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The use of deep cavity tetraformyl calix[4]arenes in the synthesis of static and dynamic macrocyclic libraries

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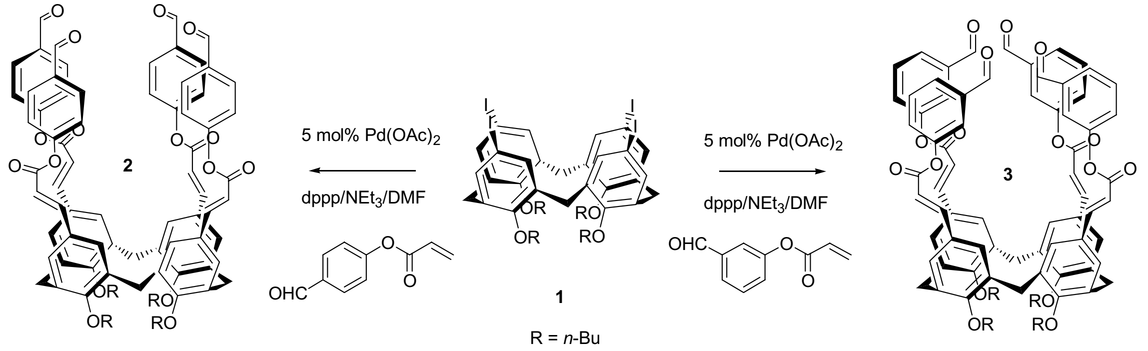
Abstract—This communication reports the first synthesis of a number of deep cavity tetraformyl calix[4]arene macrocycles and their use as key building blocks in the synthesis of a dynamic and the first static non-peptide macrocyclic library.

We have recently argued that in order to be successful in host–guest chemistry using synthetic macrocyclic receptors the principles of combinatorial chemistry should be applied. Since host–guest chemistry is guest-centred, a synthetic receptor binding to a given guest of choice with a high binding constant and high selectivity needs to be identified efficiently, necessitating the development of novel synthetic methodology for the synthesis of libraries of macrocycles.[1] These methodologies can either aim at static libraries[2] or at dynamic combinatorial libraries (DCL)[3] as proposed by Lehn[4,5] and Sanders and co-workers.[6–8] In contrast to Sanders' approach where a series of difunctional building blocks were allowed to form a DCL comprising macrocyclic receptors of various ring sizes along with open-chain receptors in the presence or absence of a guest, we present in this work a novel approach. In this approach we used a preorganised macrocycle, in our case a calix[4]arene, as an ideal platform for a macrocyclic library. The lipophilic cavity of the calix[4]arene provides a mildly attractive recess for similarly lipophilic components of a guest, without impinging on any self-assembly process of appropriately functionalised building blocks. The upper rim of the calix[4]arene should possess several functionalities suitable for further elaboration with a series of structurally diverse reagents to obtain static and dynamic libraries. Dynamic imine libraries of carcerands[9] and a series of static cyclopeptide macrocyclic libraries[10–12] have been reported.

To achieve the goal of developing a novel synthetic methodology for macrocyclic library synthesis we



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extended our recently developed Heck coupling methodology[13,14] to obtain deep cavity tetraformyl calix[4]arene acrylates **2**, **3** from tetraiodo compound **1** and the formylacrylate using palladium acetate and 1,3-bis-(diphenylphosphino)propane as a coligand. The coupling proceeded as expected to give the deep cavity calix[4]-arenes **2** and **3** in good yields as the all-*trans* isomers. All spectroscopic data were in agreement with the structure. The chemical shifts of the calix[4]arene methylene protons provided evidence for the deep cavity nature of the compounds as discussed previously.[13,15]

With the tetraformyl calix[4]arene acrylates[16] in hand we proceeded to synthesise a small library of tetra-imines using **2** and **3** along with a selection of 16 structurally diverse aromatic, aliphatic and functionalised amines **a**–**p**. We attempted the condensation of 10 selected amines **a**–**j** with 4-formyl derivative **2** to give tetra-imines **4aaaa**–**4jjjj** (each lower case letter signifies one imine linkage with a particular amine derived substituent) and the condensation of all 16 amines with 3-formyl derivative **3** to give tetra-imines **5aaaa**–**5pppp**. Imine condensation was carried out with a 2-fold excess of the amine in chloroform in the presence of molecular sieves. Within the static library 26 compounds were targeted and 21 could be isolated in analytically pure form and were fully characterised (see Table 1, entries 1–30). All the tetra-imines displayed the expected C_{4V} symmetry along with the expected spectroscopical data, supporting their structures. However, in the case of more electron-deficient amines such as **h** and **i** the reaction proceeded slowly even in the presence of small quantities of mineral or Lewis acids at elevated temperatures. Condensation reactions producing mixtures of mono-, di-, tri- and tetra-imines were characterised as mixtures by ^{1}H NMR and FAB mass spectrometry (see Table 1, entries 4, 10, 15, 24 and 30).

Reaction of the bases cytosine **j** and adenine **k** occurred to a limited extent of 2–4% and even this could only be achieved in a DMSO-d_6/CDCl$_3$ mixture (1:1) owing to their low solubility in CDCl$_3$. Similarly, the free amino acids L-alanine, L-serine, L-cysteine, L-tryptophan, L-histidine, L-valine and L-methionine failed to react despite

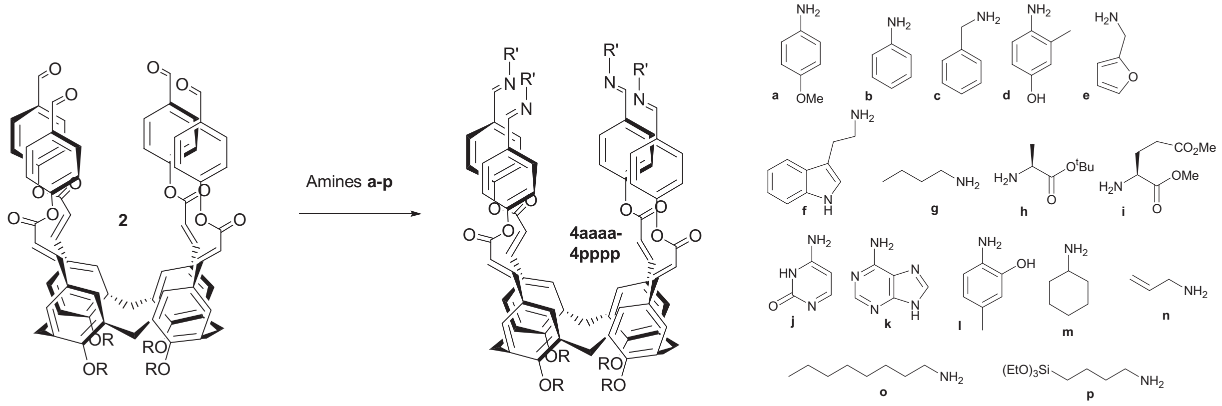


Table 1. Yields of tetra-imines **4aaaa**–**4jjjj** and **5aaaa**–**5pppp**

Entry		Major product[a]	Yield[b] (%)	Entry	Amines	Major product[a]	Yield[b] (%)
1	**a**	**4aaaa**	80	19	**e**	**5eeee**	83
2	**b**	**4bbbb**	78	20	**f**	**5ffff**	77
3	**c**	**4cccc**	88	21	**g**	**5gggg**	45
4	**d**	**4dddd**	Mixture[d]	22	**h**	**5hhhh**	49%
5	**e**	**4eeee**	54	23	**i**	**5iiii**	78
6	**f**	**4ffff**	86	24	**j**	**5jjjj**	Mixture[d]
7	**g**	**4gggg**	75	25	**k**	**5kkkk**	59
8	**h**	**4hhhh**	73	26	**l**	**5llll**	83
9	**i**	**4iiii**	74	27	**m**	**5mmmm**	39
10	**j**	**4jjjj**	Mixture[d]	28	**n**	**5nnnn**	67
11	Amino acids[c]		[c]	29	**o**	**5oooo**	84
12	**a**	**5aaaa**	75	30	**p**	**5pppp**	Mixture[d]
13	**b**	**5bbbb**	72	31	**acgf**	**4accg**	[e]
14	**c**	**5cccc**	68	32	**acgf**	**4aacf**	[g]
15	**d**	**5dddd**	Mixture[d]	33	**acgf**	**4ccg**	[f]

[a] As identified by ^{1}H NMR and FAB-MS.

[b] Isolated yield.

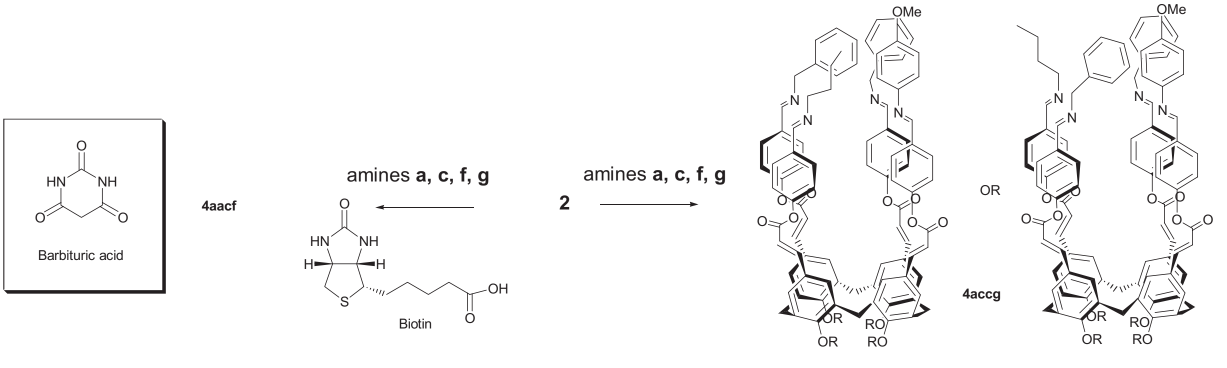
[c] No reaction occurred with L-alanine, L-serine, L-cysteine, L-tryptophan, L-histidine, L-valine and L-methionine.

[d] Mixture of isomers not separated.

[e] In the absence of external template.

[f] In the presence of biotin.

[g] In the presence of barbituric acid.



long reaction times according to the literature conditions.[17,18] As observed in non-macrocyclic cases[19,20] ester protected amino acids **h** and **i** showed an increased degree of reactivity and successfully yielded the required tetra-imines.[21]

Generally the reaction times of amines **a**–**p** loosely reflect (Table 1) their relative nucleophilicity. Within the static library, 26 compounds were targeted and 21 could be isolated in analytically pure form.

After the successful synthesis of a static library we turned our attention to a dynamic library based on the imine condensation reaction of tetraformyl compounds **2** and **3**. Imine condensation is a reversible reaction therefore allowing the exploitation of thermodynamic control in a highly modular approach. In a dynamic combinatorial library the potential number of unique calix[4]arene compounds possible when **2** or **3** are reacted with four different amines could comprise 146 different imines in the cone conformation (including mono-, di-, tri- and tetra-imines, regioisomers and possible stereoisomers). The inclusion of an additional amine adds another 105 possible permutations of imine reaction products to the dynamic library, clearly illustrating the immense diversity that can be achieved with our approach. The possibility of exerting thermodynamic control via a guest and the subsequent predominance of one (or significantly fewer than 146) compounds would certainly illustrate the potential value of the method described.

A representative example of this thermodynamic preference was given by LSIMS–MS analysis of the products, when **2** was mixed with stoichiometric amounts of amines **a**, **c**, **f** and **g**. After 12 h reaction time a statistical mixture of at least 30 imines (as judged by the intensity of the molecular ions in the LSIMS MS) was observed.[22] After a prolonged reaction time of 48 h there was strong evidence for equilibration under thermodynamic control as illustrated by the predominance of a heterocondensation product **4accg** (*m*/*z* 1684) with smaller amounts of **4aacc**, **4cccf** and **4aaaf** as judged by the relative intensities of the molecular ions in the LSIMS-MS. Longer reaction times did not change the composition of the DCL significantly. It can be assumed that one of the amines acts as a templating guest to induce the formation of the four most stable tetra-imines.

As a control experiment we added two non-amine templates (barbituric acid and biotin) to the dynamic library described above. Again LSIMS-MS allowed us to identify the major components of the library after 48 h of equilibration. The major product when barbituric acid was present was **4aacf**, which was not present in the above mixture. In the case of biotin the major reaction product was tris-imine **4ccg**.[23] The ^{1}H NMR spectra of the dynamic library support the formation of a major tetra-imine **4aacf** and tris-imine **4ccg**, respectively.[21] Additional evidence for binding of the guest template to a component of the dynamic library comes from diffusion NMR experiments,[14,24] indicating a reduced diffusion coefficient of barbituric acid and biotin benzyl ammonium salt in the presence of the dynamic library as opposed to the templates in the absence of the dynamic library. These experiments clearly indicated that when alternative guest templates were introduced to the dynamic library the equilibrium mixture shifted considerably towards a thermodynamically more stable host–guest system and result in molecular amplification of individual DCL members. Current work is focussing on the isolation and full characterisation of the novel macrocyclic receptors.

In conclusion, we have demonstrated that deep cavity tetraformyl calix[4]arenes are ideal scaffolds for the synthesis of the first static macrocyclic library and can be used successfully to create a dynamic combinatorial library. The synthetic methodology developed will allow us to exploit the libraries in supramolecular chemistry.

Acknowledgements

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16. (a) Synthesis of **2**: Triethylamine (0.335 ml, 0.157 g, 1.56 mmol) and 4-acryloylbenzaldehyde (0.276 g, 1.56 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene 25,26,27,28 tetra-*n*-butylether (0.3 g, 0.26 mmol) **1** in DMF (20 ml). After 10 min vigorous stirring at 25 °C palladium acetate (0.006 g, 0.026 mmol) and bis-diphenylphosphinopropane (0.011 g, 0.026 mmol) were added and the mixture heated to 100 °C and stirred for 48 h. After addition of (50 ml) diethylether the mixture was washed with HCl (3 × 20 ml 3 M HCl). The organic extract was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was further dried in a desiccator (SiO_2) under reduced pressure for 12 h. Purification via column chromatography (SiO_2, DCM) gave the calix[4]arene **2** (0.101 g, 32%) as cream shards mp 103–105 °C; ν_{max} (Nujol)/cm^{-1} 1748 (C=O (ester)), 1710 (C=O), 1615 (C=C); δ_H (270 MHz; $CDCl_3$) 9.99 (4H, s, CHO), 7.79 (8H, d, *J* 8.6, Ar-H (benzaldehyde)), 7.62 (4H, d, *J* 15.9, Ar-CH=), 7.28 (8H, d, *J* 8.6, Ar-H (benzenaldehyde)), 6.93 (8H, s, Ar-H), 6.37 (4H, d, *J* 15.9, Ar-CH=C*H*–C=O), 4.50 (4H, d, *J* 13.2, $\mathrm{C}\mathit{H}_\mathrm{A}\mathrm{H}_\mathrm{B}\mathrm{Ar}$), 3.97 (8H, t, *J* 6.4, CH_2O), 3.19 (4H, d, *J* 13.2, $\mathrm{CH}_\mathrm{A}\mathit{H}_\mathrm{B}\mathrm{Ar}$), 1.90 (8H, m, $\mathrm{C}\mathit{H}_2\mathrm{CH_2O}$), 1.50–1.35 (8H, m, $\mathrm{OCHCH_2C}\mathit{H}_2$), 1.00 (12H, t, *J* 8.3, $\mathrm{C}\mathit{H}_3\mathrm{CH_2}$); δ_c ($CDCl_3$) 191.5, 165.4, 156.1, 147.2, 142.3, 136.0, 131.7, 131.3, 129.7, 128.8, 123.1, 114.8, 75.6, 32.5, 31.2, 19.7, 14.3; *m*/*z* (EI) 1345 [M+]. Found: C, 68.97; H, 5.92. $C_{84}H_{80}O_{16}\cdot 6H_2O$ requires C, 69.41; H, 6.38; (b) Synthesis of **3**: Triethylamine (0.650 ml, 0.320 g, 3.12 mmol) and 3-acryloylbenzaldehyde (0.540 g, 3.12 mmol) were added to a stirred solution of 5,11,17,23-tetraiodocalixarene 25,26,27,28 tetra-*n*-butylether (0.6 g, 0.510 mmol) **1** in DMF (20 ml). After 10 min vigorous stirring at 25 °C palladium acetate (0.0120 g, 0.052 mmol) and bis-diphenylphosphinopropane (0.022 g, 0.052 mmol) were added and the mixture heated to 100 °C and stirred for 36 h. After addition of (50 ml) diethylether the mixture was washed with HCl (3 × 20 ml 3 M HCl). The organic extract was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was further dried in a desiccator (SiO_2) under reduced pressure for 12 h. Purification via column chromatography (SiO_2, DCM) gave the calix[4]arene **3** (0.429 g,68%) as cream shards; mp 98–104 °C; ν_{max} (Nujol)/cm^{-1} 1730 (C=O), 1720 (C=O), 1630 (C=C); δ_H (300 MHz, $CDCl_3$) 9.81 (4H, s, CHO), 7.76 (4H, d, *J* 6.9, Ar-H), 7.61 (4H, s, Ar-H), 7.78–7.75 (4H, m, Ar-CH=), 7.41–7.35 (8H, m, Ar-H), 6.93 (8H, s, Ar-H), 6.34 (4H, d, *J* 15.2, CH–C=O), 4.51 (4H, d, *J* 14.0, $\mathrm{C}\mathit{H}_\mathrm{A}\mathrm{H}_\mathrm{B}\mathrm{Ar}$), 3.99 (8H, q, *J* 6.9, $\mathrm{OC}\mathit{H}_2\mathrm{CH_2}$), 3.26 (4H, d, *J* 14.0, $\mathrm{CH}_\mathrm{A}\mathit{H}_\mathrm{B}\mathrm{Ar}$), 1.91–1.90 (8H, m, $\mathrm{C}\mathit{H}_2\mathrm{CH_2O}$), 1.48–1.41 (8H, m, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.00 (12H, t, *J* 8.3, $\mathrm{C}\mathit{H}_3\mathrm{CH_2}$); δ_c ($CDCl_3$) 191.2, 165.4, 151.4, 147.3, 137.7, 135.6, 129.9, 129.9, 128.7, 128.5, 128.1, 126.6, 123.3, 114.6, 75.6, 32.5, 31.3, 19.5, 14.2; *m*/*z* (LSIMS) 1368 [M+Na]; Found: C, 69.29; H, 5.92. $C_{84}H_{80}O_{16}6H_2O$ requires C, 69.41; H, 6.38.
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21. Analytical data data of representative imine **4eeee**: pale brown powder; mp 74–79 °C; ν_{max} (Nujol)/cm^{-1} 1732 (C=O), 1634 (C=N), 1602 (C=C); δ_H (300 MHz; $CDCl_3$) 8.28 (4H, s, CH=N), 7.69 (8H, d, *J* 8.5, *H*CCCH=N), 7.51 (4H, d, *J* 15.5, Ar–CH=), 7.34 (4H, s, Ar-H (furfuryl), 6.90 (8H, s, Ar-H), 6.78 (8H, d, *J* 8.5, *H*CCO), 6.34–6.30 (8H, m, CH-C=O, Ar-H (furfurylamine)), 6.12 (4H, s, Ar-H (furfurylamine)), 4.76 (8H, s, CH_2N), 4.50 (4H, d, *J* 13.9, $\mathrm{C}\mathit{H}_\mathrm{A}\mathrm{H}_\mathrm{B}\mathrm{Ar}$), 4.19 (8H, q, *J* 6.3, $\mathrm{OC}\mathit{H}_2\mathrm{CH_2}$), 3.23 (4H, d, *J* 13.85, $\mathrm{CH}_\mathrm{A}\mathit{H}_\mathrm{B}\mathrm{Ar}$), 1.91–1.88 (8H, m, $\mathrm{C}\mathit{H}_2\mathrm{CH_2O}$), 1.50–1.35 (8H, m, $\mathrm{OCH_2CH_2C}\mathit{H}_2$), 1.00 (12H, t, *J* 8.3, $\mathrm{C}\mathit{H}_3\mathrm{CH_2}$); δ_C ($CDCl_3$) 165.1, 160.3, 160.1, 152.1, 146.3, 135.8, 134.9, 133.1, 133.0, 128.9, 128.1, 127.0, 122.0, 121.5, 121.2, 118.9, 118.6, 110.7, 74.7, 61.2, 31.7, 30.4, 18.7, 13.9; *m*/*z* (LSIMS) 1662 [M+]; Found C, 68.23; H, 6.11; N, 3.10; $C_{104}H_{100}O_{16}N_4$ 1.5 $CHCl_3$ requires C, 68.83; H, 5.56; N 3.04.
22. FAB-MS spectra of representative equimolar mixtures of tetra-imines revealed differences of relative intensities of the molecular ions within 20%, indicating that LSIMS-MS is in this case a valid technique for the analysis of structurally closely related compounds of comparable molecular weight. It is furthermore worth noting that the library components could not be sufficiently resolved by HPLC. For the validity of FAB-MS quantification of compounds in mixtures see also: Manzi, A. E.; Dell, A.; Azadi, P.; Varki, A. *J. Biol. Chem.* **1990**, *265*, 8094.
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