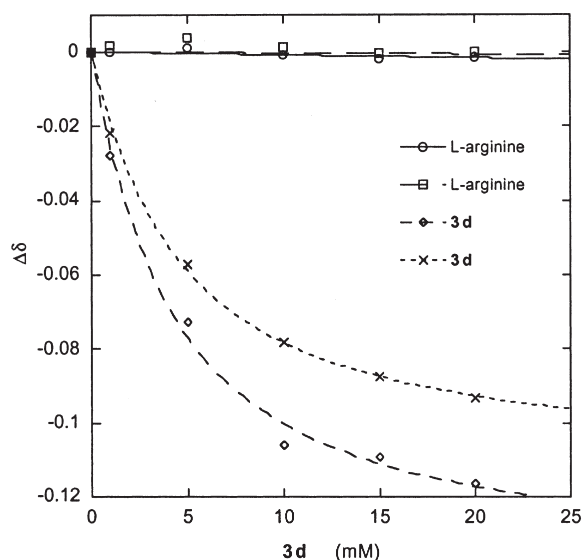

FIGURE 3 Complexation induced shifts of aromatic protons in *p*-nitrophenyl β-D-glucuronide **11** in NMR-titration experiments with **3d** and with L-arginine.

using either a Perkin–Elmer 141 polarimeter or a Perkin–Elmer Model 341 polarimeter. The TLC plates were Kieselgel 60 F_{254} (Merck). Matrex 35–70 μm 60 Å silica (Grace) was used for flash chromatography. Sep-Pak Plus C_{18} cartridges and C_{18} silica (55–105 μm 125 Å C_{18}) were from Waters. CH_3CN was dried over 4 Å molecular sieves.

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9,10-Bis-[N-(methoxycarbonylmethyl) aminomethyl]anthracene (2a)

Compound **1** [43] (200 mg, 0.73 mmol) and glycine methyl ester hydrochloride (274 mg, 2.18 mmol) were suspended in CH_3CN (7 ml) and *N*-ethyldiisopropylamine (0.56 g, 4.36 mmol) was added. The mixture was stirred at 80°C for 3 h and then concentrated. Flash chromatography (Toluene: EtOAc 3:2, $R_f = 0.12$) gave **2a** (149.5 mg, 54%); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.49 (m, 4H, Ar-H), 7.57 (m, 4H, Ar-H), 4.76 (s, 4H, CH_2NHCH_2CO), 3.82 (s, 6H, OCH_3), 3.65 (s, 4H, CH_2CO); HRMS calcd. for $C_{22}H_{25}N_2O_4$ (M+H): 381.1814; found 38l.1820.

9,10-Bis-{N-[(S)-1,2-dimethoxycarbonylethyl] aminomethyl}anthracene (2b)

Compound **1** (200 mg, 0.73 mmol) and L-aspartic acid dimethyl ester hydrochloride (431 mg, 2.18 mmol) were suspended in CH_3CN (7 ml) and *N*-ethyldiisopropylamine (560 mg, 4.36 mmol) was added. The mixture was stirred at 80°C for 3 h and then concentrated. Flash chromatography (Toluene: EtOAc 4:1, $R_f = 0.12$) gave **2b** (119.3 mg, 31%); $[\alpha]_D^{25} = +3°$ (*c* 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.43 (m, 4H, Ar-H), 7.54 (m, 4H, Ar-H), 4.85 (d, 2H, $J = 11.9$ Hz, CH_2N), 4.61 (d, 2H, $J = 11.9$ Hz, CH_2N), 3.98 (dd, 2H, $J = 8.2$, 5.2 Hz, CHCO), 3.87 (s, 6H, OCH_3), 3.62 (s, 6H, OCH_3), 2.84 (dd, 2H, $J = 15.8$, 5.4 Hz, CH_2CO), 2.68 (dd, 2H, $J = 15.8$, 8.2 Hz, CH_2CO); HRMS calcd. for $C_{28}H_{32}N_2O_8$ (M): 524.2158; found 524.2166.

9,10-Bis-{N-[(S)-1,3-dimethoxycarbonylpropyl] aminomethyl}anthracene (2c)

Compound **1** (200 mg, 0.73 mmol) and L-glutamic acid dimethyl ester hydrochloride (461 mg, 2.18 mmol) were suspended in CH_3CN (7 ml) and *N*-ethyldiisopropylamine (560 mg, 4.36 mmol) was added. The mixture was stirred at 80°C for 3 h and

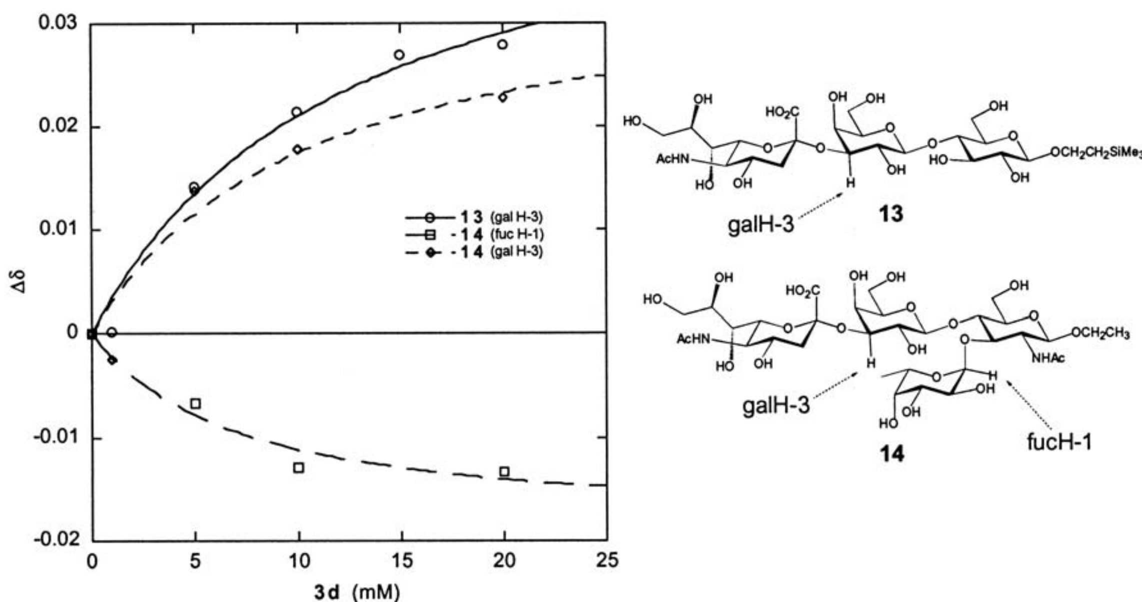

FIGURE 4 Complexation induced shifts in the sialyl oligosaccharides GM3 **13** and sialyl Lewis^X **14** in NMR-titration experiments with **3d**.

was then concentrated. Flash chromatography (Toluene:EtOAc 5:1, $R_f = 0.13$) gave **2c** (158.5 mg, 39%); $[\alpha]_D^{25} = +16°$ (c 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.41 (m, 4H, Ar-H), 7.55 (m, 4H, Ar-H), 4.75 (d, 2H, $J = 11.9$ Hz, CH_2N), 4.52 (d, 2H, $J = 11.9$ Hz, CH_2N), 3.85 (s, 6H, OCH_3), 3.57 (s, 6H, OCH_3), 3.57 (m, 2H, CHCO), 2.48 (t, 4H, $J = 7.3$ Hz, CH_2CO), 2.10 (m, 2H, $CHCH_2$), 1.87 (m, 2H, $CHCH_2$); HRMS calcd. for $C_{30}H_{37}N_2O_8$ (M+H): 553.2550; found 553.2529.

9,10-Bis-{N-[(S)-4- guanidino-1-methoxycarbonylbutyl]aminomethyl}anthracene (2d)

Compound **1** (200 mg, 0.73 mmol) and L-arginine methyl ester dihydrochloride (569 mg, 2.18 mmol) were suspended in CH_3CN (7 ml) and *N*-ethyldiisopropylamine (850 g, 6.54 mmol) was added. The mixture was stirred at 80°C for 3 h and was then concentrated. The residue was dissolved in water and applied to a C_{18} column (5 g). Elution with a water–MeOH gradient and concentration gave **2d** (226 mg, 54%); $[\alpha]_D^{25} = +14°$ (c 1.0, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 8.48 (m, 4H, Ar-H), 7.57 (m, 4H, Ar-H), 4.72 (d, 2H, $J = 12.1$ Hz, CH_2NHCH), 4.62 (d, 2H, $J = 12.4$ Hz, CH_2NHCH), 3.82 (s, 6H, OCH_3), 3.58 (m, 2H, CHCO), 3.10 (m, 4H, CH_2CH_2N), 1.75 (m, 4H, $CHCH_2$), 1,64 (m, 4H, $CH_2CH_2CH_2$); HRMS calcd. for $C_{30}H_{43}N_8O_4$ (M+H): 579.3407; found 579.3416.

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9,10-Bis-(N-carboxymethylaminomethyl) anthracene (3a)

Compound **2a** (20 mg, 52.6 mmol) was dissolved with acetone (2.1 ml) and NaOH (0.5 M aq, 0.53 ml). The mixture was stirred at room temperature for 3 h and then neutralised with Duolite C436 (H^+) resin. The Duolite C436 was filtered off and washed with MeOH and 25% NH_3(aq). The filtrate and washings were combined and concentrated. A small amount of water was added to the residue, followed by 25% aqueous NH_3 until the product dissolved. The solution was applied to a C_{28} column (1.4 g). Elution with water gave **3a** (16.3 mg, 88%); ^{1}H-NMR (300 MHz, D_2O): (δ 8.05 (m, 4H, Ar-H), 7.38 (m, 4H, Ar-H), 4.05 (s, 4H, CH_2NCH_2CO), 3.10 (s, 4H, CH_2CO); HRMS calcd. for $C_{20}H_{18}N_2O_4Na$ (M − 2H+Na): 373.1164; found 373.1160.

9,10-Bis-{N-[(S)-1,2-dicarboxyethyl] aminomethyl}anthracene (3b)

Compound **2b** (100 mg, 0.19 mmol) was dissolved in MeOH (3.1 ml) and 1 M LiOH (aq, 3.1 ml) was added. The mixture was stirred at room temperature for 24 h and then neutralised with Duolite C436 (H^+) resin. The Duolite C436 was filtered off and washed with MeOH and 25% NH_3 (aq). The filtrate and washings were combined and concentrated. The residue was dissolved in water and applied to a C_{18} column (3 g). Elution with water gave **3b** (78.8 mg, 88%); $[\alpha]_D^{25} = +8°$ (c 0.53, H_2O); ^{1}H-NMR (300 MHz, D_2O): δ 8.06 (m, 4H, Ar-H), 7.63 (m, 4H, Ar-H), 4.57 (d, 2H, $J = 13.6$ Hz, CH_2N), 4.47 (d, 2H, $J = 14.0$ Hz, CH_2N), 3.80 (dd, 2H, $J = 11.2$, 3.4 Hz, CHCO), 2.63 (dd, 2H, $J = 17.6$, 3.4 Hz, CH_2CO), 2.38 (dd, 2H, $J = 17.7$, 11.3 Hz, CH_2CO); HRMS calcd. for $C_{24}H_{23}N_2O_8$ (M − H): 467.1454; found 467.1474.

9,10-Bis-{N-[(S)-1,3-dicarboxypropyl] aminomethyl}anthracene (3c)

Compound **2c** (60 mg, 0.11 mmol) was dissolved in MeOH (1.8 ml) and LiOH (1 M aq, 1.7 ml) was added. The mixture was stirred at room temperature for 24 h and then neutralised with Duolite C436 (H^+) resin. The Duolite C436 was filtered off and washed with MeOH and 25% NH_3 (aq). The filtrate and washings were combined and concentrated. The crude product was dissolved in water and applied to a C_{18} column (5 g). Elution with water gave **3c** (32.2 mg, 60%); $[\alpha]_D^{25} = +9°$ (c 0.3, H_2O); ^{1}H-NMR (300 MHz, D_2O): δ 8.04 (m, 4H, Ar-H), 7.67 (m, 4H, Ar-H), 4.43 (d, 2H, $J = 13.7$ Hz, CH_2N), 4.30 (d, 2H, $J = 13.9$ Hz, CH_2N), 3.66 (t, 2H, $J = 5.8$ Hz, CHCO), 2.28 (m, 4H, CH_2CO), 1.91 (m, 4H, $CHCH_2$); HRMS calcd. for $C_{26}H_{27}N_2O_8$ (M − H): 495.1767; found 495.1779.

9,10-Bis-{N-[(S)-4-guanidino-1-carboxybutyl]aminomethyl}anthracene (3d)

Compound **2d** (21.0 mg, 36.3 mmol) was dissolved in MeOH (0.6 ml) and 1 M LiOH (aq, 0.3 ml) was added. The mixture was stirred at room temperature for 5.5 h and then neutralised with Duolite C436 (H^+) resin. The Duolite C436 was filtered off and washed with MeOH and 25% NH_3 (aq). The filtrate and washings were combined and concentrated. The residue was dissolved in 0.1 M HCl(aq) and applied to a C_{18} column (1.4 g). Elution with water gave **3d** (9.4 mg, 47%); $[\alpha]_D^{25} = +25°$ (c 1.0, H_2O); ^{1}H-NMR (300 MHz, D_2O): δ 7.93 (m, 4H, Ar-H), 7.59 (m, 4H, Ar-H), 4.30 (d, 2H, $J = 14.0$ Hz, CH_2NHCH), 4.14 (d, 2H, $J = 13.9$ Hz, CH_2NHCH), 3.61 (m, 2H, CHCO), 3.03 (t, 4H, $J = 6.8$ Hz, CH_2CH_2N), 1.67 (m, 4H, $CHCH_2$), 1.49 (m, 4H, $CH_2CH_2CH_2$); HRMS calcd. for $C_{28}H_{39}N_8O_4$ (M+H): 551.3094; found 551.3090.

NMR-titration Experiments

Titration experiment were performed in D_2O by observing chemical shifts of ligand (**4–14**, 1 mM) protons in the presence of increasing concentrations

of **3d**. The CIS were fitted to a 1:1 binding isotherm [44] using non-linear regression analysis.

Acknowledgements

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