Synthesis and characterization of squaramide-based supramolecular polymers

Lauria, F.

CHAPTER 3

Tripodal acids as building blocks for the Ugi multicomponent reactions

3.1 Abstract

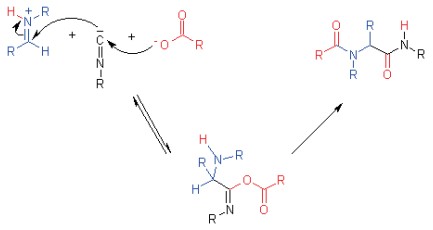
Trigonal molecules have found broad application as scaffolds in the fields of supramolecular, coordination and catalysis chemistry. However, their synthesis often requires multistep reactions to obtain the designed monomer. To expedite the synthesis of trigonal molecules, multicomponent reactions provide a viable approach to obtain functional molecules with high structural diversity and yield in a single step. The Ugi reaction is a multicomponent reaction involving an isocyanide, amine, carboxylic acid and aldehyde or ketone that generates an α-acetamido carboxamide or peptide-like bond that can analogously be seen in numerous supramolecular structures. In this chapter, the use of different acidic tripodal cores based on nitrilotriacetic or squaric acids are examined in the multicomponent Ugi reaction to prepare trigonal scaffolds. Modulation of the amine and isocyanide components and their respective concentrations and the reaction temperature were probed for their efficiency to obtain the trisubstituted product. Reaction of nitrilotriacetic acid with ammonium carbonate resulted in a mixture of mono-, di- and trisubstituted compounds emphasizing the need for a stable imine to be formed to yield the desired trisubstituted compound. In contrast, the use of a tripodal squaric acid with a primary amine, defined reagents concentration, increased temperature and longer reaction times resulted in the preferential formation of the trisubstituted product over mono- and disubstituted compounds.

3.2 Introduction

Trigonal conjugates, including -symmetric, tripodal and triskelion systems, play an important role in biological processes[1] found in Nature. In endocytosis, clathrin that regulates cellular uptake of membrane proteins and neurotransmitters through the formation of coated vesicles, is a triskelion protein with three heavy chains and three light chains.[2] Trigonal scaffolds have been also exploited in synthetic molecules for several applications in homogeneous catalysis,[3] coordination and supramolecular chemistry.[4, 5] Tripodal ligands have a higher chelating effect towards ions and tunable selectivity that can be modulated according to the bulkiness of the arms in comparison to receptors that are bi- or monopodal.[6] Additionally, when C_3-symmetric scaffolds are used as cores for supramolecular monomers, they show enhanced ability to self-assemble into supramolecular polymers when put against their C_2-symmetric counterparts.[7, 8] More specifically, a widely exploited core is based on benzene-1,3,5-tricarboxamide (BTA) that benefits from hydrogen bonding and π-π interactions to form supramolecular polymers with helical character when chiral substituents are used.[8, 9] This core has provided tremendous insight into the monomer features required for polymerization and its control in a range of media.[9] However, in order to achieve monomer with specific function, C_3-symmetric and tripodal building blocks usually require several reaction steps to obtain a designed monomer,[9] thus efficient synthetic approaches are necessary to expedite their preparation for a broad range of applications.

Multicomponent reactions are a class of reactions used to construct functional molecular scaffolds in a high yielding (70-90%), selective and rapid manner, often being performed in one pot.[10, 11] Compounds with high structural diversity can be obtained in a minimum number of synthetic steps, and have been used to generate libraries for assessing structure activity relationships (SARs) of therapeutics in the drug discovery pipeline.[12] One important multicomponent reaction is the four component Ugi reaction that involves the use of an isocyanide, aldehyde/ketone, carboxylic acid, and amine to generate α-acetamido carboxamides.[11, 13,14] In the Ugi mechanism, condensation of the amine with the aldehyde first occurs. This step is critical for the formation of the final product and to increase the yield of the reaction. Subsequently, proton transfer from the carboxylic acid to imine occurs, followed by its reaction with the terminal carbon of the isocyanide yielding the nitrilium ion. The carboxylate then participates in a second nucleophilic addition on the nitrilium ion forming an imidate derivative prior to an irreversible Mumm

rearrangement that drives the reaction and determines the structure of the final Ugi products. Because of the commercial availability of hundreds of amines, aldehydes, and carboxylic acids, a large number of Ugi-end products are synthetically feasible opening the door for use in numerous applications.[15]



General Scheme Ugi reaction

Several factors have been identified to steer the outcome of the Ugi reaction such as the type of solvent, chosen amine and carboxylic acid, the overall reactant concentrations and temperature. Notably, the solvent plays a critical role in the Ugi reaction; polar and protic solvents such as MeOH or TFE are often used because of their capacity to stabilize the polar intermediates of the reaction. The choice of amine and carboxylic acid component can also play an important role in the formation and stabilization of the imine. If the chosen amine is not nucleophilic enough, a low Ugi product yield is obtained. Moreover, the presence of a strong acid in the reaction mixture is also critical to increase the electrophilic character of the imine through its protonation for the formation of the subsequent intermediates and to ensure a high yield.[16] Additionally, the reactivity of carbonyl group is critical as aromatic and aliphatic aldehydes react more readily in the Ugi reaction than aliphatic and aromatic ketones.[17] Importantly, these factors have often been explored in the context of monofunctional adducts, however execution of two or more Ugi reaction on the same acid have been examined to a lesser extent.[18-22] In a recent work, Dehghan and co-workers successfully introduced trimesic acid as the acid component of Ugi reaction for the synthesis of novel C_3-symmetric peptide-based molecules.[23] Additionally, squaric acids have been reported for their use in the Ugi reaction to yield bifunctional squaramide adducts for use in medicinal chemistry.[22] Because of the broad utility of tripodal cores in supramolecular chemistry,[24] we became interested to examine the feasibility of using the Ugi reaction to generate tripodal scaffolds based on peptide-like amide and squaramide bonds starting from nitrilotriacetic and squaric acid.

In our research group, we are particularly interested in the use of squaramides in supramolecular systems. Squaramides are ditopic supramolecular synthons that form strong hydrogen bonds by synergizing with a gain in aromatic character of the cyclobutenedione ring on self-assembly.[25, 26] They have been exploited in the organocatalysis[27, 28] and anion receptor field.[29-33] Previously, we investigated the self-assembly of squaramide-based bolaamphiphiles into supramolecular polymers through hydrogen bonding and hydrophobic interactions in water.[34] In a follow up work, we studied the ability of a small family of tripodal squaramide-based monomers to gelate water and to encapsulate stem cells in 3D for their culture.[35] We herein examine the use of nitrilotriacetic or trisquaric acids in combination with various Ugi components to establish the optimal conditions for this multicomponent reaction to prepare a range of tripodal scaffolds for supramolecular assembly.

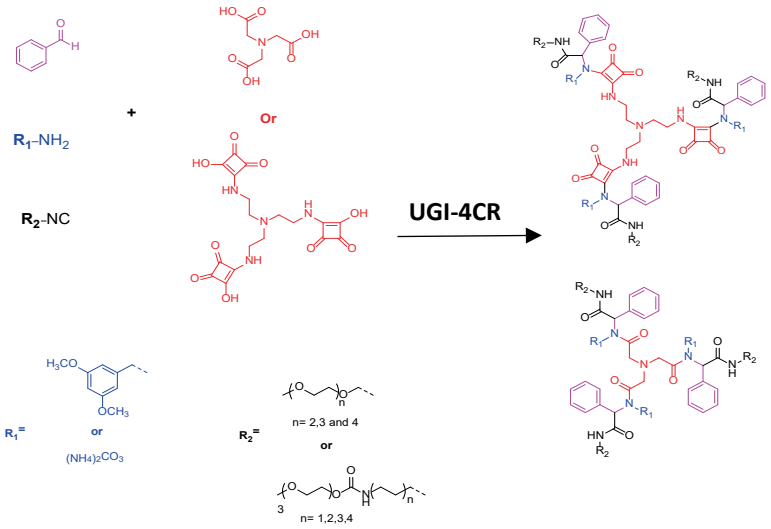


Figure 3.1 General synthetic route to synthesize tripodal compounds by the multicomponent Ugi reaction involving benzaldehyde, ammonium carbonate or 2,4-dimethoxybenzylamine as the amine component, nitrilotriacetic acid or trisquariCACid as the acid component and oligo(ethylene glycol) chains containing isocyanide. 4CR = four component reaction.

3.3 Results and discussion

Because various reaction parameters can influence the outcome of Ugi reaction as described above, their contribution on the preparation of tripodal building blocks for applications in supramolecular chemistry will be evaluated. Since the aim is to prepare a tripodal monomer that is primed for self-assembly in water, the designed Ugi monomers were amphiphilic in character with sufficient hydrophilic and hydrophobic domains and hydrogen-bonding or π-π stacking interactions through intermolecular interactions between amide or squaramide in the hydrophobic domain (**Figure 3.1**). The hydrophilic domains consist of oligo(ethylene glycol) chains that either have a directly coupled isocyanide or a variable number of methylene units (n = 1, 2, 3, 4). To introduce units that either π-stack or provide hydrogen bonds in addition to the trigonal geometry to the monomer through Ugi reaction, tripodal acids such as nitrilotriacetic (pK_{a1} = 3.03, pK_{a2} = 3.07, pK_{a3} = 10.70) and the more acidic squaric acid (pK_{a1} = 0.54, pK_{a2} = 3.48) were used. Specifically, the use of a strong acid plays a determining role in the formation of the imine and subsequently, the Ugi reaction product. Additionally, to prepare the Ugi tripodal molecules, aldehyde and amine components are necessary and thus a range of these components was tested. This chapter has been organized according to the two tripodal cores (nitrilotriacetic acid (3.3.1) and squaric acid (3.3.2)) and the capacity to form the trisubstituted reaction products was examined varying the reaction conditions and the components such as aldehyde (3.3.1.1 and 3.3.2), the isocyanide (3.3.3) and the amine (3.3.4).

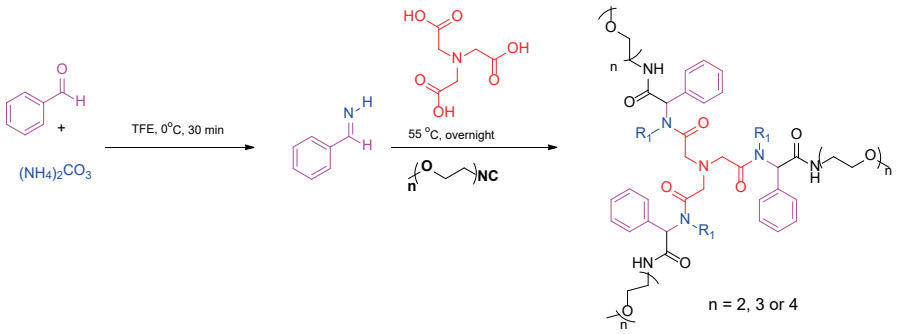
3.3.1 Use of a nitrilotriacetic acid core

In a first step, nitrilotriacetic acid was selected as a tripodal core to provide three peptide-like bonds after the Ugi reaction. The nitrilotriacetic acid core was combined with ammonium carbonate, benzaldehyde and oligo(ethylene glycol) isocyanide (OEG_2, OEG_3, OEG_4) under different reaction conditions to obtain the Ugi product. Ammonium carbonate was used as the source of the amine to avoid an additional deprotection step after the Ugi reaction. The use of ammonium carbonate was previously used by the group of Abbas and coworkers[36] in the synthesis of selenocysteine peptides. Oligo(ethylene glycol) isocyanides were prepared starting from oligo(ethylene glycol) (OEG_2, OEG_3, OEG_4) that after reaction with tosyl chloride were converted in phthalimide derivatives in the presence of potassium phthalimide. Subsequently, treatment with hydrazine monohydrate provided the oligo(ethylene glycol) amine derivatives which were quantitatively formylated using ethyl formate. The isocyanides were isolated in high yield (90%) by the reaction of the formylated oligo(ethylene glycol)s with $POCl_3$.

The Ugi reaction at 55 °C with the above components (entry 1, Table 1) using an isocyanide concentration of 0.2 M resulted in a mixture of di- (d) and tri-substituted (t) products. In order to increase the yield of the trisubstituted product, the equivalents of isocyanide, ammonium carbonate, benzaldehyde and isocyanide were varied. The products and yields of each reaction was determined by LCMS.

3.3.1.1 Modulation of the component ratios and concentration of isocyanide

In this section, the number of equivalents and concentration of isocyanide and the other components on the final product distribution of the Ugi reaction were examined (Table 1, entries 1-7).



Scheme 1

Table 1 Selected entries for the Ugi reaction conditions with nitrilotriacetic acid[a]

Entry	R-N≡C *(eq)*	*BA (eq)*	$(NH_4)_2CO_3$ *(eq)*	R-N≡C [b] *[M]*	*OEG*	*Yield**		
						t (%)	*d (%)*	*m (%)*
1	10.0	5.0	5.0	0.2	OEG_3	10	90	NO
2	7.0	5.0	5.0	1.0	OEG_3	83	17	NO
3	10.0	10.0	10.0	1.0	OEG_3	72	28	NO
4	10.0	10.0	7.5	1.0	OEG_3	72	28	NO
5	10.0	5.0	5.0	1.0	OEG_4	52	48	NO
6	10.0	5.0	5.0	0.2	OEG_4	48	52	NO
7	10.0	5.0	5.0	1.0	OEG_2	86	14	NO

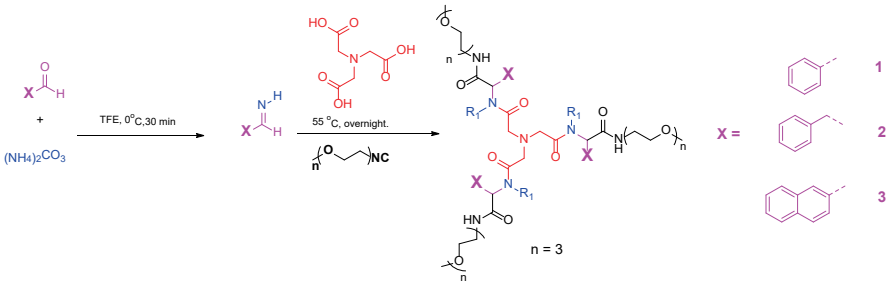
[a]Reaction conditions: nitrilotriacetic acid (0.05 mmol), isocyanide ($(OEG)_nNC$), benzaldehyde, ammonium carbonate in TFE at 55 °C, overnight. [b] The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *The yields were determined by LCMS. t = trisubstituted, d = disubstituted, m = monosubstituted, NO = not observed, R-N≡C: isocyanide, BA: benzaldehyde, $(NH_4)_2CO_3$: ammonium carbonate.

The concentration of the reagents determines the outcome of an Ugi reaction, with higher reagent concentrations resulting in increased yields.[17] While most Ugi reaction conditions are based on a (near-) equimolar distribution of the four components, we opted for an excess of isocyanide (10 eq) because of its known instability in acidic conditions[37-39] and tendency to polymerize.[40] The Ugi reaction was performed by first mixing benzaldehyde with ammonium carbonate (5 eq) at 0 °C for 30 min resulting in imine formation, followed by the addition of nitrilotrisquaric acid and OEG_n-NC (n = 2, 3, 4). As shown in Table 1 (entry 1), the nitrilotriacetic acid core in the presence of a 0.2 M concentration of isocyanide OEG_3 (10 eq) yielded predominantly the disubstituted product (90%), compared to the trisubstituted compound (10%). Performing the reaction at 1 M (entry 2) and reducing the number of isocyanide equivalents (7 eq) resulted in a higher yield of the trisubstituted compound (83%). These results confirmed the importance of the isocyanide component concentration on the Ugi reaction with entry 2 displaying the most favorable product distribution. To further optimize the formation of the desired trisubstituted compound, an excess of ammonium carbonate and benzaldehyde at a 1 M isocyanide concentration were used (entries 3, 4) resulting in the trisubstituted compound (72%) as the main product.

To further extend the library of supramolecular monomers with the nitrilotriacetic acid core, the length of the oligo(ethylene glycol) was varied. Using the successful conditions of entry 2, the Ugi reaction was performed with OEG_4-NC using fewer equivalents of ammonium carbonate (5.0 eq, entry 5). A comparable amount of di- and trisubstituted compounds were observed even though being performed at different isocyanide concentrations (0.2 and 1 M) (entries 6-7). On extending these conditions to the OEG_2-NC derivative (entry 7), the most optimal tri- and disubstituted product ratio in this study was obtained (tri-/di-substituted product ratio = 6:1). Moreover, when comparing entries 5 and 7, an effect of the oligo(ethylene glycol) chain length was observed on the reaction yield. This result suggests that the difference in solubility of the OEG isocyanides in the reaction medium have a significant influence on the formation of the trisubstituted product, with the shortest chain length OEG_2 showing the highest yield. In conclusion, the solubility, equivalents and concentration of the reaction components are critical for the success of the tripodal Ugi product.

3.3.1.2 Examination of reaction scope with varying the aldehyde component

The use of various aromatic aldehydes to prepare tripodal compounds were further examined in the Ugi reaction. Benzaldehyde (**1**) was compared against phenylacetaldehyde (**2**) or 2-naphthaldehyde (**3**), because of their increased aliphatic character and number of aromatic rings, respectively, for their ability to effect the efficiency or product distribution in the Ugi reaction. The water soluble oligo(ethylene glycol) isocyanide with three repeats units OEG_3 (10 eq) was used in combination with ammonium carbonate and nitrilotriacetic acid (5 eq) (Table 2, entries 10-15).



Scheme 2

Table 2 Selected entries for the Ugi reaction with nitrilotriacetic acid and different aldehydes[a]

Entry	*R-N≡C [M] [b]*	*Aldehyde*	*Yield**		
			m (%)	*d (%)*	*t (%)*
8	1.0	**1**	NO	23	77
9	0.2	**1**	NO	70	30
10	1.0	**2**	100	NO	NO
11	1.0	**3**	100	NO	NO
12	2.0	**2**	100	NO	NO
13	2.0	**3**	100	NO	NO
14	0.1	**2**	100	NO	NO
15	0.1	**3**	100	NO	NO

[a]Reaction conditions: nitrilotriacetic acid (0.05 mmol), isocyanide ($(OEG)_3NC$), (0.5 mmol), ammonium carbonate (0.25 mmol) and different aldehydes (0.25 momol) in TFE at 55 °C, overnight. [b]The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *The yields were determined by LCMS. t = trisubstituted, d = disubstituted, m = monosubstituted, NO= not observed, R-N≡C: isocyanide.

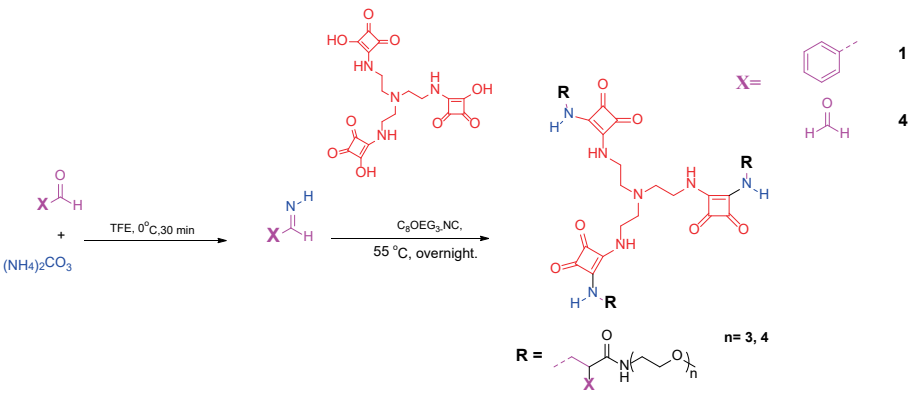
The tripodal compound was predominantly formed (77%) with benzaldehyde at 1 M isocyanide concentration. Conversely, a 0.2 M isocyanide concentration (entry 9) resulted in the disubstituted compound (70%) as the major product, confirming again the importance of concentration in the outcome of Ugi reaction.

Using similar reaction conditions developed for benzaldehyde as described above, its substitution with phenylacetaldehyde or 2-naphthaldehyde were explored (entries 10-15). The exclusive formation of the monosubtituted compound was observed when performing the Ugi reaction at a 1 M isocyanide concentration with **2** or **3** (entry 10 – 11). The same result was obtained when the reaction was carried out at a 2 M isocyanide concentration (entry 12-13). In contrast, Aknin and coworkers previously demonstrated that using a 0.1 M concentration of isocyanide the most optimal yield was obtained for bivalent compounds originating from squaric acid on several parameters including concentration, temperature and various solvents.[22] However, the exclusive formation of monosubstituted compound was still observed after executing the Ugi reaction with **2** or **3** using 0.1 M

isocyanide, (entries 14 and 15). One plausible explanation for the exclusive formation of the monosubtituted compound is the increased size of phenylacetaldehyde or 2-naphthaldehyde relative to benzaldehyde. As most Ugi reactions are performed only once on a particular molecular scaffold, sterics may not play an obvious role in their formation. However, sterics has been demonstrated by Rivera *et al.* to influence the Ugi reaction of a third substituent in tripodal peptide-podands.[41] Based on our findings, the size of the aromatic aldehyde is pivotal for the success of Ugi reaction using tripodal acidic cores. Hence, in the subsequent reaction conditions, benzaldehyde was further used as the aldehyde component.

3.3.2 Examination of the Ugi reaction on a tripodal squaric acid core

In the last decade, the squaramide synthon has been explored in the field of supramolecular chemistry for its ability to form very strong hydrogen bonds with a wide range of substrates.[24] As demonstrated through DFT calculations and NICS (Nuclear Independent Chemical Shift), this peculiar property is due to the delocalization of π electrons inside the cyclobutenedione ring that confers and increase in aromatic character at the squaramide moieties.[42, 43] Squaric acid has been used as building block for the Ugi reaction[22] and differs from nitrilotriacetic acid not only for the presence of cyclobutenedione moieties that provide distinct non-covalent interactions through their π-surface but also for its stronger acidity. Squaric acid has pKa values similar to sulfuric acid ($pK_{a1} = 0.54$, $pK_{a2} = 3.48$) is due to the formation of dianonic resonance chemical structures[26] as demonstrated by ^{17}O NMR spectroscopy. In the Ugi reaction, the strength of the acid plays an important role in the stabilization of iminium ion resulting in higher yields and faster reaction times.[17] To further examine the potential of an alternative tripodal core for the Ugi reaction and to gain access to new supramolecular scaffolds, a trisquaric acid core was synthesized. The TREN core was reacted with an excess of squaric ester, and successively treated with concentrated HCl solution in dioxane giving rise to the product quantitatively (3.6.2, Scheme S.2, SI).



Scheme 3

Table 3 Selected entries for the Ugi reaction conditions with trisquaric acid and different aldehydes[a]

Entry	*R-N≡C [M]* [b]	*Aldehyde*	*Reaction temperature (°C)*	*OEG*	*Yield**		
					t (%)	*d (%)*	*m (%)*
16	0.02	**1**	55	OEG_3	NO	100	NO
17	0.5	**1**	55	OEG_3	71	29	NO
18	1.0	**1**	55	OEG_3	66	34	NO
19	2.0	**1**	55	OEG_3	43	57	NO
20	1.0	**4**	RT	OEG_4	NO	NO	NO
21	1.0	**1**	RT	OEG_4	44	56	NO
22	1.0	**4**	55	OEG_4	NO	NO	NO

[a]Reaction conditions: trisquaric acid (0.02 mmol), isocyanide ($(OEG)_3NC$ or $(OEG)_4NC$), (0.2 mmol), ammonium carbonate (0.1 mmol) and benzaldehydes or formaldehyde (0.1 momol) in TFE at 55 °C or RT, overnight. [b] The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *The yields were determined by LCMS. t = trisubstituted, d = disubstituted, m = monosubstituted, NO= not observed, R-N≡C: isocyanide.

Reaction conditions that favoured the trisubstituted (77%) over the disubstituted (29%) product for nitriloacetic acid (entry 8) were used as a

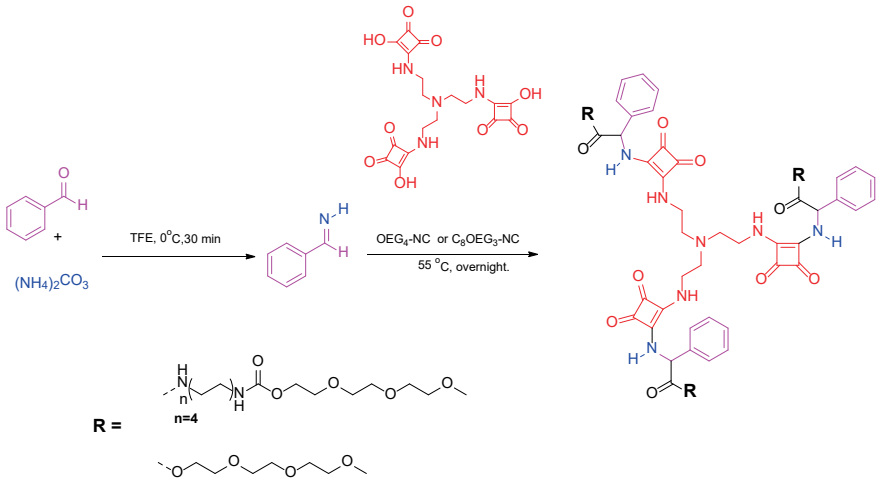
starting point for the reaction with trisquaric acid. Furthermore, the use of different isocyanide concentrations (0.02-2 M), reaction temperature (RT) and type of aldehyde (benzaldehyde or formaldehyde) were explored (Table 3, entries 16-19). In brief, the Ugi reaction with trisquaric acid was carried out mixing ammonium carbonate with benzaldehyde for 30 min at 0 °C (5 eq), followed by the addition of trisquaric acid and OEG_3-NC or OEG_4-NC (10 eq). The trisubstituted product was not observed at an isocyanide concentration of 0.02 M (entry 16), while it is the major product at 0.5 and 1 M (entries 17-18, 71%) and its further increase to 2 M favoured the disubstituted product (57 %).

In an attempt to remove the stereocenters from the tripodal structure, the Ugi reaction was performed with formaldehyde instead of benzaldehyde (entries 20 and 22). Performing the reaction at RT and at 55 °C in the presence of formaldehyde, no products were observed. The failure of the reaction with formaldehyde is likely due to the instability of iminium ion that is generated in the first step of the reaction and prevents the subsequent steps. Previously, to facilitate the coupling to the squaric core, all the Ugi reactions were carried out at 55 °C, but in the entry 21, the effect of the reaction temperature was examined. Specifically, the reaction in the presence of benzaldehyde was performed at RT instead of 55 °C. Comparing the entries 18 and 21, the yield of trisubstituted compound at RT (44%) is significantly lower compared to the reaction at 55 °C (66%). In conclusion, the use of a stronger acid (squaric acid), higher reaction temperature (55 °C), higher isocyanide concentration (1 M) and aromatic aldehyde is critical to promote the trisubstituted Ugi product, thereby minimizing the formation of the mono- and disubstituted species.

3.3.3 Use of an amphiphilic isocyanide component

To further extend the library of Ugi products that can be used as supramolecular scaffolds, an aliphatic-oligo(ethylene glycol) amphiphile isocyanide was prepared. In contrast to the synthesis of $(OEG)_3$-NC, overnight reaction was required to prepare aliphatic-oligo(ethylene glycol) amphiphiles ($C_8(OEG)_3NC$, 80-90% yield). In brief their synthesis consisted of the activation of triethylene glycol with 1,1'-carbonyldiimidazole (CDI), followed by its coupling with mono Cbz-protected 1,8-octanediamine. *In situ* hydrogenation with triethylsilane and Pd/C was performed to remove the Cbz protecting group. The primary amine was successively formylated using ethyl formate and the final amphiphile isocyanide was isolated by the reaction with $POCl_3$. Inspired by the findings of our previous work,[35] where the right balance between the hydrophilic and hydrophobic domains in the molecular structure of tripodal squaramide monomers were pivotal for their self-assembly, an aliphatic spacer of 8 carbons was used. Once the isocyanide was obtained, the Ugi reaction was executed starting with the reaction of ammonium carbonate and benzaldehyde at 0 °C to form the imine, followed by squaric acid and $C_8(OEG)_3NC$.

Starting from previous entries (entries 18-19) where an isocyanide concentration of 0.5 and 1 M and heating of the reaction mixture to 55 °C were necessary to promote the formation of trisubstituted squaramide product, an isocyanide concentration (C_8OEG_3-NC) from 0.1 to 2 M was screened (Table 4, entries 23- 25, 27).



Scheme 4

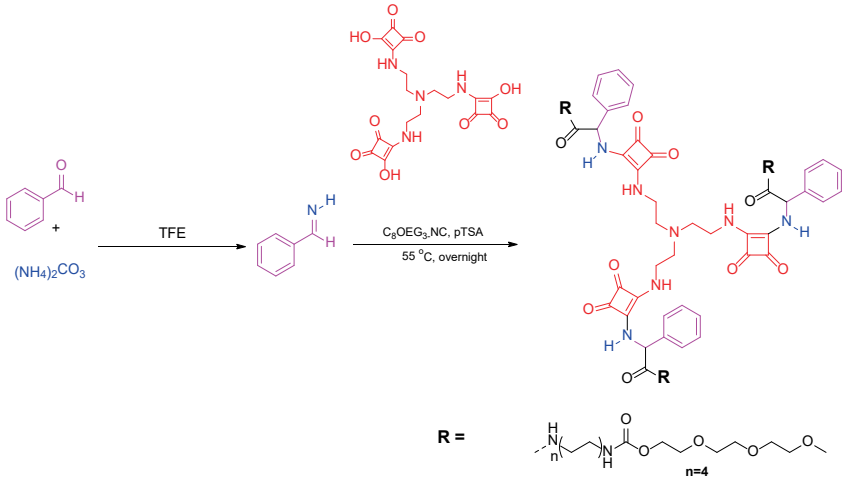
Table 4 Selected entries for the Ugi reaction with trisquaric acid and various isocyanides[a]

Entry	*Triethyl amine (eq)*	*R-N≡C [M][b]*	*Solvent*	*R-N≡C*	*Reaction temperature (°C)*	*Yield**		
						t (%)	*d (%)*	*m (%)*
23	0.0	1.0	TFE	$C_8(OEG)_3NC$	55	22	49	29
24	0.0	0.5	TFE	$C_8(OEG)_3NC$	55	32	52	16
25	0.0	0.1	TFE	$C_8(OEG)_3NC$	55	45	55	NO
26	0.0	0.5	TFE	$C_8(OEG)_3NC$	80	25	51	24
27	0.0	2.0	TFE	$C_8(OEG)_3NC$	55	12	27	62
28	5.0	0.5	TFE	$C_8(OEG)_3NC$	55	NO	NO	NO
29	5.0	0.5	MeOH	$(OEG)_4NC$	55	NO	NO	NO
30	5.0	0.5	TFE	$(OEG)_4NC$	55	NO	NO	NO
31	5.0	0.5	MeOH	$C_8(OEG)_3NC$	55	NO	NO	NO

[a]Reaction conditions: trisquaric acid (0.02 mmol), isocyanide ($C_8(OEG)_3NC$ or $(OEG)_4NC$), (0.2 mmol), ammonium carbonate (0.1 mmol) and benzaldehydes or formaldehyde (0.1 momol) in TFE or MeOH at 55 or 80 °C and in presence of triethylamine (0.1 mmol), overnight. [b] The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *The yields were determined by LCMS. t = trisubstituted, d = disubstituted, m = monosubstituted, NO = not observed, R-N≡C: isocyanide, conc.: concentration.

A significant amount of mono- and disubstituted products were observed in this concentration range of isocyanide. Further increasing the isocyanide concentration (1 and 2 M), resulted in the preferential formation of mono and disubstituted compounds. This concentration screen pointed out that an isocyanide concentration of 0.1 M yields the highest amount of trisubstituted product (45%) (entry 25). Further increasing the reaction temperature to 80 °C (entry 26), decreased the amount of trisubstituted product formed with the mono- and disubstituted products as the predominant species (*m* = 24% and *d* = 51%, respectively). In the synthesis of tripodal peptide-peptoid podands as reported by Rivera[41] and coworkers, triethylamine was used to promote the formation of the iminium ion when starting from amines as their hydrochloride salts. Therefore, triethylamine (5 eq) was added to the Ugi reaction with 0.5 M isocyanide (entries 28-31) using a reaction temperature of 55 °C, but no product was formed. Further changing the solvent (MeOH) and the type of isocyanide ($(OEG)_4NC$), also did not yield any product formation.

As the formation of the iminium ion in the Ugi reaction determines the success and the yield of reaction, conditions that further can encourage its formation when using amphiphilic isocyanides were probed (entries 32-36, Table 5).



Scheme 5

Table 5 Selected entries for the Ugi reaction with trisquaric acid and different reaction times for the imine formation step[a].

Entry	R-N≡C *(eq)* [b]	*pTSA (eq)*	*Length of imine formation step (min)*	*Reaction temperature (°C)*	*Yield**		
					t (%)	*d (%)*	*m (%)*
32	10	0.0	120	0->55	26	54	20
33	10	0.0	120	RT->55	23	36	41
34	5	0.0	30	0->55	11	26	63
35	10	1.0	30	0->55	30	48	22
36	10	3.0	30	0->55	23	43	34

[a]Reaction conditions: trisquaric acid (0.02 mmol), isocyanide ($(OEG)_4NC$), (0.2 mmol, 0.5 M), ammonium carbonate (0.1 mmol) and benzaldehyde (0.1 momol) in TFE at 55 °C and with pTSA for different reaction times in the imine formation step, overnight. [b]The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *Yields were determined by LCMS. t = trisubstituted, d = disubstituted, m = monosubstituted, NO = not observed, R-N≡C: isocyanide.

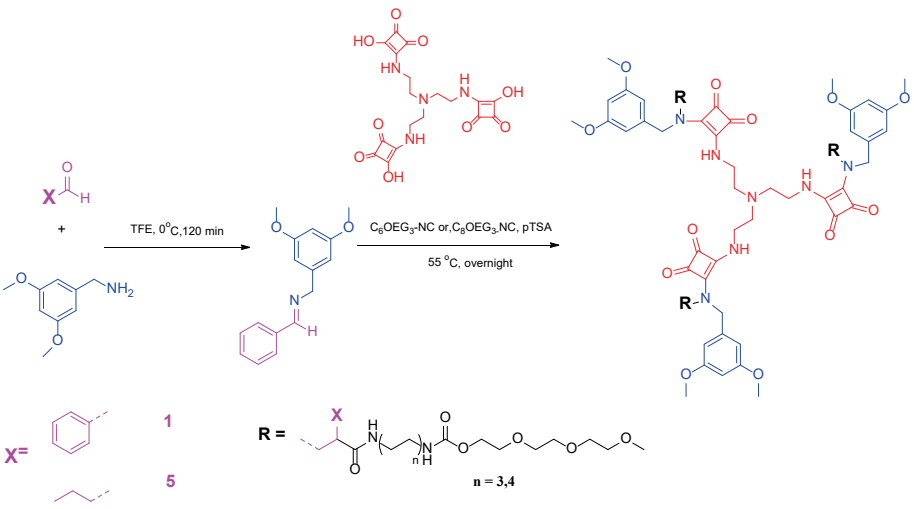
The reaction time used to form the iminium ion prior to the addition of the other components was 30 min at 0 °C. Extension of the reaction time up to 2 h did not further increase the yield of the trisubstituted product (entry 32). When the imine reaction step was carried out at RT (entry 33) based on a previous study by Aknin and coworkers,[22] an increased formation of monosubstituted compound was observed alongside the trisubstituted product in comparison to starting at 0ºC (entry 32).

To further optimize the yield of the reaction, decreasing the number of equivalents of isocyanide (5 eq) with at a concentration of 0.5 M was examined (entry 34). The importance of an excess of isocyanide on the success of the reaction was highlighted, as an increased yield of the monosubstituted compound (63%) was observed. Subsequently, the effect of adding the Brønsted acid catalyst *p*-toluensulfonic acid (pTSA) after the imine formation was examined to increase the yield of the reaction. [17,44, 45] The acid plays a pivotal role in the Ugi reaction mechanism because it increases the concentration of the imine ion in the reaction mixture.[17] Hence, pTSA (1 or 3 eq) was used to protonate the acid and to facilitate the formation of a imine ion after the addition of squaric acid (entries 35 and 36). While the use of 1 eq of pTSA slightly increased the yield of the trisubstituted compound (23-30%), the addition of more equivalents (3 eq) increased the amount of mono- and disubstituted compounds. Hence, extending the reaction time to form the iminium ion, increasing the reaction temperature and concentration of the reagents did not result in an increase in yield of the trisubstituted compound. The use of triethylamine was detrimental for the reaction with the lack of product being formed. In contrast, the addition of low amounts of pTSA (1 eq) resulted in the formation of the trisubstituted Ugi compound.

3.3.4 Modulation of the amine components

Earlier the use of ammonium carbonate as the amine component provided a low yield of the trisubstituted Ugi product (entries 23-27). This result is most likely due to the formation of an unstable imine. It was previously reported by Kazmaier and coworkers that when ammonia is used in the Ugi reaction, a side reaction can result to form a semiaminal.[46] This product can be formed when a second reaction occurs with ammonia instead of the isocyanide on the iminium ion. Thus, to prevent the formation of the semiaminal, 2,4-dimethoxybenzylamine was used.[47, 48] Additionally, the use of this amine has advantages in the purification step, as it can be easily removed from the product under acidic conditions.[49-51] To further promote the formation of the trisubstituted product, an excess of the isocyanide (10 eq C_6-OEG-NC) at a 0.5 M concentration was used (entry 37). An excess of disubstituted compound was observed (42%) in comparison to the trisubstituted compound (58%). To further enhance the formation of the trisubstituted compound, pTSA was added. However, using 1 equivalent of pTSA (entry 40), no significant improvement in the yield of trisubstituted compound was observed when compared against reaction in absence of pTSA (entry 39). Moreover, further increasing the equivalents of pTSA was detrimental for product formation (entry 41). Decreasing the amount of isocyanide (from 10 eq to 5 eq) with 1 eq of pTSA, showed a slight improvement in the yield of the trisubstituted product (58%), in contrast to the disubstituted compound (48%).

Finally, to extend the library of the supramolecular monomers, the use of butyraldehyde was further examined. Unfortunately, no reaction was observed under the same conditions (entry 38). This result is likely due to the decreased stability of the imine formed by aliphatic aldehyde as compared to benzaldehyde.



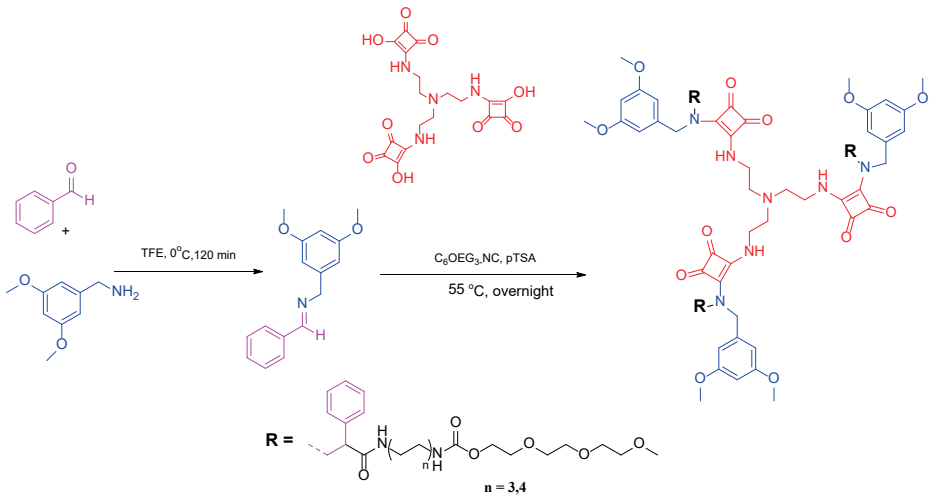
Scheme 6

Table 6 Selected entries for the Ugi reaction with trisquaric acid and primary amine[a]

Entry	R-N≡C *(eq)* [b]	*PTSA (eq)*	*Aldehyde*	R-N≡C *type*	*Yield**		
					t (%)	*d (%)*	*m (%)*
37	10.0	0.0	**1**	C_8OEG_3	58	42	NO
38	10.0	0.0	**5**	C_8OEG_3	NO	NO	NO
39	10.0	0.0	**1**	C_6OEG_3	42	57	NO
40	10.0	1.0	**1**	C_6OEG_3	45	55	NO
41	10.0	3.0	**1**	C_6OEG_3	27	73	NO
42	5.0	1.0	**1**	C_6OEG_3	58	48	NO

[a]Reaction conditions: trisquaric acid (0.02 mmol), isocyanide ($(C_8OEG)_4NC$, 0.5 M), (0.2 mmol), 2,4-dimethoxybenzylamine (0.1 mmol) and benzaldehydes or butyraldehyde (0.1 momol), with pTSA in TFE at 55 °C overnight. [b]The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *Yields were determined by LCMS. t = trisubstituted, d = disubstituted, m = monosubstituted, NO = not observed, R-N≡C: isocyanide.

Based on previous improvements of the Ugi reaction yield in the formation of the trisubstituted product (entries 43-49, Table 7), the number of equivalents of isocyanide and the reaction time for the imine formation was investigated (Scheme 7). A decrease in the isocyanide, benzaldehyde and amine components from 5 to 3.5 eq (entry 44) favoured the disubstituted compound (65%). Moreover, the addition of 1 eq of pTSA did not improve the yield of the trisubstituted compound (entry 45). Consequently, the effect of the reaction time to prepare the imine was further investigated. Increasing the reaction time from 30 min to 2 h, was found to slightly favor the formation of trisubstituted compound (31%, entry 46). In entries 47 and 48, an additional decrease in equivalents of the other components did not increase the trisubstituted product. The use of 5 eq of isocyanide, benzaldehyde, and 2,4-dimethoxybenzylamine with 1 eq of pTSA and an increased reaction time for imine formation, showed nearly full conversion to the trisubstituted product (79%) with a considerable reduction in the disubstituted product formed.



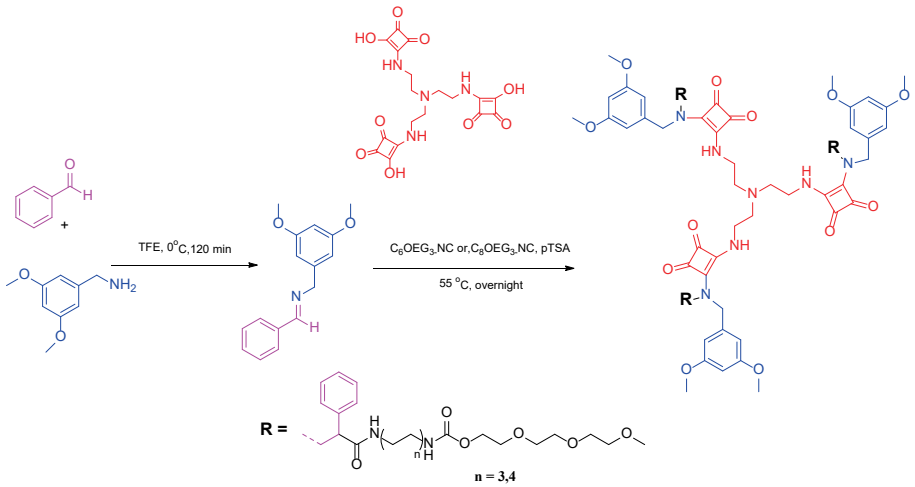
Scheme 7

Table 7 Selected entries for the Ugi reaction with trisquaric acid and different reaction times for imine formation

Entry	**R-N≡C** *(eq)*	*Aldehyde & 2,4-dimethoxy benzylamine (eq)*	*PTSA (eq)*	*Time imine-formation step (min)*	*Yield**		
					t *(%)*	***d*** *(%)*	***m*** *(%)*
43	5.0	5.0	0.0	30	47	53	NO
44	3.5	3.5	0.0	30	35	65	NO
45	3.5	3.5	1.0	30	25	75	NO
46	3.5	3.5	0.0	120	31	69	NO
47	3.05	3.05	1.0	30	14	86	NO
48	5.0	3.05	1.0	30	21	79	NO
49	5.0	5.0	1.0	120	79	21	NO

[a]Reaction conditions: trisquaric acid (0.02 mmol), isocyanide ($(C_6OEG)_4NC$ or $C_8OEG)_4NC$, 0.5 M), 2,4-dimethoxybenzylamine (0.1 mmol) and benzaldehyde (0.1 momol), in presence of pTSA, with different reaction times for imine formation, in TFE at 55 °C, overnight. [b]The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *Yields were determined by LCMS t = trisubstituted, d = disubstituted, m = monosubstituted, NO = not observed, R-N≡C: isocyanide.

The effect of the reaction time between 2,4-dimethoxyenzylamine and benzaldehyde was evaluated on the formation of the trisubstituted product (entries 43-49). After imine formation (2 h), the outcome of the Ugi reation was examined after the addition of the other Ugi components and their reflux at 55 °C after 72 h (entry 50) and 144 h (entry 51). No major differences in yield of trisubstituted product were found for the different isocyanide chain lengths (C_6OEG_3NC, C_8OEG_3NC). Although the formation of trisubstituted product was favoured (79-82%) on increasing the reaction time to 72 h (3 days) and 144 h (5 days), further increasing the reaction time resulted in the formation of an unknown byproduct.



Scheme 8

Table 8 Selected entries for the Ugi reaction conditions with trisquaric acid and different reaction times

Entry	*Reaction time (h)*	**R-N≡C** *(0.5 M)*[b]	*Percentage yield**		
			t (%)	***d (%)***	***m (%)***
50	72	C_6OEG_3NC	79	21	NO
51	144	C_8OEG_3NC	82	17	NO

[a]Reaction conditions: trisquaric acid (0.02 mmol), isocyanide ((0.1 momol, $C_6(OEG)_4NC$ or $C_8OEG)_4NC$), 2,4-dimethoxybenzylamine (0.1 mmol) and benzaldehydes (0.1 momol), in presence of pTSA (0.02 mmol), with different reaction times of imine formation, in TFE at 55 °C, for 72 or 144h. [b]The reaction conditions were designed considering the concentration of isocyanide in the reaction mixture. The addition of the solvent was modified accordingly to obtain a specific concentration of isocyanide in the reaction mixture. *Yields were determined by LCMS. t = trisubstituted, d = disubstituted, m = monosubstituted, NO = not observed, R-N≡C: isocyanide.

3.4 Self-assembly of tripodal squaramides obtained by the Ugi reaction

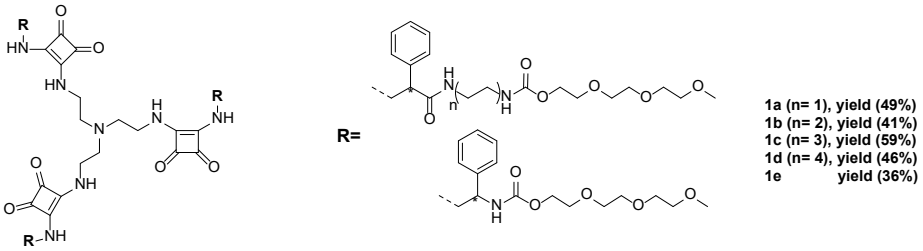


Figure 3.2 Chemical structure of the molecules synthesized by Ugi reaction.

Using the synthetic protocol described in the prior sections, a small family of tripodal compounds was prepared using squaric acid, benzaldehyde, 2,4-dimethoxybenzylamine and an amphiphilic isocyanide with different aliphatic spacer lengths and an oligoethylene glycol chain were synthesized and their capacity for self-assembly was assessed (n = 1-4, **Figure 3.2**). The various squaramide supramolecular scaffolds were synthesized and isolated in moderate yields (36-59%). Because the tripodal squaramide scaffolds consist of hydrophilic, hydrophobic and hydrogen-bonding segments, we investigated their potential for aggregate formation in water. To faciliate the self-assembly of the monomers, 2,4-dimethoxybenzyl protecting group was removed under acidic conditions revealing the squaramide. Firstly, a solubility test of the various compounds (**1a - e**) between 1 and 5 mM was executed. Whereas **1c** and **1d** precipitated at concentrations of 1 mM, **1e** and **1a** were soluble up to 5 mM concentration. Compound **1b** was soluble up to a 1 mM concentration. In all cases, no gels were formed even though typical domains encountered in gelator molecules were used. Once the solubility of the compounds was determined, atomic force microscopy (AFM), and UV-vis studies were used to provide more insight into their aggregation behavior (**Figure 3.3**). AFM imaging of compounds **1a** and **1b** at a concentration of 15 μM displayed the formation of spherical aggregates (**Figure S3.1** and **S3.2**). Self-assembly of the squaramide compounds was further probed by UV-vis spectroscopy at the molecular level. We previously demonstrated that the simultaneous red- and blue-shifting of the HOMO-LUMO and HOMO-LUMO+1 bands of the squaramides and their increased intensity is consistent with the head-to-tail

hydrogen bond assembly of the squaramide rings. However, the lack of shifting of these bands in the Ugi compounds **1a** and **1e** suggests an aggregation mode of the squaramides that is distinct from head-to-tail hydrogen bonding. One possible explanation for the observed aggregate morphology and organization of the squaramide synthons is the presence of three stereocenters observed in the Ugi products that preclude their self-assembly in a head-to-tail mode. To control the stereochemistry of Ugi products, the use a chiral catalyst as demonstrated by Zhang and coworkers should be considered.[52] Alternatively, ketones such as acetone or diethylketone can be used in the Ugi reaction to remove the stereocenters opening the use of these amphiphilic scaffolds for the formation of supramolecular polymers.

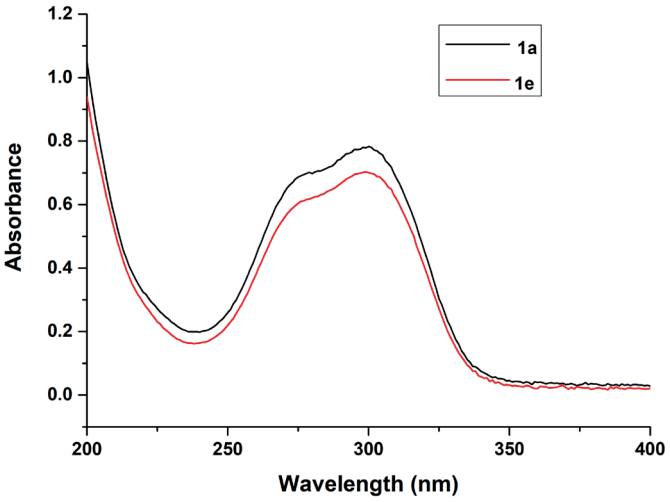


Figure 3.3 UV-vis spectra of **1a** and **1e** (c=15 μM) in water

3.5 Conclusions

In summary, several Ugi reaction conditions were tested to obtain and optimize the synthesis of the tripodal supramolecular scaffolds. These compounds consist of a hydrophilic domain (triethylene glycol) and a variable number of methylene units (n= 0, 2, 4, 6) connected to a central squaramide or amide core. More specifically, the effect of varying the aldehyde, amine, isocyanide and acidic components, such as the use of nitrilotriacetic and squaric acid were investigated. Performing the reaction with nitrilotriacetic acid, benzaldehyde, ammonium carbonate, and OEG_n-NC resulted in a distribution of di- and trisubstituted compounds. The use of 2,4-dimethoxybenzylamine in combination with squaric acid, benzaldehyde and amphiphilic isocyanides allowed the preparation of a small family of tripodal compounds to investigate their self-assembly in water. The use of an aromatic aldehyde causes the formation of diastereomers in the final products. The ability of the synthesized squaramide-based Ugi compounds to self-assemble in water was examined. Compounds **1a** and **1e** showed their aggregation in spheres. This result was supported by UV-vis results of **1a** and **1e** that lack the typical HOMO-LUMO and HOMO-LUMO+1 transitions of squaramide when assembled into a head-to-tail hydrogen bond array. The lack of self-assembly into fibrillar aggregates can be due to the existence of diastereomers in the final products. Although no fibrillar aggregates are observed, the optimized Ugi reaction with trisquaric acid core can be considered as novel strategy for the preparation of tripodal squaramide compounds.

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SUPPORTING INFORMATION

3.5 Materials and methods

3.5.1 Materials

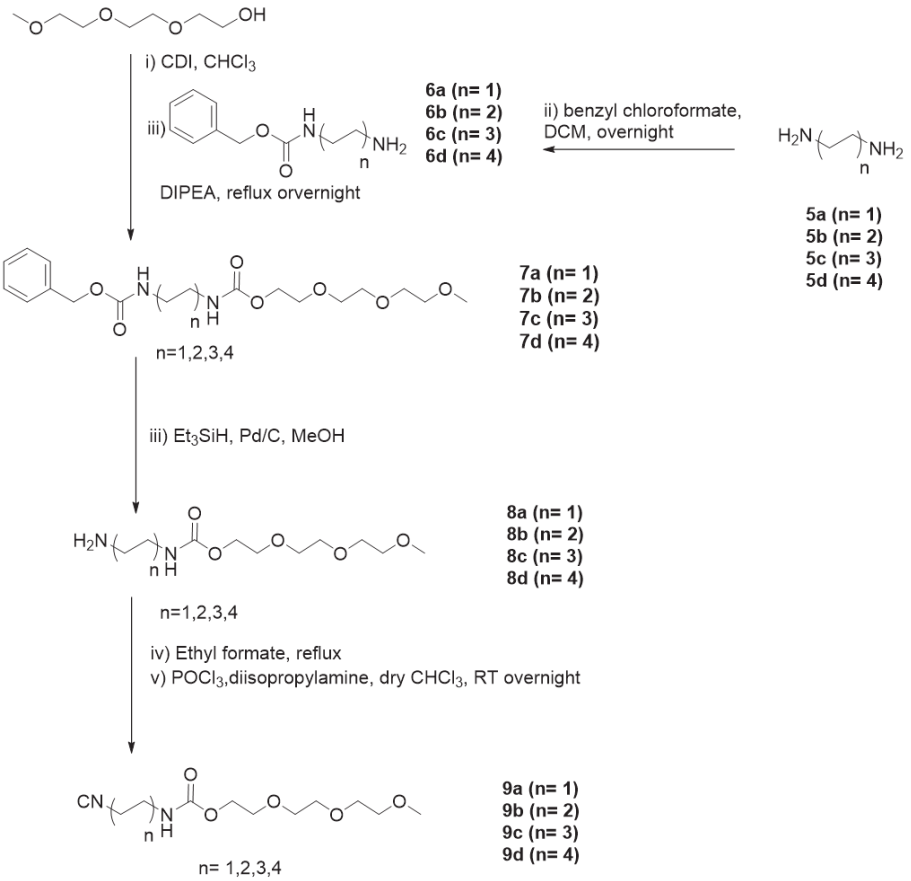
All reagents and chemicals were purchased at Sigma Aldrich and Acros Organic and were used without further purification. Deuterated chloroform was purchased from Euriso-top and Milli-Q water was employed for all the experiments. Acetonitrile for the hydrogenation reaction was dried using molecular sieves 3Å (20% w/v) and used after 24 h of equilibration.

3.5.2. Instrumentation

The compounds were purified by normal-phase silica chromatography or on X1 flash chromatography system equipped with a C18 column from Grace Reveleris using a gradient of H_2O/CH_3CN. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker (300 MHz) or Bruker DMX-400 (400 MHz) spectrometer. LC-MS analysis was performed on a Finnigan Surveyor HPLC system equipped with a Gemini C18 50 x 4.60 mm column (UV detection at 228, 214 nm) coupled to Finnigan LCQ Advantage Max mass spectrometer with ESI. For the mobile phase of LC-MS, a gradient of 10-90% of CH_3CN/ H_2O with 0.1% trifluoroacetic acid over 13.5 minutes was used. To report the various Ugi reaction conditions that were screened, the yields of the mono-, di- and trisubstituted products were calculated from the peak areas of the LCMS spectra. The peak areas were divided by the number of substituents attached to the squaric acid cores. To calculate the percentage yield for each compound in the mixture, the individual peak areas of mono-, di- and trisubstituted compounds were divided by the total area and multiplied by 100. Atomic force microscopy (AFM) images were recorded in tapping mode on a Veeco-Bruker Multimode AFM with a Nanoscope IIIa controller at room temperature. The AFM tips used were Oltespa Opus probes with a reflex aluminium coating, with a nominal spring constant of 2 N/m, a nominal resonance frequency of 70 kHz and a tip radius of 7 nm. UV-vis measurements were performed on a Cary 300 UV-VIS spectrophotometer using a quartz cuvette of a 1 cm path length.

3.6 Synthetic Schemes

3.6.1 Scheme S.1 – Synthesis of the amphiphilic isocyanide



Scheme S.1

Synthesis of compound 6

To a solution of alkyldiamine **5a-d** (**5a**: ethane-1,2-diamine (20.00 g, 0.333 mol); **5b**: butane-1,4-diamine (30.00 g, 0.312 mol), **5c**: hexane-1,6-diamine (10.00 g, 0.086 mol); **5d**: octane-1,8-diamine (8.03 g, 55.66 mmol)) in DCM (275 mL), benzyl chloroformate (**a**: 9.50 mL, 0.067 mol, **b**: 8.91 mL, 10.64 g, 0.062 mol, **c**: 2.46 mL, 2.94 g, 0.017 mol, **d**: 1.58 mL, 1.89 g, 0.011 mol) was added dropwise over 2 hours at 0°C and was stirred overnight at room temperature. The solvent was removed by rotary evaporation and the residue was redissolved in EtOAc (250 mL) and washed with water (3 x 200 mL). The combined organic layers were dried with $MgSO_4$ and after the removal of the solvent, the product was isolated as white solid.

6a: Yield: 11.35 g, 88%. ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 7.38 – 7.28 (m, 5H), 4.90 (s, 2H), 3.27 (s, 2H), 3.20 – 3.04 (m, 2H), 2.65 (t, 1H), 1.52 (q, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 128.06, 127.58, 127.44, 66.05, 48.45, 48.17, 47.89, 47.60, 47.32, 47.04, 46.75, 43.02, 40.93.

6b: Yield: 11.89 g, 86%. ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 7.39 – 7.28 (m, 5H), 5.07 (s, 2H), 3.36 – 3.06 (m, 6H), 2.64 (q, 1H), 1.51 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.42, 135.87, 128.03, 127.53, 127.34, 65.90, 48.44, 48.15, 47.87, 47.59, 47.30, 47.02, 46.74, 40.03, 31.81, 26.73

6c: Yield: 4.28 g, 99%. ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 7.35 (d, 5H), 4.88 (s, 2H), 3.19 – 3.07 (m, 2H), 2.63 (m, 2H), 1.60 – 1.29 (m, 8H). ^{13}C NMR: (300 MHz, $CDCl_3$): δ (ppm) = 157.49, 137.12, 128.05, 127.52, 127.35, 65.86, 48.47, 48.18, 47.90, 47.61, 47.33, 47.05, 46.76, 41.09, 41.03, 40.30, 32.34, 32.29, 29.47, 26.48, 26.23, 26.02.

6d: Yield: 6.20 g, 100%. ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) = 7.40 – 7.26 (m, 5H), 5.07 (s, 2H), 3.11 (m, 3H), 2.88 (m, 1H), 1.64 (m, 2H), 1.50 (m, 2H), 1.35 (q, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.67, 136.01, 128.07, 127.56, 127.34, 65.89, 48.20, 47.92, 47.63, 47.35, 47.06, 46.78, 40.33, 39.43, 29.44, 28.68, 27.31, 26.24, 25.97.

Synthesis of 7

Triethylene glycol monomethyl ether (**a**: 2.50 mL, 15.23 mmol; **b**: 2.50 mL, 15.23 mmol; **c**: 4.14 mL, 25.88 mmol; **d**: 2.63 mL, 16.44 mmol) was activated with 1,1′-carbonyldiimidazole (CDI) (**a**: 2.72 g, 16.75 mmol; **b**: 2.72 g, 16.75

mmol; **c**: 4.62 g, 28.47 mmol; **d**: 2.93 g, 18.09 mmol) for 1 h at RT. Subsequently, **6a-d** (**6a**: 4.44 g, 22.84 mmol; **6b**: 5.08 g, 22.84 mol; **6c**: 9.72 g, 38.83 mmol; **6d**: 5.95 g, 21.38 mmol) and DIPEA (**7a**: 5.30 mL, 30.45 mmol; **7b**: 5.30 mL, 30.45 mmol; **7c**: 9.02 mL, 51.77 mmol; **7d**: 5.73 mL, 32.88 mmol) were dissolved in $CHCl_3$ (70 mL) and were added to the reaction mixture and refluxed overnight. Once the reaction was complete, DCM (100 mL) was added and the reaction mixture was washed with H_2O (3 x 200 mL). The combined aqueous fractions were then back-extracted 3x with DCM (3 x 100 mL). The combined organic fractions were dried with $MgSO_4$, prior to removal of the solvent in *vacuo*. The crude product was purified by silica column chromatography using a DCM/EtOAc gradient (20-50% DCM: EtOAc). The product was isolated as a white solid.

7a: Yield: 5.59 g, 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.43 – 7.27 (m, 5H), 5.41 (d, 2H), 5.10 (s, 2H), 4.27 – 4.14 (m, 2H), 3.65 (q, 8H), 3.57 – 3.52 (m, 2H), 3.37 (s, 3H), 3.33 – 3.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 160.55, 157.14, 140.43, 128.51, 128.13, 77.49, 77.06, 76.64, 71.90, 70.53, 70.48, 69.49, 66.75, 64.05, 58.98, 41.22, 41.05.

7b: Yield: 4.15 g, 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41 – 7.27 (m, 5H), 5.10 (s, 2H), 4.95 (s, 3.26 – 3.13 (m, 4H), 1.53 (q, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.17, 156.47, 137.26, 128.51, 128.09, 77.48, 77.06, 76.63, 71.92, 70.55, 70.51, 69.61, 66.62, 63.87, 59.01, 40.55, 27.20.

7c: Yield 7.20 g, 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.34 (m, 5H), 5.08 (s, 2H), 4.27 – 4.02 (m, 3H), 3.74 – 3.49 (m, 11H), 3.36 (s, 4H), 3.15 – 3.01 (m, 5H), 1.57 – 1.41 (m, 5H), 1.41 – 1.18 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 157.52, 137.13, 128.08, 127.39, 71.57, 70.16, 70.00, 69.21, 65.88, 63.56, 57.73, 48.50, 48.22, 47.94, 47.65, 47.37, 47.09, 46.80, 40.31, 40.25, 29.45, 26.07.

7d: Yield: 5.70 g, 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.43 – 7.28 (m, 5H), 5.10 (s, 2H), 4.89 – 4.72 (m, 2H), 4.22 (t, 2H), 3.66 (d, 8H), 3.61 – 3.54 (m, 2H), 3.39 (s, 3H), 3.26 – 3.09 (m, 4H), 1.47 (q, 4H), 1.30 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.48, 156.41, 136.69, 128.05, 77.50, 77.07, 76.65, 71.93, 70.56, 70.54, 70.50, 69.66, 66.53, 63.79, 59.02, 40.96, 29.88, 29.10, 26.60.

Synthesis of 8

To perform the hydrogenation reaction **7a-d** (**7a**, n=1: 5.59 g, 14.53 mmol; **7b**, n=2: 3.25 g, 7.876 mmol; **7c**, n=3: 1.47 g, 3.35 mmol; **7d**, n=4: 1.80 g, 3.84 mmol) was dissolved in dry MeOH (20 mL), and Pd/C (**a**: 558.6 mg, 5.249 mmol; **b**: 324.9 mg, 3.053 mmol; **c**: 178.1 mg, 1.673 mmol; **d**: 204.4 mg, 1.921 mmol) was added. The solution was put under a N_2 atmosphere and triethylsilane (**a**: 34.82 mL, 218.0 mmol; **b**: 18.87 mL, 118.1 mmol; **c**: 26.73, 167.3 mmol; **d**: 61.36 mL, 384.1 mmol) was added dropwise. When the reaction was complete (TLC, 95:5 v/v DCM/MeOH), the solution was filtered through Celite to remove Pd/C. The filtrate was concentrated by rotary evaporation and afterwards, a gentle stream of N_2 gas to give the product **8** as a white sticky solid. In all cases, the reaction was quantitative as determined by LCMS.

8a: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.85 (d, 1H), 4.16 – 4.06 (m, 2H), 3.62 – 3.49 (m, 8H), 3.45 (m, 2H), 3.28 (s, 3H), 3.14 (q, 2H), 2.72 (t, 2H), 2.52 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.78, 77.65, 77.22, 76.79, 71.76, 70.38, 70.33, 69.49, 63.68, 58.87, 43.25, 41.39.

8b: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.55 (s, 1H), 4.04 (t, 2H), 3.57 – 3.44 (m, 8H), 3.43 – 3.35 (m, 2H), 3.22 (s, 3H), 3.00 (q, 2H), 2.55 (t, 2H), 2.27 (s, 2H), 1.34 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.50, 77.74, 77.31, 76.88, 72.70, 71.73, 71.69, 70.38, 70.35, 70.29, 70.20, 70.08, 69.47, 63.51, 61.03, 61.03, 58.80, 41.43, 40.60, 30.32, 27.15.

8c: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.94 (s, 1H), 4.26 – 4.17 (m, 2H), 3.72 – 3.62 (m, 8H), 3.61 – 3.55 (m, 2H), 3.39 (s, 3H), 3.24 – 3.10 (m, 2H), 2.69 (t, 2H), 1.85 (s, 2H), 1.48 (m, 4H), 1.33 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.39, 77.72, 77.29, 76.87, 71.76, 70.40, 70.37, 70.33, 69.51, 63.54, 58.84, 41.77, 40.73, 33.18, 29.77, 26.43, 26.37.

8d: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.13 (d, 1H), 4.16 – 4.09 (m, 2H), 3.65 – 3.52 (m, 8H), 3.50 – 3.44 (m, 2H), 3.30 (s, 3H), 3.10 – 3.01 (m, 2H), 2.60 (m, 2H), 1.38 (q, 4H), 1.21 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.41, 77.57, 77.15, 76.72, 71.84, 70.47, 70.44, 69.63, 63.65, 58.94, 41.85, 41.74, 40.93, 38.00, 33.09, 29.84, 29.42, 29.26, 29.14, 29.07, 26.71, 26.65, 26.61.

Synthesis of 9

The formylation reaction was performed by dissolving **8a-d** (**8a**, n=1: 3.64g, 14.54 mmol; **8b**, n=2: 2.18, 2.78 mmol; **8c**, n=3: 1.48g, 4.81 mmol; **8d**, n=4: 1.29g, 3.86 mmol) in ethylformate (20 mL) and refluxing overnight. The reaction was monitored by ^{1}H NMR and after ethyl formate was removed by rotary evaporation, the compound was used for the next step without further purification. Subsequently, the crude was dissolved in DCM (20 mL) and diisopropylamine (**a**: 3.02 mL, 21.56 mmol; **b**: 3.11 mL, 22.19 mmol; **c**: 2.03 mL, 14.48 mmol; **d**: 2.48 mL, 17.71 mmol) was added at 0 °C. Phosphorus oxychloride (**a**: 0.81 mL, 8.62 mmol; **b**: 0.83 mL, 8.88 mmol; **c**: 0.54 mL, 5.78 mmol; **d**: 0.66 mL, 7.09 mmol) was added dropwise and the reaction mixture was stirred overnight. Sodium carbonate was added to quench the reaction and was stirred for another 30 min before dilution with water. The aqueous layers were extracted with DCM (3 x 40 mL) and dried with Na_2SO_4. The solvent was removed under vacuum and purified by silica column chromatography using DCM:MeOH (95:5) as the eluent.

9a: Yield: 1.63 g, 87%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.00 (t, 1H), 4.14 – 3.89 (m, 2H), 3.50 – 3.41 (m, 8H), 3.35 (m, 4H), 3.22 (t, 2H), 3.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.47, 71.68, 70.28, 70.25, 70.22, 69.18, 64.00, 58.71, 41.53, 40.01.

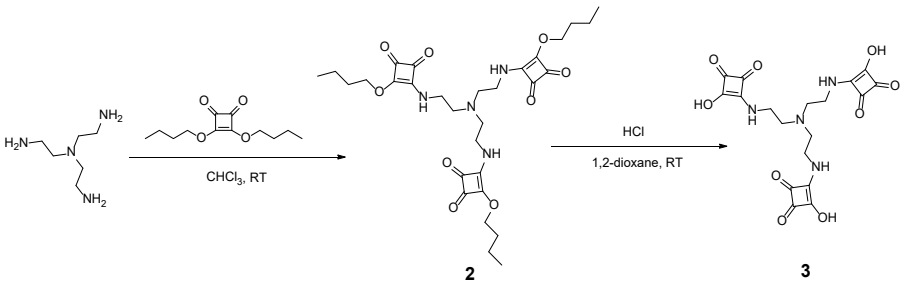
9b: Yield: 2.00 g, 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.36 – 4.96 (m, 1H), 4.25 – 4.01 (m, 2H), 3.56 (d, 10H), 3.46 (m, 2H), 3.29 (d, 3H), 3.08 (d, 2H), 1.44 (dq, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.55, 156.55, 77.82, 77.40, 76.98, 71.75, 70.52, 70.43, 70.37, 70.31, 69.42, 69.39, 65.99, 65.91, 63.70, 63.61, 58.81, 41.15, 41.07, 40.98, 40.40, 39.66, 27.01, 26.74, 26.08.

9c: Yield:1.26 g, 83%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.92 (t, 1H), 4.17 (t, 2H), 3.68 – 3.58 (m, 8H), 3.56 – 3.48 (m, 2H), 3.40 – 3.30 (m, 5H), 3.13 (q, 2H), 1.72 – 1.58 (m, 2H), 1.53 – 1.27 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.42, 77.60, 77.17, 76.74, 71.88, 70.51, 70.49, 70.46, 69.58, 63.80, 58.99, 41.52, 41.43, 41.35, 40.73, 29.74, 28.93, 25.97, 25.80.

9d: Yield: 1.82 g, 90%.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 4.22 (t, 2H), 3.66 (d, 8H), 3.56 (m, 2H), 3.39 (s, 4H), 3.17 (q, 2H), 1.76 – 1.61 (m, 2H), 1.46 (m, 4H), 1.32 (q, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.41,

155.48, 77.56, 77.13, 76.71, 71.89, 70.52, 70.50, 70.47, 69.62, 63.77, 58.99, 41.59, 41.51, 41.43, 40.91, 29.86, 29.00, 28.96, 28.56, 26.54, 26.20

3.6.2 Scheme S.2: Synthesis of trisquaric acid



Scheme S.2

Synthesis of 2

Tris(2-aminoethyl)amine (200 mg 1.37 mmol) was dissolved in $CHCl_3$ (30 mL). DIPEA (1.2 mL, 6.84 mmol) and 3,4-dibutoxy-3-cyclobutene-1,2-dione (1.18 mL, 5.47 mmol) were added to the mixture and refluxed overnight at 75 °C. The compound was purified by flash chromatography using a gradient of H_2O/CH_3CN 10-90% over 30 min and the product was isolated as yellow solid.

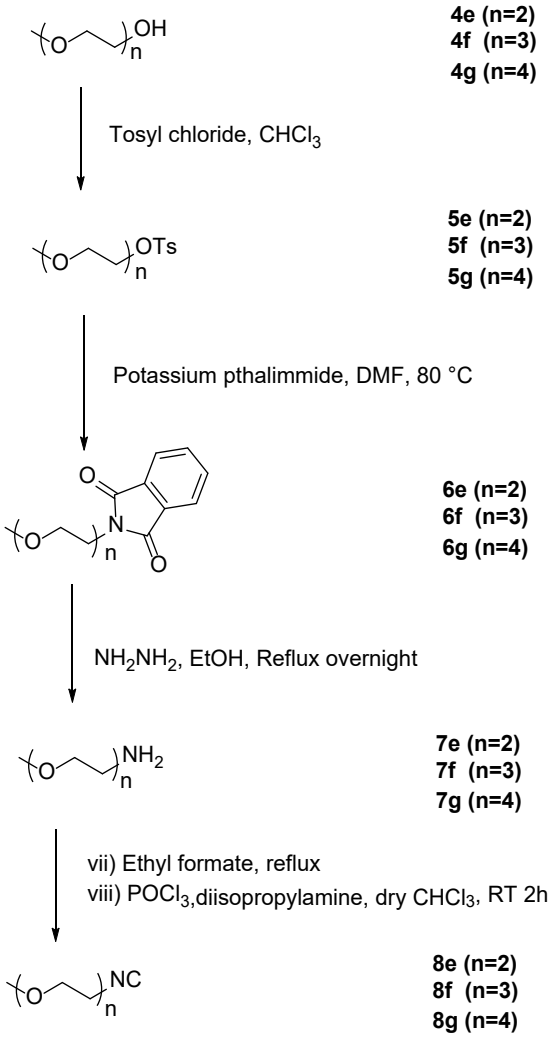
Yield: 1.25 g, 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.97 – 7.50 (m, 3H), 4.68 (t, 6H), 3.67 (d, 7H), 2.74 (s, 6H), 1.77 (p, 6H), 1.41 (m, 7H), 0.97 (t, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 160.89, 145.78, 130.66, 77.47, 77.04, 76.62, 73.67, 54.83, 42.04, 31.95, 31.95, 18.62, 13.66.

Synthesis of 3

Compound **2 (**624.8 mg, 1.04 mmol) was dissolved in 1,2-dioxane (10 mL) and HCl 37 % (2 mL) was added. The mixture was stirred overnight at room temperature and the final compound was isolated by removing the solvent with a gentle stream of N_2 gas. The white solid was washed with DCM and was used without further purification.

Yield: 464.7 mg, 100%. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.20 (t, 3H), 3.74 (q, 6H), 3.28 (t, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 187.29, 185.64, 175.14, 53.55, 43.54, 40.73, 40.45, 40.17, 39.89, 39.61, 39.33, 39.05. HRMS: m/z = 434.11 $[M+H]^+$.

3.6.3 Scheme S.3 – Synthesis of oligo(ethylene) glycol isocyanide



Scheme S.3

Synthesis of 5e, 5f, 5g

A solution of **4e-f** (**4e**: diethylene glycol methyl ether (9.75 mL, 83.23 mmol); **4f**: triethylene glycol monomethyl ether (4.87 mL, 30.45 mmol); **4g**: tetraethylene glycol monomethyl ether (4.78 mL, 24.01 mmol)) in THF (**e**: 14 mL; **f**: 7 mL; **g**: 7 mL) was reacted with a solution of NaOH (**e**: 6.09 g, 152.31 mmol; **f**: 2.23 g, 55.72 mmol; **g**: 1.76 g, 40.0 mmol) in distilled water (**e**: 17 mL; **f**: 6 mL; **g**: 6 mL) with stirring for 15 min at 0 °C. Subsequently, a solution of TsCl (**e**: 15.87 g, 30.45 mmol; **f**: 5.81 g, 30.45 mmol; **g**: 4.58 g, 24.01 mmol) in THF (**e**: 26 mL; **f**: 10 mL; **g**: 10 mL) was added dropwise at 0 ºC. The reaction mixture was stirred at RT for other 30 min. The volatile materials were removed by rotary evaporation and water (100 mL) was added. An extraction with Et_2O (3 x 100mL) was performed, and afterwards the organic layers were dried with Na_2SO_4. The products were isolated as a pale-yellow oil after rotary evaporation.

5e: Yield: 22.19 g, 97%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.83 – 7.73 (m, 2H), 7.38 – 7.30 (m, 2H), 4.21 – 4.12 (m, 2H), 3.72 – 3.62 (m, 2H), 3.58 – 3.53 (m, 2H), 3.50 – 3.43 (m, 2H), 3.34 (d, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 144.84, 129.82, 127.96, 77.55, 77.13, 76.70, 71.77, 70.63, 69.25, 68.67, 59.02, 21.63.

5f: Yield: 9.26 g, 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.76 – 7.62 (m, 1H), 7.32 – 7.22 (m, 1H), 4.10 – 4.03 (m, 1H), 3.61 – 3.56 (m, 1H), 3.56 – 3.48 (m, 3H), 3.46 – 3.40 (m, 1H), 3.26 (s, 2H), 2.35 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 144.76, 132.95, 129.79, 127.83, 77.75, 77.33, 76.90, 71.79, 70.57, 70.40, 69.28, 68.52, 58.84, 21.49.

5g: Yield: 7.40 g, 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.85 – 7.76 (m, 2H), 7.41 – 7.31 (m, 2H), 4.24 – 4.10 (m, 2H), 3.71 – 3.67 (m, 2H), 3.63 (d, 6H), 3.59 (s, 4H), 3.57 – 3.52 (m, 2H), 3.38 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 44.80, 142.79, 129.82, 127.98, 77.50, 77.07, 76.65, 71.91, 70.72, 70.58, 70.51, 69.25, 68.66, 59.02, 21.64.

Synthesis of compound 6e, 6f, 6g

Compounds **5e-f** (**5e**, n=2: 22.19 g, 80.88 mmol, **5f**, n=3: 9.26 g, 29.10 mmol; **5g**, n=4: 7.40 g, 20.42 mmol) were dissolved in DMF (**e**: 50 mL; **f**: 40 mL; **g**:

36 mL). phthalimide potassium salt (**e** 22.47 g, 121.31 mmol; **f**: 8.08 g, 43.65 mmol; **g**: 5.67 g, 30.63 mmol) was added to the solution and heated to stirring 80 °C with stirring overnight. After the removal of the solvent by rotary evaporation, water (100 mL) was added to the solid and extracted with DCM (3 x 100 mL). Subsequently, the combined organic layers were dried with $NaSO_4$ and purified by silica column chromatography (petroleum ether: EtOAc 1/4), and the product was isolated as a white solid.

6e: Yield: 15.32 g, 76%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.80 (m, 2H), 7.68 (m, 2H), 3.93 – 3.82 (m, 2H), 3.76 – 3.67 (m, 2H), 3.64 – 3.59 (m, 2H), 3.49 – 3.43 (m, 2H), 3.33 – 3.23 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.22, 133.89, 132.10, 123.17, 77.56, 77.13, 76.71, 71.85, 69.85, 67.90, 58.95, 37.12.

6f: Yield: 7.38 g, 87%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.92 – 7.82 (m, 2H), 7.77 – 7.65 (m, 2H), 3.94 – 3.85 (m, 2H), 3.74 (t, 2H), 3.71 – 3.57 (m, 6H), 3.52 – 3.44 (m, 2H), 3.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.12, 133.84, 132.07, 123.11, 77.62, 77.19, 76.76, 71.81, 70.49, 70.45, 70.07, 67.82, 58.87, 37.22.

6g: Yield: 6.89 g, 100%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.83 (m, 2H), 7.76 – 7.68 (m, 2H), 3.89 (t, 2H), 3.73 (t, 2H), 3.66 – 3.57 (m, 10H), 3.52 (m, 2H), 3.36 (d, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 171.64, 133.92, 132.32, 123.23, 77.46, 77.04, 76.61, 71.92, 70.60, 70.56, 70.49, 70.08, 67.91, 59.02, 37.26.

Synthesis of 7e, 7f and 7g

Compound **6e-g** (**6e**, n=2: 9.33 g, 25.17 mmol; **6f**, n=3: 5.74g, 19.56 mmol; **6g**, n=4: 3.34 g, 9.89 mmol) was dissolved in ethanol (100 mL) and hydrazine monohydrate (**e**: 10.40 mL, 214.05 mmol; **f**: 5.44 mL, 111.91 mmol; **g**: 2.75 mL, 56.63 mmol) was added. The mixture was refluxed overnight and a white solid precipitate was formed. the solvent was removed by rotary evaporation, the solid was dissolved in DCM (200 mL) and washed with 1M NaOH (3x 200 mL). Subsequently, the product was extracted from the aqueous layer with DCM (3 x 100 mL), dried with $NaSO_4$ and concentrated by rotary evaporation. The product was used for the next step without further purification.

7e: Yield: 1.95 g, 44%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.56 – 3.50 (m, 2H), 3.49 – 3.41 (m, 4H), 3.30 (d, 3H), 2.80 (t, 2H), 2.28 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 77.60, 77.17, 76.74, 73.02, 71.81, 70.14, 58.95, 41.45.

7f: Yield: 2.82 g, 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.62 (m, 6H), 3.56 – 3.47 (m, 4H), 3.35 (s, 3H), 2.90 – 2.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 77.53, 77.11, 76.68, 72.86, 71.88, 70.53, 70.48, 70.22, 58.99, 41.46.

7g: Yield: 1.51 g, 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.83 (m, 2H), 7.76 – 7.68 (m, 2H), 3.89 (t, 2H), 3.73 (t, 2H), 3.66 – 3.57 (m, 10H), 3.52 (m, , 2H), 3.36 (d, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.16, 133.90, 131.98, 123.12, 77.70, 77.27, 76.84, 72.63, 72.44, 70.49, 70.37, 70.27, 70.17, 69.95, 69.78, 67.80, 61.46, 61.22, 37.14.

Synthesis of 8e, 8f and 8g

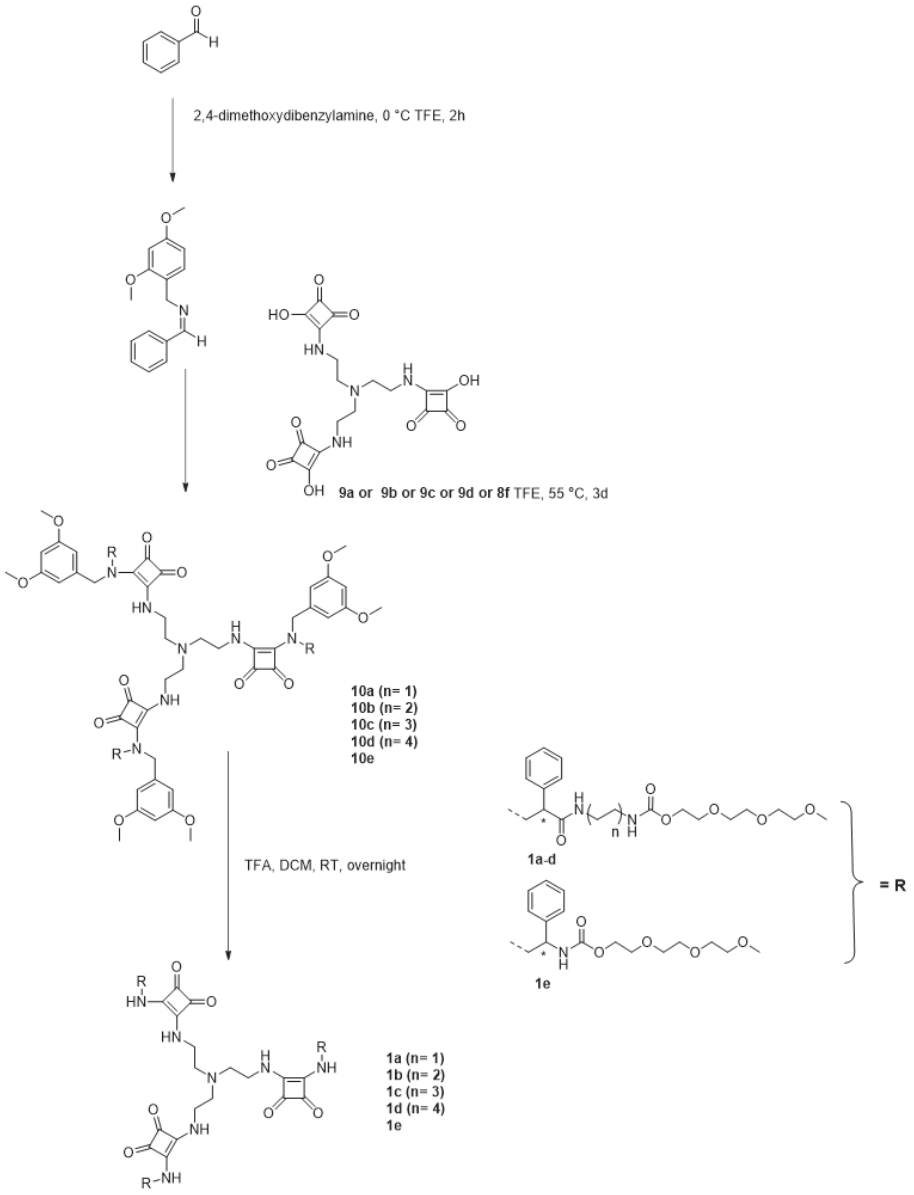
Compounds **7e-g** (**7e**, n=2: 1.95 g, 16.38 mmol; **7f**, n=3: 2.82g, 17.27 mmol; **7g**, n=4: 2.81g, 13.56 mmol) were dissolved in ethyl formate (20 mL) and refluxed for 12 hours. The volatiles were removed by rotary evaporation, (**e**, n=2: 0.91 g, 6.15 mmol; **f**, n=3: 2.30 g, 12.03 mmol; **g**, n=4: 1.53 g, 6.50 mmol), and the residue was dissolved in dry DCM (20 mL) and placed under a N_2 atmosphere. Diisopropylamine (**e**: 2.59 mL, 18.46 mmol; **f**: 5.06 mL, 36.08 mmol; **g**: 2.73 mL, 19.50 mmol) was added and the reaction mixture was cooled to 0 °C. Phosphorus oxychloride (**e**: 0.69 mL, 7.383 mmol; **f**: 1.35 mL, 14.43 mmol; **g**: 0.73 mL, 7.80 mmol) was added dropwise and brought to room temperature. The reaction mixture was stirred for additional 2 h before sodium carbonate (6.5 g in 35 mL of H_2O) was added. The resulting suspension was stirred for another 30 minutes and then diluted with water. The aqueous phase was extracted with DCM (3 x 40 mL), dried with Na_2SO_4 and the organic layers were removed by rotary evaporation. The compound was purified by silica column chromatography (95:5 DCM:MeOH).

8e: Yield: 0.6328 g, 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.74 – 3.66 (m, 4H), 3.63 – 3.52 (m, 4H), 3.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 157.51, 77.50, 77.08, 76.65, 71.84, 70.80, 68.68, 59.12, 41.82, 41.73, 41.63.

8f: Yield: 1.93 g, 93%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.71 – 3.62 (m, 8H), 3.59 – 3.51 (m, 4H), 3.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 77.57, 77.15, 76.72, 71.88, 70.81, 70.59, 70.57, 68.63, 59.02, 41.84, 41.74, 41.65.

8g: Yield: 1.19 g, 84%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.69 – 3.56 (m, 12H), 3.54 – 3.45 (m, 4H), 3.31 (d, 3H). ^{13}C NMR (75 MHz, $CDCl_3$*):* δ (ppm) = 161.46, 77.62, 77.20, 76.77, 71.88, 71.82, 70.79, 70.59, 70.54, 70.46, 70.43, 70.38, 70.09, 69.53, 68.62, 58.97, 41.83, 41.73, 41.64, 37.73.

3.6.4 Scheme S.4 – Ugi reaction



Scheme S.4

Ugi reaction

Benzaldehyde (59 µL, 0.58 mmol) and 2,4-dimethoxybenzylamine (87 µL, 0.58 mmol) were stirred at 0 °C for 2 h in TFE (0.5 mL). Subsequently, **4** (50 mg, 0.12 mmol), *p*-toluenesulfonic acid (pTSA) (1 eq, 22 mg, 0.58 mmol), and the isocyanide (**8f**: n=0 (100 mg, 0.58 mmol); **9a**: n=1 (150 mg, 0.58 mmol); **9b**: n=2 (165.96 mg, 0.58 mmol); **9c**: n=3 (182 mg, 0.58 mmol; **9d**: n=4 (198 mg, 0.58 mmol)) in TFE (0.65 mL) were added and stirred at 55 °C for an additional 72h. The reaction mixture was stirred and monitored by LCMS until no further reaction was observed. The solvent was removed by rotary evaporation and the crude was purified by flash chromatography on a C18 silica column using a gradient of 10-90% H_2O/CH_3CN over 50 min.

10a: Yield: 49%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.51 – 7.03 (m, 18H), 6.56 – 6.15 (m, 6H), 5.27 – 4.68 (m, 6H), 4.14 (m, 6H), 3.86 – 3.67 (m, 18H), 3.66 – 3.43 (m, 36H), 3.41 – 3.14 (m, 21H), 2.52 (s, 3H), 2.33 – 1.93 (m, 3H), 1.26 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 182.96, 179.20, 177.65, 169.47, 169.24, 168.49, 167.97, 160.55, 159.82, 157.04, 156.73, 156.64, 135.96, 134.81, 129.72, 128.94, 128.74, 128.38, 127.03, 118.04, 117.50, 104.79, 104.73, 98.50, 97.98, 71.73, 71.73, 70.21, 70.05, 69.29, 63.70, 58.49, 55.81, 55.62, 55.51, 54.51, 45.57, 40.80, 40.52, 40.24, 39.96, 39.68, 39.41, 39.13. MALDI: (m/z): 2003.88 $[M+Na]^+$

10b: Yield: 41%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.47 – 7.04 (m, 18H), 6.45 (m, 6H), 5.41 – 4.82 (m, 6H), 4.35 – 4.11 (m, 7H), 3.86 – 3.55 (m, 54H), 3.38 (d, 9H), 3.32 – 2.96 (m, 12H), 2.90 – 2.37 (m, 3H), 2.35 – 1.97 (m, 3H), 1.63 – 0.82 (m, 85H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 183.11, 169.57, 168.11, 161.17, 158.62, 156.66, 156.51, 130.85, 130.85, 129.69, 129.49, 129.36, 128.91, 128.73, 128.60, 128.36, 126.93, 117.01, 104.07, 98.52, 77.41, 77.09, 76.78, 71.92, 71.87, 70.52, 70.47, 70.44, 69.64, 63.77, 59.01, 55.36, 55.29, 45.15, 40.58, 40.44, 39.63, 39.43, 37.45, 37.11, 36.89, 31.95, 30.41, 29.73, 29.48, 29.39, 27.41, 27.33, 27.12, 24.49, 24.25, 22.72, 20.48, 19.98. MALDI: (m/z): 2086.64 $[M+Na]^+$

10c: Yield: 59%, ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) =7.47 – 6.99 (m, 18H), 6.97 – 6.61 (m, 3H), 6.40 (m, 6H), 6.26 – 5.95 (m, 3H), 5.47 – 4.76 (m, 9H), 4.16 (dt, 6H), 3.85 – 3.60 (m, 48H), 3.54 (t, 6H), 3.36 (s, 9H), 3.24 – 3.02 (m, 12H), 2.79 – 2.37 (m, 3H), 1.52 – 1.12 (m, 30H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 183.22, 177.81, 172.83, 169.73, 169.40, 168.21, 161.12,

160.94, 160.40, 158.63, 158.22, 157.86, 156.56, 156.47, 156.44, 136.61, 135.00, 134.01, 130.84, 129.78, 129.05, 128.90, 128.71, 128.58, 128.39, 128.21, 128.09, 127.46, 126.85, 122.18, 121.76, 116.93, 116.80, 105.21, 105.02, 104.01, 98.89, 98.65, 98.36, 98.31, 95.42, 94.69, 77.49, 77.49, 77.17, 76.85, 71.90, 70.50, 69.61, 66.46, 65.81, 63.76, 59.00, 55.71, 55.57, 55.41, 55.38, 55.27, 55.17, 54.23, 47.00, 42.21, 41.49, 40.82, 40.69, 39.97, 39.70, 39.47, 31.91, 29.78, 29.68, 29.34, 29.03, 28.57, 28.34, 26.38, 26.26, 26.13, 22.68. MALDI: (m/z): 2172.27 $[M+Na]^+$

10d: Yield: 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.22 (d, 18H), 6.92 – 6.55 (m, 3H), 6.54 – 6.21 (m, 6H), 6.20 – 5.83 (m, 3H), 5.37 – 4.76 (m, 9H), 4.21 – 4.08 (m, 6H), 3.67 (d, 48H), 3.51 (t, 6H), 3.34 (s, 9H), 3.19 – 3.04 (m, 12H), 2.69 – 2.35 (m, 3H), 1.46 – 1.15 (m, 42H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 183.23, 177.84, 169.34, 168.13, 161.12, 160.92, 160.38, 158.71, 157.87, 156.46, 135.04, 133.96, 129.98, 129.05, 128.91, 128.71, 128.55, 128.37, 128.13, 127.90, 116.86, 116.74, 116.74, 104.96, 104.26, 98.84, 98.69, 98.01, 77.53, 77.22, 76.90, 71.88, 70.50, 70.46, 69.60, 64.17, 63.70, 58.98, 55.71, 55.52, 55.38, 55.32, 55.13, 54.13, 46.84, 42.09, 40.95, 40.18, 39.95, 39.77, 39.37, 31.88, 29.85, 29.64, 29.22, 29.11, 26.81, 26.62, 22.65. MALDI: (m/z): 2256.01 $[M+Na]^+$.

10e:Yield: 36%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.37 – 7.00 (m, 18H), 6.49 – 6.17 (m, 6H), 5.15 – 4.96 (m, 3H), 3.81 – 3.64 (m, 24H), 3.56 (m, 36H), 3.34 – 3.26 (m, 9H), 2.64 (t, 3H), 2.37 – 1.83 (m, 3H), 1.49 – 0.79 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) =183.73, 183.25, 178.12, 169.44, 168.13, 161.10, 160.95, 160.37, 158.29, 157.91, 135.05, 134.91, 131.12, 130.65, 130.39, 129.86, 129.58, 129.45, 129.17, 128.93, 128.77, 128.62, 128.42, 128.22, 128.19, 127.88, 127.57, 126.81, 116.76, 116.61, 105.33, 105.24, 104.09, 103.99, 98.90, 98.76, 98.61, 98.15, 98.05, 77.50, 77.50, 77.07, 76.65, 71.85, 70.53, 70.44, 70.38, 70.22, 70.13, 69.73, 69.35, 65.67, 63.76, 58.91, 58.28, 55.81, 55.57, 55.40, 55.33, 55.24, 54.11, 47.07, 42.28, 41.37, 39.93, 39.70, 39.50, 29.68, 29.33, 28.30. MALDI: (m/z): 1742.103 $[M+H+Na]^+$.

Synthesis of 1a-e

Deprotection of compounds **10a-e (10e**, n=0: 128.7 mg, 0.067 mmol; **10a**, n=1: 98.5 mg, 0.050 mmol; **10b**, n=2: 130.30 mg, 0.063 mmol; **10c**, n=3: 212.4 mg, 0.099 mmol; **10d**, n=4: 142.80 mg, 0.064 mmol) was performed

adding 15 mL DCM/TFA (1:1) at room temperature. The reaction mixture was stirred overnight and the solvent was evaporated by a gentle stream of air. The product was purified by flash chromatography on a C18 silica column using 10-90% H_2O/CH_3CN as gradient over 30 min.

1a: Yield: 51 mg, 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.69 – 8.15 (m, 3H), 7.70 – 7.15 (m, 15H), 6.71 – 5.64 (m, 6H), 4.09 (s, 9H), 3.56 (d, 36H), 3.32 (s, 21H), 2.90 (d, 3H), 1.50 – 0.77 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 190.00, 170.78, 156.87, 148.70, 139.13, 128.96, 128.91, 127.23, 126.79, 77.49, 77.06, 76.64, 71.83, 71.81, 70.50, 70.37, 64.22, 63.87, 58.90, 54.62, 40.34, 39.85, 29.68. MALDI: (m/z): 1552.76 $[M+Na]^+$.

1b: Yield: 59 mg, 58%.^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.47 (s, 6H), 7.51 – 6.98 (m, 15H), 6.33 (m, 3H), 4.95 (s, 4H), 4.08 (s, 9H), 3.75 – 3.43 (m, 36H), 3.28 (s, 9H), 3.17 – 2.35 (m, 12H), 2.09 (d, 1.18 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 190.64, 169.32, 156.56, 144.58, 129.32, 129.31, 128.88, 128.29, 128.17, 126.92, 103.96, 98.41, 77.45, 77.02, 76.61, 71.88, 70.52, 70.44, 69.60, 66.52, 63.77, 58.97, 55.37, 53.66, 50.57, 41.92, 40.54, 39.27, 29.69, 26.19. LCMS: t=5.16 min (m/z) = 1614.19 m/z $[M]^+$.

1c: Yield: 108 mg, 65%.^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.50 (s, 3H), 7.68 – 7.02 (m, 15H), 6.16 (d, 3H), 5.45 – 5.06 (m, 3H), 4.17 (s, 9H), 3.84 – 3.48 (m, 36H), 3.35 (d, 9H), 3.05 (s, 12H), 2.68 (s, 3H), 1.88 – 0.83 (m, 30H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 188.70, 170.42, 156.52, 148.85, 139.40, 128.78, 128.56, 128.02, 127.75, 127.17, 77.51, 77.09, 76.66, 71.89, 70.53, 70.49, 70.45, 69.61, 69.61, 63.96, 63.77, 58.98, 55.11, 40.79, 39.81, 39.57, 29.70, 29.00, 26.27. MALDI: (m/z): 1721.23 $[M+Na]^+$.

1d: Yield: 59 mg, 51%,^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.48 (s, 3H), 7.77 – 7.16 (m, 15H), 6.54 – 5.95 (m, 3H), 5.25 – 4.77 (m, 3H), 4.66 – 4.01 (m, 9H), 3.99 – 3.41 (m, 36H), 3.37 (s, 9H), 3.28 – 2.82 (m, 12H), 2.67 (d, 3H), 1.48 – 0.85 (m, 42H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 187.65, 169.69, 156.51, 148.65, 138.11, 128.81, 126.61, 77.43, 77.11, 76.79, 71.93, 70.55, 69.67, 63.92, 63.82, 59.05, 53.49, 41.03, 39.86, 38.83, 29.93, 29.72, 29.17, 26.67. MALDI: (m/z): 1805.14 $[M+H+Na]^+$

1e: Yield: 42.3mg, 58%.^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.26 (dd, 6H), 7.39 (dt, 15H), 6.76 – 5.65 (m, 3H), 3.57 (d, 32H), 3.36 (d, 15H), 3.08 – 2.54 (m, 6H), 1.88 – 0.50 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) =

183.35, 182.94, 170.62, 168.59, 149.62, 139.23, 129.70, 128.93, 128.68, 128.50, 128.10, 127.89, 127.39, 127.06, 77.49, 77.17, 76.85, 71.92, 70.66, 70.42, 70.30, 69.49, 59.06, 55.11, 39.82, 29.80, 29.47, 22.80. MALDI: (m/z): 1292.88 $[M+Na]^+$.

3.6.5 Self-assembly characterization

Sample preparation protocol

Water was added to **1a-e** to prepare stock solutions from 1 - 5 mM. Subsequently, aliquots from the stock were diluted to prepare solutions at the a given concentration for further study. All samples were equilibrated overnight before measurement.

UV-vis spectroscopy

Samples for UV-vis spectroscopy were prepared at a 15 µM concentration in water as described according to the sample preparation protocol. The samples were placed in the spectrophotometer and a spectrum was recorded from 200-500 nm. The solutions were prepared in triplicate and for each solution a UV-vis spectrum was measured.

Atomic force microscopy

Compounds **1a** and **1e** were prepared according to the preparation protocol above at a concentration of 15 µM and equilibrated overnight. An aliquot (25 µL) from each of these solutions was pipetted on cleaved mica and dried overnight at RT before the measurement. The obtained AFM images were analyzed using the Nanoscope software.

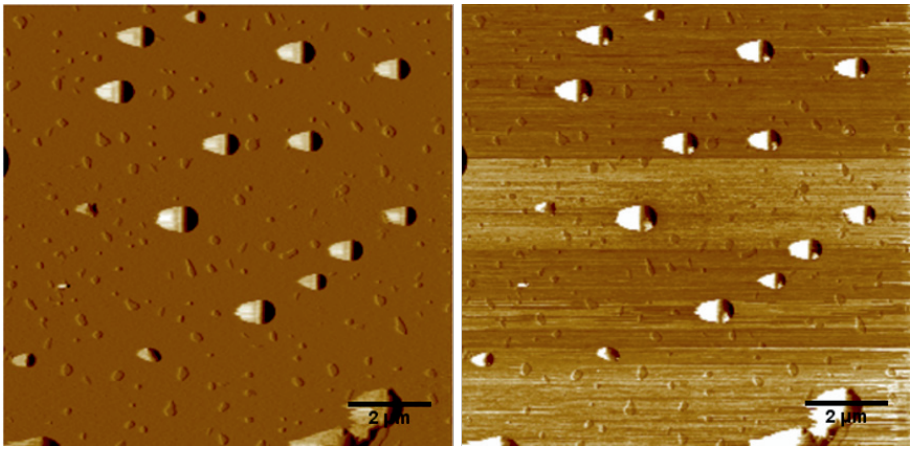


Figure S3.1 AFM micrographs of **1a** (amplitude and height, scale bar: 2 µm)

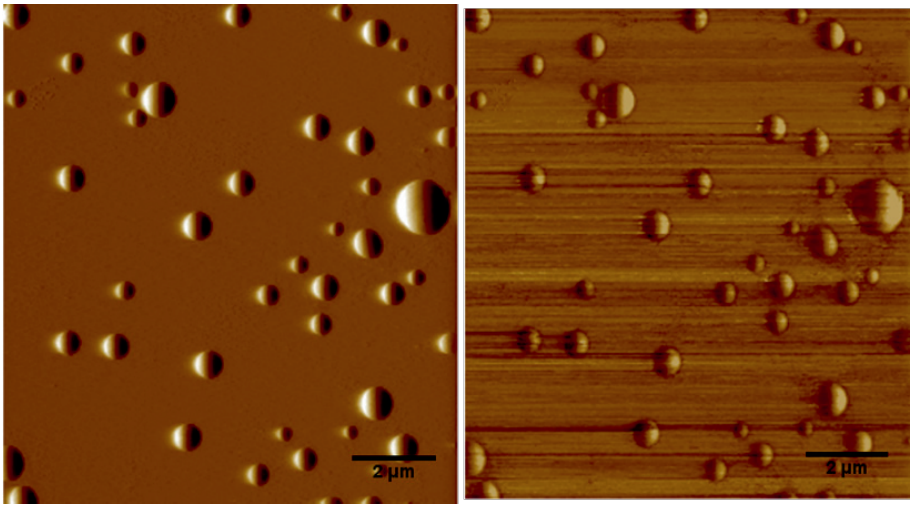


Figure S3.2 AFM micrographs of **1e** (amplitude and height image, scale bar:2 µm)

3.6.5 LCMS Spectra

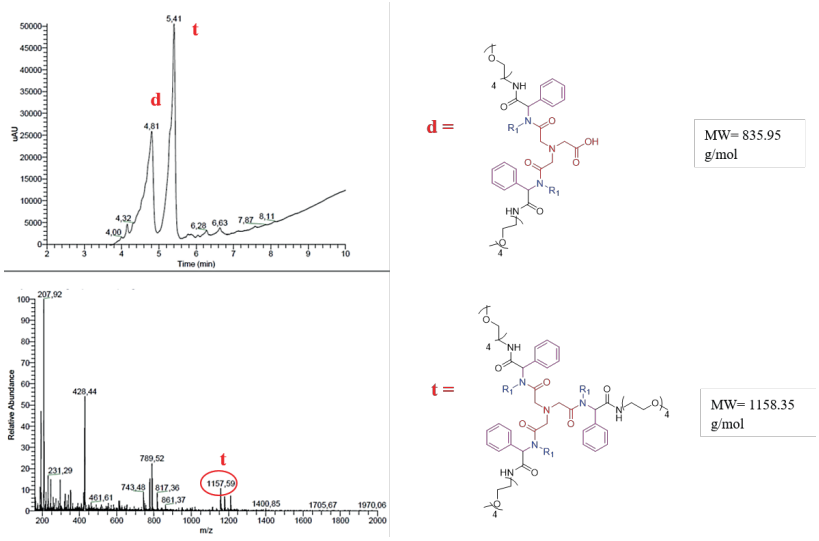


Figure S3.3 Chromatogram and corresponding mass spectrum for **entry 5** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side.

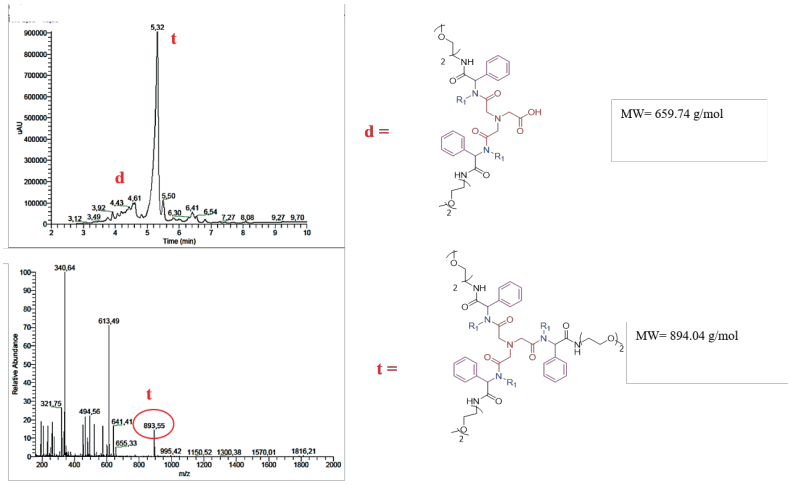


Figure S3.4 Chromatogram and corresponding mass spectrum for **entry 7** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side.

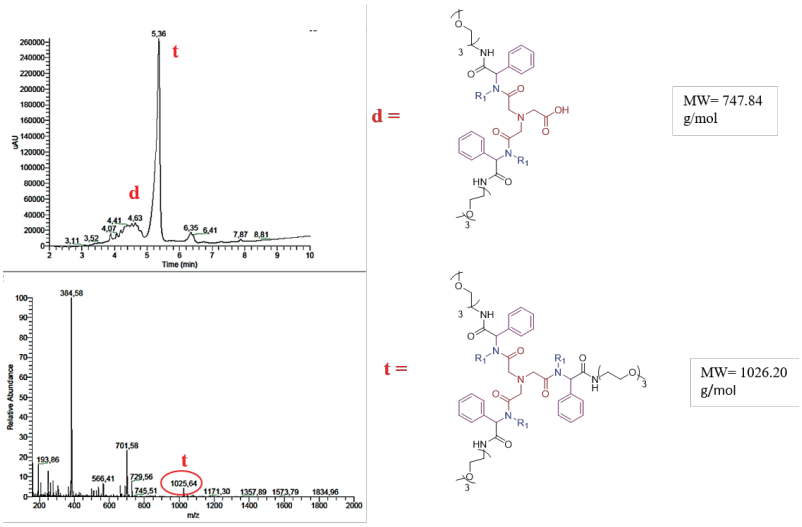


Figure S3.5 Chromatogram and corresponding mass spectrum for **entry 8** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side.

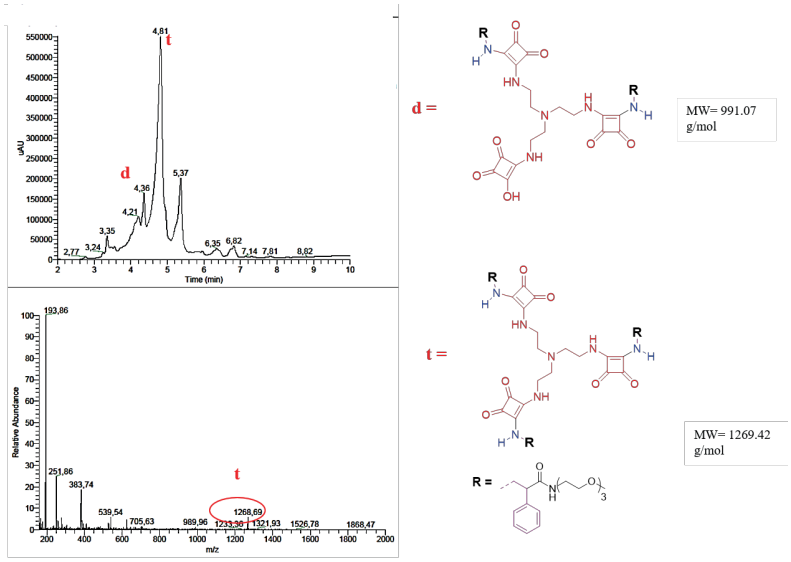


Figure S3.6 Chromatogram and corresponding mass spectrum for **entry 17** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side.

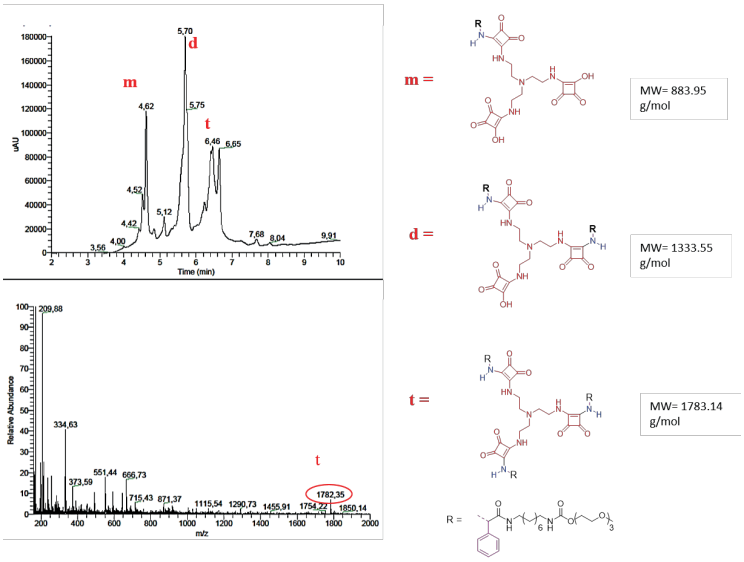


Figure S3.7 Chromatogram and corresponding mass spectrum for **entry 23** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

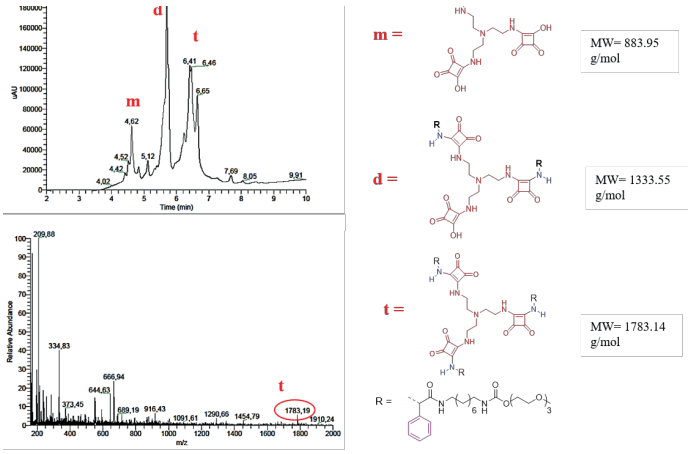


Figure S3.8 Chromatogram and corresponding mass spectrum for **entry 24** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

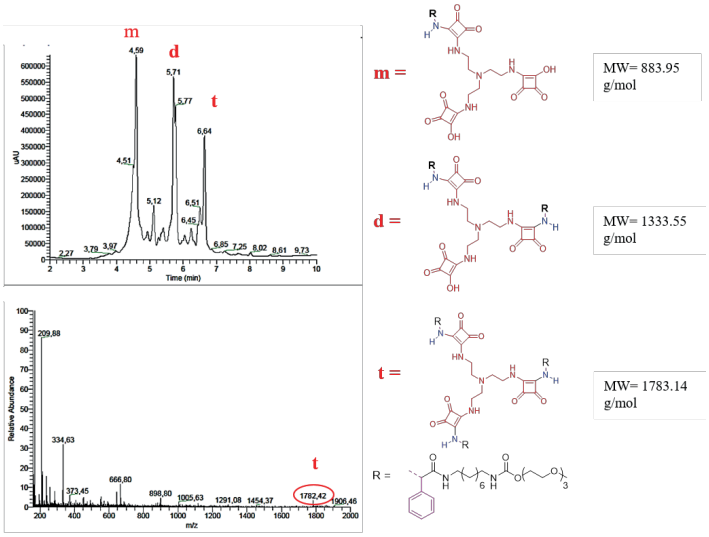


Figure S3.9 Chromatogram and corresponding mass spectrum for **entry 27** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

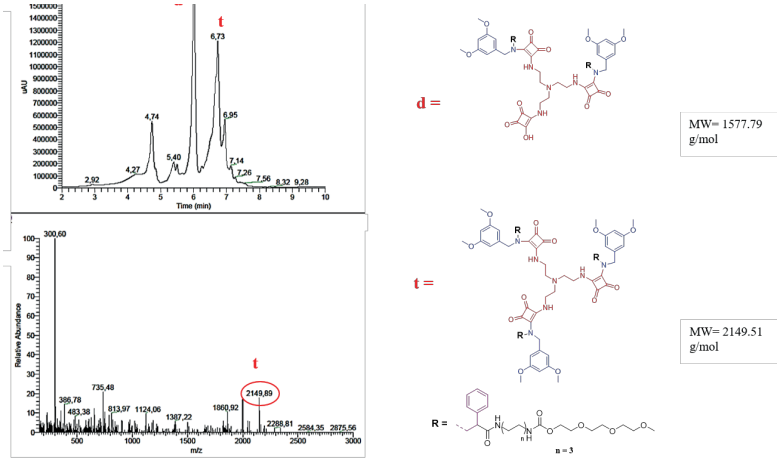


Figure S3.10 Chromatogram and corresponding mass spectrum for **entry 39** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side.

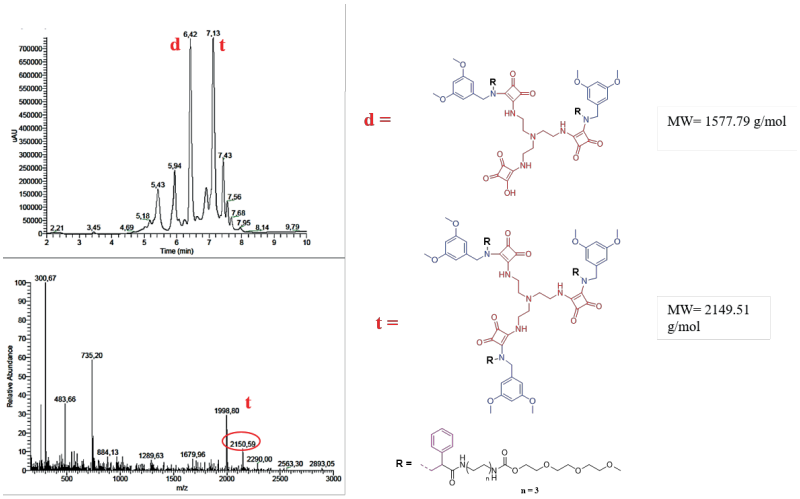


Figure S3.11 Chromatogram and corresponding mass spectrum for **entry 40** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

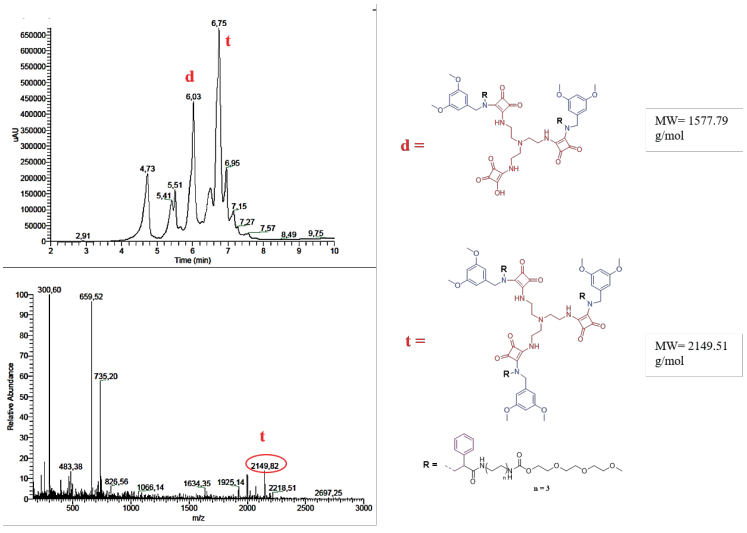


Figure S3.12 Chromatogram and corresponding mass spectrum for **entry 42** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

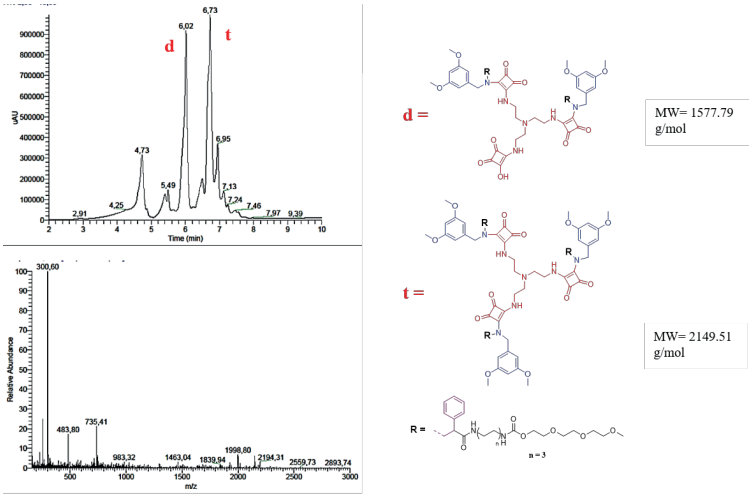


Figure S3.13 Chromatogram and corresponding mass spectrum for **entry 43** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

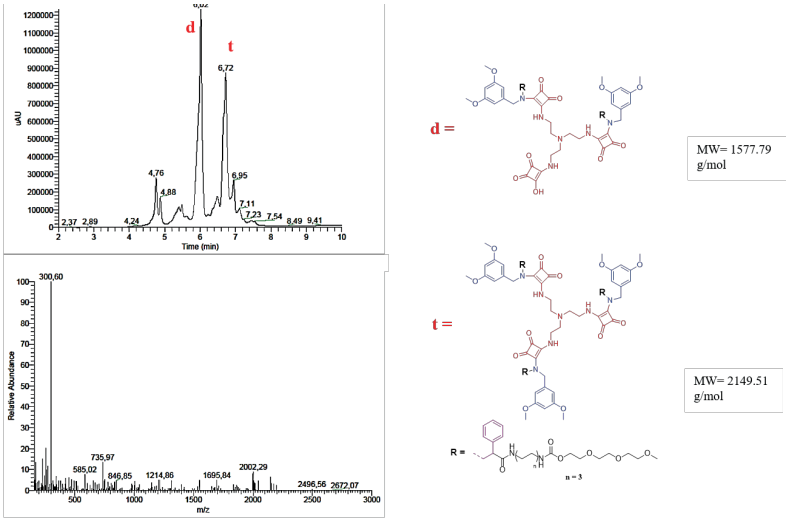


Figure S3.14 Chromatogram and corresponding mass spectrum for **entry 44** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

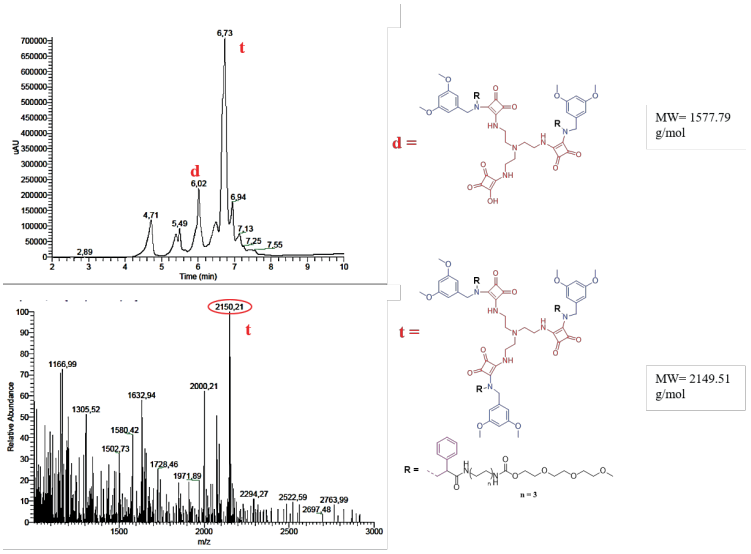


Figure S3.15 Chromatogram and corresponding mass spectrum for **entry 49** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side.

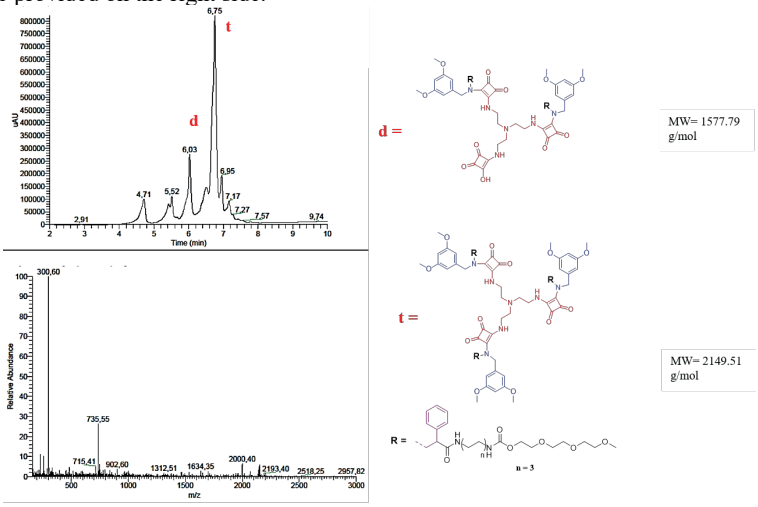


Figure S3.16 Chromatogram and corresponding mass spectrum for **entry 50** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side

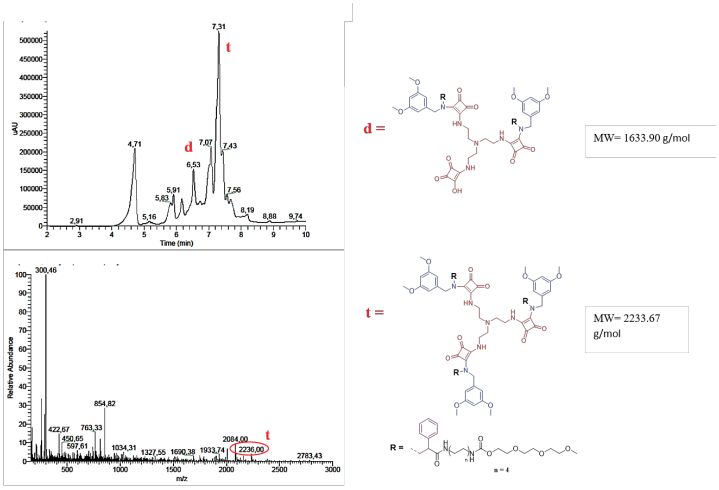


Figure S3.17 Chromatogram and corresponding mass spectrum for **entry 51** obtained by LC-MS. The relevant peaks are labelled and the chemical structure of the compounds are provided on the right side