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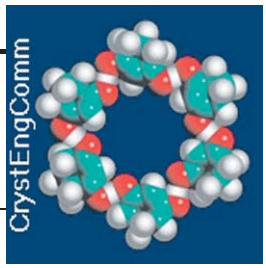

Chromogenic guest-responsive host compounds which allow rapid guest screening

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Paper

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Azo host compounds undergo rapid and clearly visible colour changes from yellow to bright orange/red on complexation with guest molecules, while no colour change is noted in the absence of complexation. This provides a rapid screening method for potential guest compounds as the first step towards the development of guest specific host compounds for use in sensors relying only on a simple, visible colour change readout mechanism.

Introduction

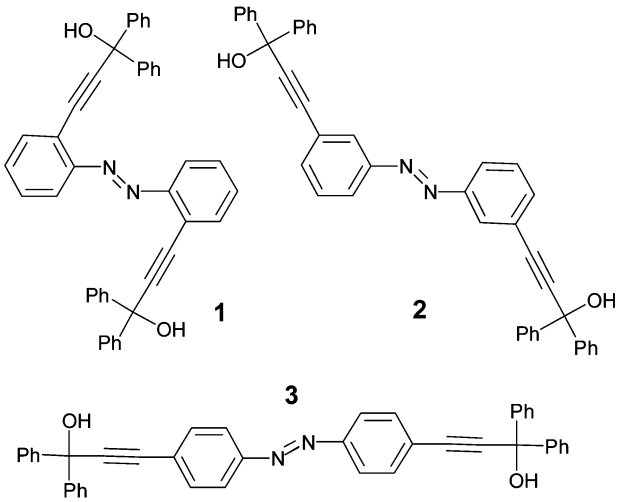
Host–guest complexation events may provide suitable sensor systems, but such events must be readily detectable without recourse to complex and/or time consuming analytical techniques if hosts are to be effectively screened for response to large numbers of potential analytes (guests). The detection of host–guest complexation events is often achieved by isolation of inclusion compounds post-(re)crystallisation followed by analysis of the molecular components of the complex by spectroscopic (UV, IR, fluorescence spectra[1,2]) or crystallographic techniques, which are relatively time consuming. Other methods for screening, including mass changes (quartz crystal microbalance or piezoelectric readout systems[3–5]) and changes in refractive index,[6] necessitate the use of sophisticated equipment, either in the readout or preparation of the sensor.

The design of simple, low cost, easily used sensors depends on simple readout mechanisms such as colour changes or chromogenicity. Host–guest binding events detected by colour changes resulting from associated conformational changes and thus shifts in energy of electronic transitions have been reported for a few imidazole compounds[7] and boronic acid derivatives.[8] We have reported the synthesis and guest-responsive colour changes of chromogenic host compounds, 3-{2-[2-(3-hydroxy-3,3-diphenyl-prop-1-ynyl)-phenylazo]-phenyl}-1,1-diphenyl-prop-2-yn-1-ol (**1**), 3-{3-[3-(3-hydroxy-3,3-diphenyl-prop-1-ynyl)-phenylazo]-phenyl}-1,1-diphenyl-prop-2-yn-1-ol (**2**) and 3-{4-[4-(3-hydroxy-3,3-diphenyl-prop-1-ynyl)-phenylazo]-phenyl}-1,1-diphenyl-prop-2-yn-1-ol (**3**).[9,10]

This phenomenon of clear change in colour upon complexation proves to be a general one for this family of hosts and colour changes, in both the solid state and in solution, allowing rapid screening of libraries of guests to determine which host might be considered as the starting point for development of an analyte-specific sensor.

Results and discussion

Each of the host compounds **1**–**3** is a yellow microcrystalline material post-grinding of pale to bright yellow host crystals obtained after recrystallisation during purification. Upon guest complexation each exhibits a distinct, easily detected, colour change to bright orange or orange/red. These colour changes may be effected by addition of liquid guest to solid host,



yielding a bright orange to orange/red solid or solution (depending on host solubility in the chosen guest) or by addition of guest to a solution of host **1**, **2** or **3** in a suitable solvent. In addition, colour changes are readily detected both by crystallisation of host–guest complexes or by absorption of guest vapours from a saturated atmosphere.[9] The colour changes occur immediately and do not fade or alter in shade with time. The ease with which these changes in absorption maximum in the visible region are detected allows rapid and accurate screening for host–guest complexation events and, to date, no colour change has been detected where subsequent guest inclusion has occurred. The application of this methodology to a small library of potential guest compounds is depicted in Fig. 1. While the effect of only a small number of guests is illustrated here, this technique has been used to discover new guest species such as *N*-methylimidazole which results in a yellow to orange colour change in each case (not pictured in Fig. 1).

Crystal structures of a number of the host–guest complexes detected in this screening experiment and some closely related guest compounds have been obtained to verify the existence of the complex and to allow analysis of intermolecular interactions and conformational changes to attempt to determine the source of the colour change. Host : guest ratios and attendant colour changes are presented Table 1, crystal structure details

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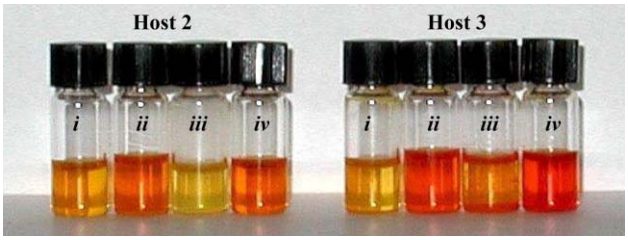

Fig. 1 Clearly visible guest-responsive colour changes of host **2** (4 vials on left) and host **3** (4 vials on right). Saturated solutions of ground hosts in toluene (note settled excess host) turn bright orange upon addition of suitable guests, left to right in each group: (*i*) no guest; (*ii*) pyridine; (*iii*) *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA); and (*iv*) dimethylformamide (DMF). No inclusion complexes of **2** and TMEDA have been prepared and this is reflected in the yellow colour of the slurry in vial *iii* for host **2**. (Orange/red crystals of the inclusion complex **3**·TMEDA form quickly and are visible on the sides of vial *iii* for host **3**.)

of inclusion complexes are presented later in Table 4 and molecular diagrams indicating chosen numbering systems in Figure 2.

As would be predicted from the yellow colour of the toluene solution of TMEDA and **2**, no inclusion complexes of **2** with TMEDA guest have been prepared although crystallisation from a range of solvents, including toluene, ethyl acetate, dichloromethane and mixtures of these has been tested. In all cases very thin yellow/pale yellow dichroic crystals of host **2** alone are isolated.

The orange/red colour of the solutions of **1** and **3** with TMEDA is reflected in the crystals grown by slow evaporation. In both complexes, the guest N atoms act as a hydrogen bond acceptors for OH donor groups of different host molecules. The host–guest–host–guest chains or ribbons thus formed pack together (aided by extensive CH···π interactions) such that ancilliary guest solvent molecules are included in channels, as depicted in Fig. 3. In the case of the complex **1**·TMEDA·

Table 1 Host : guest ratio and colour of inclusion complexes of **1**–**3**

	1		**2**		**3**	
Guest	H : G	Colour	H : G	Colour	H : G	Colour
THF	—[a]	—	1 : 2	Orange	—	—
Dioxane	—	—	1 : 2	Orange	—	—
CH_3CN	—	—	1 : 1	Orange	—	—
Cyclopentanone	—	—	1 : 2	Orange	—	—
γ-Butyrolactone	—	—	1 : 2	Orange	1 : 2	Orange
DMF	—	—	1 : 2	Orange	1 : 2	Red
DMSO	1 : 2	Red	1 : 1	Orange	1 : 2	Orange
Pyridine	1 : 2	Orange	1 : 2	Orange	1 : 3	Orange
Piperazine					1 : 1	Orange
$Me_2NCH_2NMe_2$					1 : 2	Red
$Me_2N(CH_2)_2NMe_2$	1 : 1 : (2)[b] (toluene)	Red	—	—	1 : 1 : (1)[b] (CH_2Cl_2)	Orange
N-Methylimidazole	1 : 2	Orange/red	1 : 2	Orange	?[c]	?

[a]No complexation. [b]Solvent included. [c]Colour change in solution, crystals yet to be isolated.

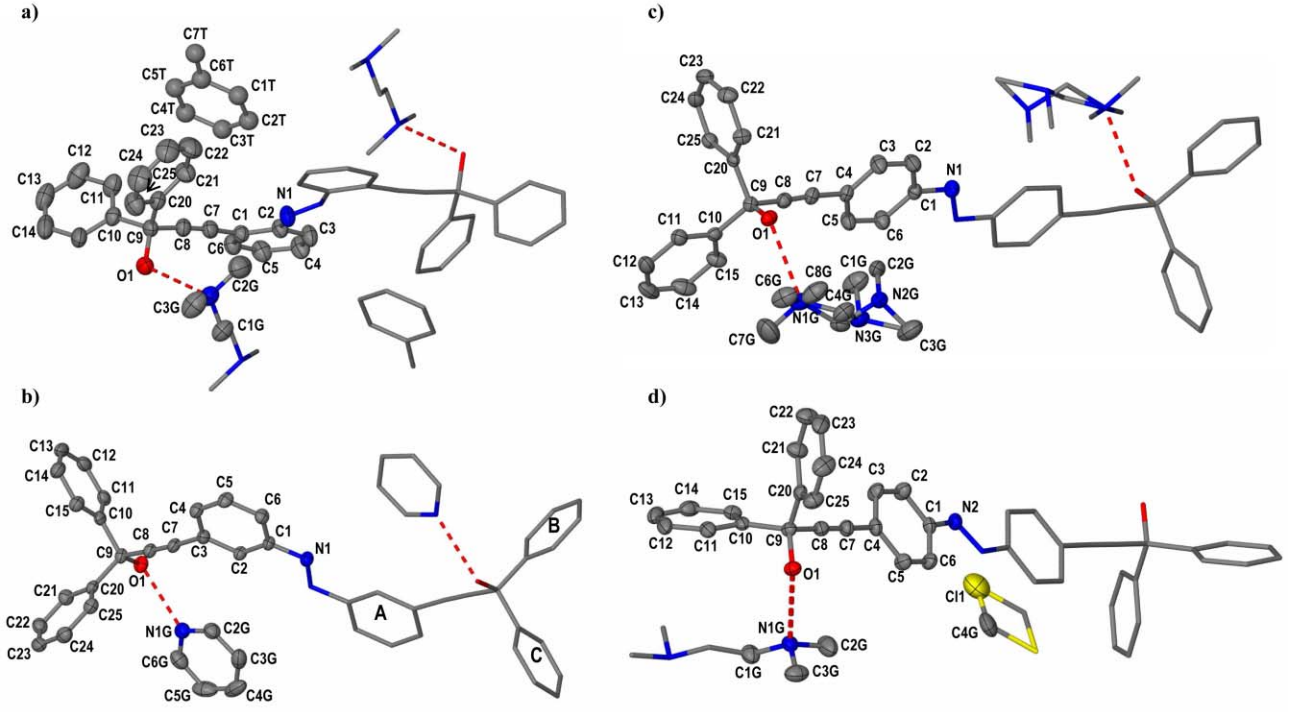

Fig. 2 Molecular diagrams of (a) **1**·TMEDA·2toluene, (b) **2**·2pyridine, (c) **3**·2TMMDA, (d) **3**·TMEDA·CH_2Cl_2. Asymmetric unit atoms are indicated as ellipsoids at the 50% probability level and host–guest hydrogen bonds as dashed lines. Disordered TMMDA and dichloromethane guest molecules are depicted but only one of the two disordered toluene molecules is depicted.

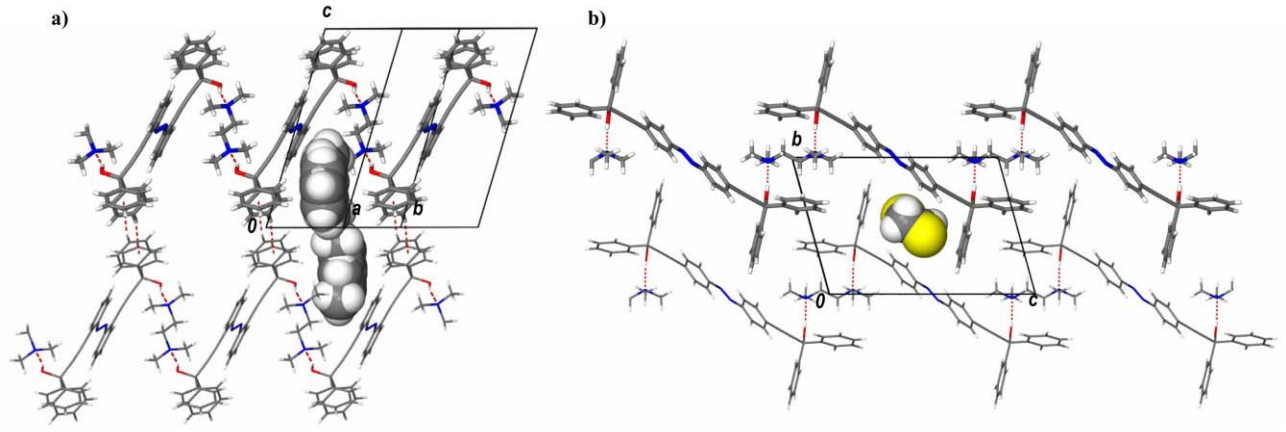

Fig. 3 Packing diagrams of (a) **1**·TMEDA·2toluene (click here to access a 3D representation), and (b) **3**·TMEDA·CH_2Cl_2 (click here to access a 3D representation). Included guest solvent molecules are depicted with van der Waals radii and hydrogen bonds, and CH···π interactions are depicted as dashed lines. One infinite –G–H–G–H– hydrogen-bonded chain is depicted with thick bonds and that adjacent with thin bonds.

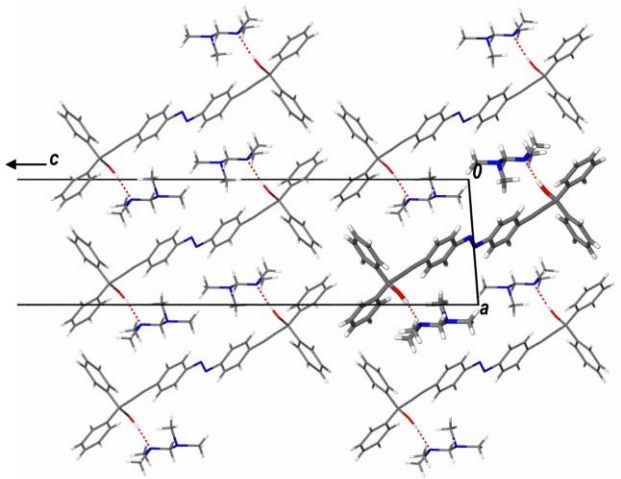

Fig. 4 Packing diagram of **3**·2TMMDA (click here to access a 3D representation). A single G–H–G hydrogen-bonded unit is depicted with thick bonds, hydrogen bonds as dashed lines and only one position of the disordered TMMDA guest molecules shown.

2toluene the toluene molecules are disordered and are modelled over two positions reflecting two possible orientations of the toluene guests in the channel. The guest dichloromethane molecule in the complex **3**·TMEDA·CH_2Cl_2 is also disordered, with two equally occupied CH_2 positions required by space group symmetry.

Table 2 Dihedral angles: terminal phenyl rings to backbone

Complex	AB[a]/°	AC/°
1·TMEDA·2toluene	42.3(1)	69.5(1)
2·2pyridine	69.84(5)	79.87(5)
3·2TMMDA	4.4(1)	88.12(5)
3·TMEDA·CH_2Cl_2	56.78(8)	59.38(6)

[a]B and C are chosen to represent each terminal phenyl ring.

Remarkably, changing the guest to *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine (TMMDA), with only one methylene group separating the N atoms, yields a completely different structure with '*para*' host **3**. The guest now behaves as a single H-bond acceptor and thus two guests are required to satisfy the H-bond capacity of the host OH groups. Guest–host–guest H-bonded units pack togther, aided by CH···π interactions of the terminal phenyl rings, as illustrated in Fig. 4. Similar guest–host–guest H-bonded units are found in the structure of **2**·2pyridine, although, once again, the packing mode adopted is completely unique and appears to arise due to maximisation of CH···π interactions, Fig. 5.

The conformation of the host molecules in each of these structures is also significantly different from each other, particularly with regard to the conformation of the terminal phenyl rings relative to the backbone of the molecule, as reflected in the dihedral interplanar angles listed in Table 2. While **3**·TMMDA has one terminal phenyl ring which adopts a conformation almost completely co-planar with the azobenezene

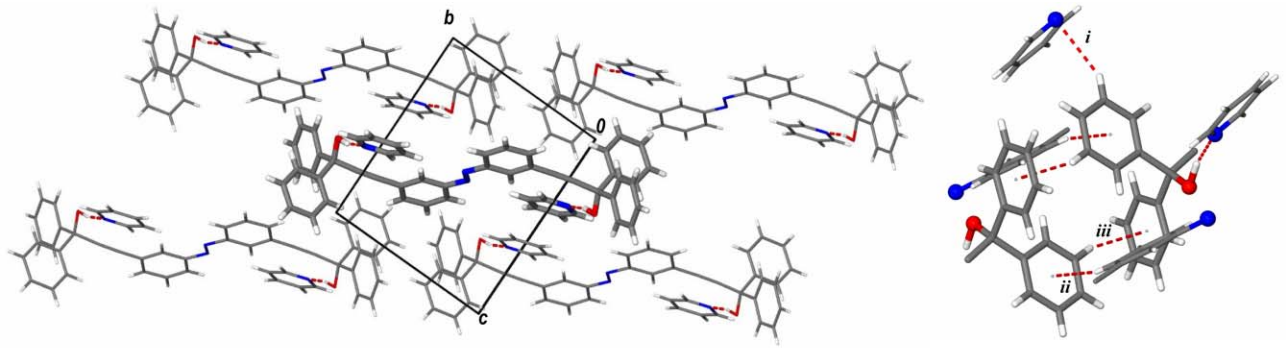

Fig. 5 Packing diagram of **2**·2pyridine with one G–H–G unit represented in bold (click here to access a 3D representation). The structure is stabilised by extensive short CH···π contacts between host backbone phenyl rings (designated A in Fig. 2) and terminal phenyl rings (designated B and C in Fig. 2) as well as H–G CH···π interactions. These are illustrated in the insert and may be characterised according to the shortest H/atom or H/centroid distance: (*i*) *d*(H12···N1G) (pyridine guest), 2.80 Å, C12–H12···N1G (pyridine guest), 151°; (*ii*) *d*(H4···centroid) (C10–C15), 2.80 Å, C4–H4···centroid (C10–C15), 149°; (*iii*) *d*(H14···centroid) (C20–C25), 2.80 Å, C14–H14···centroid (C20-C25), 163°.

Table 3 Hydrogen bond geometrical parameters

	d(D–H)/ Å	*d*(H···A)/ Å	∠(DHA)/ °	*d*(D···A)/ Å
1·TMEDA·2toluene				
O1–H1O···N1G[a]	0.83(3)	1.98(3)	159(2)	2.777(3)
2·2pyridine				
O1–H1O···N1G	1.08	1.70	168	2.768(2)
3·2TMMDA				
O1–H1O···N1G[b]	0.98(3)	1.90(2)	161(2)	2.847(2)
3·TMEDA·CH_2Cl_2				
O1–H1O···N1G	0.88(2)	1.91(4)	165(3)	2.770(3)

Symmetry operators: a = $x - 1, y, z$; b = $x + 1, y - 1, z$.

core, **3**·TMEDA·CH_2Cl_2 exhibits no co-planarity, yet both complexes form orange/red dichroic crystals and the terminal phenyl ring orientation appears to have no obvious effect on the colour of the crystalline compound, as noted previously.[10] Hydrogen bond geometries vary quite significantly from complex to complex as reflected in Table 3 and it is clear that ALL intermolecular interactions, including relatively weak CH···π interactions play, a role in determining the packing motif in each case.

The role of CH···π interactions in stabilising inclusion complexes has been discussed by Nishio, Suezawa, Takahashi and co-workers,[11,12] but, in this case, it has not yet proven possible to discern whether such interactions are important in solution. Examination of the solution phase UV-vis absorption spectra of these hosts dissolved in liquid guest demonstrates an interesting effect on change of concentration. As illustrated in Fig. 6, increasing the host concentration results in an increase in the wavelength of the absorption maximum, implying that the changes in colour noted may be due, at least in part, to host–host or host–guest–host interactions occurring in solution and in the solid, which lead to changes in energy of the electronic transitions responsible for absorption in the visible region. (There is also a substantial increase in the relative intensity of the band ascribed to the n→π* transition.[13])

Effects of solvent polarity,[14] hydrogen bonding and loss of planarity[15] on the electronic transitions in azobenzenes[16] have been described and, in particular, Robin and Simpson have suggested mixing of the 'colour band' and n→π* transition of the azo group.[13] Clearly, changes in conjugation of the N=N and aromatic groups of the azobenzene core will affect the energy of these various transitions effecting changes in absorption maxima and hence in colour. With this in mind we analysed the planarity of the azobenzene core in hosts **1**, **2** and **3** in each of the solid-state structures. This may be discerned by consideration of the N=N–C(Ar)–C(Ar) twist angle and the degree of conjugation inferred, in part, from the N=N bond lengths, which should expand with greater conjugation with the aromatic systems.[17]

Data drawn from previously published structures, as well as

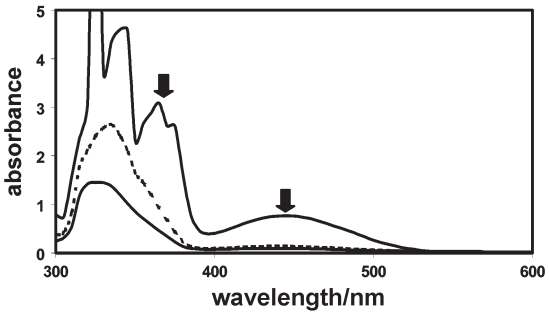

Fig. 6 UV-vis absorption spectra of **2** in pyridine at varying concentrations: solid line (top), 1.3×10^{-3} M; dashed line (middle), 6.5×10^{-4} M, and solid line (bottom) 1.3×10^{-4} M. Bold arrows indicate absorption maxima discussed in the text.

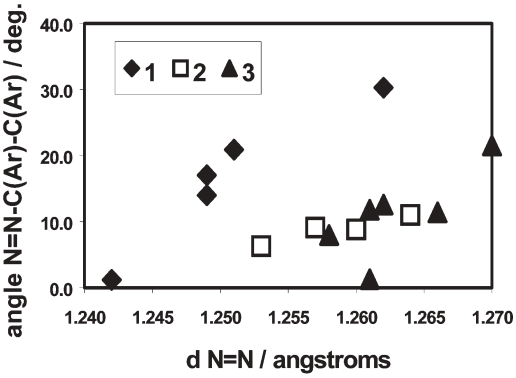

Fig. 7 Twist angle *vs.* N=N bond length in solid-state structures of compounds **1**–**3**. The longest N=N bond length and greatest twist angle occur in the two host alone structures elucidated previously.[10]

those contained in this paper, are presented in Fig. 7 and there appears to be correlation (with the exception of one example in the **3**·2DMSO structure) between the N=N bond lengths and twist angles defining the angle between the planes C–N=N–C and the aromatic ring. In each case the structures of the hosts alone exhibit both the greatest twist angles and the longest N=N bond in that series, but it should be recalled that the azo groups act as double H-bond acceptors in each case.

Thus, it is suggested that the colour of these compounds arises from absorption due to electronic transitions of the azobenzene core and that the energy of these transitions is affected by a combination of degree of conjugation of N=N and aromatic systems (reflected in the molecular geometry) and hydrogen bonding to the N=N groups. These two factors have the greatest effect on absorption in the visible region and hence the colour changes.

All complexes isolated to date avoid H-bonding to the N=N core and are of a bright orange or red colour indicating that the use of a colour change upon host–guest interaction is a useful and general screen for potential guest species, although these hosts are not highly selective, including a variety of H-bond acceptor guests.

Experimental

Crystallographic studies

Crystals suitable for single crystal X-ray diffraction experiments were grown by slow evaporation of solutions of the host in dichloromethane, toluene or a mixture of these and the chosen guest species. Data were collected on an Enraf-Nonius Kappa CCD diffratometer at 123 K using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å, 1° φ and ω scans). Structures were solved by direct methods using the program SHELXS-97[18] and refined by full matrix least squares refinement on F^2 using the programs SHELXL-97[19] and XSeed.[20] Non-hydrogen atoms of the hosts were refined anisotropically and hydrogen atoms inserted in geometrically determined positions with temperature factors fixed at 1.2 times (1.5 for methyl hydrogens) that of the parent atom. Guest molecules were refined in a similar fashion except where guests were disordered. Crystal structure details of inclusion complexes are presented in Table 4

Specific details pertaining to individual crystal structures follow. Crystals of the complex **1**·TMEDA·2toluene contain one ½ host, one ½ guest TMEDA molecule and one toluene solvent molecule in the asymmetric unit. The toluene molecule is disordered over two positions reflecting two possible orientations of the solvent molecule. These are modelled with equal site occupancy.

Crystals of the complex **2**·2pyridine have one ½ host

Table 4 Crystal and refinement data for crystalline inclusion complexes of **1**, **2** and **3**

	1·TMEDA·2toluene	**2**·2pyridine	**3**·2TMMDA	**3**·TMEDA·CH_2Cl_2
Empirical formula	$C_{62}H_{62}N_4O_2$	$C_{52}H_{40}N_4O_2$	$C_{52}H_{58}N_6O_2$	$C_{49}H_{48}N_4O_2Cl_2$
M	895.16	752.88	799.04	795.81
Crystal system	Triclinic	Triclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
a/Å	9.4585(2)	9.1559(2)	9.0344(2)	6.3341(2)
b/Å	10.2286(2)	10.5862(3)	6.3416(2)	10.9720(3)
c/Å	15.4751(4)	11.6018(4)	40.150(3)	16.0192(5)
α/°	71.744(1)	89.270(1)	90	104.947(1)
β/°	87.438(1)	84.726(2)	94.456(3)	94.277(1)
γ/°	66.696(1)	65.225(2)	90	93.557(2)
V/Å^3	1300.42(5)	1016.28(5)	2293.32(9)	1068.81(6)
Z	1	1	2	1
D_c/g cm^{-3}	1.143	1.230	1.157	1.236
μ/mm^{-1}	0.069	0.075	0.071	0.196
Reflections (unique)	6192	4889	8231	5186
Reflections [$I > 2\sigma(I)$]	2703	4889	4898	5186
R_1/wR_2 [$I > 2\sigma(I)$]	0.0793/0.2403	0.0489/0.0941	0.0539/0.1001	0.0699/0.1870
R_1/wR_2 (all data)	0.1740/0.291	0.1417/0.1176	0.1553/0.1287	0.1114/0.2100
GoF on F^2	0.959	0.888	0.897	1.071
Parameters/restraints	281/1	263/0	339/6	268/0

molecule and one hydrogen-bonded pyridine guest molecule in the asymmetric unit. Both molecules are well ordered.

The complex **3**·2TMMDA contains one ½ host molecule and one full guest TMMDA molecule, hydrogen bonded *via* one amine nitrogen atom only, per asymmetric unit. The TMMDA molecule is disordered such that the non-hydrogen-bonded amine nitrogen atom occupies two positions necessitating similar disorder in the attendant methyl and linking methylene groups.

The complex **3**·TMEDA·CH_2Cl_2 has one ½ host molecule, one ½ TMEDA guest molecule and one ½ dichloromethane solvent molecule per asymmetric unit. In common with **1**·TMEDA·2toluene, no disorder is noted in the doubly hydrogen-bonded TMEDA molecule but the dichloromethane solvent molecule is disordered over two positions reflecting its position on a centre of symmetry.

CCDC reference numbers 188478–188481.

See http://www.rsc.org/suppdata/ce/b2/b206162g/ for crystallographic data in CIF or other electronic format.

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