

Selective head-to-tail recognition in hydrazide-based molecular duplex strands induced by spectator secondary electrostatic interactions†

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Due to spectator secondary electrostatic interactions, nonsymmetric mono-Boc-mono-acetyl terminated hydrazide-based oligomers displayed a head-to-tail dimerization mode, which was evidenced by ^1H NMR, and 2D NOESY experiments. Dynamic behavior of the molecular duplex strands was also explored by variable temperature ^1H NMR experiments.

Introduction

The ability of biomolecules to adopt three-dimensional shapes and to interact specifically through cooperative action of many non-covalent attractions¹ has inspired chemists to design, synthesize, and characterize chemical models to mimic structures of biomolecules. Among the many biostructures, discovery of the double helical structure of DNA² via hydrophobic effects, hydrogen bonds, and π - π stacking interactions and elucidation of its function as genetic information carrier have founded the basis of modern molecular biology.³ Recent studies revealed that the β -sheet protein secondary structure plays an important role in many diseases, such as Alzheimer's disease, the prion disease, and other neurodegenerative disorders.⁴ Other double- and multiple-stranded complexes self-assembled from linear oligomers with encoded recognition sites are ubiquitous in nature, and are the foundation of other higher structures and functions of biomolecules. Inspired by the elegant functions of these structures in nature and for scientific and aesthetic reasons, there is currently an intensive focus of chemical research on the construction of stable molecular duplex strands from unnatural backbones for structure mimicking and potential applications.⁵ Hydrogen bonding, as adopted by natural DNA, with characteristics of strength and directionality, has been described as the "masterkey interaction in supramolecular chemistry"⁶ and is an ideal non-covalent interaction for this mission. Hydrogen bonding modules assembled with high stability, fidelity, and selectivity, are favored in this field. Heterocycle based building blocks (usually urea derivatives)⁷ and linear materials composed of arrays of hydrogen bonding sites⁸ have gained great success.

The stability of multiply hydrogen bonded complexes is determined by many factors, including the number and geometry of individual hydrogen bonds, the acidity or basicity of hydrogen bonding donor or acceptor sites, and the solvent polarity. In arrays with adjacent hydrogen bonding sites, the stability is also affected by the sequence arrangement of hydrogen bonding sites, which,

is suggested as a secondary electrostatic effect by Jorgensen *et al.* based the results of theoretical studies.⁹ Zimmerman *et al.* further provided experimental evidence for this theory.¹⁰ Based on the analysis of the stability constants of sufficiently large experimental data sets, Schneider *et al.* even derived an empirical formula for predicting the association constants for multiple hydrogen bonded systems: 7.9 kJ mol^{-1} for each primary hydrogen bond and 2.9 kJ mol^{-1} for each secondary one.¹¹ In the case of a hydrogen bonded system as shown in Fig. 1, "over-hanging" or "spectator" hydrogen bonding sites not participating in primary hydrogen bonding interaction can also affect the stability of the complex substantially due to their being adjacent to other hydrogen bonding sites in space.¹² In hydrazide-based quadruply hydrogen bonded systems we reported recently, as shown in Fig. 2, that the spectator secondary electrostatic interactions inherent with the Boc groups substantially affected the stability of the complexes: weak association was observed for **1-4** (two fold repulsive spectator secondary electrostatic interactions); $(1.4 \pm 0.1) \times 10^3 \text{ M}^{-1}$ for **2-4** (no spectator secondary electrostatic interaction) and $(5.6 \pm 0.6) \times 10^2 \text{ M}^{-1}$ for **3-4** (one repulsive spectator secondary electrostatic interaction), respectively.¹³ Further investigations revealed that the Boc groups also affected substantially the dynamic behavior of the hydrazide-based molecular duplex strands.^{13,14}

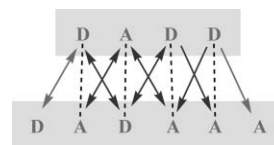


Fig. 1 Representation of secondary electrostatic interactions and spectator secondary electrostatic interactions in hydrogen bonded dimer structures (DADD·DADAAA) with adjacent hydrogen bonding sites. Double headed arrows: repulsive interactions; single headed arrows: attractive interactions.

In this paper, mono-Boc-mono-acetyl terminated non-symmetric hydrazide-based oligomers **D** series were designed and synthesized (Fig. 3). Due to spectator secondary repulsive electrostatic interactions¹² inherent with Boc groups, the Boc termini did not participate in important intermolecular hydrogen bonding interactions and a head-to-tail recognition directed dimerization mode for this series was proposed.¹⁵ Moreover,

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† Electronic supplementary information (ESI) available: Stacked partial ^1H NMR spectra of **D2-D4** and typical mono-Boc and mono-acetyl terminated oligomers at different temperatures. See DOI: 10.1039/b811272j

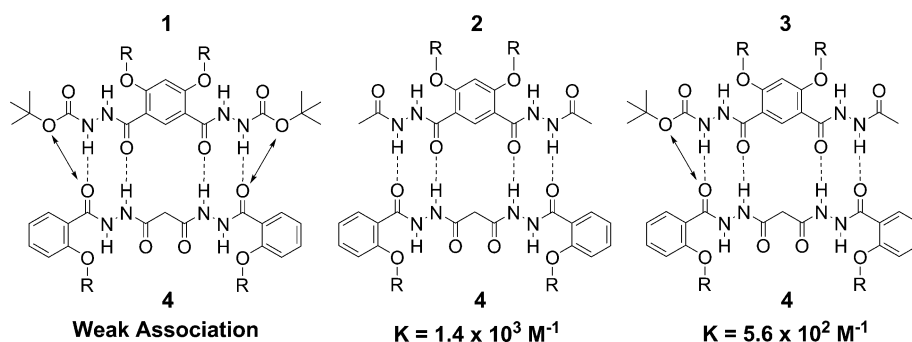


Fig. 2 Representation of spectator secondary repulsive electrostatic interactions in hydrazide-based quadruply hydrogen bonded systems.

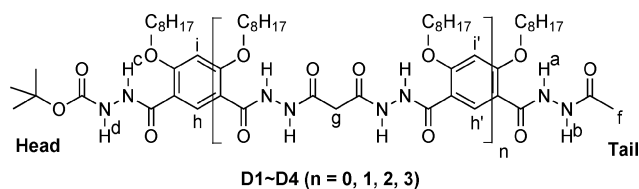


Fig. 3 Chemical structures of mono-Boc-mono-acetyl terminated oligomers **D1–D4** used in this study, with proton-labeling scheme indicated.

dynamic behavior for the duplex strands was also investigated via variable temperature ^1H NMR experiments.

Results and discussion

Synthesis

Due to the non-symmetric nature of the oligomers, an iterative sequentially homologated method has been devised (Scheme 1). Starting from the Boc termini, the oligomers were lengthened stepwise. The methyl termini were finally attached. The key step is the coupling reaction between carboxylic acid and hydrazide derivatives. It was found that EDC-HCl could be utilized as an efficient coupling reagent for this kind of reaction, and in most cases, high yields were obtained. Hydrolysis of esters was generally achieved by a solution of NaOH in THF or $\text{C}_2\text{H}_5\text{OH}$. The full synthetic methods and characterization data for new compounds are provided in the Experimental section.

^1H NMR analysis

Firstly, dilution ^1H NMR experiments on **D1** revealed that only the signal for H^b displayed a large concentration-dependency (Fig. 4), which might suggest that only H^b was involved in important intermolecular hydrogen bonding. With the chain length of this series extended to longer oligomers **D2–D4**, we found that the signals for H^c and H^d were also unaffected (Fig. 5). While for the structure-similar self-complementary mono-Boc-terminated series, the position of NHs adjacent to Boc groups shifted substantially with chain length.¹³ These findings might suggest that the Boc termini in **D** series were not involved in important intermolecular hydrogen bonding. Thus, a selectivity for acetyl termini (we call tail) over Boc termini (we call head) was obtained and a head-to-tail recognition directed dimerization mode was proposed (Scheme 2, left). In head-to-tail dimers, there were no spectator secondary repulsive electrostatic interactions; while in head-to-

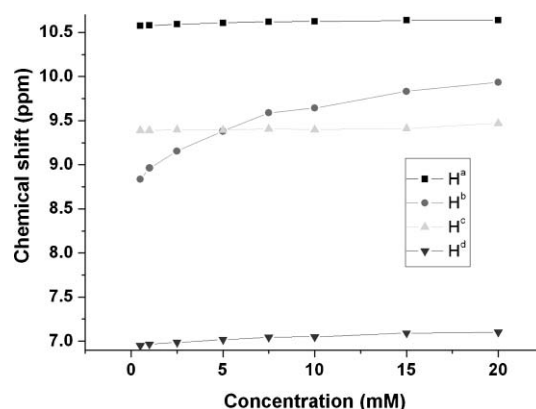


Fig. 4 Chemical shifts for NHs of **D1** at different concentrations, 300 MHz, in CDCl_3 , 298 K.

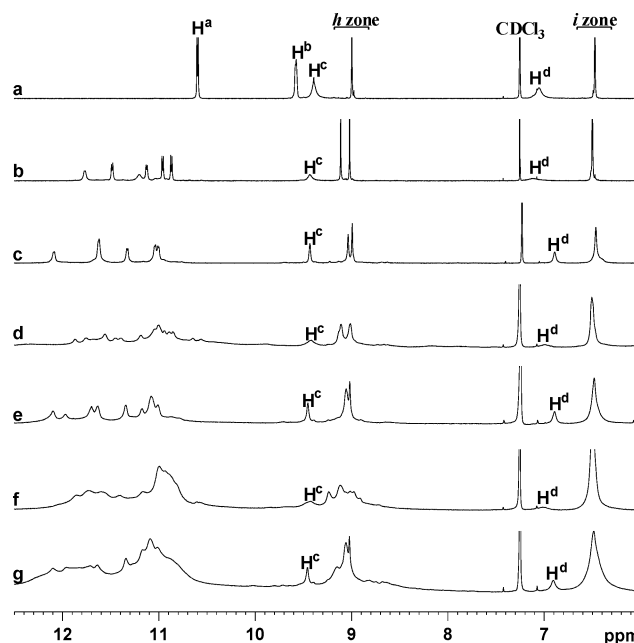
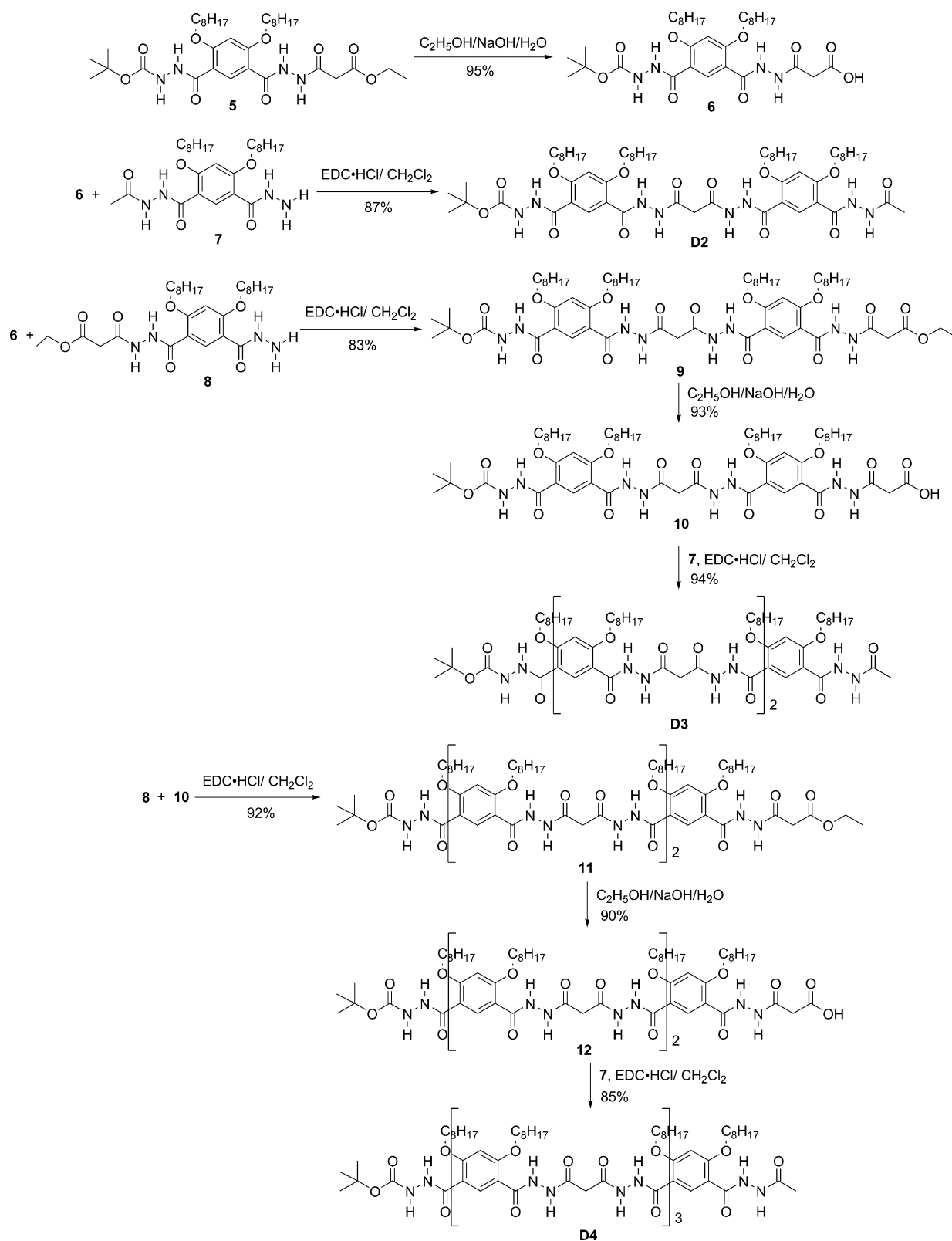


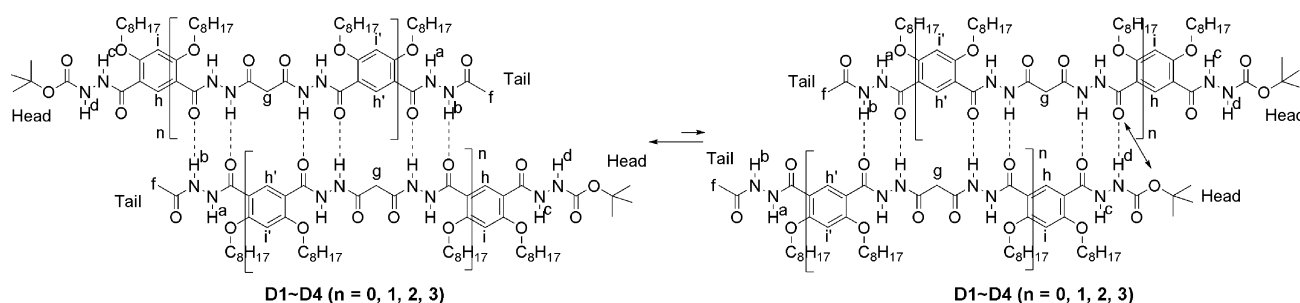
Fig. 5 Stacked partial ^1H NMR spectra (600 MHz, CDCl_3 , 10 mM) of (a) **D1**, 298K; (b) **D2**, 298K; (c) **D2**, 223K; (d) **D3**, 298K; (e) **D3**, 223K; (f) **D4**, 298K; (g) **D4**, 223K.

head dimers (Scheme 2, right), there was one spectator secondary repulsive electrostatic interaction. This difference rendered the equilibrium shift substantially to head-to-tail dimers.

Scheme 1 Synthetic routes to **D1**–**D4**.

A dimerization constant of $79 \pm 23 \text{ M}^{-1}$ was determined for **D1**–**D1** in CDCl_3 at room temperature by nonlinear regression analysis of the dilution ^1H NMR experiment data.¹⁶ Dimerization

constants for longer oligomers were not determined due to signal overlapping and no obvious chemical shift changes observed by dilution ^1H NMR experiments.



Scheme 2 Representation of equilibrium between head-to-tail dimers (left) and head-to-head dimers (right) for self-assembly of the oligomers **D1–D4**, with spectator secondary repulsive electrostatic interactions highlighted.

2D NOESY analysis and dynamic behavior

2D NOESY experiments further confirmed the above hypothesis. Cross contacts between H^f and the h zone (inter-carbonyl aromatic protons), g zone (methylene protons of malonyl groups) and h zone were observed. Variable temperature 1H NMR experiments revealed dynamic behavior for the **D** series similar to those for the mono-Boc terminated series (see ESI for more details).¹³ With lowering of temperature, in addition to signal sharpening, no apparent changes were observed (Fig. 6). While for the structure-similar mono-acetyl terminated series, new peaks corresponding to the NHs not involved in intermolecular hydrogen bonding appeared with lowering of temperature.¹³ These findings indicated that no shuttle movement perpendicular to the hydrogen bonds and no dimeric-polymeric equilibrium existed for the **D** series.

Conclusions

In summary, we presented the synthesis and self-assembly of a new series of mono-Boc-mono-acetyl terminated non-symmetric hydrazide-based oligomers (**D** series). Due to spectator secondary repulsive electrostatic interactions inherent with Boc groups, a head-to-tail dimerization mode was observed in solution for this series, which was evidenced by dilution 1H NMR and 2D NOESY experiments. Variable temperature 1H NMR experiments further revealed similar dynamic behavior for the **D** series as for those of the Boc-terminated series with complementary hydrogen bonding

sites. We believe that this selective head-to-tail dimerization and unique dynamic behavior will find practical applications in the design of hydrazide-based functional materials, which is under investigation in our laboratory.

Experimental

General procedure for the coupling reaction of carboxylic acids and hydrazide derivatives (procedure A)

To an equimolar mixture of a carboxylic acid and a hydrazide derivative in dry CH_2Cl_2 (usually 10 mL per mmol) in an ice-water bath was added 1.1 or 1.2 equiv. of EDC·HCl. The mixture was stirred at room temperature for 5 h, and then concentrated under reduced pressure. The pure product as a white solid was obtained by recrystallization from hot acetonitrile.

General procedure for hydrolysis of esters (procedure B)

To a solution or suspension of ester in THF or C_2H_5OH (usually 10 mL per mmol) was added a solution of NaOH (usually 3 equiv.) in an equal volume of water (relative to THF or C_2H_5OH). Then the mixture was stirred at room temperature and the reaction was monitored by TLC. The reaction completed in 5 h, and sometimes heating was necessary for the completion of the reaction. The organic solvent was evaporated under reduced pressure, and the residue was acidified with concentrated HCl. Upon acidification a white solid precipitated from the solution and the crude product

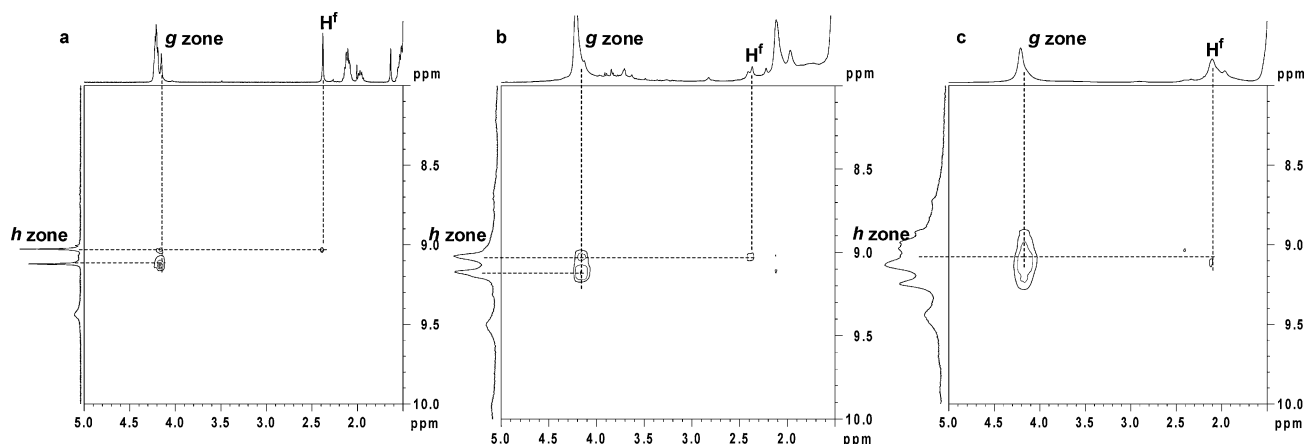


Fig. 6 Partial 2D NOESY spectra for (a) **D2**, (b) **D3**, (c) **D4**, 10 mM in $CDCl_3$, 600 MHz, 298 K, showing contacts between H^f and h zone, h zone and g zone.

was collected by filtration. The pure product as a white solid was obtained by recrystallization from hot acetonitrile.

All experiments were carried out at the 0.1–1.0 mmol scale.

Compounds **D1**, **5**, **7**, **8** were synthesized previously.¹³

Compound 6: general procedure B. Yield: 95%. Mp: 163–164 °C. ¹H NMR (300 MHz, DMSO-*d*₆, ppm): δ 12.49 (s, 1H, COOH), 10.96 (d, *J* = 3.7 Hz, 1H, *H*-N), 10.20 (d, *J* = 3.2 Hz, 1H, *H*-N), 9.40 (s, 1H, *H*-N), 9.02 (s, 1H, *H*-Ar), 8.33 (s, 1H, *H*-N), 6.81 (s, 1H, *H*-Ar), 4.29–4.22 (m, 4H, OCH₂), 3.31 (s, 2H, COCH₂CO), 1.88–1.77 (m, 4H, CH₂), 1.43–1.26 (m, 29H, CH₂ and OC(CH₃)₃), 0.86 (t, *J* = 6.9 Hz, 5.1 Hz, 6H, CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆, ppm): δ 168.8, 164.2, 162.3, 160.6, 160.3, 160.0, 155.1, 134.1, 114.0, 112.4, 97.8, 79.1, 69.6, 69.3, 31.23, 31.19, 28.8, 28.63, 28.61, 28.3, 28.0, 25.5, 22.09, 22.06, 13.89, 13.88. IR (KBr, cm⁻¹): 3369.03, 3316.96, 3218.61, 2926.45, 2858.95, 1740.44, 1713.44, 1616.06, 1466.6. MS (MALDI-TOF): *m/z* 659.1 [M + Na]⁺, 675.0 [M + K]⁺. MS (ESI): *m/z* 635.06 [M – H]⁻. Elemental analysis calcd (%) for C₃₂H₅₂N₄O₉: C 60.36, H 8.23, N 8.80; found: C 60.21, H 8.27, N 9.14.

Compound D2: general procedure A. Yield: 87%. Mp: 132–133 °C. ¹H NMR (300 MHz, CDCl₃, ppm): δ 11.78 (d, *J* = 8.0 Hz, 1H, N-*H*), 11.49 (d, *J* = 8.3 Hz, 1H, N-*H*), 11.22 (d, *J* = 8.2 Hz, 1H, N-*H*), 11.14 (d, *J* = 8.1 Hz, 1H, N-*H*), 10.97 (d, *J* = 8.2 Hz, 1H, N-*H*), 10.88 (d, *J* = 8.1 Hz, 1H, N-*H*), 9.43 (s, 1H, N-*H*), 9.12 (s, 1H, Ar-*H*), 9.03 (s, 1H, Ar-*H*), 7.22–7.05 (br, 1H, N-*H*), 6.51 (s, 2H, Ar-*H*), 4.25–4.10 (m, 10H, OCH₂ and COCH₂CO), 2.38 (s, 3H, COCH₃), 2.15–1.93 (m, 8H, CH₂), 1.55–1.20 (m, 49H, CH₂ and OC(CH₃)₃), 0.90–0.83 (m, 12H, CH₂). ¹³C NMR (75 MHz, CDCl₃, ppm): δ 165.2, 162.9, 160.9, 160.8, 160.5, 157.2, 157.0, 155.1, 136.8, 112.9, 112.3, 111.9, 96.3, 81.3, 70.3, 38.9, 31.7, 29.3, 29.2, 29.1, 29.0, 28.8, 28.6, 28.2, 26.1, 26.0, 25.9, 25.8, 22.6, 20.6, 14.1. IR (KBr, cm⁻¹): 3343.96, 3227.29, 2928.38, 2858.95, 1630.52, 1457.92. MS (ESI): *m/z* 1110.09 [M]⁻. Elemental analysis calcd (%) for C₅₈H₉₄N₈O₁₃: C 62.68, H 8.52, N 10.08; found: C 62.61, H 8.48, N 10.22.

Compound 9: general procedure A. Yield: 83%. Mp: 114–115 °C. ¹H NMR (300 MHz, CDCl₃, ppm): δ 11.66 (d, *J* = 8.2 Hz, 1H, N-*H*), 11.45 (d, *J* = 8.0 Hz, 1H, N-*H*), 11.35 (d, *J* = 7.6 Hz, 1H, N-*H*), 11.07 (d, *J* = 8.1 Hz, 1H, N-*H*), 10.94 (d, *J* = 8.0 Hz, 1H, N-*H*), 10.81 (d, *J* = 7.9 Hz, 1H, N-*H*), 9.48–9.37 (br, 1H, N-*H*), 9.09 (s, 1H, Ar-*H*), 8.97 (s, 1H, Ar-*H*), 7.37–7.26 (br, 1H, N-*H*), 6.51 (s, 1H, Ar-*H*), 6.49 (s, 1H, Ar-*H*), 4.23–4.10 (m, 12H, OCH₂ and COCH₂CO and COOCH₂CH₃), 3.75 (s, 2H, COCH₂CO), 2.13–1.92 (m, 8H, CH₂), 1.53–1.19 (m, 52H, CH₂ and COOCH₂CH₃ and OC(CH₃)₃), 0.90–0.83 (m, 12H, CH₃). ¹³C NMR (75 MHz, CDCl₃, ppm): δ 167.5, 162.7, 161.00, 160.95, 160.9, 160.8, 160.7, 160.6, 160.5, 158.1, 157.5, 157.3, 155.1, 136.7, 112.9, 112.2, 112.0, 111.7, 96.3, 81.2, 70.3, 70.1, 61.3, 40.6, 38.9, 32.0, 31.7, 29.3, 29.24, 29.20, 29.12, 29.09, 29.0, 28.8, 28.6, 28.2, 26.1, 26.0, 25.84, 25.79, 22.6, 14.0. IR (KBr, cm⁻¹): 3345.89, 3223.43, 2928.38, 2858.95, 1737.55, 1631.48, 1457.92. MS (ESI): *m/z* 1181.97 [M – H]⁻. Elemental analysis calcd (%) for C₆₁H₉₈N₈O₁₅: C 61.91, H 8.35, N 9.47; found: C 61.89, H 8.33, N 9.72.

Compound 10: general procedure B. Yield: 93%. Mp: 140–141 °C. ¹H NMR (300 MHz, CDCl₃, ppm): δ 11.66–11.18 (m, 7H, COOH and N-*H*), 9.65–9.47 (br, 1H, N-*H*), 9.12 (s, 1H,

H-Ar), 8.96 (s, 1H, Ar-*H*), 7.15–7.04 (br, 1H, *H*-Ar), 6.52 (s, 2H, Ar-*H*), 4.30–4.15 (m, 12H, OCH₂ and COCH₂CO), 2.14–1.97 (m, 8H, CH₂), 1.50–1.28 (m, 49H, CH₂ and OC(CH₃)₃), 0.90–0.83 (m, 12H, CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆, ppm): δ 168.7, 166.5, 163.1, 162.9, 162.8, 162.5, 161.3, 160.6, 160.4, 160.3, 160.1, 134.2, 113.2, 112.9, 112.8, 112.4, 98.0, 79.1, 69.7, 69.4, 31.2, 28.8, 28.63, 28.60, 28.3, 28.1, 28.0, 25.4, 22.0, 20.3, 13.9. IR (KBr, cm⁻¹): 3353.6, 3223.4, 2927.4, 2859.0, 1628.6, 1461.8.

Compound D3: general procedure A. Yield: 94%. Mp: 218–219 °C. ¹H NMR (300 MHz, CDCl₃, ppm): δ 11.72–11.50 (m, 10H, N-*H*), 9.46–9.40 (br, 1H, N-*H*), 9.15 (s, 1H, N-*H*), 9.10 (s, 1H, N-*H*), 8.97 (s, 1H, N-*H*), 7.12–6.96 (br, 1H, N-*H*), 6.53 (s, 1H, N-*H*), 6.52 (s, 1H, N-*H*), 6.47 (s, 1H, N-*H*), 4.23–4.20 (m, 16H, OCH₂ and COCH₂CO), 2.35 (s, 3H, COCH₃), 2.11–1.94 (m, 12H, CH₂), 1.50–1.25 (m, 69H, CH₂ and OC(CH₃)₃), 0.90–0.84 (m, 18H, CH₃). ¹³C NMR (75 MHz, CDCl₃, ppm): δ 165.0, 160.92, 160.87, 160.7, 160.5, 160.0, 156.8, 156.5, 155.0, 137.0, 136.7, 112.8, 112.2, 111.9, 111.8, 96.3, 81.3, 70.2, 21.8, 31.7, 29.7, 29.4, 29.32, 29.26, 29.23, 29.13, 29.0, 28.8, 28.6, 28.2, 26.1, 26.0, 25.8, 25.7, 22.60, 22.57, 20.4, 14.0. IR (KBr, cm⁻¹): 3348.78, 3228.25, 2927.41, 2857.99, 1628.59, 1457.92. MS (MALDI-TOF): *m/z* 1652.0 [M + Na]⁺. Elemental analysis calcd (%) for C₈₅H₁₃₆N₁₂O₁₉·H₂O: C 61.95, H 8.44, N 10.20; found: C 61.90, H 8.35, N 10.69.

Compound 11: general procedure A. Yield: 92%. Mp: 117–118 °C. ¹H NMR (300 MHz, CDCl₃, ppm): δ 11.82–11.17 (m, 10H, N-*H*), 9.44–9.39 (br, 1H, N-*H*), 9.20–9.08 (m, 3H, N-*H*), 7.14–7.02 (br, 1H, N-*H*), 6.52–6.50 (m, 3H, N-*H*), 4.30–4.10 (m, 20H, OCH₂ and COOCH₂ and COCH₂CO), 2.10–1.80 (m, 12H, CH₂), 1.50–1.10 (m, 72H, COOCH₂CH₃ and CH₂), 0.88–0.85 (m, 18H, CH₃). IR (KBr, cm⁻¹): 3348.78, 3225.78, 2927.41, 2857.99, 1628.59, 1457.92, 1281.47. MS (MALDI-TOF): *m/z* 1723.4 [M + Na]⁺, 1739.4 [M + K]⁺. Elemental analysis calcd (%) for C₈₈H₁₄₀N₁₂O₂₁·H₂O: C 60.81, H 8.31, N 9.67; found: C 60.66, H 8.19, N 10.12.

Compound D4: general procedure A. Yield: 85%. Mp: >215 °C, decomposition. ¹H NMR (600 MHz, CDCl₃, 10 mM, 258K, ppm): δ 12.0–11.56 (m, 14H, N-*H*), 9.46 (s, 1H, N-*H*), 9.20–9.00 (m, 4H, N-*H*), 6.97 (s, 1H, N-*H*), 6.49 (s, 4H, N-*H*), 4.30–4.15 (m, 22H, OCH₂ and COCH₂CO), 2.19–1.99 (m, 16H, CH₂), 1.36–1.00 (m, 89H, CH₂ and OC(CH₃)₃), 0.84–0.78 (m, 24H, CH₃). IR (KBr, cm⁻¹): 3356.5, 2927.41, 2858.95, 1627.63, 1459.85. Elemental analysis calcd (%) for C₁₁₂H₁₇₈N₁₆O₂₅·2H₂O: C 61.57, H 8.40, N 10.26; found: C 61.38, H 8.25, N 10.40.

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