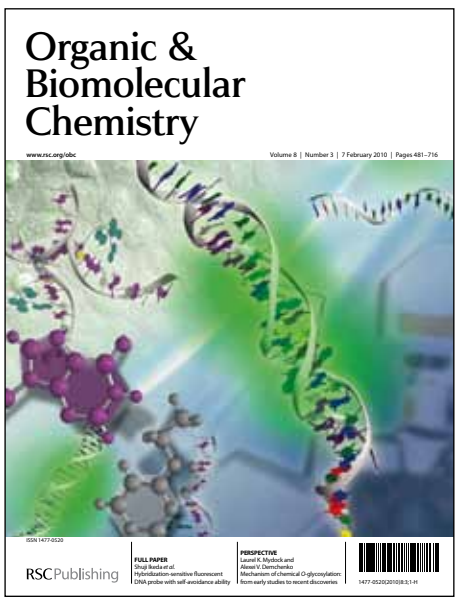
Organic & Biomolecular Chemistry

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE View Article Online

A bis(triazole)benzamide receptor for the complexation of halide anions and neutral carboxylic acid guests. Guest-controlled topicity and self-assembly

Fátima García,[a] Juan Aragó,[b] Rafael Viruela,[b] Enrique Ortí,*[b] Luis Sánchez*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Bis(triazole)benzamide **1** has been readily synthesized by means of Cu-catalyzed 1,3-dipolar cycloaddition and its ability to bind halide anions and neutral gallic acid derivative **12GA** has been theoretically and experimentally investigated. The cavity defined by the N−H amide group and the vicinal aromatic hydrogens is suitable to form H-bonding arrays with halide guests. The stability of complexes **1**•Cl^- and **1**•Br^- is very similar, as DFT calculations predict and ^{1}H NMR titration experiments confirm. The zig-zag "*anti*" conformation of the molecule generates two regions with complementary positive and negative potentials that favors the statistical complexation of two molecules of the neutral carboxylic acid **12GA**. This guest-controlled topicity demonstrates the versatility of this class of receptor to bind species of different nature. The amide group determines the complexation of both anionic and neutral species by primary acid-base interactions.

Introduction

Enzymes, hormones, and proteins are biological systems that exert a specific function in response to complexation of species of different nature. These biomolecules are endowed with functional groups able to interact with anions and carboxylic acids in natural processes such as the collapse of actin filaments by iodine or the citric acid cycle.[1] To emulate some of these natural processes, a variety of neutral receptors has been reported to bind anions by the interaction with polarized O−H or N−H groups.[2,3] The complexation of carboxylic acids occurs via an acid-base equilibrium between the carboxylic acid group and typical H-bonding donors and acceptors such as amines, carbonyls, or pyridines.[4] In the quest of new receptors for anions, 1,4-substituted-1,2,3-triazole-based macrocycles[5] and foldamers[6] are being investigated. These triazole-based receptors exhibit an array of neutral but sufficiently polarized C−H groups capable of interacting with different anions.[7] In addition to the electropositive C−H group, the triazole ring possesses two sp^2 nitrogen atoms that can interact with typical H-bonding donors. The H-bonding donor and acceptor moieties of the triazole rings have been recently combined with a derivative of gallic acid to form columnar liquid-crystalline supramolecular assemblies.[8]

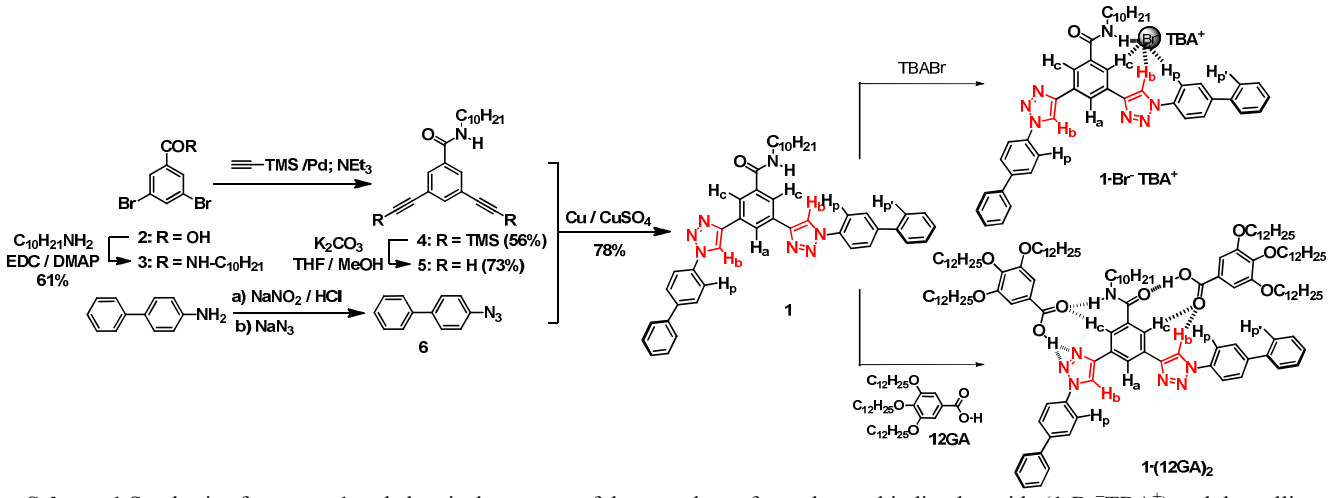
We have recently described the self-assembly of amphiphilic, open aryl triazoles, whose aggregates are disrupted upon bromide complexation. The addition of bromide to those open receptors provokes a conformational change that impedes the formation of organized supramolecular structures.[9] In this communication, we have replaced the peripheral triethylene glycol chain of our previous reported receptor by an amide functional group. The presence of the amide group in bis(triazole)benzamide **1** (Scheme 1) renders a versatile receptor that binds halide anions with a 1:1 stoichiometry and the gallic carboxylic acid derivative **12GA** with a 1:2 ratio in a non-cooperative fashion. Additionally, the complexation of anionic or neutral guests by **1** is accompanied by no remarkable conformational change of the triazole units. The neutral receptor **1**, the complexes formed by **1** and bromide anion and by **1** and the neutral carboxylic acid, are able to aggregate into highly organized supramolecular structures.

Results and Discussion

Synthesis.

Bis(triazole)benzamide **1** has been readily prepared in only five synthetic steps from commercially available 3,5-dibromobenzoic acid (**2**) (Scheme 1). Carboxylic acid **2** was reacted with *n*-decylamine in the presence of *N*-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC) and 4-(dimethylamino)-pyridine (DMAP) to yield amide **3** in 61%. The Sonogashira cross-coupling reaction between amide **3** and trimethylsilyl-acetylene and further deprotection of the silyl group with K_2CO_3 afforded *N*-decyl-3,5-diethynylbenzamide (**5**). Receptor **1** was straightforwardly synthesized with a 78% yield by following the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition[10] between **5** and 4-biphenyl azide (**6**), which was prepared by slightly modifying a previously reported procedure.[9,11] ^{1}H and ^{13}C NMR, FT-IR spectroscopy, and mass spectrometry have been used to confirm the chemical structure of all new reported compounds. The ^{1}H NMR spectrum of receptor **1** is rather simple showing seven well-defined aromatic resonances, a triplet corresponding to the N−H of the amide

functionality at δ ~ 6.7, and all the paraffinic resonances (see the Supporting Information). To achieve an antiparallel alignment of the internal electric dipoles of the triazole rings, compound **1** adopts a zig-zag ''anti'' conformation of these heterocyclic moieties as it is inferred from the NOE effects observed between the triazole proton (H_b) with the two protons of the central aromatic ring (H_a and H_c) (Scheme 1 and Figure S1).[9]



Scheme 1 Synthesis of receptor **1** and chemical structure of the complexes formed upon binding bromide (**1**•Br^-TBA^+) and the gallic acid derivative (**1•(12GA)$_2$**).

Self-assembly and complexation in solution.

Prior to the investigation of the complexation of any guest by **1**, we have studied its self-assembly in $CDCl_3$ to discard any effect from the aggregation of the receptor in the complexation process (Figure S2). Compound **1** self-assembles with a low association constant of ~7 M^{-1}. The slight upfield shift of the aromatic resonances and the deshielding of the amide proton upon increasing concentration suggests that the self-assembly of receptor **1** results from a combination of π-π stacking and H-bonding interactions.

The capability of the bis(triazole)benzamide receptor **1** to bind halide guests has been initially investigated by performing density functional theory (DFT) calculations. Geometry optimizations of **1** and its respective complexes **1**•X^- (where X^- is F^-, Cl^-, Br^-, and I^-) have been carried out at the M06-2X/6-311G** level to estimate the binding energy of the complex and to analyze the structural changes associated with the complexation process. In compound **1**, the alkyl chain attached to the nitrogen of the amide group has been substituted by a methyl group to reduce the computational cost.

The structural and electronic properties calculated for receptor **1** are first discussed. According to the orientation of the amide group, two minimum-energy conformations (A and B, Figure 1a) are obtained for **1**. Conformation A is predicted to be slightly more stable than conformation B by 2.45 kcal mol^{-1}. Nevertheless, the amide functional group in conformation A can easily rotate 180º to generate conformation B that binds anion guests more efficiently. Conformation B defines a cavity with the N−H group and the three hydrogens H_b, H_c, and H_p (Scheme 1 and Figure 1a) that can form H-bonding arrays upon binding the halide guests. The molecular electrostatic potential (MEP) computed for conformation B of receptor **1** (Figure 1b) clearly shows that the four hydrogens form a positively polarized cavity that favours the hosting of the anion guests.

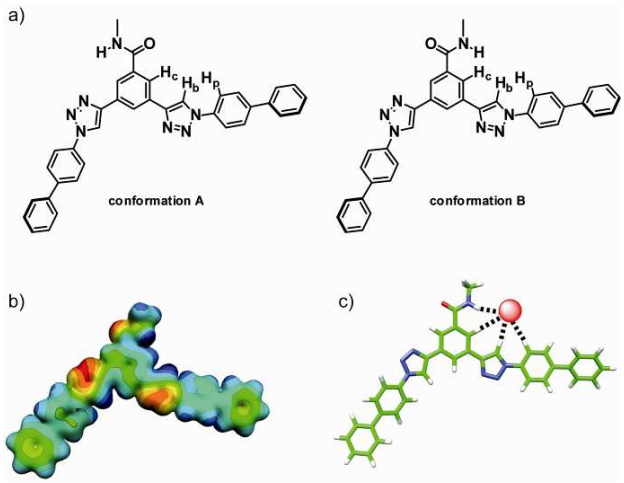


Fig. 1 (a) Minimum-energy conformations A and B computed for receptor **1**. (b) Molecular electrostatic potential calculated for conformation B of receptor **1** (red and blue are negative and positive potentials, respectively). (c) M06-2X/6-311G** optimized structure of complex **1**•Br^-.

The optimized structure of complex **1**•Br^-, which is selected as a representative example of complexes **1**•X^-, is shown in Figure 1c. In all optimized complexes, the halide ion is accommodated in the centre of the cavity surrounded by the four polarized hydrogens (see Figure 1). Table 1 collects the values of selected bond distances calculated for complexes **1**•X^- at the M06-2X level. The H···X^- distances (H being the amide H, H_b, H_c, and H_p) are all shorter than the sum of the van der Waals radii of the hydrogen atom and the corresponding X^- ion (Table 1). This is the structural signature that supports the formation of complexes **1**•X^-. The H-bonding interactions between the halide anion X^- and the surrounding protons depend on the proton, and the distances computed for the N−H···X^- and H_b···X^- contacts are

significantly shorter than those obtained for the $H_c\cdots X^-$ and especially the $H_p\cdots X^-$ contact.

Table 1. Selected bond lengths (in Å) calculated for receptor **1** and complexes **1**•X^- at the M06-2X/6-311G** level.

Bond	**1**	**1**•F^-	**1**•Cl^-	**1**•Br^-	**1**•I^-
N−H	1.007	1.048	1.018	1.017	1.014
H···X^-	-	1.645	2.346	2.508	2.741
C−H_b	1.076	1.103	1.086	1.085	1.083
$H_b\cdots X^-$	-	1.716	2.357	2.512	2.787
C−H_c	1.085	1.087	1.085	1.086	1.086
$H_c\cdots X^-$	-	1.911	2.573	2.778	3.058
C−H_p	1.083	1.089	1.087	1.087	1.086
$H_p\cdots X^-$	-	2.469	2.885	2.952	3.136
∑(vdW radii)[a]		2.670	2.950	3.050	3.180

[a] Sum of the van der Waals radii of the hydrogen atom and the corresponding X^- ion.

To investigate the stability of complexes **1**•X^-, counterpoise (CP) corrected binding energies were computed on the previously optimized M06-2X/6-311G** structures. M06-2X predicts stable molecular complexes with binding energies of –72.03, –43.26, –40.40, and –34.73 kcal mol^{-1} for complexes **1**•F^-, **1**•Cl^-, **1**•Br^-, and **1**•I^-, respectively. According to the computed binding energies, F^- ions would interact very strongly with receptor **1**, Cl^- and Br^- anions would form complexes with **1** of similar stability (the difference is less than 3.00 kcal mol^{-1}), and the voluminous I^- ions would form the less stable complexes.

The experimental evidence of the complexation of halide anions by receptor **1** was obtained by ^1H NMR titrations in $CDCl_3$. Titration of **1** with tetrabutylammonium (TBA^+) salts of F^-, Cl^-, Br^-, and I^- shows the deshielding of the resonances of the amide N−H proton and of the C−H groups corresponding to the proton in orto to the amide functionality (H_c in Scheme 1) and to the proton of the triazole ring (H_b in Scheme 1) (Figure S3). The variation of these chemical shifts confirms that the geometry of receptor **1** matches conformation B predicted by the theoretical calculations. The magnitude of the deshielding is different for the four halide complexes. Titration of receptor **1** with TBAF provides the smallest deshielding shifts for the N−H and C−H_b proton resonances, which suggests the formation of weak **1**•F^- complexes (Figure S3). This contrasts with theoretical calculations, which predict **1**•F^- as the most stable complex. The discrepancy between theoretical and experimental results has been already reported for related complexes,[12,13] and it was attributed to the difficulty of finding "free" F^- ions under common experimental conditions. The spectral shifts observed in the resonances of **1** upon adding Cl^- and Br^- anions are the most significant, whereas the titration of receptor **1** with the TBAI salt causes a smaller deshielding of the resonances of the N−H, C−H_c, and C−H_b protons (Figure S3). This is in concordance with theoretical calculations that obtain complex **1**•I^- to be less stable. The NMR experimental findings are therefore supported, except for complex **1**•F^-, by DFT calculations, which predict stable **1**•X^- complexes stabilized by strong H-bonding interactions.

Taking into account the theoretical and experimental evidence, the complexation process of chloride and bromide anions by receptor **1** was studied in further detail. The 1:1 stoichiometry of complexes **1**•Cl^- and **1**•Br^- was confirmed by a Job's plot analysis (Figure S4). The complexation of these halide anions is relatively weak since a poor saturation is observed upon the addition of 50 equivalents of the corresponding TBAX salt (Figure S5 and S6). To determine the binding features of receptor **1**, we have utilized the fitting program recently reported by P. Thordarson that performs a global analysis of multiple datasets to a single binding model.[14a] This program allows determining the binding constant K_a by fitting the variation of the chemical shifts (Δδ) of the host (*H*), directly related to the concentration of the free and bound species, upon increasing the concentration of the guest (*G*). The K_a value is calculated from Equation 1 that combines this binding constant and the mass balance equations for the total concentrations of the host $[H]_0$, guest $[G]_0$, and the concentration of the final complex *HG*. The calculated values for K_a by using the fitting program are 29.0 (± 5%) and 37.4 (± 4%) M^{-1} for complexes **1**•Cl^- and **1**•Br^-, respectively (Figure 2).

$$[HG] = 1/2\{([H]_0 + [G]_0 + 1/K_a) - \sqrt{([H]_0 + [G]_0 + 1/K_a)^2 - 4[H]_0[G]_0}\} \quad \text{Eq. 1}$$

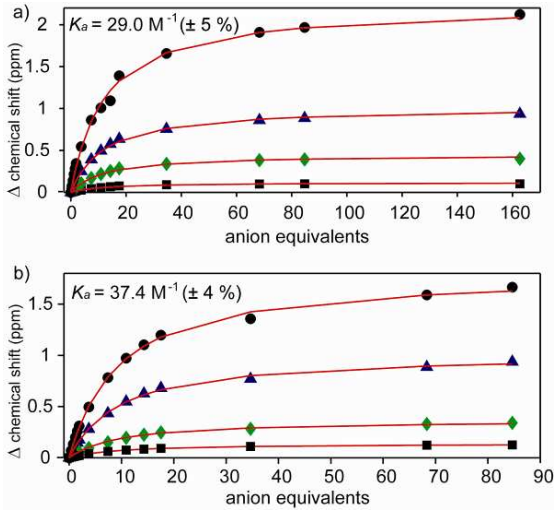


Fig. 2 Isotherms resulting from the titration of receptor **1** with TBACl (a) and TBABr (b). The binding isotherms correspond to a 1:1 complexation model by using the using the amide N−H (square), H_c (diamond), H_b (triangle) and H_p (circle) protons.

The participation of the polarized N−H proton as well as the aromatic protons H_b, H_c, and H_p in the complexation of the halide guests is confirmed by the downfield shield experienced by these resonances (Figures 2, S5 and S6) and also by the NOE effects observed upon irradiation of the triazole proton H_b in the complex formed by **1** and the Br^- anion (Figure S7). Unlike some other triazole-based receptors,[5-7,9] compound **1** possesses an acidic N−H proton that competes with the C−H groups to bind the halide anion, and no conformational changes in the 1,2,3-triazole rings occur after halide binding (Scheme 1 and Figure S7).

Considering the zig-zag "anti" conformation of the bis(triazole)benzamide receptor, we have envisioned the possibility of forming complexes by mixing **1** with a neutral guest possessing H-bonding donor and acceptor moieties. 3,4,5-tris(dodecyloxy)gallic acid[15] (**12GA** in Scheme 1) was selected as

neutral guest because the carboxylic acid functional group meets these requirements. The molecular electrostatic potential computed for receptor **1** in conformation A shows the presence of two regions with complementary positive and negative potentials (Figure S8). The negative area is determined by the amide carbonyl group and the two sp^2 nitrogens of one of the triazole rings, whereas the positive zone is determined by the polarized N−H, H_b, and H_c protons. This electronic distribution suggests that receptor **1** could behave as a ditopic host for the complexation of up two molecules of **12GA** as guest. An appealing feature of receptors with more than one binding site is the possible appearance of cooperative effects, which can be positive, like the binding of oxygen to haemoglobin,[16a] or negative, like the binding of tyrosine kinase to the EGF receptor.[16b] The complexation of **12GA** by receptor **1** and the possible cooperative effects derived from this complexation have been studied both theoretically and experimentally.

Figure 3 displays the minimum-energy optimized structure calculated for complex **1•(12GA)$_2$** at the M06-2X/6-311G** level. Table 2 compares the values calculated for selected bond lengths of receptor **1** and complex **1•(12GA)$_2$**. The complexes formed by receptor **1** and only one **12GA** molecule placed on the left **(1•12GA-*l*)** and right **(1•12GA-*r*)** sides of the amide group (Figure S10) were also computed for comparison purposes. In Figure 3, the **12GA** molecule placed on the left side of complex **1•(12GA)$_2$** is bound to receptor **1** by the primary acid-base N−H···O=C and O−H···N=N interactions with calculated bond distances of 1.952 and 1.783 Å, respectively (bonds 7 and 9, Figure 3b and Table 2). Calculations also predict short C=O···H_c and O−H···N=N contacts of 2.277 Å (bond 8) and 2.491 Å (bond 10), respectively, which reinforce the interaction between the **12GA** guest and receptor **1**. The binding of the **12GA** molecule placed on the right side of receptor **1** (Figure 3) is dominated by the strong C=O···H−O interaction (1.688 Å, bond 11) and strengthened by the short C−H_c···O=C and C−H_b···O=C contacts (2.458 and 2.048 Å, respectively; bonds 12 and 13). The computed H-bonding distances are in good agreement with those found in related complexes of triazole derivates with carboxylic acids.[8] Upon binding, the N−H, C=O, N=N, and C−H_b bonds undergo a significant elongation to accommodate the hydrogen bonds (Table 2). Theoretical calculations therefore corroborate that the **12GA** guests are stabilized in host **1** by means of an array of H-bonding interactions.

The CP-corrected binding energies for complex **1•(12GA)$_2$** (Figure 3) and for complexes **1•12GA-*l*** and **1•12GA-*r*** (Figure S9) that incorporate only one **12GA** molecule were computed at the M06-2X/6-311G** level. The theoretical calculations predict a dissimilar affinity of the two possible binding sites of receptor **1** to bind the **12GA** guest. Thus, the binding energy computed for complex **1•12GA-*r*** (Figure S9, right), formed upon binding the gallic acid guest by the C=O group of the amide and the C−H unit of the triazol ring, is –20.96 kcal mol^{-1}. However, the binding energy calculated for complex **1•12GA-*l*** (Figure S9, left), in which the gallic acid is bound to receptor **1** by the N−H unit of the amide and the N=N group of the triazole ring, is –17.77 kcal mol^{-1}. Interestingly, the sum of the binding energies computed for the single complexes **1•12GA-*l*** and **1•12GA-*r*** is practically equal to the binding energy calculated for complex **1•(12GA)$_2$** (–39.24 kcal mol^{-1}). This is indicative of a non-cooperative complexation process, in which the binding of the first **12GA** guest does not affect the complexation of the second **12GA** guest.

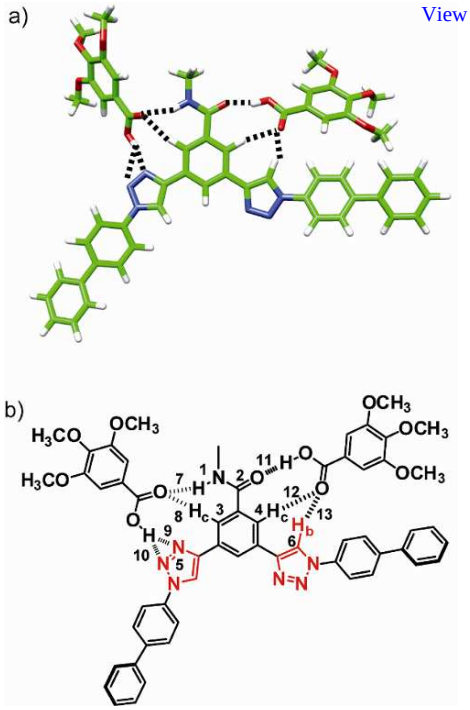


Fig. 3 (a) M06-2X/6-311G** optimized structure for complex **1•(12GA)$_2$**. (b) Chemical structure of complex **1•(12GA)$_2$** along with the bond numbering used in Table 2.

Table 2. Selected bond lengths (in Å) calculated for receptor **1** and complex **1•(12GA)$_2$** at the M06-2X/6-311G** level.

Bond	1	1•(12GA)$_2$
1	1.006	1.012
2	1.216	1.232
3	1.083	1.082
4	1.084	1.085
5	1.286	1.292
6	1.076	1.078
7	-	1.952
8	-	2.277
9	-	1.783
10	-	2.491
11	-	1.688
12	-	2.458
13	-	2.048

The formation of the complex **1•(12GA)$_2$** has been experimentally demonstrated by performing a Job's plot analysis. In good agreement with theoretical calculations, the Job's plot shows a maximum at 0.63 diagnostic of a 1:2 stoichiometry (Figure 4a). The ^{1}H NMR titration of receptor **1** with carboxylic acid **12GA** (Figures 4b and S10) reveals that both the N−H donor and the C=O acceptor H-bonding units of the amide group participate in the formation of the complex thus supporting the 1:2 stoichiometry. The primary acid-base interactions are reinforced by an array of H-bonds between the carboxylic group of **12GA** with the aromatic protons H_b and H_c. As theoretical

calculations predict, the two triazole rings are involved in binding the **12GA** guest: one of them participates as a hydrogen-donating unit by establishing H-bonds between H_b and the carbonyl group of the carboxylic acid, whereas the other acts as a hydrogen-accepting moiety by forming H-bonds between the two sp^2 nitrogen atoms of the heterocycle and the acidic O−H group of the carboxylic acid (see Scheme 1 and Figure 3). However, the benzene proton H_a located in *orto* relative to the triazole rings does not deshield in the titration experiment, which indicates that this C−H group is not participating in the complexation of the **12GA** guests (Figure S11 and Scheme 1).

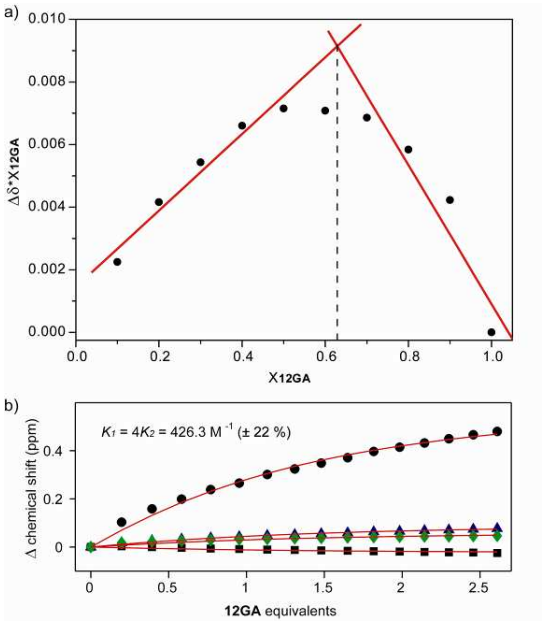


Fig. 4 (a) Job plot showing the 1:2 stoichiometry of complex **1•(12GA)$_2$**. (b) Hyperbolic binding isotherms for the binding of **12GA** to receptor **1** fitted to a 1:2 statistical association process.

The titration experiment of **1** with **12GA** did not shed sigmoidal curves but hyperbolic binding isotherms (Figure 4b), which suggests that the complexation of **12GA** by receptor **1** is non-cooperative.[17] As in the case of the complexes formed by receptor **1** and halide anions, we have fitted the experimental data by using the fitting program reported by P. Thodarson but using a 1:2 model based on cubic equation 2.[14a, 18] In this equation, K_1 and K_2 are the first and second stepwise association constants, respectively and $[G]$ is the concentration of the unbound guest.

$$[G]^3(K_1K_2)+[G]^2\{(K_1(2K_2[H]_0-K_2[G]_0)+1\}+ [G]\{K_1([H]_0-[G]_0)+1\}-[G]_0=0 \quad \text{Eq. 2}$$

In 1:2 complexes, it is necessary to consider two possibilities: *i*) a cooperative scenario in which the complexation of the first guest influences the complexation of the second one, and *ii)* a non-cooperative scenario in which the complexation of the first guest does not influence the complexation of the second one.[14b] In the first case, there must be two different values for the binding constants K_1 and K_2 but the equality $K_1 = 4K_2$ is not fulfilled. In the second case, K_1 and K_2 are different but this equality $K_1 = 4K_2$ must be fulfilled. This sequential binding implies that the two binding sites of the receptor are identical and independent of each other.[19] Fitting the variation of the chemical shifts involved in the complexation process of receptor **1** with **12GA** to a 1:2 cooperative model shed incoherent values for K_1 and K_2 with errors higher than ±400 %. However, a significant improvement is achieved by performing a global fitting of the experimental data to a statistical binding model. In this model, only one binding constant (K_1) and a global $\Delta\delta$ for the two possible HG and HG_2 complexes are averaged. The calculated K_1 and K_2 values obtained by performing the global fitting are of 426.3 and 106.5 M^{-1}, respectively, with an error of ± 22 % that allows establishing that the complexation of the neutral carboxylic acid **12GA** by receptor **1** proceeds by a statistical non-cooperative process.

Self-assembly on surfaces.

The upfield shift of some aromatic resonances observed in the titration of **1** with **12GA** (Figure S10) and with Cl^- and Br^- anions (Figure S5 and S6) and also in the self-assembly of **1** (Figure S2) suggests an aggregation phenomenon directed by π-π interactions. This aggregation was utilized to create organized supramolecular structures by slow diffusion of acetonitrile vapours into a chloroform solution of pristine **1** and also in the presence of TBABr and **12GA**. The aggregates formed have been visualized by scanning electron microscopy (SEM).

Free receptor **1** self-assembles into star-like objects composed of well-defined needle-like structures with an average thickness of ~1 μm (Figure 5a, 5b, and S11). The presence of bromide anions also gives rise to pseudo-monodimensional structures that resemble cactus prickles (Figures 5c, and S12). The anisotropic growth of the microcrystals formed from **1** in the absence or in the presence of bromide anions could be accounted for by the generation of an active plane of several molecules interacting by the paraffinic chains with a high surface free energy. These active plains grow fast in the direction perpendicular to the plane by means of π-stacking aromatic interactions.

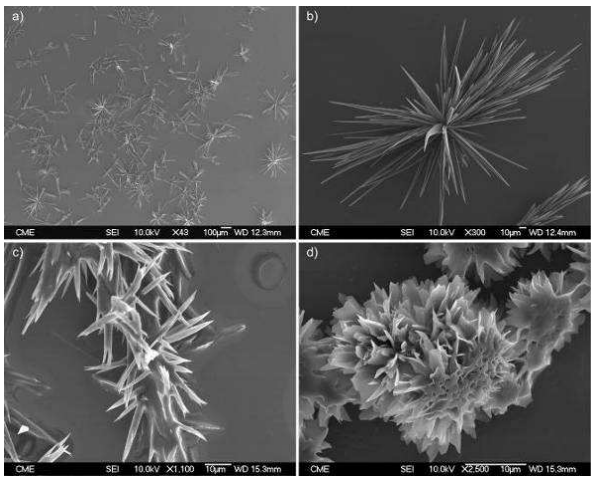


Fig. 5 SEM images of the aggregates formed by the self-assembly of **1** (a and b). The aggregation of receptor **1** in the presence of bromide anions (c) or in the presence of the gallic acid derivative **12GA** (d) results in the formation of aggregates of different morphology.

The self-assembly of **1** in the presence of the gallic acid derivative **12GA** produces flower-like structures by the

interaction of flat ribbons (Figure 5d and S13). The complexation of **12GA** by receptor **1** observed in solution could gives rise to supramolecular platforms with a larger π-surface endowed with many paraffinic chains. The interdigitation of the chains and the π-π stacking between the aromatic cages would form the lamellae constitutive of the flat ribbons.

Experimental

3,5-dibromo-N-decylbenzamide (3). 3,5-dibromobenzoic acid (1.78 g, 6.36 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.34 g, 6.99 mmol) and 4-dimethylaminopyridine (0.85 g, 6.99 mmol) were dissolved in dry dichloromethane (80 mL) under argon atmosphere at 0 ºC. The mixture was stirred for 15 minutes and then 1-decylamine (1.3 mL, 6.36 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and was stirred for 3 hours. The organic layer was washed with HCl 1M and water, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate 5:1) affording 3 as a white solid (1.63 g, 61%). Mp: 82.4-84.3 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.74 (*d*, *J* = 1.7 Hz, 2H, H_b), 7.71 (t, *J* = 1.7 Hz; 1H, H_a), 5.91 (br, 1H, H_c), 3.36 (m, 2H, H_d), 1.54 (m, 2H, H_e), 1.27-1.20 (br, 14H, $H_{f+g+h+i+j+k+l}$), 0.81 (t, *J* = 6.5 Hz, 3H, H_m); ^{13}C NMR ($CDCl_3$, 75Mz): δ ppm 165.2, 138.4, 136.9, 129.2, 123.5, 40.8, 32.2, 29.8, 29.6, 27.3, 23.0, 14.4; FTIR (neat): ν 674, 717, 739, 767, 866, 899, 1107, 1158, 1284, 1310, 1371, 1411, 1462, 1550, 1590, 1639, 2854, 2925, 3286 cm^{-1}. HRMS (ESI-FT) *m/z*: calcd. for $C_{17}H_{24}Br_2NO$ $[M-H]^+$, 416.022461; found, 416.02301.

N-decyl-3,5-bis(2-(trimethylsilyl)ethynyl)benzamide (4). 3,5-dibromo-N-decyl-benzamide (**3**) (770 mg, 1.93 mmol), bis-(triphenylphosphine)-palladium(II)-chloride (133 mg, 0.19 mmol), copper (I) iodide (19 mg, 0.10 mmol) and triethylamine (1.1 mL, 7.72 mmol) were dissolved in dry THF (4 mL). The mixture was subjected to several vacuum/argon cycles and trimethylsilylacetylene (0.8 mL, 5.80 mmol) was added. The mixture was heated at 70 ºC and stirred overnight. After evaporation of the solvent under reduced pressure, the crude was washed with HCl 1M, NH_4Cl saturated solution, water, extracted with methylenechloride, and filtered with celite. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate 20:1) affording 4 as a brownish oil (490 mg, 56%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.79 (d, *J* = 1.5 Hz, 2H, H_b), 6.69 (t, *J* = 1.5 Hz; 1H, H_a), 6.17 (br, 1H, H_d), 3.45 (m, 2H, H_e), 1.61 (q, *J* = 6.8 Hz, 2H, H_f), 1.36-1.30 (br, 14H, $H_{g+h+i+j+k+l+m}$), 0.91 (t, *J* = 6.5 Hz, 3H, Hn), 0.27 (s, 18H, Hc); ^{13}C NMR ($CDCl_3$, 75Mz): δ ppm 166.1, 137.7, 135.4, 130.2, 124.1, 103.3, 96.4, 40.4, 32.1, 29.8, 29.7, 29.5, 27.2, 22.9; FTIR (neat): ν 640, 674, 712, 767, 891, 936, 989, 1067, 1155, 1247, 1326, 1373, 1466, 1538, 1586, 1634, 1817, 2853, 2921, 2955, 3067, 3288 cm^{-1}. HRMS (ESI-FT) *m/z* calcd. for $C_{27}H_{42}NOSi_2$ $[M-H]^+$, 452.280495; found, 452.28079.

N-decyl-3,5-diethynylbenzamide (5). *N*-decyl-3,5-bis(2-(trimethylsilyl)ethynyl)-benzamide (**4**) (639 mg, 1.39 mmol) was dissolved in 20 mL of a THF:methanol mixture (1:1) and potassium carbonate was added (3.11 g, 22.50 mmol). The reaction mixture was stirred for three hours. After evaporation of the solvent under reduced pressure, the residue was washed with water, extracted with methylene chloride, dried over $MgSO_4$, and the solvent evaporated to yield compound 5 that was used without further purification (310 mg, 73%). Mp: 114.5-115.6 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.83 (d, *J* = 1.4 Hz; 2H, H_b), 7.70 (t, *J* = 1.4 Hz, 1H, H_a), 6.12 (br, 1H, H_d), 3.45 (m, 2H, H_e), 3.14 (s, 2H, H_c), 1.60 (m, 2H, H_f), 1.34-1.27 (br, 14H, $H_{g+h+i+j+k+l+m}$), 0.89 (t, *J* = 6.8 Hz; 3H, H_n); ^{13}C NMR ($CDCl_3$, 75Mz): δ ppm 165.7, 137.8, 135.6, 130.7, 123.1, 81.8, 78.9; FTIR (neat): ν 653, 692, 759, 845, 891, 982, 1075, 1167, 1251, 1329, 1425, 1461, 1545, 1585, 1640, 1814, 2159, 2856, 2926, 3073, 3310 cm^{-1}. HRMS (ESI-FT) *m/z* calcd. for $C_{21}H_{28}NO$ $[M+H]^+$, 310.217089; found, 310.21654.

N-decyl-3,5-bis(1-biphenyl-1H-1,2,3-triazol-4-yl)benzamide (1). Compound **5** (126 mg, 0.41 mmol), 4-biphenyl azide (**4**) (228 mg, 1.22 mmol), copper sulphate pentahydrate (2 mg, 0.008 mmol) and sodium ascorbate (4 mg, 0.02 mmol) were dissolved in 4 mL of a dichloromethane:water mixture (1:1) and metallic copper was added to the mixture under Argon atmosphere. The reaction mixture was stirred for 72 hours and then, the organic layer was separate, dried over $MgSO_4$, and filtered. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, chloroform:methanol 100:1) affording **1** as a light yellow solid (223 mg, 78%). Mp: 201.7-202.7 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 8.58 (br, 1H, H_a), 8.38 (s, 2H, H_c), 8.31 (d, *J* =1.3 Hz, 2H, H_b), 7.85 (d, *J* = 8.6Hz, 4H, H_d), 7.75 (d, *J* = 8.6 Hz 4H, H_e), 7.63 (m, 4H, H_f), 7.51-7.38 (m, 6H, H_{g+h}), 6.71 (t, *J* = 5.7 Hz 1H, H_i), 3.53 (m, 2H, H_j), 1.70 (q, *J* = 6.8 Hz, 2H, H_k), 1.46-1.28 (br, 14H, $H_{l+m+n+o+p+q+r}$), 0.89 (t, *J* = 6.7 Hz, 3H, H_s); ^{13}C NMR ($CDCl_3$, 75Mz): δ ppm 166.7, 147.2, 141.9, 139.5, 136.2, 135.9, 131.3, 129.0, 128.4, 128.0, 127.1, 125.3, 123.9, 120.7, 118.3, 40.4, 31.9, 29.7, 29.6, 29.4, 29.3, 27.1, 22.7, 14.1; FTIR (neat): ν 626, 647, 658, 695, 722, 763, 841, 892, 991, 1042, 1117, 1234, 1296, 1402, 1459, 1491, 1527, 1610, 1643, 2363, 2854, 2924, 3062, 3138, 3291 cm^{-1}; HRMS (ESI-FT) *m/z* calcd. for $[C_{45}H_{46}N_7O]^+$: 700.37584; found, 700.37608.

Computational details.

All theoretical calculations were carried out within the density functional theory (DFT) approach by using the C.01 revision of the Gaussian 09 program package.[20] DFT calculations were performed using the hybrid meta exchange-correlation M06-2X functional, which has been specially designed to account for noncovalent interactions.[21] Geometry optimizations were carried out with the M06-2X functional in combination with the standard 6-311G** basis set.[22] The alkyl chains attached to the nitrogen of the amide group in receptor **1** and forming the alkoxy groups of **12GA** were substituted by methyl groups to reduce the computational cost. On the previously optimized structures, single-energy calculations at the M06-2X/6-311G** level were performed to compute the binding energies. The basis set superposition error (BSSE) affecting the binding energies was corrected by using the standard counterpoise method.[23] The BSSE is estimated to be almost negligible for **1**•X^- complexes

(1−2 kcal mol^{-1} for Cl^-, Br^-, and I^-). For complex **1•(12GA)$_2$**, the BSSE increases to 6.4 kcal mol^{-1} that only represents a 15 % of the total binding energy. These results suggest that the calculation of binding energies for this kind of supramolecular complexes, for which the association is determined by strong electrostatic and H-bonding interactions, can be quite accurately estimated without taken into account the BSSE correction.[24]

Conclusions

The synergy between experimental evidences and theoretical calculations has demonstrated the versatility of the bis(triazole)benzamide receptor **1** to bind species of different nature and, hence, an interesting guest-controlled topicity. Compound **1** binds halide anions forming complexes with a 1:1 stoichiometry with similar binding constants of 29.0 (± 5%) and 37.4 (± 4%) M^{-1} for chloride and bromide anions, respectively. However, receptor **1** is able to bind a neutral carboxylic acid forming the corresponding 1:2 complexes in a non-cooperative statistical fashion, that is, the binding of the first guest does not influence the interaction with the second guest. The calculated binding constants for the formation of the complex **1·[12GA]$_2$** are K_1 = 426 M^{-1} and K_2 = 106 M^{-1}. The presence of the amide functionality plays a pivotal role in the complexation of both anionic and neutral species, which are bound by means of H-bonding arrays involving N−H, O−H, and C−H groups. The initial zig-zag "anti" conformation of the receptor is not altered upon the complexation. The aromatic surface of the free receptor, of complex **1**•Br^-TBA^+, and of complex **1•(12GA)$_2$** allows the generation of organized supramolecular structures.

Acknowledgements

Financial support by the MICINN of Spain (CTQ2011-22581, CTQ2009-08970, CTQ2008-00795, and Consolider-Ingenio CSD2007-00010 in Molecular Nanoscience), the Generalitat Valenciana (PROMETEO/2012/053), and UCM (GR42/10-962027) is acknowledged. F. G. is indebted to MEC for a FPU studentship.

Notes and references

[a] *Departamento de Química Orgánica, Facultad de Ciencias Químicas, Ciudad Universitaria s/n. 28040 Madrid (Spain), e-mail: lusamar@quim.ucm.es*

[b] *Instituto de Ciencia Molecular, Universidad de Valencia, 46980 Valencia (Spain), e-mail: enrique.orti@uv.es*

† Electronic Supplementary Information (ESI) available: NOE experiments, concentration dependent ^{1}H NMR experiments, MEP for **1** in its conformation A, optimized structures of **1·(12GA-*l*)** and **1·(12GA-r)** complexes; SEM images, experimental details, and atomic coordinates and total energy for all optimized molecular structures at the M06-2X/6-311G** level. See DOI: 10.1039/b000000x/

1 (*a*) F. Guba, *Nature* 1950, **165**, 439; (*b*) H. A. Krebs and W. A. Johnson, *FEBS Letters* 1980, **117**, 148.

2 (*a*) M. Boiocchi, L. Del Boca, D. E. Gomez, L. Fabbrizzi, M. Licchelli and E. J. M.; Monzani, *J. Am. Chem. Soc.* 2004, **126**, 16507; (*b*) S. J. Brooks, P. A. Gale and M. E. Light, *Chem. Commun* 2005, 4696; (*c*) X. He, F. Herranz, E. Chung-Chin Cheng, R. Vilar and V. Wing-Wah Yam, *Chem. Eur. J.* 2010, **16**, 9123.

3 (*a*) K. A. Nielsen, W. S. Cho, J. Lyskawa, E. Levillain, V. M. Lynch, J. L. Sessler and J. O. Jeppesen, *J. Am. Chem. Soc.* 2006, **128**, 2444; (*b*) C. H. Lee, H. Miyaji, D. W. Yoon and J. L. Sessler, *Chem. Commun*. 2008, 24.

4 (*a*) Y. Furusho, T. Kimura, T. Mizuno and T. Aida, *J. Am. Chem. Soc.* 1997, **119**, 5267; (*b*) E. Yashima, K. Maeda and Y. Okamoto, *Nature* 1999, **399**, 449; (*c*) T. Ishi-i, M. Crego-Calama, P. Timmerman, D. N. Reinhoudt and S. Shinkai, *Angew. Chem. Int. Ed.* 2002, **41**, 1924.

5 (*a*) Y. Li and A. H. Flood, *Angew. Chem. Int. Ed.* 2008, **47**, 2649; (*b*) Y. Li and A. H. Flood, *J. Am. Chem. Soc.* 2008, **130**, 12111; (*c*) Y. Li, M. Pink, J. A. Karty and A. H. Flood, *J. Am. Chem. Soc*. 2008, **130**, 17293.

6 (*a*) R. M. Meudtner, M. Ostermeier, R. Goddard, C. Limberg and S. Hecht, *Chem. Eur. J.* 2007, **13**, 9834; (*b*) H. Juwarker, J. M. Lenhardt, D. M. Pham and S. L. Craig, *Angew. Chem. Int. Ed.* 2008, **47**, 3740; (*c*) H. Juwarker, J. M. Lenhardt, J. C. Castillo, E. Zhao, S. Krishnamurthy, R. M. Jamiolkowski, K.-H. Kim and S. L. Craig, *J. Org. Chem.* 2009, **74**, 8924; (*d*) Y. Hua and A. H. Flood, *J. Am. Chem. Soc.* 2010, **132**, 12838.

7 Y. Hua and A. H. Flood, *Chem. Soc. Rev.* 2010, **39**, 1262.

8 M.-H. Ryu, J.-W. Choi, H.-J. Kim, N. Park and B. K. Cho, *Angew. Chem. Int. Ed.* 2011, **50**, 5737.

9 F. García, M. R. Torres, E. Matesanz and L. Sánchez, *Chem. Commun.* 2011, **47**, 5016.

10 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.* 2002, **41**, 2596.

11 M. Hu, J. Li and S. Q. Yao, *Org. Lett.* 2008, **10**, 5529.

12 I. Bandyopadhyay, K. Raghavachari and A. H. Flood, *ChemPhysChem* 2009, **10**, 2535.

13 R. Schwesinger, R. Link, P. Wenzl and S. Kossek, *Chem. Eur. J.* 2006, **12**, 438.

14 (a) P. Thordarson, *Chem. Soc. Rev*., 2011, **40**, 1305; (b) Binding Constants: The Measurements of Molecular Complex Stability, (ed. K. A. Connors) Wiley, New York, 1987;

15 M. Shirakawa, N. Fujita, T. Tani, K. Kaneko and S. Shinkai, *Chem. Commun.* 2005, 4149.

16 (*a*) M. F. Perutz, *Annu. Rev. Biochem.* 1979, **48**, 327; (*b*) J. L. Macdonald and L. J. Pike, *Proc. Natl. Acad. Sci. U.S.A.* 2008, **105**, 112.

17 (*a*) A. V. Hill, *Biochem. J.* 1913, **7**, 471; (*b*) S. Shinkai, M. Ikeda, A. Sugasaki and M. Takeuchi, *Acc. Chem. Res.* 2001, **34**, 494; (*c*) C. A. Hunter and H. L. Anderson, *Angew. Chem. Int. Ed.* 2009, **48**, 7488.

18 H. Tsukube, H. Furuta, A. Odani, Y. Takeda, Y. Kudo, Y. Inoue, Y. Liu, H. Sakamoto and K. Kimura, in *Comprehensive Supramolecular Chemistry*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, Pergamon, Oxford, 1996, vol. 8, ch. 10, pp. 425–482.

19 (a) B. Perlmutter-Hayman, *Acc. Chem. Res*., 1986, **19**, 90; (b) A. J. Lowe, F. M. Pfeffer and P. Thordarson, *Supramolec. Chem.* 2012, **24**, 585.

20 Gaussian 09, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian, Inc., Wallingford CT,* 2009.

21 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.* 2008, **120**, 215.

22 (*a*) R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.* 1980, **72**, 650; (*b*) M. N. Glukhovstev, A. Pross, M. P. McGrath and L. Radom, *J. Chem. Phys.* 1995, **103**, 1878.

23 S. F. Boys and F. Bernardi, *Mol. Phys.* 1970, **19**, 553.

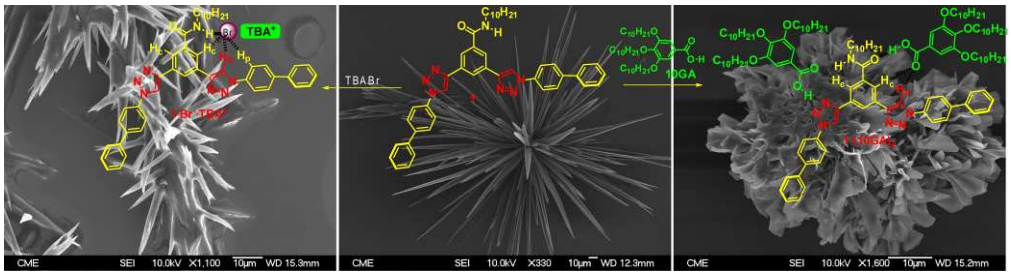
24 F. García, P. M. Viruela, E. Matesanz, E. Ortí and L. Sánchez, *Chem. Eur. J*. 2011, **17**, 7755.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE View Article Online

Table of contents



The cavity defined by the N−H amide group and the vicinal aromatic hydrogens of bis(triazole)benzamide **1** is suitable to form H-bonding arrays with halide guests and neutral gallic acid derivative **12GA** with 1:1 and 1:2 stoichiometries, respectively.