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Glaser-Eglinton-Hay sp-sp coupling and macrocyclization: construction of a new class of polyether macrocycles having a 1,3-diyne unit †

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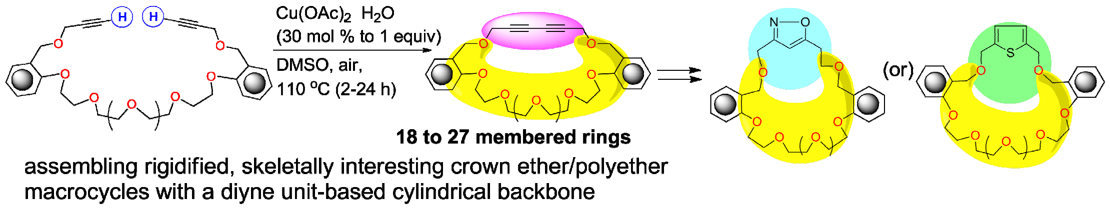
Glaser-Eglinton-Hay-type sp–sp coupling, macrocyclization and the construction of skeletally interesting, 18-27 membered, polyether macrocycles having a 1,3-diyne unit-based cylindrical backbone are reported. The utility of polyether macrocycles having the 1,3-diyne units is shown by incorporating isoxazole and thiophene moieties into the macrocycles. The structures of representative crown ether/polyether-type macrocycles were unambiguously established from the single crystal X-ray structure analyses. Investigation of the X-ray structures of representative macrocycles revealed that the 1,3-diyne unit was not linear and the same was found to be bent.

Introduction

Macrocycles are fascinating molecular frameworks, present as core units in numerous natural products and biologically active molecules.[1] The construction of macrocycles is one of the interesting chemical transformations.[1,2] Rigidified and strained macrocycles have found significant applications in several areas of scientific field because of their shape persistent skeletons and distinctive properties.[2] Various methods are available for the assembling of macrocycles and A large number of macrocycles has been synthesized by using standard peptide coupling, the Yamaguchi lactonization, ring closing metathesis and other techniques.[1c,3,4]

Along this line, Cu or Pd-based Glaser-Eglinton-Hay-type reaction is a highly attractive tactic for the synthesis of diyne-based shape persistent macrocycles and linear conjugated diynes.[5-8] Macrocyclization was also reported with the aid of a conformational control element, if a normal ring closing metathesis reaction (RCM) or Glaser-Eglinton-Hay-type reaction is ineffective.[8e]

Notably, diyne-based molecules are important building blocks in industrial and synthetic chemistry and electronic/optical materials, and exhibit prominent biological activities.[7,8] The incorporation of a diyne unit in the molecular frameworks can be considered as important molecular tools to constrain the molecular conformation and the inherent rigidity and directionally defined precise cylindrical symmetry of diyne units have been well exploited in different areas of chemical science.[6-9] Diverse families of shape persistent unsaturated macrocycles, especially, having the diyne unit-based rigid backbones, e.g. annulenes, rotanes, cyclophanes, cage compounds and artificial receptors with novel structures and



Scheme 1 Theme of this work.

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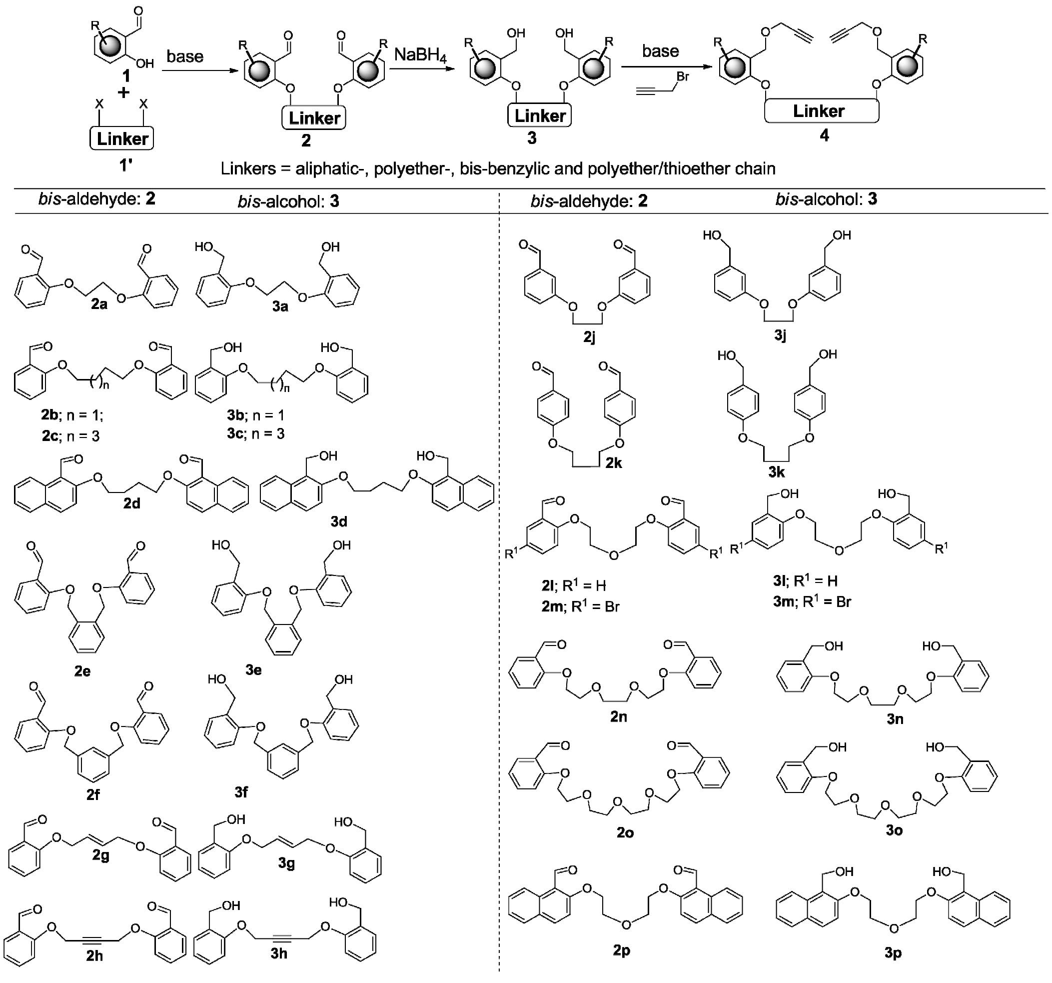
† Electronic Supplementary Information (ESI) available: [Copies of NMR spectra of all compounds and details of the single crystal X-ray data (CIF) of the compounds **5a, 5f, 5g, 5h, 5i, 5k, 6a, 6c, 6g, 7b, 7d, 8a, 9a** and **9c**]. See DOI: 10.1039/b000000x/

appreciable physicochemical properties have been constructed using the Glaser-Eglinton-Hay-type coupling strategy.[2,7-9]

Crown ether/polyether-type macrocycles including lariat crown ethers can be considered as the cornerstones of supramolecular chemistry[1d,10] and they exhibit unique properties and numerous applications in chemical and biological sciences, including anticancer, DNA interaction and other biological activities.[11] Due to the very high importance of crown ether/polyether-type macrocycles in various branches of science, study of the synthesis and supramolecular chemistry of new crown ether/polyether macrocycles has become one of the attractive areas of chemical research.[10-12] However, despite the existing developments in a pivotal research area involving the synthesis of new polyether macrocycles and the functional derivatization or periphery modification of crown ethers; the synthesis of crown ether-type macrocycle having a diyne unit-based cylindrical rigid backbone has not been well explored. The incorporation of a diyne unit as a part of crown ether/polyether macrocycles could provide directionally precise rigidity to polyether macrocycles and perhaps, new insights on their supramolecular chemistry including the stereochemical conformations. However, to the best of our knowledge and a survey of literature revealed that there exist only two preliminary reports[9] dealing on the synthesis of macrocycles appended with crown ether skeleton, which is linked *via* a 1,3-diyne unit-based backbone.

Motivated by the existing developments related to the synthesis and applications of macrocyclic materials having the diyne units-based backbones[7,8] and in line with our objectives directed toward displaying the construction of functionally modified and rigidified crown ether/polyether macrocyclic compounds; we herein report our preliminary works on the production of a new class of crown ether/polyether macrocycles having a 1,3-diyne unit-based cylindrical backbone and their utility for the incorporation of isoxazole and thiophene moieties into the new crown ether/polyether macrocyclic derivatives (Scheme 1).

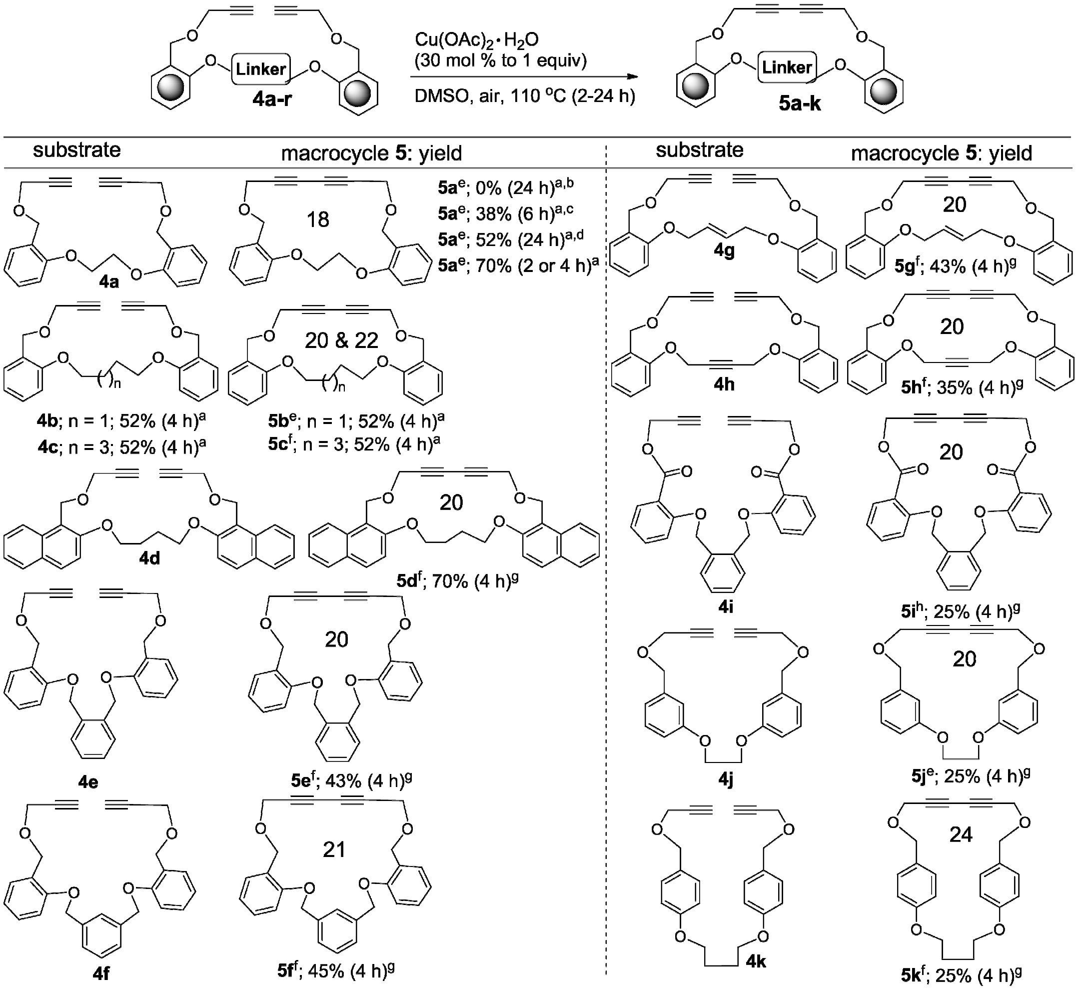


Scheme 2 Assembling of the starting materials **4**, having the terminal alkyne units.

Results and Discussion

At the outset, to prepare crown ether/polyether-based unsaturated macrocycles possessing a 1,3-diyne unit-based rigid backbone, we prepared the required starting materials possessing terminal alkyne units with the generalized structure **4**, starting from different *o*-hydroxy benzaldehydes (Scheme 2). Various *o*-hydroxy benzaldehydes (**1**) were treated with a variety of linkers (**1′**) using standard procedures, which furnished several *bis*-aldehydes with the generalized structure **2**. Next, treatment of the *bis*-aldehydes (**2**) with $NaBH_4$ followed by base-mediated O-propargylation afforded a variety of starting materials containing the terminal alkyne units with the generalized structure **4** (Scheme 2).

reaction condition. The Glaser-Eglinton-Hay-type macrocyclization reaction of substrate **4a** in the presence of $Cu(OAc)_2{\cdot}H_2O$ in toluene at refluxing temperature under an open-air atmosphere for 24 h did not afford the expected macrocycle **5a** (Scheme 3). Similarly, the Glaser-Eglinton-Hay-type macrocyclization reaction of substrate **4a** failed to afford the expected macrocycle **5a** when the reaction was carried out in 1,4-dioxane (Scheme 3).

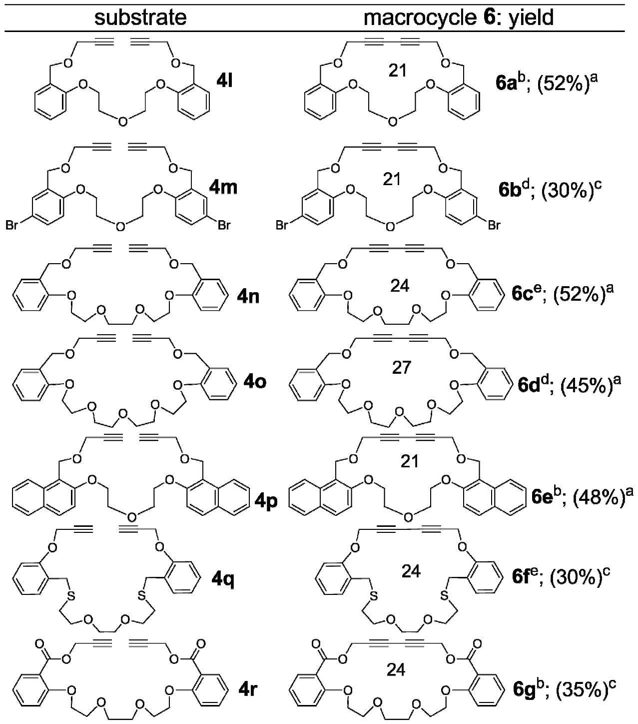


[a] 1 Equiv of $Cu(OAc)_2{\cdot}H_2O$ was used. [b] The reaction was done in toluene or 1,4-dioxane at refluxing temperature. [c] The reaction was done in DMF at 110 °C. [d] The reaction was done in refluxing MeCN. [e] The reaction was performed using 0.25 mmol of the starting material. [f] The reaction was performed using 0.5 mmol of the starting material. [g] 30 mol % of catalyst was used. [h] The reaction was performed using 0.12 mmol of starting material.

Scheme 3 Assembling of 18-24-membered, rigidified crown ether/polyether-type macrocycles having a 1,3-diyne unit-based backbone.[13c]

Then, we began our investigations on the sp–sp carbon–carbon bond forming macrocyclization of the substrates **4a-r** (Scheme 3 and Fig. 1). Initially, we carried out the Glaser-Eglinton-Hay-type macrocyclization reaction of substrate **4a** in the presence of $Cu(OAc)_2{\cdot}H_2O$ in various solvents to find out a suitable

Successively, we tried the macrocyclization of **4a** in DMF and the Glaser-Eglinton-Hay-type macrocyclization of substrate **4a** in DMF at 110 °C afforded the rigidified macrocycle **5a**, possessing a 1,3-diyne unit-based backbone in 38% yield. Further, the macrocycle **5a** was obtained with an improved yield (52%) when the reaction was performed in refluxing MeCN. Next, the Glaser-Eglinton-Hay-type macrocyclization of substrate **4a** in the presence of $Cu(OAc)_2{\cdot}H_2O$ in DMSO at 110 °C under an open-air atmosphere gave the macrocycle **5a** in 70% yield (Scheme 3). Likewise, the macrocyclization of the substrates containing two terminal alkynes **4b-f**, which were derived from different aliphatic- and benzylic chain linkers afforded the corresponding macrocycles **5b-f** in 43-70% yields (Scheme 3).



[a] Reaction condition A:[13a] $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), DMSO, 110 °C, 4 h and open-air atm. [b] The reaction was done using 0.3 mmol of the corresponding starting material. [c] Reaction condition B:[13b] $Cu(OAc)_2{\cdot}H_2O$ (1 equiv), DMSO, 110 °C, 4 h and open-air atm. [d] The reaction was done using 0.5 mmol of the corresponding starting material. [e] The reaction was done using 0.2 mmol of the respective starting material.

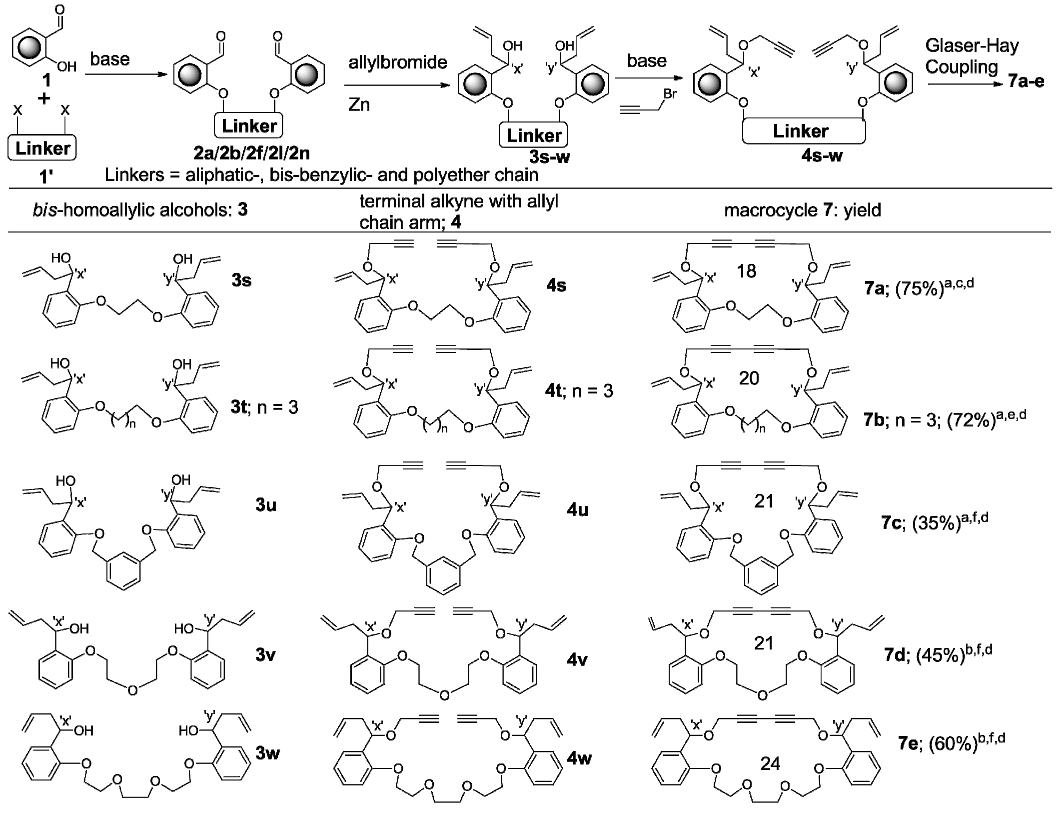
Fig. 1 21-27-Membered, rigidified crown ether/polyether-type macrocycles having a 1,3-diyne unit-based backbone.[13c]

Subsequently, the substrates **4g** and **4h**, which were derived from the linkers containing an unsaturated backbone underwent the intramolecular acetylenic coupling and gave the corresponding rigidified macrocycles **5g** (43%) and **5h** (35%), connected through a diyne moiety. The Glaser-Eglinton-Hay coupling reaction of the benzoate derivative **4i**, having two terminal alkyne units gave the macrocycle **5i** in 25% yield. The intramolecular acetylenic coupling of the starting materials **4j** and **4k** derived from *meta*- and *para*-hydroxy benzaldehydes furnished the respective macrocycles **5j** and **5k** in 25% yields (Scheme 3).

To execute the scope of this protocol, we carried out the Glaser-Eglinton-Hay coupling reaction using the substrates **4l-p** having two terminal alkyne units, which were assembled by employing various polyether units-based linkers. The intramolecular Glaser-Eglinton-Hay coupling reaction of the substrates **4l-p** in the presence of $Cu(OAc)_2{\cdot}H_2O$ in DMSO at 110 °C under an open-air atmosphere gave the novel and structurally interesting crown ether/polyether macrocycles **6a-e** in 30-52% yields, respectively (Fig. 1). The macrocyclization reaction of the substrates **4q**, which was assembled by using a polythioether unit-based linker afforded an interesting crown-type macrocycle **6f** in 30% yield. Next, in this line the Glaser-Eglinton-Hay coupling reaction of the benzoate derivative **4r** possessing two terminal alkyne units gave the crown-type macrocycle **6g** in 35% yield (Fig. 1).

Further, to elaborate the substrate scope, we aimed to prepare substrates containing two terminal alkyne units from *bis*-homoallylic alcohol which can be assembled *via* the Zn-mediated allylation strategy (Scheme 4). In this line, salicylaldehyde was treated with a variety of linkers (**1′**) using standard procedures to afford the corresponding *bis*-aldehydes (**2**), which were subsequently treated with allyl bromide and zinc dust. The Zn-mediated allylation of *bis*-aldehydes gave different *bis*-homoallylic alcohols (**3s-w**) as a mixture of diastereomers (*dr* 1:1). Further, the base-mediated O-propargylation of the *bis*-homoallylic alcohols (**3s-w**) afforded a variety of starting materials comprising of two terminal alkyne units **4s-w** incorporated with the allylic chains as the side-arms (Scheme 4). Before discussing the Glaser-Eglinton-Hay macrocyclization of the substrates **4s-w**, it is worth to mention here that in some of the crown ethers reported in the literature, the incorporation of an allylic chain as a sidearm was found to be important to induce an effective encapsulation of metals.[12e,f] For example, Gokel and co-workers have reported a solid state evidence that neutral double bonds attached to flexible side-arm of a lariat crown ether, serving as the intramolecular π-donors for a ring-bound Na^+ cation.[12f]

Taking an impetus from the Gokel's substrate,[12f] we performed the intramolecular Glaser-Eglinton-Hay coupling reactions of the substrates **4s-w** in the presence of $Cu(OAc)_2{\cdot}H_2O$ in DMSO at 110 °C under an open-air atmosphere. These reactions led to the synthesis of structurally interesting C-pivot lariat crown ether/polyether-type macrocycles **7a-e** having a 1,3-diyne unit in 35-75% yields, respectively (Scheme 4). Since the starting substrates **4s-w** were isolated as a mixture of diastereomers (*dr* 50:50, Scheme 4) in the previous step, the Glaser-Eglinton-Hay macrocyclization of the substrates **4s-w** resulted the corresponding macrocycles **7a-e** having two remote stereocenters ('x' and ' y') and as a mixture of diastereomers (*dr* 60:40). Unfortunately, all our attempts to separate the diastereomers were not successful.

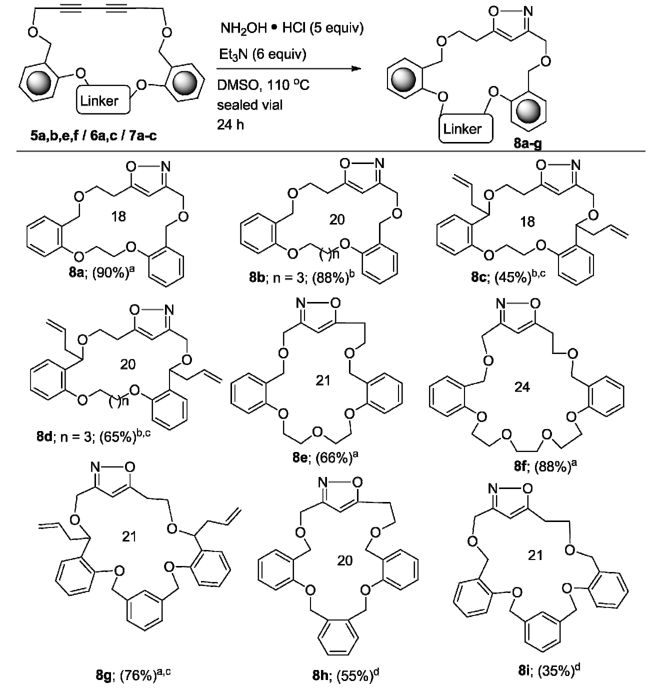


[a] Reaction condition A:[13a] $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), DMSO, 110 ºC, 4 h and open-air atm. [b] Reaction condition B.[13b] [c] The reaction was done using 0.4 mmol of the respective starting material. [d] The observed *dr* = 60:40. [e] The reaction was done using 1 mmol of the respective starting material. [f] The reaction was done using 0.2 mmol of the respective starting material.

Scheme 4 18-24-Membered rigidified crown ether/polyether-type macrocycles having a 1,3-diyne unit-based backbone.[13c]

Subsequently, as a part of our interest in the post ring-closure functional derivatization of polyether macrocycles, next we focused our attention to execute the utility of the macrocyclic compounds possessing the 1,3-diyne units, which were obtained in this work. Recently, Yu and Bao reported an efficient method for the synthesis of 3,5-disubstituted isoxazoles *via* the Cope-type hydroamination of the 1,3-dialkyne units.[13d] Along this line, some of the 1,3-diyne units containing macrocycles prepared *via* the Glaser-Eglinton-Hay macrocyclization were examined for the construction of a variety of new examples of isoxazole appended crown ether-type macrocycles by using recently procedures.[13d,e] The reaction of **5a,5b,5e,5f, 6a,6c** and **7a-c** having the 1,3-diyne units with $NH_2OH{\cdot}HCl$ and Et_3N gave the corresponding isoxazole moiety appended, a new class of 18-21-membered crown ether-type macrocycles **8a-i** in satisfactory yields (Scheme 5). It is noteworthy to mention that the isoxazole is an important structural unit, present in several bioactive molecules and natural products.[14] Further, these crown ether-type macrocycles **8a-i** appended with the isoxazole moiety can be considered as crownophane-type molecules.

Inspired by an another work reported by the Jiang and co-workers, which deals on the Cu(I)-catalyzed synthesis of 2,5-disubstituted thiophenes from the 1,3-diyne units, we decided to examine the construction of thiophene ring appended crown ether-type macrocycles from the macrocycles having the 1,3-diyne units, which were prepared in this work. By employing the reaction condition reported by the Jiang's group,[13e] we performed the reactions of various macrocycles **5c**, **6a**, **6d** and **6f** with $Na_2S{\cdot}xH_2O$ in the presence of 1,10-phenanthroline and CuI in DMF at 90 °C under an open-air atmosphere. These reactions afforded the corresponding thiophene moiety appended 20-26-membered, new crown ether-type macrocycles **9a-d** in 17-55% yields (Scheme 6).

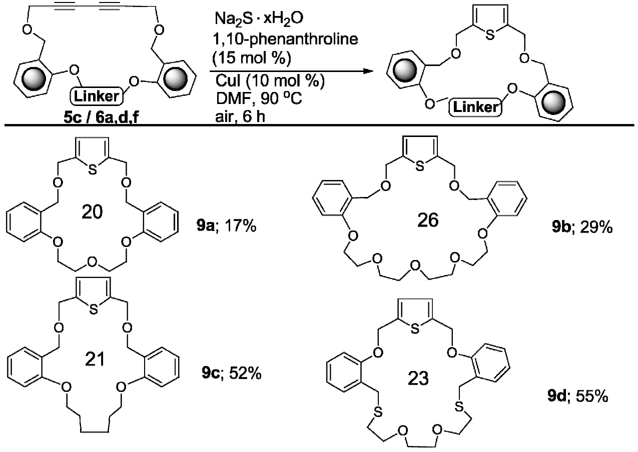


[a] The reaction was done using 0.18 mmol of the corresponding starting material. [b] The reaction was done using 0.25 mmol of the corresponding starting material. [c] *Dr* = 60:40. The reaction was done using the corresponding mixture of diastereomers **7a-c**. [d] The reaction was done using 0.12 mmol of the corresponding starting material.

Scheme 5 Synthesis of isoxazole ring-appended 18-24-membered, crown ether-type macrocycles via the cope-type hydroamination of the substrates **5**/**6**/**7**.

The Glaser-Eglinton-Hay-type sp–sp carbon–carbon bond forming macrocyclization of various substrates with the generalized structure **4** afforded a simple route for the synthesis of skeletally interesting, rigidified crown ether/polyether macrocycles possessing a 1,3-diyne unit-based cylindrical backbone. The structures of all the crown ether/polyether-type macrocycles obtained in this work were characterized by the ^{1}H and ^{13}C NMR analysis and mass spectrometry. Further, the structures of representative crown ether/polyether-type macrocycles were unambiguously established from the preliminary single crystal X-ray diffraction studies.[13f,g] Single crystal data and the results of the structure refinement details are listed in the Table 1, which can be found in the Electronic Supplementary Information (ESI).

All the molecules reported in this manuscript contains $R_3C–C≡C–C≡C–CR_3$ moiety, which is ideally expected to be linear with all the four ∠–C≡C–C– type angles to be equal to 180°. It has been found that all these angles have been deviated from 180°. Therefore, the bend angle for the $R_3C–C≡C–C≡C–CR_3$ moiety has been calculated by subtracting the sum of all the four angles from the sum of their ideal values *i.e.*, $720^o – (\theta_1 + \theta_2 + \theta_3 + \theta_4)$, where $\theta_{1\text{-}4}$ are the corresponding observed (from single crystal X-ray data) bond angles. The bend angles have been incorporated in the Table 1.



[a] The reactions were done using the corresponding starting materials as given in the parenthesis, (for **9a**; 0.25 mmol of **6a**) (for **9b**; 0.39 mmol of **6d**) (for **9c**; 0.3 mmol of **5c**) (for **9d**; 0.06 mmol of **6f**).

Scheme 6 Thiophene ring appended 20-26-membered crown ether-type macrocycles.

Description of the crystal structures of representative crown ether/polyether macrocycles containing a 1,3-diyne unit.

The single crystal X-ray diffraction study revealed that the molecule **5a** was found to crystallize in the space group $P2_1/c$ with two independent 18-membered macrocyclic molecules in the asymmetric unit (Fig. 2). In each molecule, the two phenyl rings have been found to be inclined at an angle of ~90° to each other and both the conformers majorly differ with respect to the torsion angles of the 1,3-diyne linkage, which is about <1° and ~7° respectively. The distance between phenyl rings in the both the conformations was same (~8 Å) and in each conformer the 1,3-diyne linkage has been found to be bent with an angle of ~15°. In the crystal packing of these molecules, majorly C–H···O and C–H···π hydrogen bonds have been found (Fig. 1 and 2 in the Electronic Supplementary Information (ESI)). No π···π interactions were found in the crystal structure of these molecules.

The single crystal X-ray structure revealed that the molecule **5f** was found to crystallize in the space group $P2_1/c$ with one 21-membered macrocyclic molecule in the asymmetric unit (Fig. 3). In contrast to the molecule **5a**, with the incorporation of the benzene ring in to the linker, the distance between the phenyal rings has increased by ~3 Å

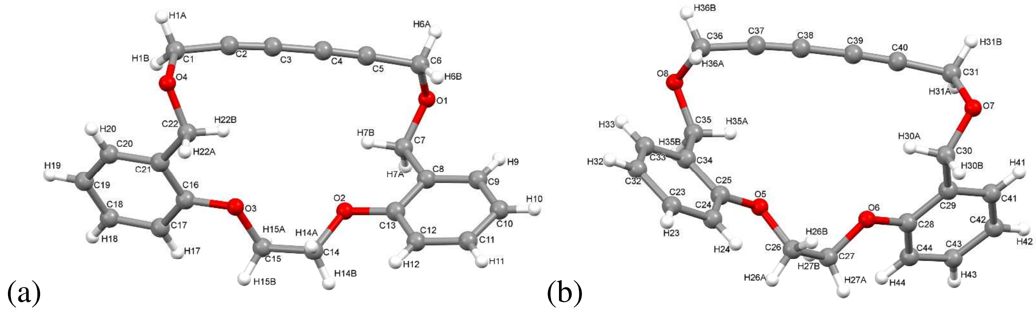


Fig. 2 (a) Ball and stick model (X-ray structure) of **5a_1** and (b) Ball and stick model (X-ray structure) of **5a_2** were drawn at 0.15 times to atomic van der Waals radius.

and the bending angle of the 1,3-diyne unit was found to be ~11 °. The interplanar angles between the linker phenyl group (having substitutions at the 1,3-positions) and the two phenyl rings (having substitutions at the 1,2-positions) was ~21° and ~77°, respectively. The two phenyl rings (having substitutions at the 1,2-positions) have been found to be inclined at an angle of ~56°. Whereas, the torsion angle for the 1,3-diyne unit was ~13°. C–H···O and C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 3 and 4 in the Electronic Supplementary Information (ESI)). Interestingly, the phenyl ring, which act as a linker, has been found to be involved in π···π stacking (Fig. 3).

The X-ray structure analysis revealed that the molecule **5g** was found to crystallize in the space group $P2_1/c$ with one 20-membered macrocyclic molecule in the asymetric unit (Fig. 4). With reference to the molecule **5a**, the incorporation of an extra *trans* alkene (ethylene) linkage led the distance between the phenyl rings to increase by ~2 Å. The bending and torsion angles of the 1,3-diyne linkage were found to be ~14° and ~11°, respectively. The interplanar angle between the two phenyl rings was found to be ~53°. C–H···O and C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 5 and 6 in the Electronic Supplementary Information (ESI)). No π···π interactions have been found in the crystal structure of this molecule.

The single crystal X-ray diffraction study revealed that the molecule **5h** was found to crystallize in the space group $P2_1/c$ with one 20-membered macrocyclic molecule (Fig. 4). With reference to the molecule **5a**, the incorporation of the alkyne (acetylenic, (C15 and C16)) group in to the linkage led the distance between the phenyl rings to increase by ~3Å. The bending and torsion angles of the 1,3-diyne linkage were found to be ~8° and ~115°, respectively. Two phenyl rings are inclined at an angle of ~61°. The bending angle of the (mono) acetylenic unit was found to be ~11°. C–H···O and C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 7 and 8 in the Electronic Supplementary Information (ESI)). No π···π interactions have been found in the crystal structure of this molecule.

The X-ray structure analysis showed that the molecule **5i** contains a 20-membered macrocyclic ring and was found to crystallize in the space group $P2_1/c$ with one molecule in the asymmetric unit. In this molecule, two phenyl groups (having substitutions at 1,2-positions such as C8/C13 and C22/C27) have been found to be inclined at an angle of ~73°. The interplanar angles between the phenyl rings having substitutions at 1,2-positions and the phenyl group (C15 to C20), which acts as a linker were found to be ~86° and ~47° (Fig. 4). The torsion angle for the 1,3-diyne unit is ~10°. The 1,3-diyne unit found to be not linear, the bending angle was found to be ~17°. C–H···O and C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 9 and 10 in the Electronic Supplementary Information (ESI)). No π···π interactions have been found in the crystal structure of this molecule.

The single crystal X-ray diffraction study revealed that the molecule **5k** was found to crystallize in the space group $P\bar{1}$ with one 24-membered macrocyclic molecule (Fig. 5) and this compound was prepared using 4-hydroxybenzaldehyde. When compared to the molecule **5a** (which was prepared from 2-hydroxybenzaldehyde) in this structure, the distance between the phenyl rings was found to

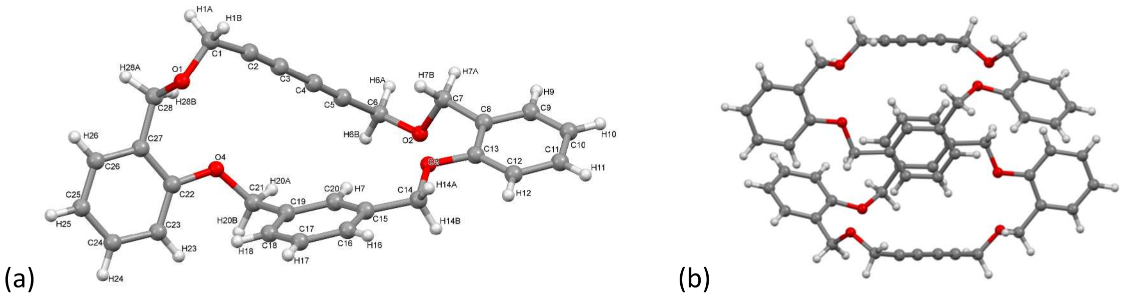


Fig. 3 (a) Ball and stick model (X-ray structure) of **5f** was drawn at 0.15 times to atomic van der Waals radius. (b) π···π Stacking between the phenyl rings which act as the linker in the compound **5f**.

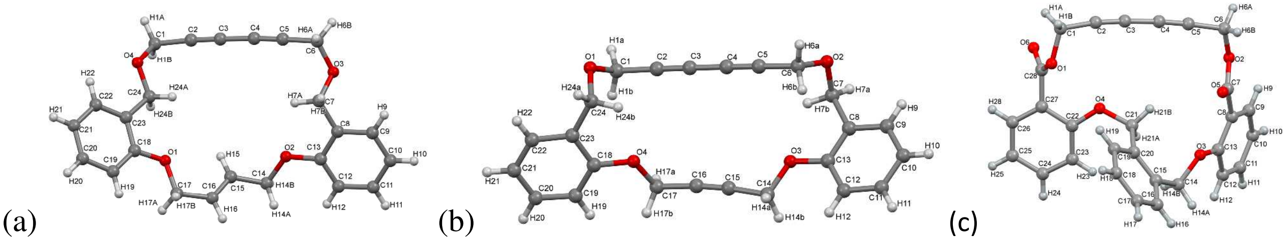


Fig. 4 Ball and stick model (X-ray structures **5g-i**) was drawn at 0.15 times to atomic van der Waals radius; (a) **5g** (b) **5h** (c) **5i**.

decrease by ~2 Å and the bending and torsion angles of the 1,3-diyne unit were found to be ~16° and ~15°, respectively. The interplanar angle between the two phenyl rings has been found to be ~70°. The C–H···O and C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 11 and 12 in the Electronic Supplementary Information (ESI)). No π···π interactions have been found in the crystal structure of this molecule.

The single crystal X-ray diffraction study revealed that the molecule **6a** was found to crystallize in the space group $P2_1/c$ with one 21-membered macrocyclic molecule in the asymetric unit (Fig.5). The incorporation of an oxygen atom at the center of the butyl linkage led the distance between the phenyl rings to increase by ~2 Å (with respect to **5a**). The bending and torsion angles of the 1,3-diyne linkage were found to be ~12° and ~19°, respectively. The inerplanar angle between two phenyl rings was found to be ~41°. C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 13 in the Electronic Supplementary Information (ESI)). No π···π interactions have been found in the crystal structure of this molecule.

Preliminary single crystal X-ray diffraction study of the 24-membered macrocyclic compound **6c** indicated that only half of the molecule is present in the asymmetric unit due to crystallographic imposed two fold symmetry and the structure having a center of inversion symmetry (Fig. 5). The 1,3-diyne unit between the two phenyl groups was found to be bent and the bending angle was found to be ~19^{o} and the angle between the phenyl rings was found to be ~56^{o}. The distance between the phenyl rings is ~13 Å. The crystal packing doesn't contain any strong hydrogen bonds other than van der Waals interactions.

The compound **6g** doesn't have any center of symmetry and one full molecule was found to be present in the asymmetric unit as a 24-membered macrocyclic ring (Fig. 6). The bending angle of the 1,3-diyne unit was found to be ~11^{o}. The interplanar angle between two phenyl rings was found to be ~73^{o} and those rings are ~13 Å distance apart from each other, which is similar to the structure **6c**. Out of two ester groups, one carbonyl group (C26/O8) was found to be in-plane to benzene ring whereas the other group was found to be out of the plane by an angle of ~36^{o}, which has led the molecule to be in an unsymmetrical form. The molecules are found to be interconnected by only C–H···O hydrogen bonds (Fig. 14 in the Electronic Supplementary Information (ESI)).

The 20-membered macrocyclic compound **7b**, doesn't have any center of inversion symmetry and one full molecule was found to be present in the asymmetric unit (Fig. 6). This molecule contains a flexible sidearm group (allyl chain) at the benzylic carbons (C7 and C24) and the bending angle of the 1,3-diyne unit was found to be ~5^{o} and the inter-planer angle between the two phenyl rings was found to be ~57^{o}. No π···π interactions have been found in the crystal structure of this molecule.

The single crystal X-ray diffraction study revealed that the molecule **7d** was found to crystallize in $P\bar{1}$ space group and asymmetric unit was found to contain two independent molecules (Fig. 7). In the molecule **7d_1**, the bending angle of the 1,3-diyne unit was found to be ~12^{o}, however, in the case of **7d_2** the bending angle of the 1,3-diyne unit was found to be ~7^{o}. The interplanar angle between two phenyl rings of the conformers **7d_1** and **7d_2** were found to be ~64^{o} and ~66^{o}, respectively. Two different conformations were found in the crystal packing and the interplanar angles between phenyl rings were almost same. The C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 15 in the Electronic Supplementary Information (ESI)).

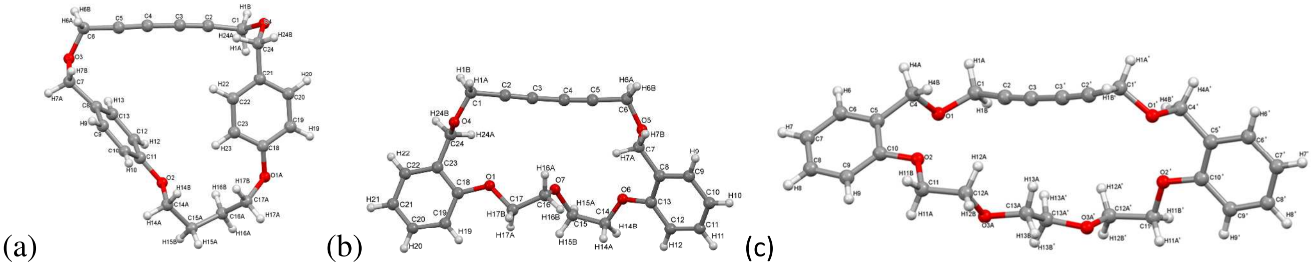


Fig. 5 Ball and stick model (X-ray structures **5k** and **6a, 6c**) was drawn at 0.15 times to atomic van der Waals radius; (a) **5k** (b) **6a** (c) **6c**. Only half of the molecule is present in the asymmetric unit of the X-ray structure of the compound **6c**. Therefore, the atoms at the right hand side of X-ray structure of **6c** (shown with a prime (') label) are at equivalent position (1-x, y, ½-z) with respect to the atoms on the left hand side.

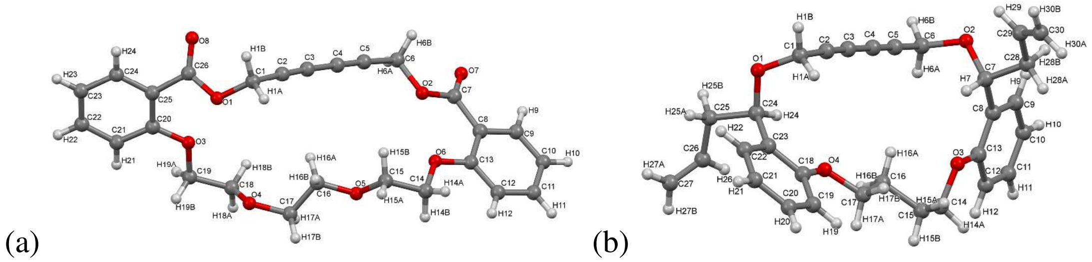


Fig. 6 Ball and stick model (X-ray structures **6g** and **7b**) was drawn at 0.15 times to atomic van der Waals radius; (a) **6g** (b) **7b**.

The single crystal X-ray structure analysis showed that the 18-membered macrocyclic compound **8a** was found to crystallize in the $P2_1/c$ space group and the asymmetric unit contained one full molecule (Fig. 8). The interplanar angle between two phenyl rings was found to be ~76^o and the interplanar angle between phenyl and isoxazole rings was found to be ~61 ^{o} and ~73^o (with respect to each phenyl ring), respectively. The distance between the phenyl rings was found to be ~8 Å and the distances between phenyl and isoxazole ring were found to be ~6 Å and ~7 Å (with respect to each phenyl ring), respectively. No π···π interactions have been found in the crystal structure of this molecule.

Preliminary single crystal X-ray diffraction study revealed that the 20-memberd macrocyclic compound **9a** was found to crystallize in the *Pnma* space group with half the molecule in the asymmetric unit. The molecule has a crystallographically-imposed mirror symmetry which leads to the appearance of the half of the molecule in the asymmetric unit (Fig. 8). The both the methoxymethyl linkages connecting the thiophene and phenyl ring were found to be in the same plane. The interplanar angle between the two phenyl rings was found to be ~77^o and the interplanar angle between the phenyl and thiophene rings was found to be ~77^o. The C–H···π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 16 in the Electronic Supplementary Information (ESI)).

The single crystal X-ray structure analysis revealed that the 21-membered macrocyclic compound **9c** was found to pack in $P\bar{1}$ space group and one full molecule was found in the asymmetric unit (Fig. 8). While considering that the methoxymethyl thiophene linkage between the phenyl rings is same in the structures **9c** and **9a**, however, the change of linker from polyether unit-based linker (**9a**) in to a flexible alkyl chain-based linker (**9c**) has led to increase the distance between two phenyl rings (centriods) by ~2 Å and the interplanar angle between two phenyl rings was reduced to ~42^o. This increment has led desymetrizitation in the molecule. The crystal packing of **9c** was majorly found to have van der Waals intreactions among its molecules. No π···π interactions have been found in the crystal structure of this molecule.

Subsequently, we calculated the cavity dimensions in the X-ray structures of representative crown ether/polyether macrocycles obtained in this work. The cavities in the X-ray structure of representative crown ether/polyether macrocycles can be approximated to be a rectangular box and the cavity dimensions are mentioned in Table 1.[13f,g] From all the above deliberations about the X-ray structures of representative macrocycles presented in this work , it was observed that in these set of molecules the 1,3-diyne unit was not able to hold the linearity.[21b] It seems that the substituents attached to the benzylic carbon, size and nature of the linkers are playing some significant roles to control the conformation including the shape of the 1,3-diyne unit of the macrocycles synthesized in this work. In this line, we further scrutinized and compared some of the X-ray structures to find out the effect of the substituents attached to the benzylic carbon, size and nature of the linkers on the conformation of macrocycles having the 1,3-diyne units.

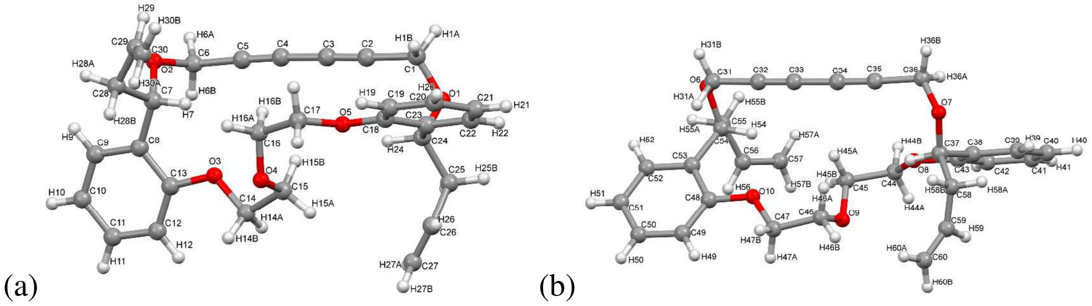


Fig. 7 (a) Ball and stick model (X-ray structure) of **7d_1** and (b) Ball and stick model (X-ray structure) of **7d_2** was drawn at 0.15 times to atomic van der Waals radius.

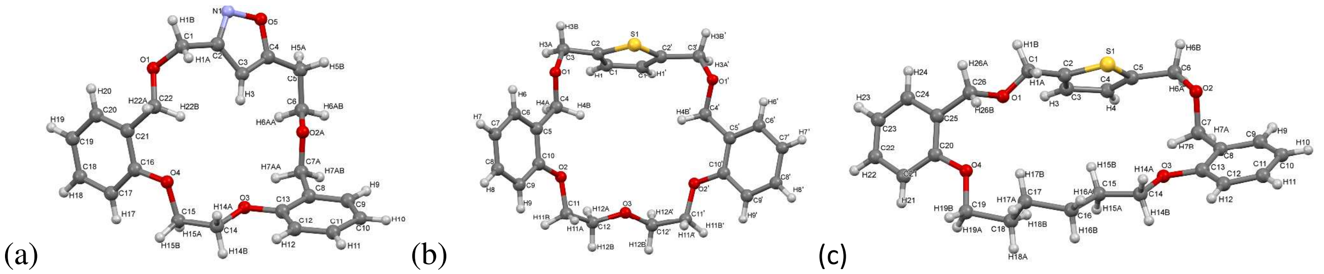


Fig. 8 Ball and stick model (X-ray structures **8a**, **9a** and **9c**) was drawn at 0.15 times to atomic van der Waals radius; (a) **8a** (b) **9a** (c) **9c**. Only half of the molecule is present in the asymmetric unit of the X-ray structure of the compound **9a**. Therefore, the atoms at the right hand side of X-ray structure of **9a** (shown with a prime (') label) are at equivalent position (x, 3/2-y, z) with respect to the atoms on the left hand side.

First of all, to see the effect of the substituent on the benzylic carbon and on the bending angle of the 1,3-diyne unit, we have compared the structures of the compounds **6a** and **7d**, in which the ring size (21-membered) and the linkers are same, while an allyl group has been incorporated at the benzylic carbons (C7/C24, Fig 7a) in **7d**. In these cases it was observed that the allylic groups at the benzylic carbons have not brought much change in the cavity size of these molecules (entries 8,12 and 13, Table 1) as well as on the bending angles of the 1,3-diyne unit (bending angle ~11° in **7d** and bending angle = ~11° in **6a**). Thus, apparently the allyl group was not playing any role in controlling the strain, cavity size or the bending angle of the 1,3-diyne unit and the conformation of the molecule **7d**.

Table 1. Cavity dimensions (in Å) of the crown ether/polyether macrocycle from their X-ray structures

entry	compound	ring size	approximate cavity dimensions (m^a x n^b in Å) from X-ray structure[c,d]	approximate bend angle of 1,3-diyne unit /°
1	**5a_1**	18	4 x 7	15
2	**5a_2**	18	4 x 7	15
3	**5f***	21	4 x 8	11
4	**5g**	20	5 x 7	14
5	**5h**	20	3 x 8	8
6	**5i**	20	4 x 7	17
7	**5k**	24	6 x 8	16
8	**6a**	21	4 x 8	12
9	**6c***	24	4 x 8	18
10	**6g***	24	4 x 8	11
11	**7b**	20	4 x 8	5
12	**7d_1**	21	4 x 8	12
13	**7d_2**	21	4 x 8	7
14	**8a**	18	4 x 6	-
15	**9a**	20	6 x 6	-
16	**9c**	21	5 x 8	-

[a] Center to center distance between the 1,3-diyne bridges and the linkers. [b] Center to center distance between two benzylic carbons, except the compounds **5f, 6c,** and **6g**. [c] In all the compounds, the cavity dimensions are calculated from the center to center distance between the 1,3-diyne bridges and the linkers as well as the center to center distance between two benzylic carbons, except the compounds **5f, 6c,** and **6g**. [d] In the cases of the compounds **5f, 6c,** and **6g**, the cavity dimensions are calculated from the center to center distance between the 1,3-diyne bridges and the linkers as well as the distance between the two oxygen atoms, which are attached to the benzylic carbons.

Then, to study the effect of the size or nature of the linkers on the bending angle of the 1,3-diyne unit, the X-ray structures of **5a** and **7b**, which have different linkers were compared. In the compound **5a**, the linker is an ethyl group (–CH_2–CH_2–), while butyl group acts as a linker in the case of **7b** (–CH_2–CH_2–CH_2–CH_2–). Compound **7b** contains the allyl groups at the benzylic carbons, which is not there in the compound **5a**. It has already been discussed that the allyl group was not playing any role in altering the cavity size and bending angle of the 1,3-dialkyne unit and hence, we envisaged to compare the structures of both the macrocycles (**5a** and **7b**) on the basis of ring size. It has been found that with the increase in the size of the ring from 18-membered (structure **5a**) to 20-membered (structure **7b**), the cavity size has increased (entries 1,2 and 11, Table 1). Consequently, there is a decrease in the bending angle of the 1,3-dialkyne unit in **7b** (bending angle ~5°) by ~10° when compared to **5a** (bending angle = ~15°).

Increase in the size of the macrocyclic ring from 20-membered (structure **7b**) to 21-membered (compound **6a**) by the incorporation of an oxygen atom in the linker of **6a** (–CH_2–CH_2–O–CH_2–CH_2–) has resulted a decrease in the cavity size in the structure of **6a** (entries 8 and 11, Table 1) and as a result the bending angle of the 1,3-dialkyne unit has increased by ~7° in the structure of **6a** (bending angle ~12°) when compared to the structure of **7b** (bending angle ~5°).

When the size of the macrocyclic ring was increased from 21-membered (compound **6a**) to 24-membered (compound **6c**) by the incorporation of another –CH_2–O–CH_2– group in the linker of **6a**, not surprisingly the cavity size has got increased (entries 8 and 9, Table 1) and it is expected that the bending angle of the 1,3-dialkyne unit in the structure **6c** has to decrease when compared to the structure **6a**. However, the bending angle of the 1,3-dialkyne unit in the macrocycle **6c** (bending angle ~18°) was found to increase by ~6° when compared to the structure of **6a** (bending angle = ~12°).

In the compounds **6g** and **6c** the ring size is same (24-membered) and in the compound **6c** the 1,3-diyne unit is connected *via* the benzylic carbons (C4 carbon, (Ph–CH_2–O unit)) while in the compound **6g**, the 1,3-diyne unit is connected *via* the Ph–COO (benzoyl carboxyl) groups (C7 and C24). In the case of the compound **6g** the carbonyl group has been found to play an important role in controlling the bending of the 1,3-diyne unit; though the ring size is same in the compounds **6g** and **6c** (entries 9 and 10, Table 1). However, the incorporation of the –COO (benzoyl carboxyl) group has altered the cavity size of **6g**. Furthermore, the bending angle of the 1,3-dialkyne unit in the macrocycle **6g** (bending angle ~11°) was found to decrease by ~7° when compared to the structure of **6c** (bending angle = ~18°).

Additionally, to explore the effect of the nature of the linker by keeping the ring size constant, we have compared the structures of **7b**, **5g** and **5h**. In the structure **7b**, where the linker is the butyl group (–CH_2–CH_2–CH_2–CH_2– (C14 to C17 unit)), the bending angle of the 1,3-dialkyne unit was found to be ~5°. Varying the linker from butyl group (see compound **7b**) in to the 2,3-*trans* butenyl group (–CH_2–CH=CH–CH_2– (C14 to C17 unit), see the compound **5g**), the cavity size of the macrocyclic ring **5g** was found to be smaller when compared to the structure of **7b** (entries 4 and 11, Table 1), consequently, the ring strain is expected to increase. Hence, the bend angle of the 1,3-dialkyne unit in the macrocycle **5g** (bend angle ~14°) was found to increase by ~9° when compared to the structure **7b** (bend angle ~5°).

Similarly, varying the linker from the 2,3-*trans* butenyl group (–CH_2–CH=CH–CH_2– (C14 to C17 unit), see the compound **5g**) in to the –CH_2–C≡C–CH_2– group (C14 to C17 unit), see the compound **5h**), the cavity size of the macrocyclic ring **5h** was found to be smaller when compared to the structure of **5g** (entries 4 and 5, Table 1). Surprisingly, the bending angle of the 1,3-dialkyne unit in the macrocycle **5h** (bending angle ~8°) did not increase more than the bending angle of the 1,3-dialkyne unit of the macrocycle **5g** (bending angle ~14°). On the other hand, interestingly, the mono acetylenic unit linker (C14 to C17 unit) present in the structure **5h** was found to be bent and the the bending angle of the mono acetylenic unit linker was found to be ~11°, which indicated that in order to accommodate the ring strain, the (mono) acetylenic unit, which act as a linker (C14 to C17 unit) is also bending. From the preliminary analysis of the X-ray structures of representative macrocycles, it has been found that the ring size and the nature of the linkers have been found to play vital role to accommodate the ring strain and control the conformation including the shape of the 1,3-diyne unit of macrocycles.

Conclusion

In summary, we have reported the production of skeletally interesting, a new class of rigidified crown ether/polyether macrocycles having a 1,3-diyne unit-based cylindrical backbone *via* the Glaser-Eglinton-Hay macrocyclization route. We have also shown the utility of polyether macrocycles possessing the 1,3-diyne units by incorporating the isoxazole and thiophene moieties into the macrocycles. The structures of selected crown ether/polyether-type macrocycles were unambiguously confirmed from the single crystal X-ray analyses of representative compounds. It has been found that in the crystal structures of representative macrocyclic compounds, the cylindrical backbone comprising a 1,3-diyne unit is not linear and the 1,3-diyne unit has been found to be bent. Amongst the X-ray structures which were scrutinized, in the X-ray structure of the macrocycle **5f**, the phenyl ring which is acting as a linker has been found to be involved in π···π stacking. Currently, we are working to find potential applications and metal binding properties of the crown ether/polyether-type macrocycles obtained in this work.

Experimental Section

General Considerations

Melting points are uncorrected. FT-IR spectra were recorded as thin films or KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz spectrometers, respectively using TMS as an internal standard. Compounds were purified by column chromatography using silica gel (100-200 mesh). Reactions were carried out in anhydrous solvent and under a nitrogen atm, wherever necessary. Solutions were dried using anhydrous Na_2SO_4. Thin layer chromatography (TLC) analysis was performed on silica gel plates and the components were visualized by observation under iodine. Isolated yields of products were reported and yields were not optimized.

Typical experimental procedures and characterization data for representative compounds are given below. The experimental procedures for the synthesis of starting materials and the characterization data of starting materials and all products reported in this work can be found in the Electronic Supplementary Information (ESI).

Typical procedure for the syntheses of the macrocycles 5a-k, 6a-g and 7a-7e.[13a-c] A mixture of **4a** (0.20 mmol), $Cu(OAc)_2{\cdot}H_2O$ (30 mol % or 1 equiv as mentioned the respective Scheme/Table/Fig.) and DMSO (2 mL) was taken in a vial (10 mL capacity) or round bottom flask (10 or 20 mL capacity). The reaction mixture was stirred at 110 °C under an open air atmosphere for 4 h. After this period, the resulting mixture was cooled to room temperature and diluted with water (4 mL). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 x 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc : Hexane) which gave the crown/polyether-type macrocycles **5a-k, 6a-g and 7a-7e**. See the corresponding Schemes 3 and 4 and Fig. 1 for specific examples.

Typical characterization data for a representative compound 5a. Following the procedure described above, the compound **5a** was obtained after purification by column chromatography on silica gel (EtOAc : Hexanes = 10:90) as a white solid, mp: 142-144 °C; Yield: 0.061 g, 70%; FT-IR (CH_2Cl_2): 3031, 1702, 1599, 1486 and 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 5.8 Hz, 2H), 7.26 (t, *J* =6.9 Hz, 2H), 6.98 (t, *J* = 7.0 Hz, 2H,), 6.88 (d, *J* = 7.6 Hz, 2H), 4.81 (s, 4H), 4.41 (s, 4H), 4.28 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 129.3, 128.9, 126.1, 121.1, 111.7, 76.5, 72.1, 67.6, 64.5, 57.3; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{20}O_4Na$: 371.1259; found 371.1263. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by the single crystal X-ray structure analysis.

Typical procedure for the syntheses of the macrocycles 8a-f. A mixture of **5a** (0.20 mmol), $NH_2OH{\cdot}HCl$ (5 equiv), Et_3N (6 equiv) and DMSO (1 mL) was taken in a vial (10 mL capacity). The reaction mixture was sealed using a vial cap and stirred at 110 °C for 24 h. After this period, the vial was cooled to room temperature. Then, the resulting mixture was diluted with water (4 ml). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 x 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc : Hexane) which gave the crown/polyether macrocycles **8a-f**. See the corresponding Scheme 5 for specific examples.

Typical characterization data for a representative compound 8a: Following the procedure described above, the compound **8a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a white solid, mp: 141-143 °C; Yield: 0.062 g, 90%; FT-IR (CH_2Cl_2): 2925, 2875, 1603, 1495 and 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.33 (m, 1H), 7.28-7.21 (m, 3H), 6.95-6.89 (m, 2H), 6.86-6.83 (m, 2H), 6.30 (s, 1H), 4.60 (s, 2H), 4.50 (s, 2H), 4.54 (s, 2H), 4.33-4.27 (m, 4H), 3.79 (t, *J* = 5.08 Hz, 2H), 2.92 (t, *J* = 5.20 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 161.9, 156.9, 156.6, 130.9, 129.9, 129.5, 129.2, 126.6, 126.2, 121.2, 120.9, 111.0, 111.8, 101.5, 69.0, 67.6, 67.5, 67.3, 67.2, 63.5, 28.1; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{23}NO_5Na$: 404.1474; found 404.1483. This compound was crystallized using a mixture of MeOH, DCM and Hexanes and confirmed by the single crystal X-ray structure analysis.

Typical procedure for the syntheses of the macrocycles 9a-d. A mixture of **6f** (0.06 mmol), $Na_2S.xH_2O$ (70 mg), CuI (10 mol %), 1,10-phen (15 mol %) and DMF (0.5 mL) was stirred at 90 °C for 6h under an open air atmosphere. After this period, the vial was cooled to room temperature. Then, the resulting mixture was diluted with water (4 ml). The mixture was filtered through a filtration funnel and the washed with ethyl acetate (4 x 5 mL). The combined layers were extracted using ethyl acetate (3 x 5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc : Hexane) which gave the crown/polyether macrocycles **9a-d**. See the corresponding Scheme 6 for specific examples.

Typical characterization data for a representative compound 9a: Following the procedure described above, the compound **9a** was obtained after purification by column chromatography on silica gel (EtOAc:Hexanes = 50:50) as a white solid, mp: 90-92 °C; Yield: 0.018 g, 17%; FT-IR (CH_2Cl_2): 2872, 1602, 1493,1358 and 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 2H), 6.90 (t, *J* = 7.4 Hz, 2H), 6.80 (s, 2H), 6.76 (d, *J* =8.2 Hz, 2H), 4.67 (s, 4H), 4.47 (s, 4H), 4.01 (t, *J* = 4.7 Hz, 4H), 3.82 (t, *J* = 4.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 141.6, 129.6, 128.9,126.8, 126.5, 121.1, 111.9, 70.5, 68.8, 66.6, 65.8; HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{24}H_{26}O_5SNa$: 449.1399; found 449.1408. This compound was crystallized using a mixture of EtOAc and Hexanes and confirmed by the single crystal X-ray structure analysis.

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13 (a) Reaction condition A: $Cu(OAc)_2{\cdot}H_2O$ (30 mol%), DMSO, 110 ^oC, 4 h and open air atm. (b) Reaction condition B: $Cu(OAc)_2{\cdot}H_2O$ (1 equiv), DMSO, 110 ^oC, 4 h and open air atm. (c) For 0.2 mmol of starting material 2 mL DMSO was used. The amount of DMSO was changed appropriately for other reactions. (d) L. Wang, X. Yu, X. Feng and M. Bao, *Org. Lett.,* 2012, **14**, 2418. (e) H. Jiang, W. Zeng, Y. Li, W. Wu, L. Huang and W. Fu, *J. Org. Chem.,* 2012, **77**, 5179; (f) Crystallographic data of the X-ray structures of the compounds **5a** (CCDC 978362), **5f** (CCDC 970700), **5g** (CCDC 970701), **5h** (CCDC 970702), **5i** (CCDC 978447), **5k** (CCDC 970703), **6a** (CCDC 970704), **6c** (CCDC 970705), **6g** (CCDC 970706), **7b** (CCDC 970707), **7d** (CCDC 970708) **8a** (CCDC 970709), **9a** (CCDC 970710), and **9c** (CCDC 970711) have been deposited with the Cambridge Crystallographic Data Centre. (g) For a some selected papers describing the X-ray structural properties of 1,3-diyene units, see ref.[7k,7l, 8c]

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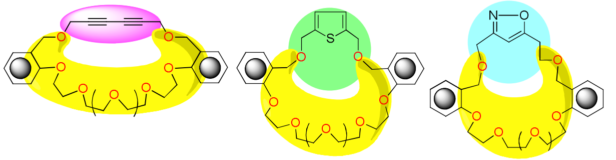
Glaser-Eglinton-Hay-type sp–sp coupling, macrocyclization and assembling of skeletally interesting 1,3-diyne unit-based crown ether/polyether macrocycles are presented.



1,3-diyne unit-based polyether macrocycles

thiophene or isoxazole moieties-based crownophane-type macrocycles