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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

Naveen, Srinivasarao Arulananda Babu,* Gurpreet Kaur, Nayyar Ahmad Aslam and Maheswararao Karanam

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. The construction of macrocycles is one of the interesting chemical transformations. Rigidified and strained macrocycles have found significant applications in several areas of scientific field because of their shape persistent skeletons and distinctive properties. 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. 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. 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.

Notably, diyne-based molecules are important building blocks in industrial and synthetic chemistry and electronic/optical materials, and exhibit prominent biological activities. 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. 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
appreciable physicochemical properties have been constructed using the Glaser-Eglinton-Hay-type coupling strategy.2–9

Crown ether/polyether-type macrocycles including lariat crown ethers can be considered as the cornerstones of supramolecular chemistry1d,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 reports9 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 backbones7,8 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.](image)

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 \( \alpha \)-hydroxy benzaldehydes (Scheme 2). Various \( \alpha \)-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).

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 \( \text{Cu(OAc)}_2\cdot \text{H}_2\text{O} \) 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). 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)$_2$·H$_2$O 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).

<table>
<thead>
<tr>
<th>substrate</th>
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<tr>
<td>4i</td>
<td>6a$^c$ (52%)</td>
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<tr>
<td>4m</td>
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<td>4n</td>
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<td>4r</td>
<td>6f$^c$ (60%)</td>
</tr>
<tr>
<td>4s-w</td>
<td>6g (35%)</td>
</tr>
</tbody>
</table>

* Reaction condition A: Cu(OAc)$_2$·H$_2$O (30 mol%), DMSO, 110 °C, 4 h and open-air atm. * The reaction was done using 0.3 mmol of the corresponding starting material. * Reaction condition B: Cu(OAc)$_2$·H$_2$O (1 equiv), DMSO, 110 °C, 4 h and open-air atm. * The reaction was done using 0.5 mmol of the corresponding starting material. * The reaction was done using 0.2 mmol of the respective starting material.

![Fig. 1](image)

**Fig. 1.** 21-27-Membered, rigidified crown ether/polyether-type macrocycles having a 1,3-diyne unit-based backbone.$^{13}$

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)$_2$·H$_2$O 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.$^{12a,c}$ 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)$_2$·H$_2$O 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.
Subsequently, as a part of our interest in the post ring-closure functional derivatization of polyether macrocycles, 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. 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. The reaction of 5a, 5b, 5c, 5f, 6a, 6c and 7a-c having the 1,3-diyne units with NH$_2$OH·HCl and Et$_3$N gave the corresponding isoxazole moiety appended, a new class of 18-21-membered, new 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. Further, these crown ether-type macrocycles 8a-i appended with the isoxazole moiety can be considered as crownophane-type molecules.

Inspired by 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, we performed the reactions of various macrocycles 5c, 6a, 6d and 6f with Na$_2$S·xH$_2$O 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).
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. The single crystal X-ray structure revealed that the molecule 5a was found to crystallize in the space group $P_2_1/c$ 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 $\sim 90^\circ$ to each other and both the conformers majorly differ with respect to the torsion angles of the 1,3-diyne linkage, which is about $<1^\circ$ and $\sim 7^\circ$ respectively. The distance between phenyl rings in the both the conformations was same ($\sim 8$ Å) and in each conformer the 1,3-diyne linkage has been found to be bent with an angle of $\sim 15^\circ$. 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 $P_2_1/c$ 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 phenyl rings has increased by $\sim 3$ Å.

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 5e) (for 9d; 0.06 mmol of 6f).
and the bending angle of the 1,3-diyne unit was found to be \( \approx 11^\circ \). 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) were \( \approx 21^\circ \) and \( \approx 77^\circ \), respectively. The two phenyl rings (having substitutions at the 1,2-positions) have been found to be inclined at an angle of \( \approx 56^\circ \). Whereas, the torsion angle for the 1,3-diyne unit was \( \approx 13^\circ \). 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 acts 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 asymmetric 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 \( \approx 2 \AA \). The bending and torsion angles of the 1,3-diyne linkage were found to be \( \approx 8^\circ \) and \( \approx 115^\circ \), respectively. Two phenyl rings are inclined at an angle of \( \approx 61^\circ \). The bending angle of the (mono) acetylenic unit was found to be \( \approx 11^\circ \). 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 5f was found to crystallize in the space group \( P \overline{1} \) 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. 2](image_url) (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.

![Fig. 3](image_url) (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.
decrease by ∼2 Å and the bending and torsion angles of the 1,3-diynes were found to be ∼16° and ∼15°, respectively. The interplanar angle between the two phenyl rings was 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 P2₁/c with one 21-membered macrocyclic molecule in the asymmetric 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-diynes were found to be ∼12° and ∼19°, respectively. The interplanar 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-diynes between the two phenyl groups was found to be bent and the bending angle was found to be ∼19° and the angle between the phenyl rings was found to be ∼56°. 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-diynes was found to be ∼11°. The interplanar angle between two phenyl rings was found to be ∼73° 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°, 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 single crystal X-ray diffraction study revealed that the molecule 7d was found to crystallize in P 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-diynes was found to be ∼12°, however, in the case of 7d_2 the bending angle of the 1,3-diynes was found to be ∼7°. The interplanar angle between two phenyl rings of the conformers 7d_1 and 7d_2 were found to be ∼64° and ∼66°, respectively. Two different conformations were found in the crystal packing and the interplanar angles between phenyl rings were almost same. C−H⋯π hydrogen bonds have been found to pack the molecules in the crystal lattice (Fig. 15 in the Electronic Supplementary Information (ESI)).
The single crystal X-ray structure analysis showed that the 18-membered macrocyclic compound $8a$ was found to crystallize in the $P_2_1/c$ space group and the asymmetric unit contained one full molecule (Fig. 8). The interplanar angle between two phenyl rings was found to be $\sim 76^\circ$ and the interplanar angle between phenyl and isoxazole rings was found to be $\sim 61^\circ$ and $\sim 73^\circ$ (with respect to each phenyl ring), respectively. The distance between the phenyl rings was found to be $\sim 8$ Å and the distances between phenyl and isoxazole ring were found to be $\sim 6$ Å and $\sim 7$ Å (with respect to each phenyl ring), respectively. No $\pi\cdots\pi$ interactions have been found in the crystal structure of this molecule.

Preliminary single crystal X-ray diffraction study revealed that the 20-membered 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 $\sim 77^\circ$ and the interplanar angle between the phenyl and thiophene rings was found to be $\sim 77^\circ$. The C–H⋯$\pi$ 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 (centroids) by $\sim 2$ Å and the interplanar angle between two phenyl rings was reduced to $\sim 42^\circ$. This increment has led desymmetrization in the molecule. The crystal packing of $9c$ was majorly found to have van der Waals interactions among its molecules. No $\pi\cdots\pi$ 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. 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-diynie unit was not able to hold the linearity. 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-diynie 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-diynie units.
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

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>ring size</th>
<th>approximate cavity dimensions (m x n in Å) from X-ray structure</th>
<th>approximate bend angle of 1,3-diyne unit</th>
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<tr>
<td>1</td>
<td>5a.1</td>
<td>18</td>
<td>4 x 7</td>
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<td>9c</td>
<td>21</td>
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</table>

* Center to center distance between the 1,3-diyne bridges and the linkers. † Center to center distance between two benzylic carbons, except the compounds 5f, 6c, and 6g. ‡ 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. § 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 (–CH₂–CH₂–), while butyl group acts as a linker in the case of 7b (–CH₃–CH₂–CH₂–CH₂–). 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 (–CH₂–CH₂–O–CH₂–CH₂–) 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 –CH₂–O–CH₂– 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 benzyllic carbons (C4 carbon, (Ph–CH₂–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 (–CH₂–CH₂–CH₂–CH₂– (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 (–CH₂–CH=CH– (C14 to C17 unit)), 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 (–CH₂–CH=CH–CH₂– (C14 to C17 unit), see the compound 5g) to the –CH₂–C≡C–CH₂– 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 polycyclic 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-diynyl 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. 1H NMR and 13C 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 Na2SO4. 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. A mixture of 4a (0.20 mmol), Cu(OAc)2·H2O (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 a nitrogen atm, wherever necessary. Solutions were dried using anhydrous Na2SO4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc : Hexanes = 10:90) as a white solid, mp: 142 -144 °C.

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 (CHCl3): 2925, 2875, 1603, 1495 and 752 cm⁻¹; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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]+ calc for C25H24O2Na: 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), Na2S·xH2O (70 mg), Cul (10 mol %), 1,10-phen (15 mol %) and DMF (0.5 mL) was stirred at 90 °C for 6 h 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 Na2SO4. 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 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 (CHCl3): 2925, 2875, 1603, 1495 and 752 cm⁻¹; 1H NMR (400 MHz, CDCl3): 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); 13C NMR (100 MHz, CDCl3): 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]+ calc for C25H24O2Na: 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 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 (CHCl3): 2872, 1602, 1493,1358 and 754 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 7.34 (d, J = 7.5 Hz, 2H), 7.14 (t, J = 7.5 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); 13C NMR (100 MHz, CDCl3): δ 156.6, 141.6, 129.6, 128.9, 128.1, 121.1, 111.7, 76.5, 72.1, 67.6, 64.5, 57.3; HRMS (ESI): m/z [M + Na]+ calc for C25H24O2Na: 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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References


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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.