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Synthesis and preliminary investigations into norbornane-based amphiphiles and their self-assembly†

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A range of norbornane based amphiphiles, which possess a rigid 'kink' in the centre of amphiphiles, were accessed *via* a concise four step synthesis. The self-assembly properties of these novel compounds were then investigated and the critical aggregation concentration (CAC), hydrodynamic diameter (D_H) by dynamic light scattering (DLS) and their morphology by cryogenic transmission electron microscopy (cryoTEM) and negatively stained transmission electron microscopy (TEM) were determined. These compounds while possessing similar CAC values (50–70 μM) exhibited a wide variety of particle size (60–140 nm) and morphologies, including vesicles, cigar-shaped aggregates and rod-like micelles. Considering the similarities in molecular structure we have proposed that the unique nature of the molecular 'kink' is affecting molecular assembly in which subtle changes in molecular structure have large ramifications on aggregate size and morphology.

Introduction

Self-assembly of amphiphilic compounds has been of incredible interest to the scientific community and is at the core of many cutting-edge technologies in areas of medicine, nutraceuticals, gene-delivery and in the various aspects of materials science.[1–4] It has been noted that even small changes in molecular structure of the individual amphiphile can have major ramifications on the morphology of the self-assembled nanostructures that they produce. Therefore, in the continual search for more advanced and 'tailorable' nanostructures, the correlation between the molecular structure of amphiphiles and the characteristics of the aggregates they form is of utmost importance as this provides insights into molecular features which contribute to potentially desirable properties for a given system.

Recently, Matisons and co-workers[5] stated that the inclusion of a rigid portion in the centre of an amphiphile could lead to the formation of lipid bi-layers and, depending on angular displacement between hydrophobic tails caused by this rigidity, may lead to the formation of ribbons or tube-like structures. The rigid groups referred to by Matisons were typically a conjugated series of unsaturated carbon–carbon bonds placed between the polar head group and an unconstrained hydrophobic tail.

In this work we have installed a norbornane unit within the core of a range of amphiphiles as this scaffold provides rigidity, angular displacement while being entirely based on a saturated hydrocarbon scaffold. We hypothesised that the inclusion of a norbornane unit at the core of the amphiphile structure should promote the formation of vesicles due to the aforementioned effects. The norbornane scaffold, bearing a primary amine, has been employed as a counter-ion in a study by Bordes *at al.*[6,7] In this instance the amino portion of the norbornane was a 60/40 mixture of *endo–exo* and this system demonstrated large variations in assembly size with minor changes in molecular feature. This was largely attributed to the unique bicyclic structure of the norbornane scaffold and its effect on ion pairing and assembly. The inclusion of the norbornane within

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the amphiphiles has provided the architecture with what we have termed a molecular 'kink' and will be another area of novelty explored in this work. Additionally, the synthetic methodology employed within our group using the norbornane scaffold is well established.[8]

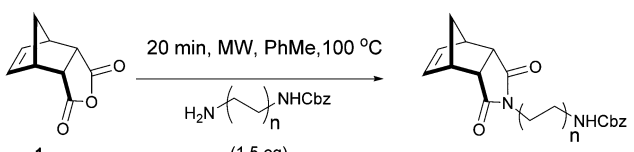
In this manuscript we present a highly versatile synthesis for accessing norbornane based amphiphilic compounds using reagents which are ubiquitous within organic chemistry laboratories worldwide. Additionally, we present preliminary findings on the physicochemical properties of several amphiphiles which include critical aggregation concentration (CAC), hydrodynamic diameter (D_H) and morphology using dynamic light scattering (DLS) and cryogenic transmission electronic microscopy (cryoTEM) and TEM.

Results and discussion

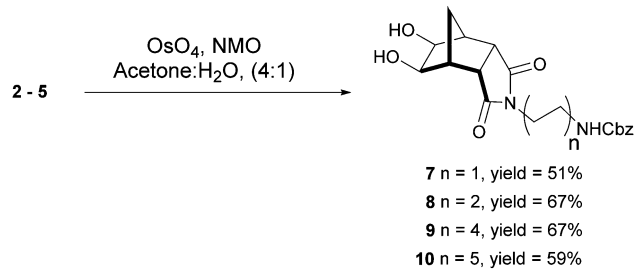
When considering the synthetic pathway to give amphiphiles of general structure shown in Scheme 1, we were conscious of developing a route that could be easily modified to facilitate analogue synthesis. We began by using mono-protected alkyldiamines,[8,9] with which we have had previous experience, of various lengths to access imides **2–5** using microwave irradiation and a slight excess (1.5 equivalents) of the mono-protected amine.

This protocol worked well for most mono-protected amines giving high to excellent yields of the corresponding imides (**2**, **3** and **5**) however, compounds **4** and **6** were initially isolated in very poor yields (typically $<20\%$). Given these low yields brief microwave optimisations were investigated for these two amines, slightly increasing the reaction time, temperature and equivalents of amine (55 min, 120 °C, 2 eq. of amine, highlighted in Scheme 1 with asterisk) these compounds could be isolated in synthetically useful yields shown in Scheme 1 (for optimisation table refer to ESI†).

With imides **2–5** in hand, our attention turned to installing the hydrophobic portion of the amphiphiles. Imides **2–5** were dihydroxylated using a typical osmium tetroxide–*N*-methylmorpholine-*N*-oxide (OsO_4–NMO) in acetone system to exclusively give the *exo*-vicinal diols **7–10** (Scheme 2),[8] the selective formation of the diol moiety in this orientation is imperative to the overarching 'kink' in the amphiphile. Note that treatment of **6** under these dihydroxylation conditions gave very low yields (typically 10–20%). Despite attempts at optimisation of this step synthetically viable yields remained elusive; as such this imide was no longer pursued for further study.



Scheme 1 Synthesis of imides **2–6**.



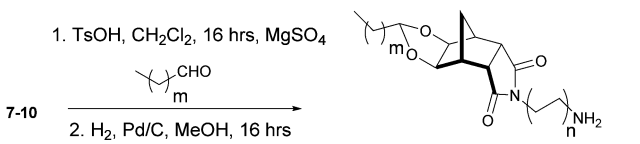
Scheme 2 OsO_4–NMO mediated dihydroxylation of imides **7–10**.

Again, reasonable yields were realised with most compounds, though it should be noted that the purification of these compounds proved troublesome.

Installation of the hydrophobic portion of the amphiphiles was carried out using a cyclodehydration protocol to give a 1,3-dioxolane (acetal) moiety under mildly acidic conditions.[10] These acetals were purified and immediately deprotected by catalytic hydrogenolysis to give the neutral amphiphiles which were obtained in good yields over two steps (Scheme 3). The overall yield for the synthesis of these novel norbornane-based amphiphiles ranged from 42% to 12% in four steps.

As we were interested in the properties of the amphiphiles in the cationic state, each of the amphiphiles **11–18** were converted to their corresponding hydrochloride salt using gaseous HCl.[11] It is worth noting that the described synthetic route can easily incorporate any amine or aldehyde combination, whether they are commercially available or tailored for a specific means. For example, the nitrogen unit used for imide formation could form part of small peptides, proteins or aptamers for targeted therapeutic purposes.

Given the unusual structural nature of the amphiphiles synthesised in this study we were curious about the lipophilic nature of these compounds. Specifically, we were interested whether the norbornane core is considered part of the lipophilic region and how much the cationic spacer unit *versus* the alkyl chain (*i.e. n versus m*, Fig. 1) contributes to the overall lipophilicity of these compounds.



Scheme 3 Installation of linear hydrophobic chain *via* an acetal moiety and removal of the Cbz protecting group.

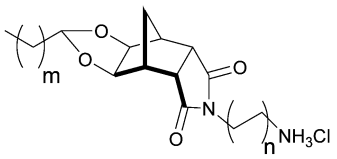


Fig. 1 Core scaffold for evaluation highlighting *m* and *n* spacer units.

Table 1 Predicted and determined lipophilicity values

Entry	Compound	*n*	*m*	nC[a]	log *P*	log k_w' [b]
1	Norbornane	—	—	—	−1.65[c]	—
2	**11**	1	10	13	1.77	1.01
3	**12**	1	14	17	3.28	1.13
4	**13**	2	10	15	2.00	0.89
5	**14**	2	14	19	3.44	1.18
6	**15**	4	10	19	3.13	1.25
7	**16**	4	14	23	4.22	1.30
8	**17**	5	10	21	3.66	1.33
9	**18**	5	14	25	4.65	1.33
10	$C_{12}H_{23}NH_3Cl$	—	—	12	1.64	—
11	$C_{14}H_{29}NH_3Cl$	—	—	14	2.53	—
12	$C_{16}H_{33}NH_3Cl$	—	—	16	3.26	—
13	$C_{18}H_{37}NH_3Cl$	—	—	18	3.95	—

[a] Number of alkyl carbons within amphiphiles, for norbornane-based compounds nC = (2*n* + *m* + 1), the acetal carbon being omitted. [b] Determined by RP-HPLC. [c] Data from ref. 7.

Therefore, the partition coefficients of **11–18** were predicted using the software ALOGPS[12,13] and the values are given in Table 1. The norbornane (Table 1, entry 1) is reported here as an indication of what the core unit lipophilic properties are and thus how the inclusion of separation between the units *m* and *n* have on this overall characteristic. In addition to the calculated values we experimentally determined the log k_w', a parameter closely associated with log *P* which is commonly used for small molecules and amphiphiles.[14] For the sake of comparison, with respect to log *P* linear *n*-alkylammonium chloride compounds were added as well (Table 1, entries 10–13).

In comparing the partition coefficient for compounds **11** and **12**, it can be seen that extension of the alkyl chain installed *via* the acetal moiety (*m*) by four methylene units results in a significant increase of the overall lipophilicity by ~1.9 times. A similar scenario is observed when comparing compounds **13** and **14**, compounds **15** and **16** and compounds **17** and **18**, where installation of four carbons on the aliphatic chain has corresponded to an increase of the lipophilicity by ~1.7, 1.3 and 1.3 times, respectively. This clearly shows that the predicted effect of extending the alkyl chain on the lipophilicity is more pronounced when the diamino spacer is short (Fig. 2).

Comparison of these same compounds (**11** and **12**, **13** and **14**, **15** and **16**, **17** and **18**) with respect to the determined log k_w' values shows the same trend though the variation in lipophilicity is much smaller.

Continuing with this theme, analysis of compounds, **11** and **13**, increasing *n* by two carbons shows only a mild increase in log *P* value (~1.1 times) whereas, as expected, six (**15**) or eight (**17**) carbons of the spacer length led to much more lipophilic compounds, respectively, 1.8 and 2.1 times when compared to

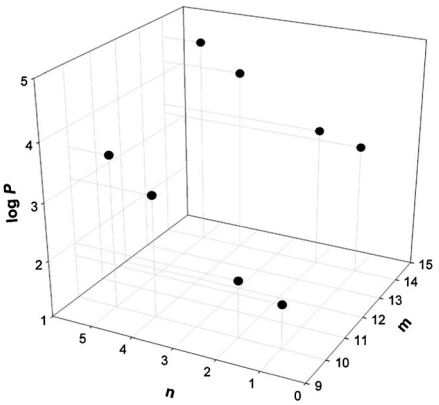


Fig. 2 Graphical representation of *A* log *P* values *versus* number of methylene units.

compound **11** (Fig. 2). A similar scenario was observed when comparing the *n* value in compounds **12**, **14**, **16** and **18** (Fig. 2). Note that a correlation of both the log *P* and log k_w' with the number of methylene units present in these compounds has been undertaken and is presented in the ESI.†

These differences suggest that the choice of diamine which is used for the synthesis has a much less pivotal role in determining overall lipophilicy of the target compound. The general trends observed by comparison of log *P* are supported by log k_w' though, again, the magnitude of variation is much smaller in the latter. Disparate results between the classical octanol partitioning method and the HPLC methods have been observed for short cationic peptides, most likely because of interactions with the stationary phase of the column. Due to the cationic nature of the polar heads, similar interactions may explain the variation between the predicted and the experimental values.[15]

Comparing the lipophilicity of the norbornane-based amphiphiles to that of their linear *n*-alkyl ammonium chloride derivatives of similar chain length, it appears that the norbornane scaffold does not contribute much to the overall lipophilicity despite being mostly hydrocarbon based (Table 1). A reason for the lack of lipophilicity demonstrated by the norbornane core may be due to the presence of the polar oxygens within the acetal and carbonyls at each end of the scaffold; this in effect may negate the lipophilic hydrocarbon core of the bicycle.

Indeed *n*-dodecylammonium chloride exhibits a log *P* value (1.64) very close to that of compound **11** (1.77) having **13** alkyl carbons. With longer alkyl chains, more pronounced differences are observed as the *n*-octadecylammonium chloride exhibits a higher lipophilicity than compounds **14** and **15** although both have an overall number of alkyl carbons of 19 suggesting that the norbornane scaffold is not lipophilic by itself. With this data in hand our attention turned to an investigation of aggregation properties focusing on compounds **11–14**. The selection of these four compounds provides a comparison of alkyl chain length and amine spacer unit when incorporated into this novel scaffold, additionally compounds **15–18** proved very insoluble in aqueous solution.

Determination of critical aggregation concentration (CAC) by encapsulation of pyrene

The critical aggregation concentration (CAC) of amphiphilic species is of paramount importance when considering their application to biological systems. In our hands, these compounds proved troublesome to dissolve in water but adequate solubilisation was achieved by heating at 60 °C under ultrasonic agitation for an hour (see experimental section for details). Once dissolved in water the CAC was determined by monitoring the ratio of fluorescence emitted by the encapsulation of pyrene.[16,17]

The ratio of pyrene emission peaks at 386 nm and 393 nm ($I_{386/393}$) was monitored over a series of concentrations ranging from 1–0.0001 mg mL^{-1}, as per literature procedures.[16,18] An example of the CAC determination of compound **11** is shown in the ESI† (Page S18), where a sharp increase in the $I_{386/393}$ value can be seen at 30.8 mg L^{-1} (70 μM) suggesting that this is the concentration at which aggregation has occurred, allowing the encapsulation of pyrene in the aggregate core. The CAC data for all compounds are summarised in Table 2.

As shown in Table 2, determination of CAC demonstrated behaviour consistent with log k_w' data as the CAC values exhibited by compounds **11–14** were fairly insensitive to changes made to amphiphile structure. This observation correlates well with those reported by Kunitake *et al.*[19] who also used a rigid scaffold in simple ammonium-based single chain amphiphiles.[16] When comparing **11** and **12**, only a slight decrease of the CAC, 22.6 mg L^{-1} (50 μM), was observed for the latter although it is has an additional four methylene longer alkyl chain.

As frequently reported for a given polar head group, the addition of two methylene units to the hydrocarbon chain of a surfactant decreases 5–15 times the critical aggregation concentration.[20,21] A similar observation was made with compounds **13** and **14**, the more hydrophobic derivative exhibited a CAC value only 1.2 times lower than that of **13** (70 μM *vs.* 60 μM, respectively) which possesses four fewer carbons. When comparing the CAC of compounds **11–14** to that of linear *n*-alkyl ammonium compounds, we found out that they were somehow in relative good agreement with a C_{16} surfactant. Indeed, the CAC of *n*-decyl ammonium chloride was reported to be ~0.05 M[22] while that of its *n*-tetradecyl derivative is ~3 mM[23] and that of the hexadecyl ammonium bromide ~30 μM.[24] Similarly, *n*-hexadecyl-D-maltosylamine and *n*-hexadecyl-D-lactosylamine were found to form aggregates at a threshold concentration of ~12 μM using fluorescence technique.[25] Therefore, this suggests that compounds **11–14** having CAC values ranging from 50 to 70 μM behave more or less like a C_{16} surfactant with no significant effect of *n* and *m* on the aggregation concentration.

When considering the effect of the length of the diamino spacer, *n*, a singular behaviour was also observed as for a given alkyl chain, similar CAC values were observed for the butyl diamino derivatives (**13** and **14**) when compared to the ethyl diamino ones (**11** and **12**). This is, however, in agreement with the partition coefficients as we showed that increasing the length of the spacer unit from 2C to 4C did not significantly affect the overall lipophilicity (Table 1). This, again, correlates well to our previous hypothesis that the length of the diamino spacer incorporated into this scaffold does not play a pivotal role in overall compound hydrophobicity.

This further confirms the peculiar behaviour of these compounds as they exhibit similar critical aggregation concentrations to that of C_{16} surfactants.[24,25] Moreover, such a magnitude of concentration is consistent with other single-chain surfactants forming bilayer aggregates.[19,25]

We have attributed these unusual results, which contradict commonly observed trends, to the unique architecture which is present in these amphiphiles. Indeed, due to the weakly non-polar nature of the norbornane core as discussed previously (see partition coefficient section), as well as its rigid structure and the kink it provides to the overall molecular architecture, its insertion within the hydrophobic part of the amphiphile may alter aggregation and therefore could explain unexpected behaviour. For instance, although the sulfur atom is usually considered as a hydrophobic unit when inserted within the hydrophobic chain of a surfactant, Menger and co-workers found out that the insertion of a sulfide group causes an increase in the CAC by 2- to 3-fold, the deeper the insertion, the higher the increase.[26,27]

Taking this into account, on one hand, an increased CAC may be explained by attractive interactions between the norbornane core and water such as hydrogen bonding leading to increased solubility. The norbornane group could also decrease the entropic gain on micellisation by changing the water structure around the monomer into a less ordered one. On the other hand, packing constraints could arise from the rigid and bulky norbornane inserted group. These effects will be further studied in future work.

Table 2 CAC data for **11–14** *via* pyrene encapsulation

					CAC[a]	
Entry	Cpds	*n*	*m*	nC	(mg L^{-1})	(μmol L^{-1})
1	**11**	1	10	13	30.8 2.1	70 5
2	**12**	1	14	17	22.6 3.1	50 7
3	**13**	2	10	15	34.4 1.1	70 2
4	**14**	2	14	19	29.3 3.7	60 7

[a] Results are the average of triplicate experiments carried out at 18 °C in MilliQ water.

Determination of hydrodynamic diameter (D_H) by DLS

The hydrodynamic diameter of each amphiphile solution was determined by Dynamic Light Scattering (DLS) at 25 °C. Hydrodynamic diameter for **11** showed a D_H of 59 nm. Examination of **12** in an aqueous system showed a bimodal distribution (Table 3, entry 2) of 79 and 24 nm, these data suggest that the aggregates formed by **12** are in two distinct populations. DLS analysis of **13** and **14**, gave polydisperse aggregates of 142 and 91 nm, respectively.

Aggregates of ~60–160 nm diameter is consistent with the formation of vesicles as it has been observed with other

Table 3 D_H of aggregates

Entry	Compound	D_H [a] (nm)
1	**11**	59 (100%)
2	**12**	79 (89%)
		24 (10%)
3	**13**	142 (100%)
4	**14**	91 (100%)

[a] Hydrodynamic diameter, determined at 10× the CAC value at 25 °C with volume distribution.

single-chain surfactants.[19,25,28] For instance, a recently designed triazole-based single-chain surfactant was found to form vesicles whose size varies from 80–100 nm by TEM to ~170 nm by DLS.[29] Moreover, Bhattacharya and Acharya reported that freshly prepared solution of the single chain *n*-hexadecyl-D-maltosylamine and *n*-hexadecyl-D-lactosylamine compounds form vesicles of 50 to 80 nm diameter. Upon aging, these vesicles transformed into tubular and lamellar microstructures.[25]

Considering the data obtained by DLS, our attention turned to obtaining morphological information of these aggregates under cryoTEM conditions.

TEM and CryoTEM imaging

Compound **11** presented in the form of small vesicle aggregates (Fig. 3) which were visualised by negative stain. Despite potential morphological changes that can occur by negative staining, there was excellent agreement between the D_H obtained *via* DLS and the observed vesicles, *cf.* 59 nm *vs.* 65 nm, respectively.

Analysis of **12** (Fig. 4) gave a bimodal distribution in DLS and proved very interesting when visualized by cryoTEM showing two morphological forms, both of which were cylindrical. Examination in low contrast revealed elongated forms of cigar-shaped vesicles as seen in Fig. 4 (labelled A). These elongated vesicles were the dominant feature of the colloid, though a number of striated tube-like structures were also seen, although these were not as common as the cigar like vesicles but are still considered to be a real feature of the sample (Fig. 4, labelled B).

Interestingly, **13** has formed large vesicles of classical liposomal structure (Fig. 5), a morphology very similar to that observed by Bordes *et al.*[7] which was attributed to the stacking

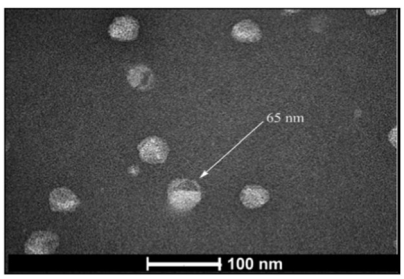


Fig. 3 Compound **11** negatively stained showing vesicles approximately 65 nm in diameter.

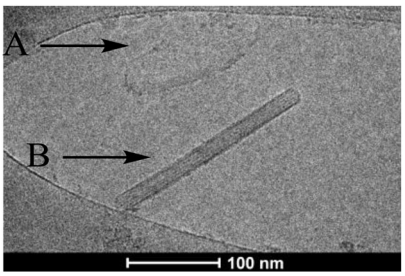


Fig. 4 Compound **12** showing two morphologies, A, cigar shaped vesicle (57 nm wide, 163 nm long); B, rod-like micelle (20 nm wide, 245 nm long).

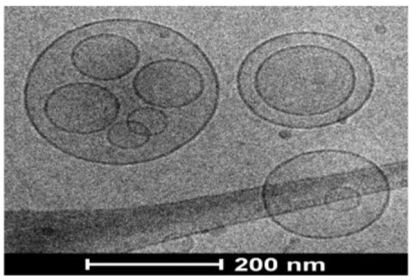


Fig. 5 CryoTEM images of **13** showing the formation of vesicles ranging from 150–250 nm.

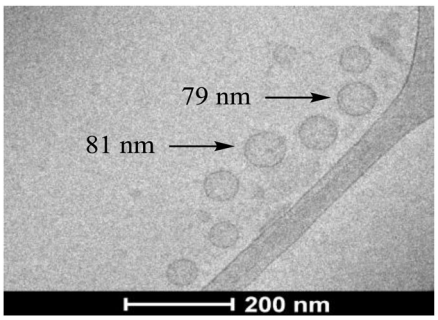


Fig. 6 Compound **14** showing vesicle formation ranging from 70–90 nm.

of their norbornane bicyclic structure. Compound **14** also showed classic spherical vesicles (Fig. 6) which are quite polydisperse in size, with a range of 30–500 nm, however the majority are observed to be between 70–90 nm, corresponding well to the values obtained from DLS (*cf.* 91 nm). Most of the vesicles are smooth with no substructure although occasional smaller vesicles observed with a slight ''orange peel'' texture.

We have attributed these differences in morphology to the ability of the amphiphiles to stack together, thus creating the lipid bilayer. It has been shown that the position of the ''rigid portion'' of amphiphiles can have ramifications on the overall morphology of the self assemblies.[30] In this study by varying the value of *n* and *m* we have effectively moved the rigid 'kink' within the overall architecture of the amphiphiles. As such their ability to stack must be determined by a delicate balance of *n* and *m* which, in turn, dictates the aggregate morphology, CAC and size. It was noted that during the course of the CAC studies

via surface tension measurements that the calculated head group area at the interface is larger than typically seen in these systems (data not shown). This may indicate unusual interactions at the surface, possibly arising due to stacking phenomena arising from the kink present in the amphiphile. The assembly of these compounds may occur in a complementary fashion, with all the kinks facing in the same direction or, conversely, in an opposing orientation. Each of these assembling motifs will result in vastly different effective critical packing parameter (CPP)[31] thus shedding light on the unusual behaviour of these compounds. The molecular interactions of these compounds and their potential assembly modes are currently under investigation using computational methods and will be reported in due course.

Conclusions

In conclusion, this manuscript has presented the synthesis and preliminary investigations into the self-assembly characteristics of several amphiphiles based on a norbornane scaffold. This scaffold, while rigid in structure, provides a central 'kink' to the amphiphile which has a major effect on how they assemble in aqueous media. Prediction of partition coefficient values *in silico* suggested that the rigid norbornane core has little-to-no effect on overall compound hydrophobicity. This was reinforced by the determination of log k_w' which showed very small variation in lipophlicity among compounds investigated. Additionally the length of the linking group between the norbornane core and hydrophilic head group has minimal effect on CAC value and aggregate morphology as is consistent with log k_w' values. Despite compounds 11–14 possessing similar CAC values they demonstrated large variations in aggregate size and morphology. Subtle changes in the distribution of methylene groups throughout the compounds influenced the aggregate size (approximately 60–140 nm) and their morphology in aqueous solution.

Experimental

Dynamic light scattering

The light scattering measurements were performed with a Zetasizer Nano ZS (Malvern Instruments) at a scattering angle of 173°. The concentrations of the surfactants were sufficiently low enough (0.46–0.72 mM) to avoid multiple scattering from the aggregates. Solutions were prepared at 10 × CAC from a stock solution of 1 mg mL^{-1} in Milli-Q water and sonicated for 30 min to ensure adequate dissolving before being left to equilibrate overnight. All solutions were filtered with 0.45 μm filter directly into the cuvette immediately before measurement to avoid interference from dust particles. Measurements were taken at 25 °C unless otherwise stated.

Pyrene encapsulation measurements

The fluorescence properties of pyrene were determined using a Varian Cary Eclipse fluorescence spectrophotometer. The surfactant solutions were prepared 24 h prior to the measurements using Milli-Q water (resistivity of 18.2 MΩ cm) at a range of concentrations (1–0.0001 mg mL^{-1}). Excess crystalline pyrene was then added to the surfactant aqueous solutions and heated at 30 °C for 30 min in a sonic bath before allowing to equilibrate at room temperature 23 hours. The solutions were then filtered through a 0.45 μM filter prior to measurement. The emission spectra of pyrene were acquired by exciting samples at 335 nm (Ex slit width 5 nm, Em slit width 5 nm). The spectra were then used to determine the ratio of $I_{386/393}$.

Determination of log k_w'

The analytes were sequentially injected onto the column with increasing amounts of organic modifier in the eluent (water–methanol). Runs were undertaken at ratios of 90 : 10, 70 : 30 and 50 : 50 methanol–water. The value of k_w was determined by extrapolation of the k *vs.* conc. of organic modifier back to pure water. The log (base 10) of this value was then carried out to give the log k_w value. Dead time of the system was determined by injecting acetone through the system and monitoring its retention time.

CryoTEM and TEM

A laboratory-built humidity-controlled vitrification system was used to prepare the samples for Cryo-TEM. Humidity was kept close to 80% for all experiments, and ambient temperature was 22 °C. 200-Mesh copper grids coated with perforated carbon film (Lacey carbon film: ProSciTech, Qld, Australia) were glow discharged in nitrogen to render them hydrophilic. 4 μL Aliquots of the sample were pipetted onto each grid prior to plunging. After 30 seconds adsorption time the grid was blotted manually using Whatman 541 filter paper, for approximately 2 seconds. Blotting time was optimised for each sample. The grid was then plunged into liquid ethane cooled by liquid nitrogen. Frozen grids were stored in liquid nitrogen until required. The samples were examined using a Gatan 626 cryoholder (Gatan, Pleasanton, CA, USA) and Tecnai 12 Transmission Electron Microscope (FEI, Eindhoven, The Netherlands) at an operating voltage of 120 KV. At all times low dose procedures were followed, using an electron dose of 8–10 electrons per Å^2 for all imaging. Images were recorded using an Eagle 4k × 4k CCD camera (FEI, Eindhoven, The Netherlands) using magnifications in the range 15 000–60 000×

Synthesis of *N*-(benzyloxy carbonyl)-1,4-butanediamine

A solution of 1,4-diaminobutane (5.72 mL, 5.67 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and a solution of benzylchloroformate (1.62 mL, 11.3 mmol) and CH_2Cl_2 (150 mL) was added dropwise over 1 h. The reaction was then stirred at rt for 24 h. The resulting mixture was transferred to a separating funnel where it was washed with saturated aqueous NaCl (3 × 30 mL). The organic phase was dried ($MgSO_4$), filtered and solvents removed *in vacuo* to afford a white powder. ^{1}H NMR spectroscopy data was found to be consistent with literature values[8] for the desired monobenzylcarbamate diamine (2.07 g, 82%) in >95% purity which was then used without further purification.

Synthesis of *N*-(benzyloxy carbonyl)-1,2-diaminoethane

Synthesis of *N*-(benzyloxy carbonyl)-1,2-diaminoethane was carried out as per previously described for *N*-(benzyloxy carbonyl)-1,4-butanediamine, with 1,2-diaminoethane (6.67 mL, 10 mmol) and benzylchloroformate (2.85 mL, 20 mmol mol) to afford a white paste. ^{1}H NMR spectroscopy data was found to be consistent with literature values[8] for the desired monobenzylcarbamate diamine (3.48 g, 90%) in >95% purity which was then used without further purification.

Synthesis of *N*-(benzyloxy carbonyl)-1,8-octyldiamine

Synthesis of *N*-(benzyloxy carbonyl)-1,8-octyldiamine was carried out as per previously described *N*-(benzyloxy carbonyl)-1,4-butanediamine, with 1,8-diaminooctane (3.00 g, 0.021 mol) and benzylchloroformate (0.6 mL, 0.0042 mol) to afford a white powder. ^{1}H NMR spectroscopy data was found to be consistent with literature values[8] for the desired monobenzylcarbamate diamine (0.985 g, 84%) in >95% purity which was then used without further purification.

Synthesis of *N*-(benzyloxy carbonyl)-1,10-decyldiamine

Synthesis of *N*-(benzyloxy carbonyl)-1,10-decyldiamine was carried out as per previously described for *N*-(benzyloxy carbonyl)-1,4-butanediamine, with 1,10-diaminodecane (1.00 g, 0.0058 mol) and benzylchloroformate (0.17 mL, 0.0012 mol) to afford a white powder. ^{1}H NMR spectroscopy data was found to be consistent with literature values[8] for the desired monobenzylcarbamate diamine (0.208 g, 57%) in >95% purity which was then used without further purification.

Synthesis of *N*-(benzyloxy carbonyl)-1,12-dodecyldiamine

Synthesis of *N*-(benzyloxy carbonyl)-1,12-dodecyldiamine was carried out as per previously described for *N*-(benzyloxy carbonyl)-1,4-butanediamine, with 1,10-diaminodecane (2.00 g, 0.010 mol) and benzylchloroformate (0.28 mL, 0.002 mol) to afford a white powder. ^{1}H NMR spectroscopy data was found to be consistent with literature values[8] for the desired monobenzylcarbamate diamine (0.556 g, 83%) in >95% purity which was then used without further purification.

Synthesis of benzyl [2-(1,3-dioxo-1,3,3*a*,4,7,7*a*-hexahydro-2*H*-4,7-methanoisoindol-2-yl)butyl]carbamate 3

To a 35 mL microwave vial containing mono-protected diaminobutane (873 mg, 3.90 mmol), norbornene anhydride (430 mg, 2.6 mmol) was added and dissolved with toluene (15 mL). The solution was then subjected to microwave irradiation at 100 °C for 30 min. The resulting solution was diluted with CH_2Cl_2 (30 mL) and was transferred to a separating funnel where it was washed with saturated aqueous NaCl (2 × 25 mL) followed by a wash with HCl (2 M, 20 mL) and finally $NaHCO_3$ (3 × 25 mL). The combined organic phases were dried ($MgSO_4$) and solvent removed *in vacuo* to give reddish brown viscous oil. ^{1}H NMR spectroscopy analysis showed it to be the desired diaminobutane imide **3** (1.29 g, 90%) in >95% purity which was then used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.34–7.19 (5H, s), 6.01 (2H, s), 5.01 (2H, s,), 3.28–3.26 (4H, m), 3.18–3.08 (4H, m), 1.73–1.68 (1H, d, J = 13.5 Hz), 1.52–1.42 (5H, m, 2 × CH_2); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.87, 156.59–156.49, 136.71, 134.51, 129.91–128.16, 66.82–66.64, 52.31, 45.79, 44.96, 40.56, 37.91, 27.31, 25.16; HRMS (ESI *m*/*z*): calcd for $[C_{21}H_{25}N_2O_4]^+$ 369.1809, found 369.1837; $\nu_{(max)}$ cm^{-1}: 3338 m, 2942 m, 2870 m, 1683 s, 1527 m, 1172 m.

Synthesis of benzyl [2-(1,3-dioxo-1,3,3*a*,4,7,7*a*-hexahydro-2*H*-4,7-methanoisoindol-2-yl)ethyl]carbamate 2

Synthesis of imide **2** was carried out as previously describe for compound **3** with mono-protected diaminoethane (2 g, 0.01 mol) and norbornene anhydride (1.13 g, 7.0 mmol) to produce a yellow oil. ^{1}H NMR spectroscopy analysis showed it to be the desired diaminoethane imide **2** (2.2 g, 94%) in >95% purity which was then used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.47–7.31 (5H, s) 6.03 (2H, s) 5.04 (2H, s) 3.46–3.48 (2H, d, J = 5.4 Hz) 3.27–3.32 (2H, m) 3.17 (2H, s) 1.67–1.69 (1H, d, J = 5.4 Hz) 1.46–1.49 (1H, d, J = 8.1 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.96, 156.35, 136.63, 134.51, 128.57–128.17, 66.77, 52.31, 45.87, 44.94, 37.80; HRMS (ESI *m*/*z*): calcd for $[C_{19}H_{21}N_2O_4]^+$ 341.1496, found 341.1478; $\nu_{(max)}$ cm^{-1}: 3349 m, 2945 m, 1691 s, 1525 m, 1188 m.

Synthesis of benzyl [2-(1,3-dioxo-1,3,3*a*,4,7,7*a*-hexahydro-2*H*-4,7-methanoisoindol-2-yl)octyl]carbamate 4

Synthesis of imide **4** was carried out as previously describe for compound **3** with mono-protected diaminooctane (100 mg, 0.359 mmol) and norbornene anhydride (29.5 mg, 0.180 mmol) to produce a yellow oil. ^{1}H NMR spectroscopy analysis showed it to be the desired diaminooctane imide **4** (49 mg, 64%) in >95% purity which was then used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.33–7.35 (5H, s), 6.15 (2H, s), 5.10 (2H, s), 3.21–3.56 (6H, m), 1.69–1.72 (1H, d, J = 8.1 Hz), 1.43–1.48 (5H, m), 1.22 (8H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.51, 156.20, 136.49, 128.80, 128.37, 65.99, 52.30, 45.80, 44.98, 41.34, 38.34, 29.18, 26.85, 26.68; HRMS (ESI *m*/*z*): calcd for $[C_{25}H_{33}N_2O_4]^+$ 425.2435 found 425.2428; $\nu_{(max)}$ cm^{-1}: 3333 m, 2935 m, 2854 m, 1687 s, 1558 m, 1137 m.

Synthesis of benzyl [2-(1,3-dioxo-1,3,3*a*,4,7,7*a*-hexahydro-2*H*-4,7-methanoisoindol-2-yl)dodecanyl]carbamate 5

Synthesis of imide **5** was carried out as previously describe for compound **3** with mono-protected diaminodecane (1.05 g, 0.003 mol) and norbornene anhydride (563 mg, 0.002 mol) to produce a yellow oil. ^{1}H NMR spectroscopy analysis showed it to be the desired diaminodecane imide **5** (1.22 g, 79%) in >95% purity which was then used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.32–7.30 (5H, s), 6.11 (2H, s), 5.05 (2H, s), 3.34–3.18 (8H, m), 1.68–1.71 (1H, d, J = 8.1 Hz), 1.47–1.45 (5H, m), 1.23 (10H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.86, 156.48, 137.01, 134.47, 128.57–128.12, 66.59, 52.27, 45.77, 44.96, 38.49, 29.42, 29.36, 26.92; HRMS (ESI *m*/*z*): calcd for $[C_{27}H_{37}N_2O_4]^+$ 453.2748, found 453.2763; $\nu_{(max)}$ cm^{-1}: 3348 m, 2926 m, 2854 m, 1692 s, 1531 m, 1129 m.

Synthesis of benzyl [2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-4,7-methanoisoindol-2-yl)butyl]carbamate 8

Diaminobutane imide **3** (1.03 g, 2.70 mmol) was dissolved in a 4 : 1 solution of acetone–water (30 mL) and NMO (493 mg, 4.0 mmol) was added and stirred until dissolved. Osmium tetroxide (0.3 mL, 4% in H_2O) was added and the black solution stirred for 72 h at room temperature. The reaction was quenched with sodium metabisulfite (2 mL, 0.53 M) and the solution diluted with EtOAc (30 mL) before being transferred to a separating funnel where it was washed with saturated aqueous NaCl (3 × 25 mL). The organic phase was dried ($MgSO_4$) and solvent was removed *in vacuo* to afford a dark brown oil. Purification by silica gel column chromatography was performed with 80% EtOAc–20% petroleum spirit solution and the resulting brown oil was shown by ^{1}H NMR spectroscopy to be the desired diaminobutane diol **8** (733 mg, 67%). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.30–7.27 (5H, s), 5.01 (2H, s), 3.98 (2H, s), 3.64 (2H, s), 3.44–3.39 (2H, t, J = 8.1 Hz), 3.11–3.09 (2H, d, J = 5.4 Hz), 2.63 (2H, s), 2.39 (2H, br s), 2.08–2.04 (2H, d, J = 10.8 Hz), 1.48–1.40 (4H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.30, 156.85, 136.40, 128.64, 70.19, 66.92, 45.82, 45.75, 40.68, 38.27, 36.00, 29.75, 27.55, 25.16 HRMS (ESI *m*/*z*): calcd for $[C_{21}H_{26}N_2NaO_6]^+$ 425.1683, found 425.1657; $\nu_{(max)}$ cm^{-1}: 3368 br, 2942 m, 1689 s, 1537 m, 1139 m.

Synthesis of benzyl [2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-4,7-methanoisoindol-2-yl)ethyl]carbamate 7

Synthesis of diaminoethane diol **7** was carried out as previously describe for compound **8** with diaminoethane imide **2** (1.04 g, 3.0 mmol) and NMO (539 mg, 4.6 mmol) to produce a dark brown oil. Purification by silica gel column chromatography was performed with 90% EtOAc–10% petroleum spirit solution and the resulting light brown oil was shown by ^{1}H NMR spectroscopy to be the desired diaminoethane diol **7** (578 mg, 51%). ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.32 (5H, s), 5.09 (2H, s), 3.64 (2H, s), 3.58–3.55 (4H, m), 3.37–3.35 (2H, d, J = 5.4 Hz), 2.90 (2H, s), 2.61 (2H, s), 2.11–2.09 (1H, d, J = 5.4 Hz), 1.43–1.39 (1H, t, J = 5.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.54, 156.92, 136.39, 128.63–128.32, 70.15, 67.12, 45.76, 39.22, 35.99 HRMS (ESI *m*/*z*): calcd for $[C_{19}H_{23}N_2O_6]^+$ 375.1551, found 375.1578; $\nu_{(max)}$ cm^{-1}: 3368 br, 2924 m, 2854 m, 1692 s, 1533 m, 1145 m.

Synthesis of benzyl [2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-4,7-methanoisoindol-2-yl)octyl]carbamate 9

Synthesis of diaminooctane diol **9** was carried out as previously describe for compound **8** with diaminooctane imide **4** (228 mg, 0.54 mmol) and NMO (94.4 mg, 0.81 mmol) to produce a dark brown oil which was then used without further purification. Purification by silica gel column chromatography was attempted for analysis purposes with 80% EtOAc–20% petroleum spirit solution and the resulting light brown oil was shown by ^{1}H NMR spectroscopy to be the desired diaminooctane diol **9**. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.34 (5H, s), 5.07 (2H, s), 3.73 (2H, s), 3.43 (2H, s,), 3.17–3.15 (2H, d, J = 8.1 Hz), 3.04 (1H, s), 2.67 (1H, s), 2.14–2.11 (1H, d, J = 12.0 Hz), 1.73 (1H, s), 1.52–1.47 (4H, d, J = 20 Hz), 1.28 (2H, s), 1.25 (8H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.04, 156.85, 136.47, 128.63–128.23, 70.26, 66.93, 46.01, 45.76, 40.77, 36.02, 29.85, 28.60, 27.80, 26.63, 26.01 HRMS (ESI *m*/*z*): calcd for $[C_{25}H_{35}N_2O_6]^+$ 459.2490, found 459.2475; $\nu_{(max)}$ cm^{-1}: 3347 br, 2929 m, 2856 m, 1692 s, 1534 m, 1139 m.

Synthesis of benzyl [2-(5,6-dihydroxy-1,3-dioxooctahydro-2*H*-4,7-methanoisoindol-2-yl)dodecanyl]carbamate 10

Synthesis of diaminodecane diol **10** was carried out as previously describe for compound **8** with diaminodecane imide **5** (673 mg, 1.5 mmol) and NMO (262 mg, 2.23 mmol) to produce a black oil which was shown by ^{1}H NMR spectroscopy to be the desired diaminodecane diol **10** (334 mg, 46%). Numerous attempts at purification by silica gel column chromatography were unsuccessful so the crude product was used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.32–7.29 (5H, m), 5.08 (2H, s), 3.66 (3H, br s), 3.40–3.34 (2H, t, J = 8.1 Hz), 2.64–2.62 (2H, m), 2.01–1.97 (2H, br s), 1.44–1.41 (7H, m), 1.22–1.16 (13H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 177.13, 156.67, 136.64, 128.60–128.19, 70.15, 66.74, 45.97, 38.76, 35.97, 29.93–29.07, 28.91, 26.86 HRMS (ESI *m*/*z*): calcd for $[C_{27}H_{38}N_2NaO_6]^+$ 509.2622, found 509.2614; $\nu_{(max)}$ cm^{-1}: 3350 br, 2926 m, 2854 m, 1685 s, 1533 m, 1151 m.

Synthesis of benzyl [2-(2-dodecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)butyl]carbamate and the corresponding deprotected amphiphile 13

To a solution of dodecyl aldehyde (0.3 mL, 1.36 mmol) in CH_2Cl_2 (30 mL), diaminobutane diol **8** (366 mg, 0.909 mmol) was added and stirred until dissolved. $MgSO_4$ was added, followed by the addition of *p*-toluenesulfonic acid (692 mg, 3.64 mmol). The resulting solution was warmed to 35 °C and stirred for 24 h before being filtered and the solvent was removed *in vacuo* to give a light brown oil. Purification by silica gel column chromatography was performed with a 70% petroleum spirit–30% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminobutane dodecyl acetal (314 mg, 61%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.33 (5H, s), 5.07 (2H, s), 4.63–4.60 (1H, t, J = 2.7 Hz), 3.84 (2H, s), 3.43 (2H, d, J = 5.4 Hz, 2 × CH), 3.20–3.18 (2H, d, J = 5.4 Hz), 3.07 (2H, s, 2 × CH), 2.83 (2H, s), 2.35–2.29 (1H, t, J = 16.2 Hz), 2.01–1.98 (1H, d, J = 8.1 Hz), 1.61–1.51 (6H, m, 3 × CH_2), 1.24 (18H, bs), 0.88 (3H, t, J = 13.5 Hz, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 176.4, 156.5, 136.6, 128.6–128.20, 104.2, 101.8, 77.5–76.64, 66.8, 44.5, 42.7, 40.5, 38.2, 37.4, 35.9, 32.7, 31.9, 29.8–29.2, 27.5, 25.1, 24.3, 22.8, 14.2; HRMS (ESI *m*/*z*): calcd for $[C_{33}H_{49}N_2O_6]^+$ 569.3585, found 569.3592; $\nu_{(max)}$ cm^{-1}: 2923 s, 2853 s, 1698 s, 1521 m, 1132 m. Palladium on activated carbon (31 mg, 10% w/w) was then suspended in methanol (50 mL) and left to stir before the addition of the diaminobutane dodecyl acetal (314 mg, 0.55 mmol) in methanol (50 mL). The reaction mixture was stirred under $H_{2(g)}$ for 24 h before being vacuum filtrated

through a celite plug and the filtrate removed *in vacuo* to give a white paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.07 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **13** (211 mg, 88%) in >95% purity which was then used without further purification. HRMS (ESI *m*/*z*): calcd for $[C_{25}H_{43}N_2O_4\ H^+]$ 435.3217, found 435.3233; $\nu_{(max)}$ cm^{-1}: 2923 s, 2853 s, 1697 s.

Synthesis of benzyl [2-(2hexaodecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)butyl]carbamate and the corresponding deprotected amphiphiles 14

Synthesis of diaminobutane hexadecyl acetal was performed as per previously described for diaminobutane dodecyl acetal with diaminobutane diol **8** (246 mg, 0.613 mmol) and hexadecyl aldehyde (221 mg, 0.919 mmol) to afford a light yellow oil. Purification by silica gel column chromatography was performed with a 70% petroleum spirit–30% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminobutane hexadecyl acetal (286 mg, 75%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.38–7.28 (5H, m), 5.06 (2H, s), 4.62–4.59 (1H, t, J = 5.4 Hz), 3.84 (2H, s), 3.44–3.40 (2H, t, J = 5.4 Hz, 2 × CH), 3.22–3.17 (2H, d, J = 13.5 Hz), 3.08–3.06 (2H, m, 2 × CH), 2.83–2.81 (2H, m, 2 × CH), 2.02–1.97 (2H, d, J = 13.5 Hz), 1.62–1.32 (6H, m, 3 × CH_2), 1.22 (26H, bs), 0.88–0.83 (3H, t, J = 5.4 Hz) ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 179.7, 176.4, 156.5, 139.4, 136.5, 128.6–128.2, 114.4, 104.1, 77.6–76.6, 66.8, 44.5, 42.7, 40.5, 38.2, 35.9, 34.2, 32.7, 32.0, 29.8–29.03, 27.5, 25.1, 24.7, 24.3, 22.8, 14.2; HRMS (ESI *m*/*z*): calcd for $[C_{37}H_{57}N_2O_6]^+$ 625.4211, found 625.4200; $\nu_{(max)}$ cm^{-1}: 3368 m, 2924 s, 2853 s, 1697 s, 1532 m, 1137 m. Deprotection of diaminobutane hexadecyl acetal (377 mg, 0.60 mmol) was then carried out as per previously described for diaminobutane dodecyl acetal with palladium on activated carbon (38 mg, 10% w/w) to afford a white paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.06 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **14** (263 mg, 89%) in >95% purity which was then used without further purification. HRMS (ESI *m*/*z*): calcd for $[C_{29}H_{51}N_2O_4]^+$ 491.3843, found 491.3824; $\nu_{(max)}$ cm^{-1}: 2920 s, 2851 s, 1698 s.

Synthesis of benzyl [2-(2-dodecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)ethyl]carbamate and the corresponding deprotected amphiphile 11

Synthesis of diaminoethane dodecyl acetal **11** was performed as per previously described for diaminobutane dodecyl acetal with diaminoethane diol **7** (212 mg, 0.566 mmol) and dodecyl aldehyde (0.19 mL, 0.849 mmol) to afford a light yellow oil. Purification by silica gel column chromatography was performed with a 60% petroleum spirit–40% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminoethane dodecyl acetal (188 mg, 61%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.32 (5H, s), 5.02 (2H, s), 4.59–4.55 (1H, t, J = 10.8 Hz), 3.83 (2H, s), 3.58–3.57 (2H, t, J = 4.0 Hz, 2 × CH), 3.38–3.36 (2H, d, J = 5.4 Hz), 2.96–2.95 (1H, d, J = 2.7 Hz, 1 × CH), 2.78 (1H, s, 1 × CH), 2.33–2.27 (1H, t, J = 8.1 Hz), 1.99–1.95 (1H, d, J = 10.8 Hz), 1.58–1.57 (2H, m, CH_2), 1.31 (18H, bs), 0.88–0.84 (3H, t, J = 10.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 176.8, 156.6, 136.5, 128.6–128.3, 104.3, 78.4–76.7, 66.9, 44.6, 42.6, 39.8, 38.3, 35.9, 34.0, 32.7, 32.0, 31.10, 29.7–29.5, 24.33, 22.8, 14.3; calcd for $[C_{31}H_{45}N_2O_6]^+$ 541.3272, found 541.3301; $\nu_{(max)}$ cm^{-1}: 3360 m, 2924 s, 2854 s, 1699 s, 1522 m, 1142 m. Deprotection of the diaminoethane dodecyl acetal (459 mg, 0.85 mmol) was then carried out as per previously described for diaminobutane dodecyl acetal with palladium on activated carbon (46 mg, 10% w/w) to afford a white paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.02 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **11** (319 mg, 92%) in >95% purity which was then used without further purification. HRMS (ESI *m*/*z*): calcd for $[C_{23}H_{39}N_2O_4]^+$ 407.2911, found 407.2931; $\nu_{(max)}$ cm^{-1}: 2954 s, 2853 s, 1699 s.

Synthesis of benzyl [2-(2-hexadecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)butyl]carbamate and the corresponding deprotected amphiphile 12

Synthesis of diaminoethane hexadecyl acetal **12** was performed as per previously described for diaminobutane dodecyl acetal with diaminoethane diol **7** (250 mg, 0.668 mmol) and hexadecyl aldehyde (240 mg, 1.00 mmol) to afford a light yellow oil. Purification by silica gel column chromatography was performed with a 70% petroleum spirit–30% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminoethane hexadecyl acetal (276 mg, 70%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.32 (5H, s), 5.02 (2H, s), 4.58–4.55 (1H, t, J = 2.7 Hz), 3.83 (2H, s), 3.60–3.56 (2H, t, J = 5.4 Hz, 2 × CH), 3.40–3.34 (2H, d, J = 5.4 Hz), 2.97–2.93 (2H, m, 2 × CH), 2.79–2.78 (2H, t, J = 2.7, 2 × CH), 2.34–2.28 (1H, t, J = 8.1 Hz), 1.99–1.95 (1H, d, J = 10.8 Hz), 1.60–1.57 (2H, m, CH_2), 1.34 (26H, bs), 0.88 (3H, t, J = 13.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 174.7, 156.6, 136.4, 128.6–128.4, 104.1, 77.7–76.6, 66.9, 44.5, 42.6, 39.6, 38.3, 37.2, 34.0, 32.7, 32.0, 29.8–29.2, 24.8, 24.3, 22.7, 14.21; HRMS (ESI *m*/*z*): calcd for $[C_{35}H_{53}N_2O_6]^+$ 597.3898, found 597.3912; $\nu_{(max)}$ cm^{-1}: 3354 m, 2922 s, 2853 s, 1698 s, 1526 m, 1120 m. Deprotection of the diaminoethane hexadecyl acetal (62 mg, 0.10 mmol) was then carried out as per previously described for diaminobutane dodecyl acetal with palladium on activated carbon (6 mg, 10% w/w) to afford a white paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.02 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **12** (40 mg, 83%) in >95% purity which was then used without further purification. HRMS (ESI *m*/*z*): calcd for $[C_{27}H_{47}N_2O_4]^+$ 463.3530, found 463.3527; $\nu_{(max)}$ cm^{-1}: 2916 s, 2849 s, 1698 s.

Synthesis of benzyl [2-(2-dodecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)octyl]carbamate and the corresponding deprotected amphiphiles 15

Synthesis of acetal **15** was performed as per previously described for diaminobutane dodecyl acetal with diaminooctane diol **9** (135 mg, 0.294 mmol) and dodecyl aldehyde (0.13 mL, 0.589 mmol) to afford a brown oil. Purification by silica gel column chromatography was performed with a 60% petroleum spirit–40% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminooctane dodecyl acetal (235 mg, 64%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.34–7.33 (5H, m), 5.07 (2H, s), 4.60–4.58 (1H, t, J = 2.7 Hz), 3.85 (1H, s), 3.42–3.37 (2H, t, J = 8.1 Hz, 2 × CH), 3.19–3.12 (2H, q, J = 5.4 Hz), 3.08–3.05 (2H, m, 2 × CH), 2.83 (2H, br s, 2 × CH), 2.34–2.26 (1H, m, bridge-H) 1.97 (1H, s, bridge-H), 1.65–1.58 (5H, m, 2 × CH_2) 1.48–1.46 (2H, m, 1 × CH_2), 1.26–1.24 (27H, m), 0.85 (3H, t, J = 5.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 176.41–176.36, 156.48, 136.75, 128.60–128.54, 128.18, 128.14, 104.14, 78.32, 66.63, 44.48, 42.70, 41.12, 38.68, 35.87, 33.95, 32.69, 31.97, 29.69, 29.67–29.16, 27.76, 26.89, 26.66, 24.87, 24.24, 22.76, 22.75, 22.74, 21.10, 14.18; HRMS (ESI m/z): calcd for $[C_{37}H_{57}N_2O_6]^+$ 625.4211, found 625.4224; $\nu_{(max)}$ cm^{-1}: 3365 m, 2965 m, 2850 m, 1694 s, 1537 m, 1129 m. Deprotection of the diaminooctane dodecyl acetal (235 mg, 0.375 mmol) was then carried out as per previously described for diaminobutane dodecyl acetal with palladium on activated carbon (24 mg, 10% w/w) to afford a cream paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.02 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **15** (147 mg, 89%) in >95% purity which was then used without further purification. HRMS (ESI m/z): calcd for $[C_{29}H_{51}N_2O_4]^+$ 491.3843, found 491.3861; $\nu_{(max)}$ cm^{-1}: 2927 s, 2850 s, 1699 s.

Synthesis of benzyl [2-(2hexadecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)octyl]carbamate and the corresponding deprotected amphiphiles 16

Synthesis of diaminooctane hexadecyl acetal **16** was performed as per previously described for diaminobutane dodecyl acetal with diaminooctane diol **9** (164 mg, 0.358 mmol) and hexadecyl aldehyde (129 mg, 0.537 mmol) to afford a brown oil. Purification by silica gel column chromatography was performed with a 60% petroleum spirit–40% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminooctane hexadecyl acetal (95 mg, 39%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.35–7.33 (5H, m), 5.12 (2H, s), 4.60–4.58 (1H, t, J = 2.7 Hz), 3.85 (1H, s), 3.40–3.37 (2H, t, J = 8.1 Hz, 2 × CH), 3.20–3.12 (2H, q, J = 5.4 Hz), 3.07–3.06 (2H, m, 2 × CH), 2.88–2.83 (4H, m, 2 × CH), 2.35–2.29 (1H, t, J = 8.1 Hz) 2.01–1.97 (1H, d, J = 10.8 Hz), 1.48–1.46 (6H, m, 3 × CH_2), 1.40–1.35 (6H, m, 3 × CH_2) 1.23–1.20 (30H, m), 0.87 (3H, t, J = 2.7 Hz, CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): 176.37, 156.47, 136.74, 128.89–128.20, 104.08, 78.33, 66.69, 44.58, 42.73, 41.14, 38.72, 32.69, 32.11, 29.78, 27.80, 26.67, 24.22, 22.80, 14.22; HRMS (ESI m/z): calcd for $[C_{41}H_{65}N_2O_6]^+$ 681.4837, found 681.4862; $\nu_{(max)}$ cm^{-1}: 3368 m, 2924 m, 2853 m, 1697 s, 1532 m, 1137 m. Deprotection of the diaminooctane hexadecyl acetal (95 mg, 0.140 mmol) was then carried out as per previously described for diaminobutane dodecyl acetal with palladium on activated carbon (20 mg, 10% w/w) to afford a cream paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.02 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **16** (80 mg, 84%) in >95% purity which was then used without further purification. HRMS (ESI m/z): calcd for $[C_{33}H_{59}N_2O_4]^+$ 547.4469, found 547.4476; $\nu_{(max)}$ cm^{-1}: 2920 s, 2851 s, 1699 s.

Synthesis of benzyl [2-(2-dodecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)decyl]carbamate and the corresponding deprotected amphiphile 17

Synthesis of diaminodecane dodecyl acetal **17** was performed as per previously described for diaminobutane dodecyl acetal with diaminodecane diol **10** (361 mg, 0.742 mmol) and dodecyl aldehyde (0.25 mL, 1.11 mmol) to afford a brown oil. Purification by silica gel column chromatography was performed with a 60% petroleum spirit–40% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminodecane dodecyl acetal (368 mg, 76%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.33 (5H, br s), 5.08 (2H, s), 4.61–4.57 (1H, t, J = 5.4 Hz), 3.85 (3H, br s), 3.43–3.37 (1H, t, J = 8.1 Hz), 3.18–3.15 (1H, d, J = 8.1 Hz), 3.09–3.06 (2H, q, J = 5.4 Hz) 2.83 (2H, br s), 2.36–2.20 (1H, m) 2.01–1.97 (1H, d, J = 10.8 Hz), 1.64–1.59 (7H, m), 1.24 (35H, m), 0.88–0.84 (3H, t, J = 5.4 Hz); δ ^{13}C NMR (67.5 MHz, $CDCl_3$): 174.32, 156.50, 136.73, 128.59–128.22, 104.34, 78.33, 66.67, 44.48, 42.71, 38.79, 35.89, 34.06, 32.69, 31.99, 30.00–29.09, 27.02, 24.78, 24.26, 22.77, 14.20; HRMS (ESI m/z): calcd for $[C_{39}H_{61}N_2O_6]^+$ 653.4524, found 653.4543; $\nu_{(max)}$ cm^{-1}: 3349 m, 2922 m, 2870 m, 1695 s, 1538 m, 1142 m. Deprotection of the diaminodecane dodecyl acetal (368 mg, 0.564 mmol) was then carried out as per previously described for diaminobutane dodecyl acetal with palladium on activated carbon (37 mg, 10% w/w) to afford a cream paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.02 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **17** (234 mg, 80%) in >95% purity which was then used without further purification. HRMS (ESI m/z): calcd for $[C_{31}H_{56}N_2O_4]^+$ 463.3537, found 463.3627; $\nu_{(max)}$ cm^{-1}: 2922 s, 2870 s, 1699 s.

Synthesis of benzyl [2-(2-hexaecyl-5,7-dioxooctahydro-6*H*-4,8-methano[1,3]dioxolo[4,5-*f*]isoindol-6-yl)decyl]carbamate and the corresponding deprotected amphiphiles 18

Synthesis of diaminodecane hexadecyl acetal **18** was performed as per previously described for diaminobutane dodecyl acetal with diaminodecane diol **10** (132 mg, 0.271 mmol) and hexadecyl aldehyde (98 mg, 0.406 mmol) to afford a brown oil. Purification by silica gel column chromatography was performed

with a 70% petroleum spirit–30% EtOAc solution and the resulting caramel oil was shown by ^{1}H NMR spectroscopy analysis showed it to be the desired diaminodecane hexadecyl acetal (165 mg, 88%) in >95% purity which was then used immediately in the next deprotection step. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.34–7.33 (5H, m), 5.08 (2H, s), 4.59–4.57 (1H, t, J = 2.7 Hz), 3.85 (3H, br s), 3.43–3.37 (1H, t, J = 8.1 Hz, 1 × CH), 3.20–3.13 (1H, q, J = 5.4 Hz, CH), 3.08–3.05 (2H, q, J = 2.7 Hz, 2 × CH), 2.83 (2H, br s, 2 × CH), 2.34–2.29 (1H, m) 2.01–1.97 (1H, d, J = 10.8 Hz), 1.60–1.36 (7H, m, 3 × CH_2), 1.27–1.19 (39H, m), 0.85 (3H, t, J = 5.4 Hz) δ ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 176.42, 156.54, 136.76, 128.45–128.00, 104.03, 78.26, 66.50, 44.40, 42.64, 38.65–38.59, 35.76, 34.02, 32.63, 31.95- 31.93, 27.74–27.70, 26.92–26.69, 25.78, 25.34, 24.77–24.17, 22.72–22.33, 20.93, 14.14; HRMS (ESI m/z): calcd for $[C_{43}H_{68}N_2NaO_6]^+$ 731.4969, 731.4952; found $\nu_{(max)}$ cm^{-1}: 3359 m, 2923 m, 2853 m, 1699 s, 1558 m, 1144 m. Deprotection of the diaminodecane hexadecyl acetal (46 mg, 0.066 mmol) was then carried out as per previously described for diaminobutane dodecyl acetal with palladium on activated carbon (4.6 mg, 10% w/w) to afford a cream paste. Analysis by ^{1}H NMR spectroscopy determined the loss of the singlet resonance at δ 5.02 ppm indicating the successful deprotection of the benzyl carbamate to afford compound **18** (26 mg, 67%) in >95% purity which was then used without further purification. HRMS (ESI m/z): calcd for $[C_{35}H_{62}N_2O_4H]^+$ 575.4789, found 575.4863; $\nu_{(max)}$ cm^{-1}: 2920 s, 2851 s, 1698 s.

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