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Halide binding and self-assembling behavior of Triazole-based acyclic and cyclic molecules

V. Haridas [a,*], Srikanta Sahu [a], P. Venugopalan [b]

[a] Department of Chemistry, Indian Institute of Technology, Hauz Khas, New Delhi-110016, India
[b] Department of Chemistry, Panjab University, Chandigarh, India

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ABSTRACT

The present study demonstrates the use of triazole moiety in designing molecules endowed with the ability for self-assembly and molecular recognition. The receptors **7a** and **9a** having open structures bind to fluoride ion with good affinity. Various cyclophanes with 19-, 20-, 21-, 38-, and 40-membered rings containing triazole units were designed and synthesized. X-ray crystal structure of macrocycle **16** showed a tubular like architecture. Triazolophane **22** possesses bifurcated CH···N intramolecular hydrogen bonds and it further organizes in the solid state using CH···N interactions. Triazole based compounds are potential store house for exploiting CH···O and CH···N hydrogen bonding interactions for molecular self-assembly.

1. Introduction

The ever-increasing number of receptor designs for ions and neutral molecules has been highlighted in the literature, especially exotic structures with unusual binding abilities.[1–4] However, despite a large number of efforts directed towards receptor design; general design strategies for receptors with high affinity and specificity for a given analyte are rare. This lacuna is partly due to the intricacies of the weak forces involved in binding *inter alia* and the precise requirement of spatial and temporal factors.[5–7] These limitations stem from our inability to predict the conformation of receptor in solution a priori and the innumerable non-covalent interactions that play an integral role in deciding whether or not a molecule can act as a receptor for specific guest. The design of receptors incorporating non-conventional hydrogen bonding interactions continues to be challenging even though enormous advancements have been made during the last two decades in the understanding of non-conventional hydrogen bonding.[8–10]

Molecular engineering of receptors requires a precise control of binding interactions, correct cavity size and solvation among other parameters.[11,12] One path for successful molecular engineering is design and synthesis of preorganized receptors that will have an energetic advantage over other flexible structures.[13,17c] However, a conformationally rigid system may hamper the torsional motion of bonds to organize around a guest molecule. Most often it is difficult to design highly preorganized and rigid receptors with accurate atomic level complementarity with the guest molecule. Therefore, a semi-rigid system that can adopt a favorable conformation with less bond rotation to fit the guest molecule is especially useful. The advantage of such design is the possibility to generate receptors for any given guest molecule through simple modulation of the receptor. We report a simple, uncharged triazole-based semi-rigid receptor molecule capable of anion recognition utilizing non-conventional hydrogen bonding and also report triazolophanes with tubular and string-like architecture in the solid state.

2. Results and discussion

The Huisgen reaction (or 1,3-dipolar cycloaddition) involving an alkyne and azide unit is the simplest method to introduce a triazole entity. This reaction has been central to many investigations in recent years for applications in bioconjugation and in supramolecular chemistry.[14–16] Triazole derivatives[17] and triazolophanes[18] have been demonstrated as excellent entities for molecular recognition utilizing the CH···O and CH···N interactions. A triazole ring with three nitrogens and a C–H donor site can be engineered to make a specific receptor exploiting the donor/acceptor interactions. Making use of these hydrogen bond donor/acceptor sites for molecular recognition requires a precise arrangement of the triazole moiety in appropriate spatial disposition to maximize the interaction with the guest molecule. This requires use of an

* Corresponding author. Tel.: +91 11 26591380; e-mail address: h_haridas@hotmail.com (V. Haridas).

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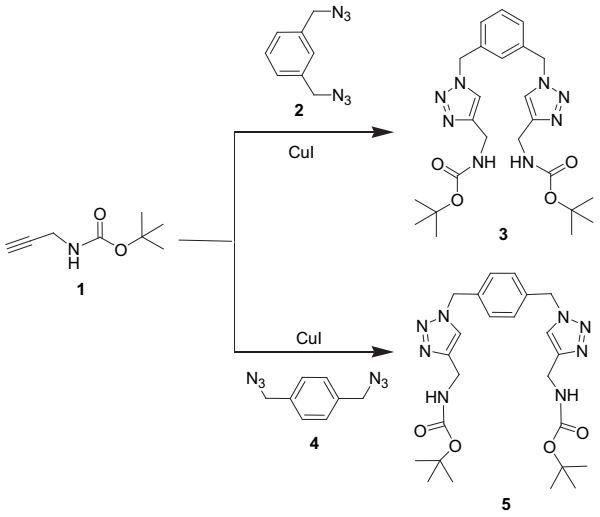
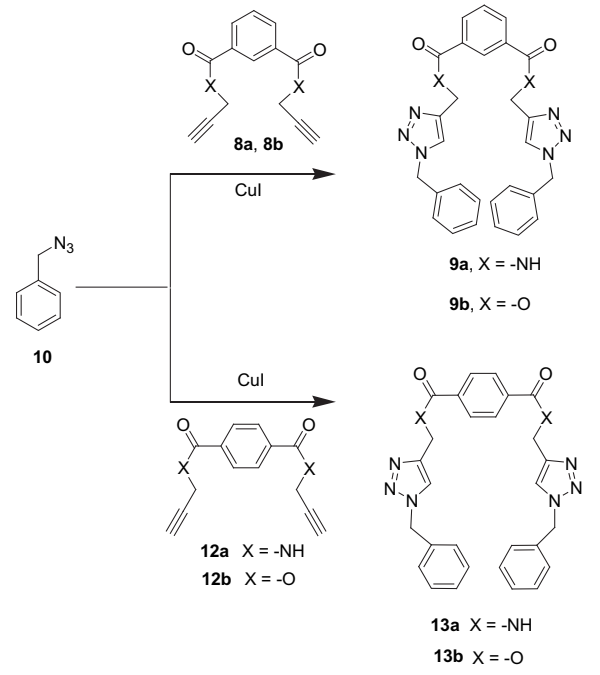
appropriate scaffold that can display the triazole units in the right orientation for binding to anions.

In search of a molecular scaffold for the ideal disposition of triazole units, we embarked on a systematic analysis of rigid aromatic scaffolds. Anchoring triazole moieties on a benzenoid scaffold may provide rigidity, and thus may act as receptors for anions. We synthesized molecules **3** and **5** embodying two triazole moieties in their structures and evaluated their binding affinities toward anions. The Boc protected propargylamine was reacted with *m*-xylylene diazide in the presence of catalytic amounts of CuI to yield **3**. Similarly, **5** was synthesized from *p*-xylylene diazide and Boc-propargylamine (Scheme 1).



Scheme 1. Synthesis of **3** and **5**.

The anion binding properties of all the synthesized compounds were investigated using a ^{1}H NMR titration technique. The addition of tetrabutylammonium halide (TBAX) to a solution of **3** and **5** in $CDCl_3$ showed no noticeable changes in the NMR spectra, indicating no binding of anions. Therefore, we designed compounds **9a** and **13a** (Scheme 2), anticipating that the incorporation of the amide close to the aryl ring may provide a suitable environment for the relatively acidic C2H of the aromatic ring to participate in binding. Upon addition of tetrabutylammonium halide (TBAX) to **9a** in $CDCl_3$ resulted in shifting of amide NHs, aromatic ring hydrogen (C2H) and both triazole ring CHs to downfield (Fig. 1). The detailed NMR titration experiments performed on **9a** showed that



Scheme 2. Synthesis of **9a**, **9b**, **13a** and **13b**.

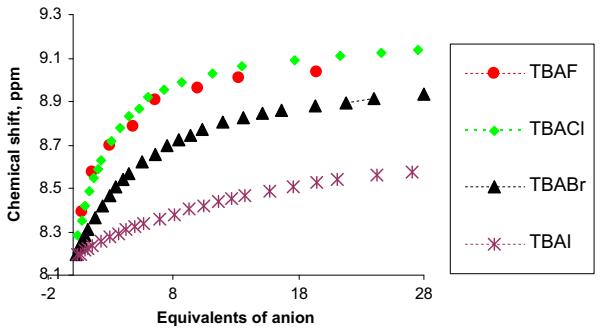


Fig. 1. Variation of aromatic CH (isopthaloyl) proton chemical shift upon addition of TBAX to a solution of **9a** in $CDCl_3$ at room temperature.

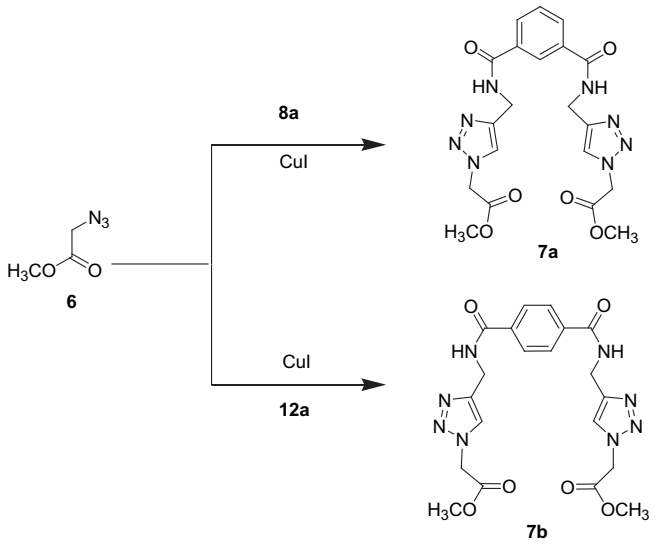
it indeed binds to F^-, Cl^-, Br^-, and I^- (Fig. 1 and Table 1). The binding constants were determined using WinEQ NMR analysis of the NMR data (Supplementary data).[19] Receptor **9a** binds to fluoride strongly (K_a 1973±150 M^{-1}), followed by weak binding to Cl^-, Br^-, and I^- (Table 1). Job plots indicated the formation of 1:1 complex (Supplementary data). Receptor **13a** with triazole entities

Table 1
Binding constants of triazole derivatives **9a** and **7a** along with dialkyne **8a** as the control

Anion salts	K_a (M^{-1}) (**9a**)	K_a (M^{-1}) (**7a**)	K_a (M^{-1}) (**8a**)
F^-	1973±150	1383±90	1028±97
Cl^-	914±15	1606±41	548±34
Br^-	436±7	553±8	222±5
I^-	115±3	248±15	104±7

on the 1,4-positions of an aromatic ring was insoluble in $CDCl_3$ and the binding studies were carried out in DMSO-d_6. The NMR titration experiments show that molecule **13a** binds only to the fluoride ion with weak binding (K_a ~ 82 M^{-1}) affinity. The change from amide linkages to ester linkages (**9a** and **9b** or **13a** and **13b**) resulted in complete lack of anion binding. The two amide NHs and two acidic triazole CHs, in concert with an aromatic proton in close proximity are essential for binding. The influence of phenyl rings at the terminal positions were investigated by using azidomethyl acetate instead of benzylazide in the reaction (Scheme 3). The receptors **7a** and **7b** showed improved solubility behavior; additionally the selectivity towards anions was also changed as a result of change in the terminal groups. Receptor **7a** binds to chloride stronger than fluoride (Table 1, Fig. 2), unlike receptor **9a** that binds fluoride more strongly than chloride. The different affinities of **7a** and **9a** towards anions might be due to flexibility of the structure as a result of the change in terminal groups. As control experiments, dialkyne **8a** was analyzed for binding towards various anions and found that the K_a values (Table 1) are lesser than that of the receptors **7a** and **9a**. Receptors with triazole units on the 1,3 positions of the benzene ring are better binders of anions than the receptors wherein the triazole units were attached to 1,4-positions of the phenyl ring implying the right cavity size is essential for binding. Mere introduction of triazole units on the aromatic scaffold is also not sufficient as receptor **3** bound anions

with lesser affinity than **7a** and **9a**. The amide bonds are essential for halide binding as none of the ester-linked molecules (**9b**, **13b**) showed affinity for halide ions. These results clearly demonstrate that triazole units provide additional hydrogen bond donor sites, which in concert with the precise arrangement of additional hydrogen bond donor moieties such as amide bonds can enhance binding affinities.



Scheme 3. Synthesis of **7a** and **7b**.

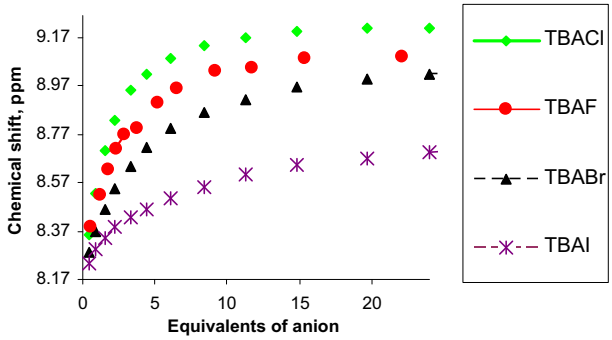
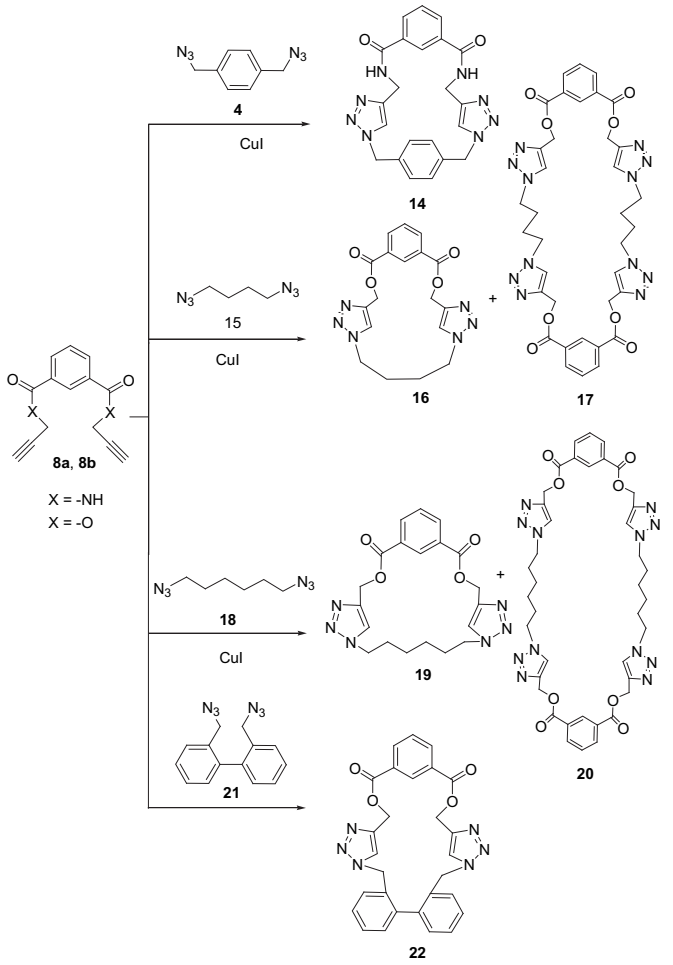


Fig. 2. Variation of aromatic CH (isopthaloyl) proton chemical shift upon addition of TBAX to a solution of **7a** in $CDCl_3$ at room temperature.

We then turned our attention to restricting the conformation of the receptors by synthesizing various triazole-based macrocycles with the intention that the triazolophanes will act as constrained analogs of the open chain structures. We envisaged that triazolophanes with highly preorganized structure may bind anions very strongly and with better selectivity. We anticipated that these triazolophanes may also serve as a good model system for studying their supramolecular interaction using non-conventional hydrogen bonding. Therefore, various triazolophanes were designed and synthesized (Scheme 4) to find application as receptors and also to study their organization in the solid state. The *p*-xylylene diazide **4** was reacted with dialkyne **8a** to provide the macrocycle **14** in 70% yield. The ^{1}H NMR spectrum of **14** indicated that it has a symmetric structure as evident from the appearance of a singlet for benzylic protons at δ 5.52 ppm. Reaction of diazide **4** with terephthaloyl-anchored dialkyne **12a** resulted in highly insoluble material and was unable to be characterized. Macrocycle **14** with 21-membered ring showed very weak binding to halide anions in spite of its rigid cyclic structure and amide linkages. Similarly, ester-linked biphenyl macrocycle **22** with a 21-membered ring showed no affinity for the halide ions. Our observation is that all the amide-based triazole compounds synthesized had poorer solubility than their ester counterparts. Therefore, we believe that the rigid triazolophanes with amide linkages might arrange in the solid state using very strong intermolecular hydrogen bonding interactions.



Scheme 4. Synthesis of **14**, **16** **17**, **19**, **20**, and **22**.

This prompted us to use a more flexible linker to tether the two triazole units. Semi-rigid amide/ester-linked triazolophanes with four and six-methylenes in the ring were synthesized from the corresponding diazides and dialkynes. For example, reaction of 1,4-diazidobutane with dialkyne **8b** resulted in 19- and 38-membered macrocycles **16** and **17** in 67% and 12% yield, respectively. Similarly, reaction of 1,6-diazidohexane with **8b** provided 20 and 40-membered triazolophanes **19** and **20** in 56% and 15% yield, respectively. It is noteworthy to mention that macrocycles **17** and **20** embody four triazole units in their structures. Macrocycles **16**–**20** are highly symmetric as evident form their ^{1}H NMR spectra. Macrocycles **16** and **17** display two sets of peaks for the methylene protons of the butyl chains, one singlet for the triazole CHs and one singlet representing the methylenes attached to the ester oxygens. 38-membered macrocycle **20** with four triazole units showed only one singlet for the triazole CHs at δ 7.68 ppm ($CDCl_3$) and very symmetric distributions of methylene protons in the ^{1}H NMR spectrum. The ^{1}H NMR spectrum of **19** showed one singlet for the two triazole CHs and highly symmetric distributions of methylene protons. These tetra-triazole compounds **17** and **20** open up new opportunities for developing molecules with metal uptake ability. The attempted

synthesis of various amide analogs of triazolophanes by reaction of **8a** with diazides **15**, **18**, and **21** resulted in highly insoluble material. This hampered their characterization and the binding studies. Macrocycles **16**, **17**, **19**, **20**, and **22** with ester linkages showed no noticeable changes in their ^{1}H NMR spectra after addition of variable amounts of TBAX in $CDCl_3$. The results underscore the stringent requirements of the precise conformation; an adequate number of binding moieties and flexibility of the structure are of paramount importance in the design of receptors.

The ester-linked cyclophanes are interesting candidates for studying their self-assembling properties since they do not have any conventional hydrogen bond donor sites. These macrocyclic structures without any conventional hydrogen bond donor sites may organize in the solid state using CH···O and CH···N interactions.[20] Therefore, these compounds may serve as good models for studying non-conventional and non-covalent hydrogen bonding interactions.

Triazolophane **16** was crystallized from a mixture of chloroform and methanol. It crystallized in monoclinic crystal system (space group, $P2_1/c$) with four molecules in the unit cell. Each macrocycle used triazole nitrogen (N4) and oxygen of the ester carbonyl (O1) as hydrogen bond acceptors, whereas the aromatic proton (H4) and triazole hydrogen (H14) acted as the donors. The aliphatic butyl moiety that links the two triazole units is disordered over two positions. Moreover, the benzene ring of the molecule takes an approximate perpendicular juxtaposition, in which it makes an angle of 66.6° with N1 bearing triazole and 82.3° with N4 bearing triazole ring. The lattice stabilization is achieved through weak C–H···X (X=O, N) hydrogen bonds and π···π stacking interactions. Two centrosymmetrically related benzene rings are π stacked with a shearing in such a way that the C2···C2 distance is 3.413 Å and the distance between the best least squares plane through these rings is 3.356 Å (Supplementary data). Between these π-stacked molecules there is an additional C–H···N interaction between H6 and N4 (H6A···N4=2.611 Å, C6–H6A···N4=152.1°), thus generating a dimer through a unison of C–H···N and π···π interactions (Fig. 3a). Two such dimers that are related by c glide are interconnected through another C–H…O (H14A···O1=2.611 Å, C14–H14A···O1=133.3°) hydrogen bond. This pattern is infinitely repeated to build up the lattice as shown in Fig. 3b. When the packing is viewed down b axis, because of the π-stacking, nanotube-like arrangements[21] are formed (Fig. 3b) and this arrangement is held in place through weak C–H···O interactions.

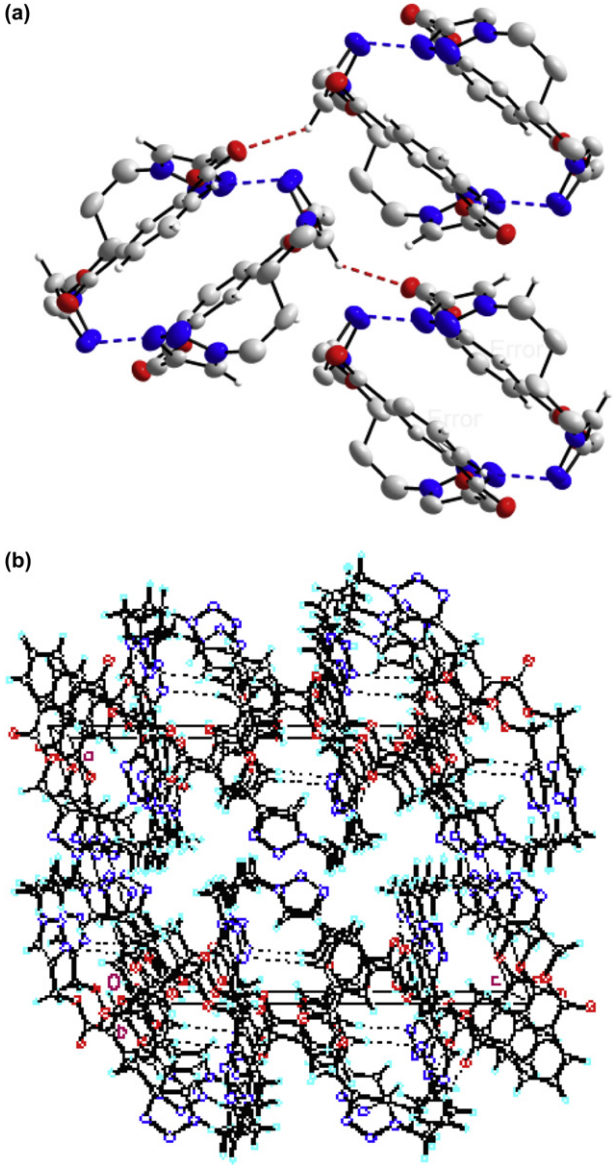


Fig. 3. (a) The dimeric arrangement of **16** showing the π–πand hydrogen bonding interactions (b) Packing diagram of **16**.

The biphenyl linked cyclophane **22** was synthesized from **8b** to 2,2′-bis(azidomethyl)biphenyl **21** in 63% yield. Macrocycle **22** was crystallized from a mixture of chloroform and methanol (2:1). The X-ray crystal structure analysis (Fig. 4) revealed a string-like arrangement of macrocycles connected by intermolecular CH···N hydrogen bonding (H12A···N5=2.732 Å, C12–H12A–N5=137.89°) and (H12A···N4=2.678 Å, C12–H12A–N4=134.80°). One triazole ring hydrogen (CH) is pointing inside the cavity, and the CH of second triazole ring is projecting outwards, thus ideal for intramolecular and intermolecular interactions. The intramolecular

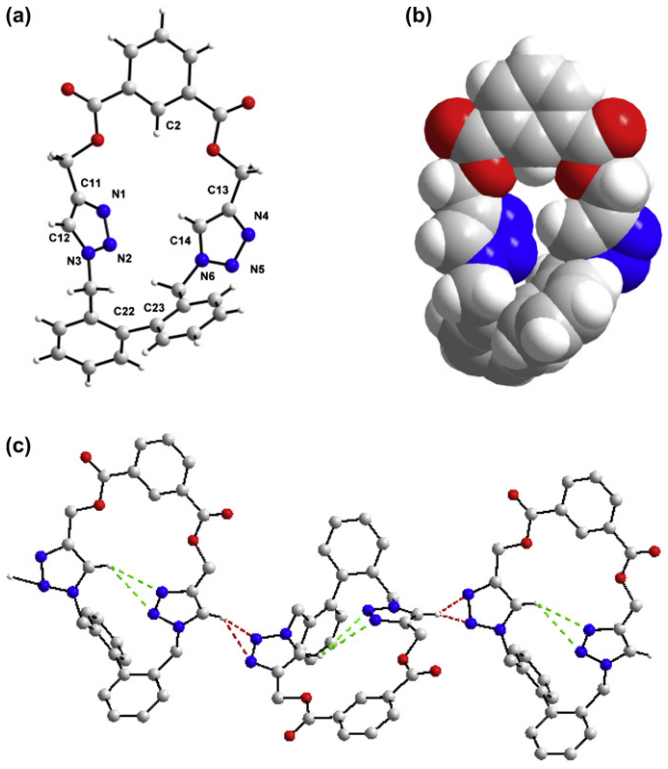


Fig. 4. (a) X-ray crystal structure of **22** (b) CPK model of the molecule showing the internal cavity (c) The arrangement of **22** showing the intramolecular and intermolecular CH···N interactions.

hydrogen bonding is between the triazole nitrogens (N1 and N2) and the CH (H14A) of the other triazole unit (N1···H14A=2.99 Å, N2···H14A=2.99 Å). The biphenyl system has an orthogonal arrangement of phenyl rings, and the cavity size of the macrocycle is different in the vertical and horizontal direction. The distance between the atoms C12 and C14 is 5.53 Å. The distance between N2 and C14 is ~3.64 Å. The vertical distance between the atoms C2 and C22 is 8.52 Å. X-ray crystal structures of two triazolophanes **16** and **22** thus demonstrated the intrinsic tendency to assemble in the solid state using non-conventional hydrogen bonding interactions.

3. Conclusions

We demonstrated that placing triazole moieties on different positions of an aromatic scaffold can change the binding affinity towards anions. Various receptor designs described here emphasize that simple triazole moiety is a potential CH hydrogen bond donor for binding anions and for designing self-assembling systems. Macrocycles **14**, **16**, **17**, **19**, **20**, and **22** containing triazole units with small and large rings can be designed and synthesized using click chemistry. The self-assembling properties of macrocycles **16** and **22** were investigated by X-ray crystallographic analysis. The macrocycle **16** assembles as a nanotubular structure in the solid state using entirely non-conventional non-covalent interactions. The molecules synthesized here will be of potential use in biological ion-transport and thus may have nanobiotechnological applications. The intrinsic tendency of the triazole moiety to organize in the solid state using non-conventional hydrogen bonding will be a harbinger for further studies in the area of crystal engineering.

4. Experimental section

4.1. General method of preparation of 3 and 5

To an ice cold solution of Boc-propargylamine (**1**) (413 mg, 2.66 mmol) in dry acetonitrile was added diisopropylethylamine (DIEA) (0.45 mL, 2.7 mmol), followed by diazide (200 mg, 1.06 mmol) under an N_2 atmosphere. CuI (21 mg, 0.11 mmol) was added and the reaction mixture was stirred for 24 h under an N_2 atmosphere. The solvent was evaporated and the residue was dissolved in chloroform and washed with aqueous solution of NH_4Cl+NH_4OH (9:1), 2 N H_2SO_4, saturated solution of $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain the product.

*4.1.1. Compound **3**.* Yield 80%; mp 93–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 18H), 4.38 (d, J=5.7 Hz, 4H), 5.19 (br s, 2H), 5.48 (s, 4H), 7.11 (s, 1H), 7.22 (d, J=7.5 Hz, 2H), 7.37 (t, J=7.5 Hz, 1H), 7.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 36.1, 53.6, 79.6, 121.9, 127.3, 128.1, 129.8, 135.7, 146.1, 155.8; IR (KBr): 3348, 3140, 2979, 2938, 1694, 1526, 1443, 1365, 1281, 1248, 1171, 1046 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{34}N_8O_4Na$: 521.2601, found: 521.2617.

*4.1.2. Compound **5**.* Yield 90%; mp 184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 18H), 4.36 (d, J=6.0 Hz, 4H), 5.08 (br s, 2H), 5.49 (s, 4H), 7.25 (m, 4H), 7.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 36.1, 53.6, 79.7, 121.8, 128.7, 135.3, 146.0, 155.8; IR (KBr): 3399, 3115, 3066, 2977, 2938, 1691, 1511, 1434, 1365, 1332, 1266, 1167, 1050 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{24}H_{35}N_8O_4$: 499.2781, found: 499.2785.

4.2. General method for the preparation of 8a and 12a

To an ice cold solution of propargylamine (0.34 mL, 4.9 mmol) in dry dichloromethane was added triethylamine (1.4 mL, 9.8 mmol) followed by dropwise addition of acid chloride (2.5 mmol) in dry dichloromethane over 30 min. The reaction mixture was stirred for 12 h. The solvent was evaporated and the residue was washed sequentially with 2 N H_2SO_4, saturated solution of $NaHCO_3$, water and diethylether. The solid obtained was recrystallized from a mixture of chloroform and methanol.

*4.2.1. Compound **8a**.* Yield 96%; mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.13 (s, 2H), 4.06 (d, J=2.7 Hz, 4H), 7.56 (t, J=7.8 Hz, 1H), 7.97 (d, J=7.5 Hz, 2H), 8.31 (s, 1H), 9.03 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.6, 72.9, 81.1, 126.4, 128.5, 130.0, 134.1, 165.5; IR (KBr): 3315, 3256, 3079, 2928, 2113, 1649 (br), 1535, 1476, 1418, 1301, 1177, 1055, 1010 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{13}N_2O_2$: 241.0977, found: 241.0980.

*4.2.2. Compound **12a**.* Yield 95%; mp 247–250 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.15 (s, 2H), 4.08 (s, 4H), 7.95 (s, 4H), 9.08 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.0, 73.43, 81.6, 127.8, 136.7, 165.7; IR (KBr): 3285 (br), 3062, 2955, 2903, 2859, 2119, 1638, 1543, 1494, 1443, 1356, 1285, 1231, 1161, 1113, 1064 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{12}N_2O_2Na$: 263.0796, found: 263.0802.

4.3. General method of preparation of 7a, 7b, 9a, 9b, 13a, and 13b

To an ice cold and homogeneous solution of dialkyne (1.03 mmol) in dry acetonitrile was added DIEA (0.35 mL, 2.1 mmol), followed by benzylazide **10** or azidomethyl acetate **6** (2.07 mmol) under an N_2 atmosphere. To the reaction mixture under nitrogen, was added CuI (19.67 mg, 0.11 mmol) and stirred for 24 h. The reaction mixture was evaporated and the solid obtained was washed sequentially with aqueous solution of NH_4Cl+NH_4OH (9:1), 2 N H_2SO_4, saturated solution of $NaHCO_3$, water, and diethylether. The solid obtained was recrystallized from a mixture of chloroform and methanol.

*4.3.1. Compound **7a**.* Yield 89%; mp 159–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 6H), 4.63 (d, J=4.2 Hz, 4H), 5.46 (s, 4H), 7.66 (t, J=7.95 Hz, 1H), 8.02–8.15 (m, 4H), 8.46 (s, 1H), 9.27 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.3, 50.6, 52.9, 124.9, 126.9, 128.9, 130.4, 134.8, 145.5, 166.2, 168.2; IR (KBr): 3413, 3278, 3138, 3067, 2993, 2954, 1754, 1643, 1534, 1443, 1377, 1291, 1226 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{22}N_8O_6Na$: 493.1560, found: 493.1556.

*4.3.2. Compound **7b**.* Yield: 92%; mp 222–224 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.70 (s, 6H), 4.54 (d, J=5.1 Hz, 4H), 5.37 (s, 4H), 7.95 (s, 4H), 7.99 (s, 2H), 9.21 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.3, 50.6, 52.9, 124.9, 127.9, 136.8, 145.4, 165.9, 168.2; IR (KBr): 3333, 3291, 3146, 3080, 3007, 2957, 1739, 1660, 1634, 1554, 1499, 1444, 1416, 1372, 1293, 1248, 1149, 1052 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{23}N_8O_6$: 471.1741, found: 471.1737.

*4.3.3. Compound **9a**.* Yield: 90%; mp 196–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 4.66 (d, J=5.1 Hz, 4H), 5.49 (s, 4H), 7.24–7.44 (m, 10H), 7.48 (t, J=6.0 Hz, 1H), 7.62 (s, 2H), 8.04 (d, J=7.5 Hz, 2H), 8.31 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.4, 51.2, 121.6, 124.9, 126.5, 126.6, 126.9, 127.2, 128.4, 132.7, 134.6, 143.6, 164.2; IR (KBr): 3289, 3122, 3070, 2939, 1642, 1537, 1427, 1353, 1303, 1231, 1131, 1050 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{28}H_{27}N_8O_2$: 507.2257, found: 507.2269.

*4.3.4. Compound **9b**.* Yield: 98.7%; mp 122–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.45 (s, 4H), 5.54 (s, 4H), 7.25–7.45 (m, 10H), 7.49 (t, J=7.8 Hz, 1H), 7.62 (s, 2H), 8.20 (d, J=7.5 Hz, 2H), 8.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.2, 58.3, 123.9, 128.1, 128.6, 128.8,

129.1, 130.2, 131.0, 134.1, 134.3, 142.9, 165.5; IR (KBr): 3133, 3081, 3037, 2959, 1723, 1601, 1445, 1383, 1339, 1296, 1234, 1167, 1124, 1084 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{28}H_{25}N_6O_4$: 509.1937, found: 509.1927.

4.3.5. Compound ***13a***. Yield: 93%; mp 246–248 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 4.52 (d, *J*=5.4 Hz, 4H), 5.56 (s, 4H), 7.35 (m, 10H), 7.93 (s, 4H), 8.04 (s, 2H), 9.13 (t, *J*=5.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.9, 52.7, 123.1, 127.3, 128.0, 128.1, 128.7, 136.1, 136.4, 145.2, 165.5; IR (KBr): 3366, 3122, 3067, 2946, 1638, 1541, 1496, 1450, 1366, 1301, 1232, 1164, 1125, 1055 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{28}H_{27}N_8O_2$: 507.2257, found: 507.2256.

4.3.6. Compound ***13b***. Yield: 93%; mp 206–208 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 5.45 (s, 4H), 5.53 (s, 4H), 7.28 (m, 4H), 7.37 (m, 6H), 7.60 (s, 2H), 8.05 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.3, 58.4, 123.9, 128.2, 128.9, 129.2, 129.7, 133.7, 134.3, 142.9, 165.5; IR (KBr): 3119, 3063, 2958, 1717, 1499, 1450, 1400, 1274, 1219, 1106, 1057, 1023 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{28}H_{25}N_6O_4$: 509.1937, found: 509.1923.

4.4. Preparation of 14

To an ice cold and well-stirred solution of **8a** (149 mg, 0.62 mmol) in dry acetonitrile was added DIEA (0.23 mL, 1.4 mmol), **4** (130 mg, 0.68 mmol), and CuI (12 mg, 0.062 mmol). The reaction mixture was left stirred under nitrogen for 24 h. Afterwards, the solvent was evaporated and the residue was washed sequentially with saturated solution of NH_4Cl+NH_4OH (9:1), 2 N H_2SO_4, saturated solution of $NaHCO_3$, water, and ether. The solid obtained was subjected to vacuum to obtain the product **14**. Yield: 70%; mp above 250 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 4.50 (s, 4H), 5.52 (s, 4H), 7.29 (s, 4H), 7.54 (t, *J*=7.5 Hz, 1H), 7.96 (d, *J*=7.5 Hz, 2H), 8.02 (s, 2H), 8.32 (s, 1H), 9.06 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.9, 52.4, 123.2, 126.4, 128.4, 129.9, 134.2, 135.9, 145.3, 165.7; IR (KBr): 3284, 1646, 1535, 1428, 1275, 1177, 1129, 1054 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{20}N_8O_2Na$: 451.1607, found: 451.1614.

4.5. General method of preparation of 16, 17, 19, 20 and 22

To an ice cold and well-stirred solution of **8b** (150 mg, 0.62 mmol) in dry acetonitrile was added DIEA (0.21 mL, 1.25 mmol), followed by diazide (0.68 mmol) under N_2 atmosphere. CuI (21 mg, 0.11 mmol) was added to the reaction mixture and stirred for 24 h. The solvent was evaporated and the residue was dissolved in chloroform. The chloroform soluble part was washed sequentially with an aqueous solution of NH_4Cl+NH_4OH (9:1), 2 N H_2SO_4, saturated solution of $NaHCO_3$ and water. The chloroform part was dried over anhydrous Na_2SO_4, evaporated, and purified by silica gel column chromatography using chloroform/methanol as the eluents.

4.5.1. Compound ***16***. Yield: 67%; mp 212–214 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.86 (br s, 4H), 4.53 (br s, 4H), 5.41 (s, 4H), 7.61 (s, 3H), 8.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.9, 49.7, 59.3, 122.8, 129.1, 129.7, 130.3, 134.6, 143.2, 164.9; IR (KBr): 3573, 3379, 3142, 3094, 2956, 1719, 1563, 1459, 1389, 1309, 1226, 1145, 1068 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{19}N_6O_4$: 383.1468, found: 383.1474.

4.5.2. Compound ***17***. Yield: 12%; mp above 300 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.77 (br s, 8H), 4.38 (br s, 8H), 5.38 (s, 8H), 7.65 (t, *J*=7.8 Hz, 2H), 8.05–8.25 (m, 8H), 8.35 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 49.1, 58.7, 125.3, 129.9, 130.1, 130.3, 134.3, 142.0, 165.0; IR (KBr): 3421, 3132, 2955, 2877, 1713, 1609, 1444, 1387, 1301, 1231 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{36}H_{37}N_{12}O_8$: 765.2857, found: 765.2862.

4.5.3. Compound ***19***. Yield: 56%; mp 206–207 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (br s, 4H), 1.87 (br s, 4H), 4.41 (t, *J*=4.8 Hz, 4H), 5.46 (br s, 4H), 7.59 (s, 2H), 7.62 (s, 1H), 8.32 (d, *J*=7.8 Hz, 2H), 8.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4, 29.9, 50.0, 58.9, 123.1, 128.9, 129.7, 130.0, 134.7, 142.6, 165.5; IR (KBr): 3410, 3136, 3093, 2947, 2866, 1715, 1561, 1459, 1387, 1307, 1229, 1142, 1079 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{23}N_6O_4$: 411.1781, found: 411.1793.

4.5.4. Compound ***20***. Yield: 15%; mp 228–230 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (br s, 8H), 1.90 (br s, 8H), 4.34 (t, *J*=6.3 Hz, 8H), 5.47 (s, 8H), 7.51 (t, *J*=7.35 Hz, 2H), 7.68 (s, 4H), 8.23 (d, *J*=7.2 Hz, 4H), 8.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 29.9, 50.1, 58.5, 124.0, 128.8, 130.2, 130.9, 134.3, 142.6, 165.5; IR (KBr): 3427, 3138, 2928, 2860, 1725, 1611, 1443 (br), 1381, 1305, 1232, 1129, 1084 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{40}H_{45}N_{12}O_8$: 821.3483, found: 821.3501.

4.5.5. Compound ***22***. Yield: 63%; mp 322–324 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 5.35–5.70 (m, 8H), 7.03 (d, *J*=7.2 Hz, 2H), 7.20–7.50 (m, 6H), 7.58 (t, *J*=7.65 Hz, 1H), 7.76 (s, 2H), 8.26 (d, *J*=7.5 Hz, 2H), 8.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.8, 59.5, 122.1, 128.2, 128.8, 129.0, 130.1, 130.2, 131.4, 133.3, 134.1, 138.8, 143.4, 164.9; IR (KBr): 3431, 3136, 3097, 2945, 1724, 1452, 1362, 1313, 1231, 1155, 1103, 1048 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{28}H_{23}N_6O_4$: 507.1781, found: 507.1790.

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Supplementary data

Detailed experimental procedures and compound characterization. Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.11.078.

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