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A new binding motif in molecular clips: 1-D polymeric self-inclusion in a phenol complex of a bis(methoxyphenyl)glycoluril

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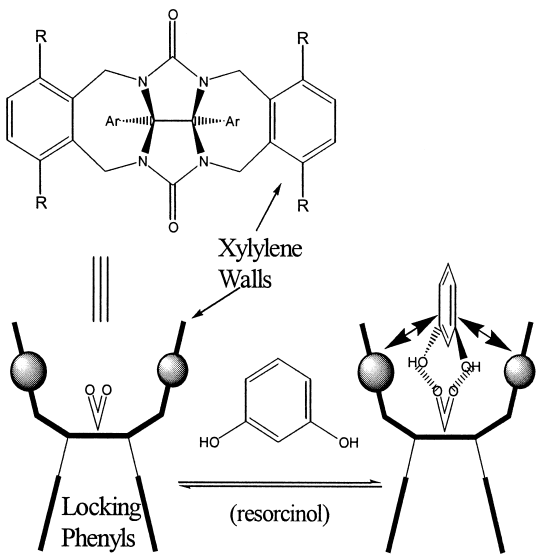
Dedicated to Professor Rory More O'Ferrall in his Emeritus Year

Abstract—Nolte's bis(*o*-xylylenyl)diphenylglycoluril molecular clips, in which the phenyls act as conformational 'locks' of the receptor site, have been modified with *p*-methoxy substituents on the phenyls. While this change does not have a major effect on the complexation of guests such as resorcinol (*m*-dihydroxybenzene) in chloroform solution, it allows for new binding geometries in the solid state. The crystal structure of new host 1,6:3,4-bis(1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)-imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (**11**) complexed with 4-phenylphenol (4-PP) has been determined as its toluene solvate [(**11**):2(4-PP):0.5(C_7H_8)]. Molecules of **11** aggregate in 1-D chains through polymeric self-inclusion via C–H···π(aromatic) interactions: 2-D sheets form via aryl stacking of the 1-D chains and the 3-D structure consists of alternating sheets of **11** in between which sheets of (4-PP):0.5(C_7H_8) reside.

1. Introduction

Molecular recognition continues to be of major interest in the fields of host–guest chemistry and biomimetic chemistry.[1] Depending upon the need for selectivity in the recognition process, several types of interactions can play a role. In aqueous solution, the hydrophobic effect is often the main driving force for host–guest complex formation.[2] The selectivity of binding can be improved if additional interactions are involved, such as hydrogen bonding, electrostatic interactions, van der Waals forces, aryl stacking interactions[3] and metal-to-ligand interactions. The approach of using a combination of interactions is particularly important for receptors in organic solvents, because here the hydrophobic effect is lacking. Rebek[4] and Nolte,[5] amongst others, have used this approach to develop host systems that can bind guests based on hydrogen bonding and aryl stacking.

Nolte's bis(*o*-xylylenyl)diphenylglycoluril molecular clip has a cavity which is selective—in terms of shape and binding functions—for resorcinol (1,3-dihydroxybenzene), complexing it via two hydrogen bonds and two aryl stacking interactions in orthogonal dimensions (see Scheme 1).[5] The



Scheme 1.

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phenyl substituents act as conformational 'locks', preventing the xylylene 'walls' from populating non-convergent conformations. They have also been able to control the self-assembly of derivatives of the glycoluril building block in such a manner that 3-D architectures of well-defined shape and dimension are formed: when long alkyl chains were attached to the phenyl substituents, interesting self-assembled architectures resulted.[6] The molecules adopt a bilayer structure through a mutual cavity-filling process (dimerisation) which, when combined with aryl stacking interactions, generates malleable crystalline thin films. Similarly, placing pyridine on the locking phenyls gives water-soluble clips that form well-defined nanoscale aggregates.[7] In the case of a naphthalene-walled clip, the complexation-induced NMR shifts observed indicated that two modes of self-association occurred, a 'head-to-head' dimerisation and a 'head-to-tail' one in which the pyridyl groups of one clip are docked in the cavities of a neighbour.[7]

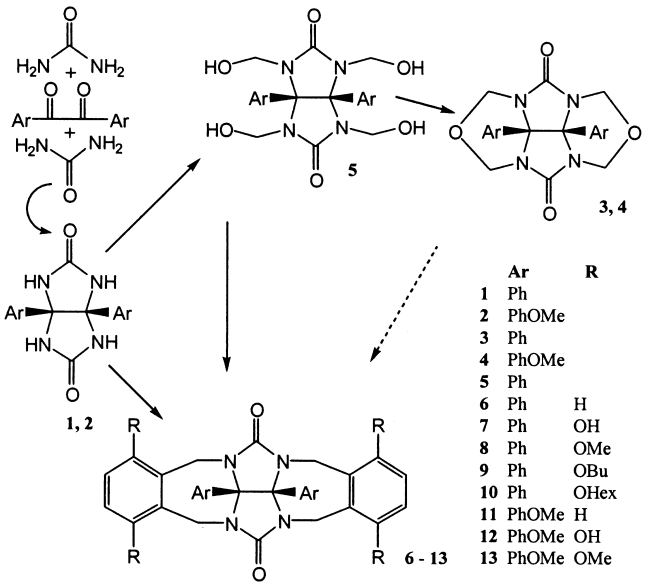
One of the goals of our research has been the design and synthesis of new types of cleft-shaped host molecules that can be functionalised with catalytically active components. Towards this goal, we have designed and studied receptor systems based on diphenylglycoluril (DPG) that can bind dihydroxybenzenes.[8] To examine the binding forces in our host–guest complexes more precisely, we have synthesised a series of new receptor molecules containing *p*-methoxy groups on one or both phenyls of the DPG building block. During this work, we carried out a series of co-crystallisation reactions between the methoxy-clips obtained and various mono- and di-hydroxy benzenes. The crystal structure of one such co-crystallisation is presented here. The new locking group appears to have little adverse effect on binding resorcinol in solution but opens up new intermolecular possibilities in the solid state.

2. Results and discussion

The coupling of DPG **1** (Ar=Ph, prepared from benzil and two ureas), its bis-ether **3** (Ar=Ph) and other tetramethylene derivatives of DPG with aromatic moieties belongs to a type of reaction known as amidoalkylation, or indeed in this case a ureidoalkylation (see Scheme 2). Two literature procedures have been employed in this communication.[5,8] By using these generalised methods the molecular clips **6** (Ar=Ph; R=H), **7** (Ar=Ph; R=OH), and **8** (Ar=Ph; R=OMe), were synthesised in good yields. These clips can then be used as starting points for further derivatisation of the clip structure.

From the tetrahydroxy-clip **7**, butyl- and hexyl-ethers (**9**, **10**; Ar=Ph; R=OBu, OHex) can also be formed by base-catalysed alkylation with the appropriate alkyl bromide.

Another less time-consuming procedure has previously been reported for the synthesis of the bis(xylenyl) clip **6**.[8a] This method cuts out the need to form the tetramethylene derivatives. The synthesis involves heating **1** (DPG) and potassium hydroxide in DMSO with α,α′-dibromo-*o*-xylene for 1–4 h. When the reaction is complete, it is simply added to water and the required product precipitates out in, typically, 80% yield. This reaction has three main



Scheme 2.

advantages: (i) it saves synthesising the tetramethylene derivatives, (ii) a much purer product is obtained more quickly, and (iii) because the tetramethylene compounds will not readily form with all glycolurils, it provides a synthesis for otherwise inaccessible clips. The main limitation, however, is that it is less convenient for clip receptors with substituted xylylene walls, since substituted dibromo-*o*-xylene compounds are not easily accessible.

4,4′-Dimethoxybenzil is commercially available, and we considered it as a potentially interesting alternative to benzil in the synthesis of clips. Besides observing the effects that a *para*-methoxy group would have on the binding properties of a molecular clip, it also opens up a variety of methods for further structural elaboration of the locking groups. Despite its obvious possibilities, it appears to have been bypassed in the literature as a candidate for use as the locking group: the focus elsewhere has been on bipyridyl, halide, and acid functionalities.[6,7] The ring-activating *p*-methoxy group on the locking phenyl could allow the possibility of electrophilic aromatic substitution *ortho*- to it. Alternatively, the methoxy group could be demethylated to give the more reactive hydroxyl for the purpose of immobilising/linking a molecular clip to a solid phase, or for producing phenolate salts to facilitate aqueous solubility, or for binding transition metal cations.

The glycoluril **2** (Ar=Ph-*p*-OMe) which was produced from 4,4′-dimethoxybenzil was synthesised using the same procedure as for **1** (DPG).[8] The substituted benzil was refluxed with urea in trifluoroacetic acid (TFA) and toluene, producing a precipitate. Using this method 4,4′-bis(methoxyphenyl)glycoluril **2** was isolated in 81% yield. The next step with **2** (as for **1**) was to form the tetramethylene derivatives. Proceeding as for **1**, 4,4′-bis(methoxyphenyl)glycoluril **2** and paraformaldehyde were dissolved in DMSO by the careful addition of base and stirred overnight, then following adjustment to pH 1 the tetramethylol intermediate **5** was heated to reflux to form the 4,4′-bis(methoxyphenyl)bisether **4** (Ar=Ph-*p*-OMe). The tetrakis(hydroxymethyl) derivative **5** could not be isolated: any attempts to

isolate this compound from DMSO failed. The bis(xylenyl) clip **11** (Ar=Ph-*p*-OMe; R=H) was formed by reacting **2** with excess dibromo-*o*-xylene under basic conditions, then precipitating the product by adding to water. Reactions of **2** with hydroquinone and 1,4-dimethoxybenzene, respectively, were also carried out to form the clips **12** and **13** (Ar=Ph-*p*-OMe; R=OH, OMe) in 97 and 77% yields.

Clip molecules **6**–**13** contain a cleft with a cavity size of approximately 6.35 Å [6.347(3) Å centroid-to-centroid distance for **11**, 4.167(2) Å for the centroids on the opposite or R group side] which has been shown to be ideal for the binding of aromatic guests.[5a,9] From these studies it is known that the main binding interactions in the formation of complexes of dihydroxybenzenes with molecular clip **6** in chloroform are: (a) hydrogen bonding between the OH groups of the guest and the urea carbonyl functions of the host, and (b) aryl stacking interactions between the aromatic surfaces of the guest and host. While independent research by our[8a,b] and Nolte's[5,9] group has involved the replacement of one or both carbonyl O atoms by S atoms, the design of clip molecules possessing zero, one or two cavity walls and the design of clips containing larger aromatic side-walls has been achieved by Nolte.[5,8,9] Furthermore, when clips with extended walls were built, i.e. naphthalene walls instead of phenyl walls, weak binding was found.[9] This weak binding has been ascribed to a repulsive aryl-stacking interaction between the aromatic guest and the naphthalene side walls. These studies have been carried out on a wide variety of clip molecules, all of which contain unsubstituted phenyl groups as the locking unit.

We have synthesised several molecular clips containing two 4-methoxyphenyl groups as the locking units (see Scheme 2). Complexation of a series of dihydroxybenzene guests with the molecular clips **6**–**13** were investigated by ^{1}H NMR titrations in $CDCl_3$. Table 1 shows the binding strength of the host–guest complex formed. On examination of this data, the two dihydroxy-substituted aromatics resorcinol and catechol show a remarkable difference in K_c, e.g. 3200 M^{-1} for resorcinol, and 95 M^{-1} for catechol when complexed with **13** compared to 200 M^{-1} for resorcinol, and 70 M^{-1} for catechol when complexed with **6**. On comparison with the values obtained for **8**, which has the methoxy groups only present on the walls, we observe quite similar values to **13**, that is 2400 M^{-1} for resorcinol, and 90 M^{-1} for catechol. This suggests that the perturbation of placing methoxy substituents on the locking phenyls has a minimal effect on the binding of resorcinol and catechol in solution. This point is further reinforced when a comparison of the binding of both **6** and **11** with resorcinol shows similar values (200 M^{-1} for **6** and 100 M^{-1} for **11**).

Table 1. The complexation constants, K_c/M^{-1}, of the molecular clips **6**–**13** with resorcinol (1,3-hydroxybenzene), catechol (1,2-hydroxybenzene), and orcinol (5-methyl-1,3-dihydroxybenzene) guests, measured at ~20 °C in $CDCl_3$, by titration of host (typically ~1 mM) with guest

Host	Resorcinol	Catechol	Orcinol
6	200 (±15)	70 (±10)	170 (±15)
7	370 (±40)	45 (±10)	–
8	2400 (±200)	90 (±15)	2300 (±200)
9	5100 (±400)	100 (±15)	4600 (±300)
10	4400 (±300)	60 (±10)	–
11	100 (±15)	–	–
12	350 (±40)	–	–
13	3200 (±250)	95 (±15)	2500 (±200)

Table 1 shows that binding decreased slightly using orcinol (5-methylresorcinol) as guest, as the electron-releasing methyl group decreases the acidity of the OH groups, thus weakening the hydrogen bonding, an effect seen by Nolte with other electron-releasing substituents.[9a,10]

The Table also shows the complexation results for a number of wall-substituted molecular clip receptors with resorcinol. On examination of this data we see an increase in K_c on going from H to OH to OCH_3 substituents in the aromatic walls of the hosts. The aromatic ring of the guest molecule can be considered to be π-rich overall. The position (e.g., *o*-, *m*-, *p*-) of the substituents on the aromatic ring alters the 'π-richness' of the individual atoms on that ring. This can leave some atoms more electron rich than others. The hosts increase in π-richness as we go from H to OH, i.e. **12** is more π-rich than **11**, and the further significant increase in complexation constant going from OH to OCH_3 substituents (i.e. from **12** to **13**) indicates a favourable 'cavity extension' effect. These trends are also seen in the diphenylglycoluril H/OH/OCH_3 series, **6**, **7**, and **8**, reaching a maximum (for the receptors we have prepared) at the tetrabutyloxy derivative, **9**. The lower K_c for tetrahexyloxy clip **10** may be entropic in nature: its melting point is also significantly lower than that of **9**.

The presence of oxy substituents on the cavity walls of some of the receptors (i.e., hydroxy in **7**, and alkoxy in **8**, **9**, and **10**) raises the possibility of: (i) alternative hydrogen bonding modes to dihydroxybenzene guests, with (ii) additional alternatives introduced for the new receptors with methoxies on the 'locking' phenyl moieties (i.e., **11**, **12**, and **13**). However, we did not observe any sign of an incursion of such binding modes in solution in our titration studies, nor—to our knowledge—has Nolte. Specifically, if a significant fraction of the host–guest complex in such a case were to involve a guest OH hydrogen bonding to a host oxygen other than the carbonyls, it is likely to be observed as an anomalous complexation-induced chemical shift change. For the example of hexamethoxy clip **13** and resorcinol, the wall or 'locking phenyl' methoxy singlet might be affected, and its associated aromatic hydrogens, and the induced changes in the aromatic hydrogens of resorcinol attendant on insertion into the cleft would be absent or attenuated. No such anomalous behaviour was observed.

While in theory chloroform's poor donor ability and its inability to act as an acceptor favour all host–guest hydrogen-bonding motifs by default, we believe there are sound theoretical reasons why alternative geometries would be insignificant in our case. Specifically, resorcinol and orcinol (and to a lesser extent catechol) have their hydroxyls optimally placed for the 5.8 Å spacing[8a] of the urea carbonyls of the host, an arrangement which also leaves the guest's aromatic ring sandwiched between the aromatic walls. Alternative hydrogen-bonding modes are unlikely to be as entropically favoured. Enthalpically, they would likely need two hydrogen bonds and two favourable aryl–stacking

interactions to compete. If an alkoxy oxygen accepts a hydrogen bond from resorcinol [alternative (i) above], the second OH cannot reach the opposite wall, and is not optimally placed for one of the carbonyls. An even less favourable arrangement pertains at the locking groups [alternative (ii)], where neither carbonyl can be employed. Ternary complexes—in which resorcinol hydrogen bonds to two separate clip molecules—should be insignificant at our concentrations.

A recent report[11] details measurements for self-association of 15 clips at high concentrations, including two in Table 1: **6** and **8**. The values reported (K_{dimer}=7 and 16 M^{-1}, respectively) suggest that dimerisation is a minor side reaction under our titration conditions. Dilution of 1 mM solutions of representative clips in Table 1 showed negligible changes in chemical shift.

Given the strong binding in many of these cases, we decided to look at the binding of monohydroxybenzenes, to see if reasonable complexation could be attained while sacrificing one host–guest hydrogen bond. In particular, we looked at 4-phenylphenol (4-PP), with the prototypical dimethoxy clip **11**. Attempts to carry out titration studies were thwarted by the poor solubility of this phenol in chloroform (a problem which also occurs for phenol itself). The complexation between two equivalents of 4-PP and one equivalent of the clip **11** was tried in toluene, heated to reflux temperature, since 4-phenylphenol has higher solubility in this solvent. A crystalline material was obtained from the reaction and the X-ray crystal structure determined.[12,13]

The structure of (**11**):2(4-PP):0.5(toluene) (Fig. 1) confirms the 1:2 nature of the interaction between **11** and 4-phenylphenol, with toluene present as a (hemi)solvent of crystallisation. The hydroxyl of each phenol is hydrogen-bonded to a carbonyl oxygen of **11** [O–H···O distances and angles of 2.700(4) and 2.733(4) Å, and 169 and 165°, respectively], but neither 4-PP resides within the cleft/cavity. Instead, a methoxy group from the locking phenyl system of a neighbouring molecule is enclathrated there (see Figure 1b).[14–16] Interestingly, the two methoxy groups are observed as identical in $CDCl_3$ solution in both ^1H and ^{13}C NMR.

The crystal structure of (**11**):2(4-PP):0.5(toluene) can be rationalised as having molecules of **11** aggregate in 1-D chains along the *a*-axis, through polymeric self-inclusion processes via complementary methyl C–H···π(C_6H_4) and phenyl C–H···π(C_6H_4)/offset π···π stacking interactions,[14] (depicted in Figure 2, left): these 1-D chains pack and form 2-D sheets through further π···π stacking contacts while the overall 3-D structure consists of alternating 2-D sheets of **11** (Fig. 2, right) in between which 2-D sheets of the hydrogen-bonded guest/solvate 2(4-PP):0.5(C_7H_8) reside. The 2-D sheets are of course linked by the stronger O–H···O=C bonds.

The complementary self-inclusion process and encapsulation in the crystal structure of (**11**):2(4-PP):0.5(toluene) often arises in macrocyclic hosts e.g. calix[*n*]arenes.[14–18] These systems contain molecular cavities and the inclusion process typically arises when the stronger hydrogen bond donors and acceptors e.g. O–H···O pair off and molecular aggregation and crystal stability is enhanced by multiple weaker C–H···π(aromatic) interactions which ensue on formation of the 3-D crystal structure. In (**11**):2(4-PP):0.5(toluene), two strong C=O acceptors form hydrogen bonds with the two strong O–H (4-PP) donors. The remaining possible donor/acceptors facilitate the filling of the larger molecular cavity of **11** by the *para*-methoxyphenyl group of a symmetry-related molecule **11***: this in turn has its smaller *para*-methoxyphenyl cleft filled by the *o*-phenylene group of **11**. The 1-D chain builds up from these complementary head-to-tail interactions. The crystal structure then aggregates as described above.

In summary, the molecular recognition properties of glycoluril-based molecular clips have prompted many groups to broaden the range of study of these hosts. We have synthesised and studied molecular clips based on the 4,4′-bis(methoxyphenyl)glycoluril. We find an interesting aggregation occurring in the solid state when a monohydroxyaromatic is used as guest rather than the *meta*- or *ortho*-dihydroxyaromatics previously studied. We are currently investigating the solid-state interaction between

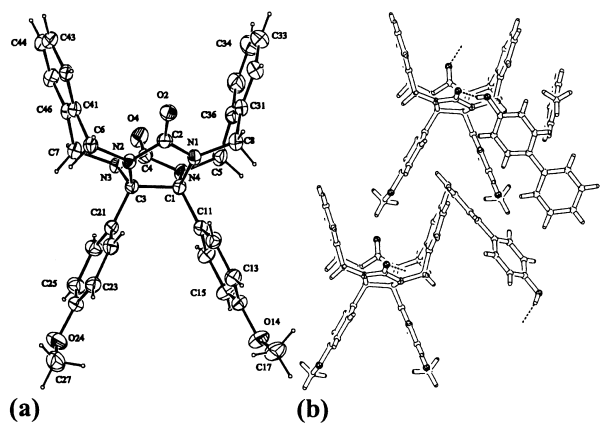


Figure 1. Crystal structure of (**11**):2(4-phenylphenol): (a) labeled structure of molecular clip (**11**) moiety; (b) highlight of clip/clip and clip/4-PP interactions (toluene hemi-solvent of crystallization omitted for clarity).

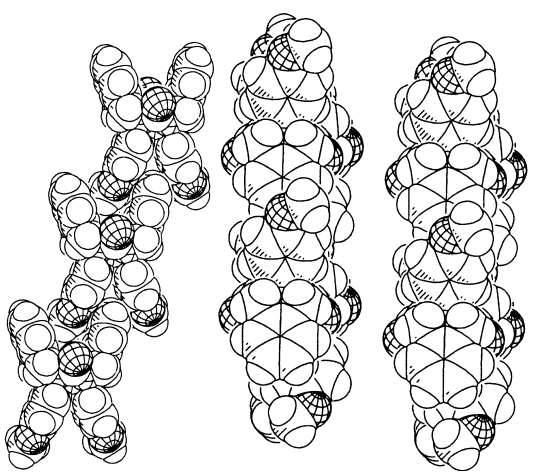


Figure 2. Side-on views of clip moieties in the co-crystal.

the prototype clip **6** and 4-phenylphenol, and also solution studies of the bis(dimethoxyphenyl) clips in toluene. In addition, the minimal effect that the remote methoxy groups have on binding guests in solution holds out considerable promise. Future demethylation of these receptors can provide free phenol functions to facilitate alkaline solubility, complexation of transition metal ions, or covalent attachment to solid-phase support.

3. Experimental

3.1. General

All syntheses were carried out under an inert nitrogen atmosphere. All solvents were distilled using standard procedures. All chemicals were commercial materials used without further purification. Compounds **1**, **3**, **5**, **6**, **7**, and **8** were prepared as described in the literature.[8a] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) with Me_4Si as internal standard using a JEOL JNM-LA300 FT NMR spectrometer, with resolutions of 0.18 Hz and 0.01 ppm, respectively. IR spectra (KBr disc) were measured on a Nicolet Impact 410 FT-IR. Melting points were >300 °C (except **10**). Elemental analyses were carried out at the Microanalytical Laboratory of University College, Dublin.

Table 2 below shows ^{1}H and ^{13}C NMR data for the new compounds, organized by atom type. All were white solids. Details of their syntheses, together with elemental analytical and other data, are also provided below.

3.1.1. 3a,6a-Bis(4-methoxyphenyl)-tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (2).

Urea (3.0 g, 50 mmol), 4,4′-dimethoxybenzil (6.76 g, 25 mmol), TFA (6 mL), and dried toluene (75 mL) were heated to reflux using a Dean and Stark apparatus for 4 h. After cooling, the reaction solution was kept at 0 °C overnight. The resulting precipitate was collected by filtration, washed with IMS (3×100 mL) and acetone (3×50 mL), and then dried to a constant weight under vacuum: yield 7.2 g (81%). IR/cm^{-1}: 3220 (NH), 1684 (C═O). $C_{18}H_{18}N_4O_4$ theory: C, 61.01; H, 5.12; N, 15.81. Found: C, 61.05; H, 5.15; N, 15.92.

3.1.2. 1,6:3,4,-Bis(2-oxapropylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (4).

4,4′-Bis(methoxyphenyl)glycoluril (**2**) (0.74 g, 2.1 mmol) and paraformaldehyde (0.33 g, 11 mmol monomer, 30% excess) were stirred in DMSO (6 mL) at ambient temperature. The reaction was adjusted to pH 9 with a 10% aqueous NaOH solution (dropwise, very slowly, until solution is just attained), and stirred at room temperature for 18 h. After this time, the clear solution was brought to pH 1 with conc. HCl and heated to reflux for 2 h. After cooling, the white precipitate that formed was collected by filtration, washed with water (2×100 mL) and ethanol (3×50 mL) and dried to a constant weight under vacuum: yield 0.90 g (99%). IR: 1717 (C═O). $C_{22}H_{22}N_4O_6$ theory: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.45; H, 5.10; N, 12.88.

3.1.3. 1,6:3,4-Bis(3,6-dibutyloxy-(9) and 1,6:3,4-bis(3,6-dihexyloxy-1,2-xylylene)tetrahydro-3a,6a-diphenylimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)dione (10).

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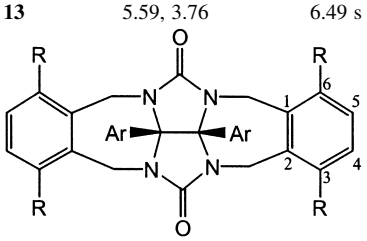
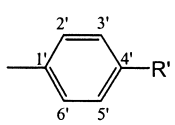
Table 2. ^{1}H (top) and ^{13}C (bottom) NMR data for **2**, **4**, **9**, **10**, **11**, **12**, and **13**: wall aryl ring numbered 1–6 and locking phenyl numbered 1′–6′, as per structure (centre)

#	H_a–C–H_b	$H_{3,6}/H_{4,5}$	$H_{2',6'}/H_{3',5'}/H_{4'}$	Me
2			6.97/6.64/–	3.62
4	5.65, 4.57		7.08/6.68/–	3.72
9	5.57, 3.87	6.65 s	7.04 (m, 10H)	
10	5.55, 3.89	6.65 s	7.04 (m, 10H)	
11	4.78, 4.19	7.25–7.08m	7.03/6.69/–	3.72
12	5.37, 3.58	6.55 s	6.92/6.77/–	3.65
13	5.59, 3.76	6.49 s	6.98/6.65/–	3.70



Ar =



#	CO	C_qN	H_aCH_b	$C_{1,2}/C_{3,6}/C_{4,5}$	$C_{1'}/C_{2',6'}/C_{3',5'}/C_{4'}$	Me
2	165.9	86.7			130.2/129.2/116.6 /161.6	57.5
4	160.2	79.5	71.9		124.5/129.2/114.1/158.5	55.3
9	157.9	85.1	37.0	135.1/151.3/114.0	128.6/128.2/127.9/127.1*	
10	158.0	85.1	37.1	134.6/150.7/113.5	128.3/128.2/128.1/128.0*	
11	159.9	85.3	45.3	136.9/129.4/127.7	125.6/129.5/114.1/157.9	55.3
12	159.0	84.5	36.5	129.2/146.9/115.1	125.0/128.0/113.9/156.8	55.1
13	160.1	84.5	36.7	128.0/151.5/113.9	126.2/129.5/112.6/157.5	55.9

(a) NMR in $CDCl_3$, at ~20 °C, except DMSO-d_6 for **2**, **12**. (b) ^{1}H coupling constants/Hz for CH_2=11.1, 15.8, 16.0, 15.6, 15.8, 16.0 (**4**, **9**–**13**); for *p*-MeOPh=8.6–8.8 (**2**, **4**, **11**, **12**, **13**). (c) Other NMR signals: NH of **2**=7.64 (exch. D_2O); butyl of **9**=3.95, 1.84, 1.60, 0.98; 69.9, 31.7, 19.3, 13.9; hexyl of **10**=3.81, 1.83, 1.50, 1.35, 1.34, 0.91; 70.3, 31.6, 29.6, 25.8, 22.6, 14.1; OH of **12** not seen; methyl (on aromatic wall) of **13**=3.80; 55.2. *CHs not individually assigned.

clip **7** (0.45 g, 0.80 mmol), 1-bromobutane (0.43 mL, 0.55 g, 4.0 mmol, 25% excess) in DMSO (20 mL) were dissolved at 110 °C. Anhydrous potassium carbonate (1.72 g, 12.5 mmol) was then added in one portion and heating continued for 48 h. The reaction was poured onto water (150 mL) and stirred for 20 min. After addition of Hyflo-Supercel (6 g) to the solution, it was filtered and washed thoroughly with water. Extraction with $CHCl_3$ (50 mL×3), followed by drying with $MgSO_4$ yielded 0.41 g **9** (65%). IR: 1674 (C═O). $C_{48}H_{58}N_4O_6$ theory: C, 73.26; H, 7.43; N, 7.12. Found: C, 73.67; H, 7.55; N, 7.24. Compound **10** was similarly prepared using 1-bromohexane. Yield: 1.17 g (73%); mp 260–265 °C. IR: 1657 (C═O). $C_{56}H_{74}N_4O_6$ theory: C, 74.80; H, 8.29; N, 6.23. Found: C, 75.08; H, 8.33; N, 6.19.

3.1.4. 1,6:3,4-Bis(1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxy-phenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (11). 4,4′-Bis(methoxyphenyl)glycoluril (**2**) (0.49 g, 1.4 mmol) and freshly ground potassium hydroxide (0.80 g, 14 mmol) in DMSO (10 mL) were heated to 120 °C with vigorous stirring for 20 min. α,α′-Dibromo-*o*-xylene (0.80 g, 3.0 mmol) was added in one portion and stirring was continued at this temperature for 2 h. On cooling, the reaction mixture was added to water (100 mL) and stirred for 30 min. The resulting precipitate was collected by filtration, washed with water (3×100 mL) and ether (3×50 mL), and reduced to dryness under vacuum to yield 0.50 g (65%). IR: 1690 (C═O). $C_{34}H_{30}N_4O_4$ theory: C, 73.10; H, 5.41; N, 10.03. Found: C, 72.89; H, 5.36; N, 9.93.

3.1.5. 1,6:3,4-Bis(3,6-dihydroxy-1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (12). 4,4′-Bis(methoxyphenyl)glycoluril bisether (**4**) (0.34 g, 0.78 mmol), *p*-toluenesulfonic acid monohydrate (0.60 g, 3.2 mmol) and 1,2-dichloroethane (7 mL) were placed in a 25 mL round-bottomed flask fitted with a Dean and Stark apparatus containing 4 Å molecular sieves, and heated to reflux with stirring for 10 min. Hydroquinone (0.33 g, 3.0 mmol) was added in one portion and the reaction was further refluxed for 2 h. A brown precipitate formed. On cooling, 1,2-dichloroethane (12 mL) was added. The resulting solid was collected by filtration, washed with water (2×50 mL), ethanol (2×50 mL), and ether (3×30 mL), and dried to constant weight under vacuum to yield 0.47 g (97%). IR: 3400 (OH), 1710 (C═O). $C_{34}H_{30}N_4O_8$ theory: C, 65.59; H, 4.86; N, 9.00. Found: C, 65.17; H, 4.71; N, 8.93.

3.1.6. 1,6:3,4-Bis(3,6-dimethoxy-1,2-xylylene)tetrahydro-3a,6a-bis(4-methoxyphenyl)imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (13). 4,4′-Bis(methoxyphenyl)glycoluril bis-ether (**4**) (0.219 g, 0.50 mmol), acetic anhydride (0.5 mL), and trifluoroacetic acid (0.5 mL) were heated with stirring to 95 °C for 30 min. 1,4-Dimethoxybenzene (0.15 g, 1.1 mmol) was added in one portion; stirring and heating were maintained for 1 h. On cooling, methanol (2 mL) was cautiously added, and the resulting precipitate was collected by filtration, washed with water (2×50 mL), and reduced to dryness under vacuum: yield 0.26 g (77%). IR: 1729 (C═O). $C_{38}H_{38}N_4O_8$ theory: C, 67.25; H, 5.64; N, 8.26. Found: C, 66.99; H, 5.61; N, 7.95.

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12. Crystallographic data: chemical formula $C_{61.5}H_{54}N_4O_6$, molecular weight 945.09 g mol^{-1}, triclinic, space group $P\bar{1}$ (No. 2), a=11.5618(16), b=14.1207(19), c=15.7993(19) Å, α=88.368(10), β=74.618(12), γ=86.119(12),

V=2481.2(6) Å^3, Z=2, T=296(2) K, density=1.265 g cm^{-3} (calc.), F(000)=998, μ=0.082 cm^{-1}, 8615 reflections in the range 2–25°, 8171 unique (4153 with $I>2\sigma I$), 670 parameters, R-factor is 0.066, wR_2=0.136 (based on F^2 for reflections with $I>2\sigma I$), Gof=1.02, density range in final Δ-map is −0.26 to +0.29 e A^{-3}, (solved in SHELXL97, refined in SHELXL97).

13. The crystallographic data for **11**:2($C_{12}H_{10}O$):0.5(C_7H_8) have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 190122. Copies may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).
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