ORIGINAL ARTICLE

Effect of remote substituents on solid state packing interactions in macrocyclic crownophanes derived from 1,3,5-triaroylbenzenes

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Abstract A series of four structurally related crownophanes has been prepared and characterized by X-ray crystallography. The crownophanes are based upon a 1,3,5-triaroyl benzene framework and were synthesized via enaminone/alkyne cyclotrimerization. The crownophanes differ in the identity of a peripheral substituent attached to a remote arene ring that is not part of the cyclophane macrocycle. Solid state structural characterization reveals that crownophanes with remote phenyl and phenol substituents self-assemble to form centrosymmetric dimers. Incorporation of remote alkoxy groups (methoxy or ethoxy) disrupts dimerization and leads to catameric networks. Each crownophane crystallized as an inclusion complex or a hydrate and, in one instance, water was found to occupy the macrocyclic cavity.

Keywords Crownophane · Head-to-tail dimerization · Solid state packing · Triaroylbenzene · X-ray crystal structure

Introduction

Hybrid molecules that possess structural features common to cyclophanes and crown ethers have emerged as inter-

esting and potentially valuable building blocks in supramolecular chemistry. The term crownophane is used to describe such materials and recently reported derivatives have been shown to display a range of useful properties [1]. For example, crownophanes imbued with hydrogen bonding and/or metal ligating sites within the macrocyclic cavity have been shown to function as receptors for small molecule, metal ion, and anion guests [2–5]. Certain crownophanes have also been utilized as components of novel rotaxanes that retain cation-binding functions [6–8].

We have recently disclosed the synthesis of an architecturally distinct series of crownophanes based on a 1,3,5-triaroylbenzene platform. Specifically, concomitant benzannulation–macrocyclization of bis(ethynyl ketone)s **1** and enaminone **2** produces crownophane derivatives **3** in moderate to good yield depending on the length and position (*o*, *m*, or *p*) of the ethylene glycol linker (Scheme 1) [9]. While several crownophanes of this type were prepared, these compounds were found to be poor solution phase alkali metal and ammonium cation binding agents. In an effort to determine the basis for this absence of ionophoric activity, the X-ray crystal structure of crownophane **4** was determined. The molecular structure revealed a large, roughly bowl-shaped and seemingly rigid macrocyclic cavity that possessed dimensions ill-suited for complexation of spherical alkali metal cations [9]. An interesting feature of the solid state structure of **4**, however, became evident upon examination of the extended packing. Two molecules of **4** self-assemble into head-to-tail dimers in which the "dangling" aromatic ring of one crownophane is partially inserted into the macrocyclic cavity of a second molecule (Fig. 1). In particular, one of the *meta* aryl hydrogen atoms is directed into the wide bowl-shaped crownophane opening defined by the

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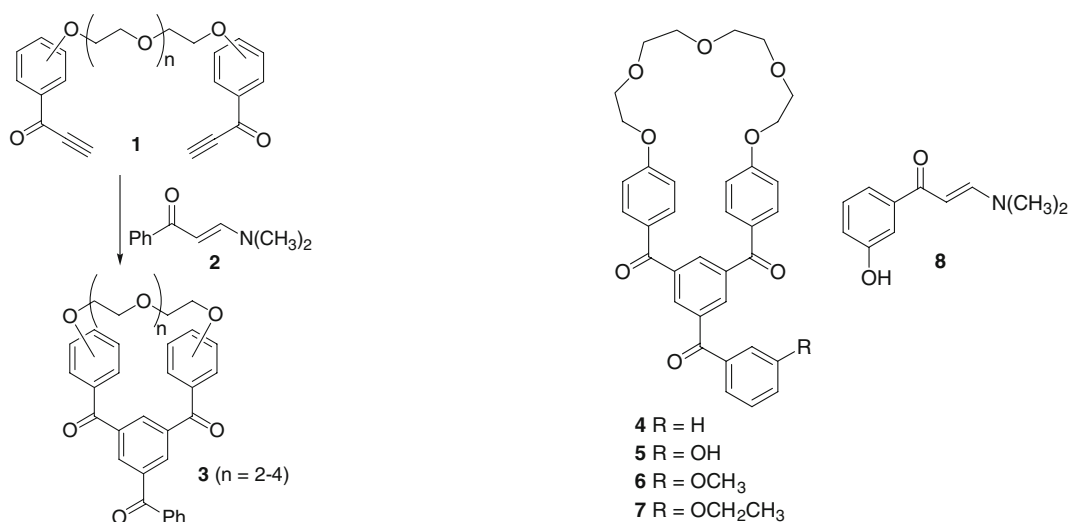
Scheme 1 Preparation of triaroylbenzene-based crownophanes
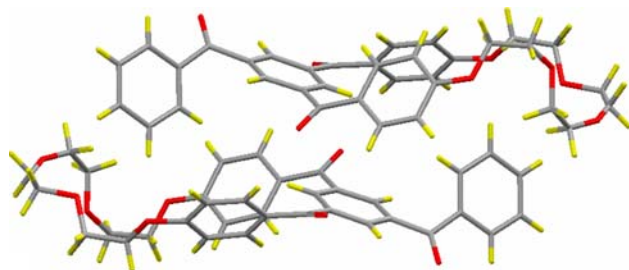
Fig. 1 Head-to-tail dimerization in the solid state structure of **4**

cyclophane arene rings and the crown ether moiety. This dimerization appears to be governed by van der Waals interactions, while discrete dimeric pairs are connected via a variety of weak C–H···O hydrogen bonds (not shown in Fig. 1).

Intrigued by this mode of solid state assembly, we initiated a study to examine what effect *meta* substituents attached to the peripheral arene ring would exert on the solid state supramolecular organization of the resulting crownophanes. Three analogues of **4** were prepared (**5–7**) possessing hydroxyl, methoxy, and ethoxy substituents, respectively. The single crystal X-ray structure of each of these compounds was determined, in addition to a new acetone inclusion complex of **4**. A common feature of all the structures is the positioning of an arene ring at the concave face of the macrocyclic ring, although the head-to-tail arrangement found in **4** is not universally observed. Finally, each of these crownophane derivatives forms solvated crystalline complexes incorporating either water (**5** and **7**) or an organic solvent (**4** and **6**).

Experimental

All commercially available reagents and solvents were used as received unless otherwise noted. Tetrahydrofuran was distilled from Na-benzophenone, toluene was distilled from CaH_2. ^{1}H- and ^{13}C-NMR chemical shifts (δ) are reported relative to residual solvent ($CHCl_3$) peaks (7.27 and 77.23 ppm for ^{1}H- and ^{13}C-NMR, respectively). Melting points are uncorrected. High-resolution mass spectra were obtained using a JEOL M-Station 700 spectrometer. Combustion analyses were obtained from Atlantic Microlabs, Norcross, GA. The preparation of **4** and **6** has been previously reported [9].

Crownophane 5

The *para*-tetra(ethylene glycol)-linked bis ethynyl ketone **1** [9] (0.59 g, 1.30 mmol) and hydroxyl-substituted enaminone **8** [10] (0.25 g, 1.3 mmol) were combined in 250 mL toluene and heated to reflux for 5 d. After this time TLC indicated complete consumption of the starting enaminone and the solvent was evaporated. The residue was subjected to flash column chromatography (5:1 $CHCl_3$:Et_2O) to afford **5** (96 mg, 12%) as a yellow solid. An analytical sample was obtained upon recrystallization from benzene. M.p. 220–221 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (3.69–3.76 (m, 8H), 3.90 (t, $J = 4.2$ Hz, 4H), 4.23 (t, $J = 4.2$ Hz, 4H), 7.00 (d, $J = 8.8$ Hz, 4H), 7.11–7.15 (m, 1H), 7.33–7.34 (m, 4H), 7.78 (d, $J = 8.8$ Hz, 4H), 7.87 (t, $J = 1.6$ Hz, 1H), 8.53 (d, $J = 1.6$ Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (194.2, 163.4, 156.8, 140.1, 138.6, 138.1, 136.3, 134.4, 132.7, 130.4, 130.0, 123.0, 120.9, 117.1, 114.7, 71.3, 71.1, 69.9, 68.6. IR (thin film) v (cm^{-1})

3407, 2878, 1656, 1601. HRMS (FAB$^+$, NBA) calcd. for C$_{35}$H$_{33}$O$_9$ [M + H]$^+$: 597.2125; found: 597.2125. Anal. Calcd. for C$_{35}$H$_{32}$O$_9$ · (H$_2$O)$_{1.25}$: C 67.89, H 5.62. Found: C 67.88, H 5.46.

Crownophane 7

Phenol-substituted crownophane **5** (93 mg, 0.156 mmol), ethyl bromide (175 mg, 2.34 mmol), and K$_2$CO$_3$ (625 mg, 4.50 mmol) were combined in acetone (∼5 mL) and heated to reflux for 12 h. The reaction was allowed to cool to rt and the solids were removed by filtration. The filtrate was concentrated in vacuo and the residue was dissolved in CH$_2$Cl$_2$. This solution was washed sequentially with H$_2$O and brine, and dried over anhydrous MgSO$_4$. Filtration and removal of the solvent afforded a residue that was recrystallized from benzene to give **7** (76 mg, 78%) as a yellow solid. M.p. 159–160 °C. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 1.45 (t, J = 7.0 Hz, 3H), 3.67–3.75 (m, 8H), 3.90 (t, J = 4.2 Hz, 4H), 4.12 (q, J = 7.0 Hz, 2H), 4.24 (t, J = 4.2 Hz, 4H), 7.01 (d, J = 8.8 Hz, 4H), 7.16–7.20 (m, 1H), 7.37–7.45 (m, 3H), 7.81 (d, J = 8.8 Hz, 4H), 7.92 (t, J = 1.6 Hz, 1H), 8.57 (d, J = 1.6 Hz, 2H). ^{13}C-NMR (75 MHz, CDCl$_3$) δ 195.2, 193.8, 162.9, 159.4, 140.1, 138.0, 137.6, 135.8, 134.1, 132.4, 129.8, 129.6, 123.1, 120.5, 115.0, 114.4, 70.9, 70.7, 69.4, 68.0, 64.0, 14.9. IR (thin film) ν (cm^{-1}) 2,878, 1,661, 1,602. HRMS (FAB$^+$, NBA) calcd. for C$_{37}$H$_{37}$O$_9$ [M + H]$^+$: 625.2438; found 625.2441. Anal.

Calcd. for C$_{37}$H$_{36}$O$_9$ · (CH$_2$Cl$_2$)$_{0.75}$: C 65.86, H 5.49. Found: C 65.61, H 5.62.

X-ray crystal structure determinations

Single crystals of a new inclusion complex **4** · acetone were obtained from slow evaporation of an acetone solution. Crystals of **5**–**7** were grown from CHCl$_3$/hexanes solutions. The structures of **5** and **7** were obtained as hydrates exhibiting a 1:1 crownophane:H$_2$O stoichiometry while **6** formed an inclusion complex with CHCl$_3$ (stoichiometry **6** · (CHCl$_3$)$_{0.5}$). Crystal data for all new structures is shown in Table 1.

Preliminary examination and data collection were performed using a Bruker SMART charge coupled device (CCD) area detector system single crystal X-ray diffractometer. SMART and SAINT software packages were used for data collection and integration [11]. Collected data were corrected for systematic errors using SADABS based on the Laue symmetry using equivalent reflections [12]. Structure solution and refinement were carried out using the SHELXTL-PLUS software package [13]. The structures were solved by direct methods using full-matrix least squares refinement on F^2.

Crystallographic data (cif) has been deposited with the Cambridge Crystallographic Data Center (CCDC, deposition numbers 673,773–673,776). Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. E-mail: deposit@ccdc.cam.ac.uk.
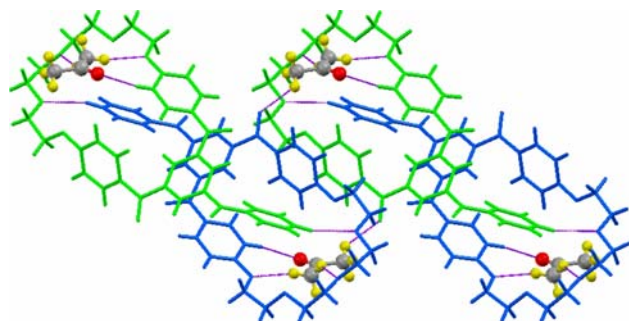
Table 1 Crystallographic data

	4 · acetone	**5** · H$_2$O	**6** · (CHCl$_3$)$_{0.5}$	**7** · H$_2$O
Cryst syst	Triclinic	Triclinic	Monoclinic	Orthorhombic
Space group	$P\bar{1}$	$P\bar{1}$	P2$_1$/c	Pbca
a (Å)	9.24110 (10)	10.2780 (5)	18.692 (5)	9.2830 (4)
b (Å)	13.8094 (2)	12.1363 (6)	11.844 (3)	18.8458 (8)
c (Å)	14.3183 (2)	12.6445 (6)	15.143 (5)	37.5453 (16)
α (°)	69.2200 (10)	78.551 (2)	90	90
β (°)	86.3890 (10)	74.304 (2)	98.260 (19)	90
γ (°)	71.4240 (10)	85.349 (2)	90	90
V (Å^3)	1616.77 (4)	1487.58 (13)	3317.9 (16)	6568.4 (5)
Z	2	2	2	8
D_{calc} (mg/m^3)	1.312	1.372	1.342	1.300
μ (mm^{-1})	0.093	0.101	0.211	0.094
T (K)	155 (2)	165 (2)	218 (2)	295 (2)
No. of reflns	26,284	25,953	53,075	123,290
No. of unique reflns	7,057	5,842	5,517	7,932
No. of parameters	424	410	434	444
R1 [$I > 2\sigma(I)$]	0.0660	0.1360	0.0653	0.0548
wR2	0.2034	0.1435	0.1746	0.1447

Results and discussion

Many simpler 1,3,5-triaroylbenzene derivatives have shown a propensity to form crystalline inclusion complexes with various small molecule (solvent) guests [14–16]. While crystals of **4** grown from CHCl₃/hexanes yielded a close-packed non-solvated structure upon X-ray analysis (vide supra), crystals deposited from acetone solution were found to contain an included acetone molecule of solvation. Acetone solvates occupy positions along the convex faces of the macrocyclic cavity, with the wider concave faces cradling a dangling phenyl ring from a second molecule of **4** (Fig. 2). Thus, the head-to-tail dimerization observed in the non-solvated form of **4** (see Fig. 1 above) is preserved in the acetone inclusion complex. Indeed, the peripheral arene ring is inserted even deeper into the macrocyclic cavity resulting in concomitant formation of an arene C–H···O hydrogen bond with one of the crown ether oxygen atoms (purple line in Fig. 2, H···O distance = 2.526 Å). The acetone solvates participate in numerous solid state hydrogen bonding interactions, some of which are indicated in Fig. 2. These contacts serve not only to position acetone solvates at the convex (narrow) face of the crownophane ring but also to connect adjacent dimeric units of **4** resulting in formation of two-dimensional layers. Face-to-face π–π interactions are also observed between adjacent molecules of **4** (arene–arene distance ~ 3.72 Å). Compared to the non-solvated structure of **4**, the acetone inclusion complex features a more compact head-to-tail dimerization motif arrayed in 2D layers mediated (in part) by acetone–crownophane hydrogen bonding interactions.
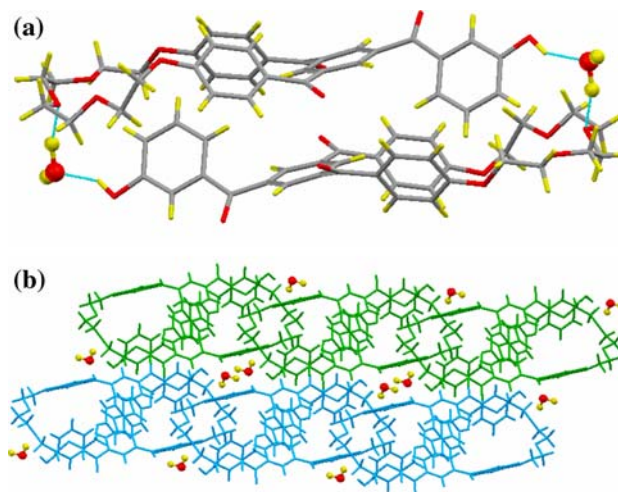
The hydroxyl-substituted crownophane **5** was prepared from enaminone **8** and the appropriate bis(ethynyl ketone) according to the procedure illustrated in Scheme 1. While the isolated yield was modest due to formation of intractable tars during the reaction, **5** could be easily isolated via flash column chromatography. Single crystals suitable for X-ray analysis were subsequently grown from a mixture of CHCl₃ and hexanes.

Given the packing motif previously observed in **4** (see Figs. 1, 2), it was envisioned that a peripheral phenolic residue capable of engaging in hydrogen bonding interactions with the macrocyclic oxygen atoms may reinforce head-to-tail dimerization. This notion proved to be partially correct in that **5** does self-assemble via dimerization outwardly similar to that observed in **4**, however a water molecule positioned above the concave face of the macrocyclic cavity serves as a hydrogen bond relay between a phenol group and the crown ring (Fig. 3a). The phenolic arene is rotated with respect to the crownophane cavity such that the OH substituent is pointed away from the macrocycle. The water molecule acts as a hydrogen bond donor toward a macrocyclic oxygen atom (HO–H···O distance = 1.659 Å) and a hydrogen bond acceptor toward the phenol residue (ArO–H···OH₂ distance = 1.833 Å). The remaining hydrogen from included water forms a hydrogen bond with a carbonyl oxygen from an adjacent molecule of **5** ($d_{\text{H···O}} = 1.765$ Å) as part of a 2D layer motif. Adjacent layers then stack about an inversion center as depicted in Fig. 3b.
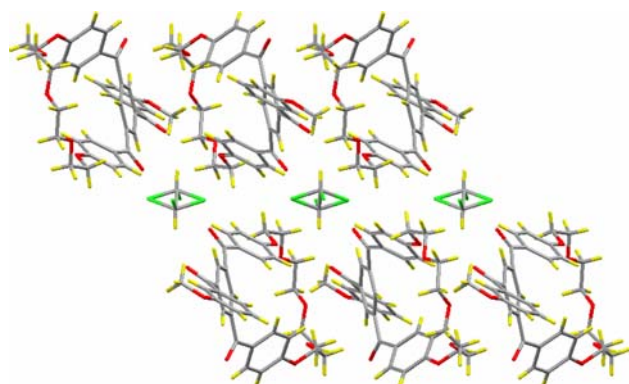
A significantly different packing arrangement is encountered in the crystal structure of **6** · (CHCl₃)₀.₅. Rather than forming discrete dimers via head-to-tail interactions, molecules of **6** arrange in a zig-zag fashion mediated by partial insertion of a methoxy group from one crownophane into the convex face of a second crownophane (Fig. 4a). Close contact between a C–H group from the methoxy residue and a crown ether oxygen atom ($d = 2.432$) may represent a solid state C–H···O hydrogen bond [17]. One-dimensional ribbons formed from this intermolecular arrangement stack upon each other to generate close-packed 2D sheets as indicated in Fig. 4b. The included CHCl₃ molecules are disordered about an

Fig. 2 View of the extended packing found in **4** · acetone (down *a*). Hydrogen bonding interactions indicated by purple lines

Fig. 3 (**a**) Water-mediated dimerization of **5** (hydrogen bonds shown in light blue). (**b**) 2D sheet-like packing observed in **5** · H₂O
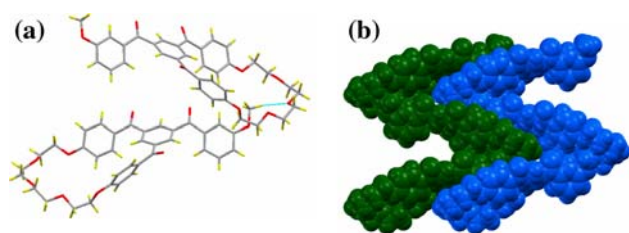
Fig. 4 (**a**) Zig-zag ribbon formed from **6**. (**b**) Stacking of individual ribbons (viewed down *a*) to form 2D sheets in **6** · (CHCl$_3$)$_{0.5}$. Chloroform solvates omitted for clarity
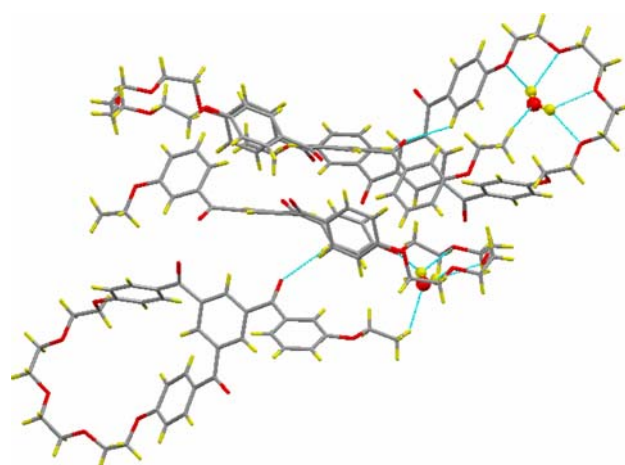

Fig. 5 Packing (down *b*) of **6** · (CHCl$_3$)$_{0.5}$

Fig. 6 View of the extended packing found in **7** · H$_2$O. Hydrogen bonding interactions indicated in light blue. Only two included water molecules shown for clarity

inversion center and occupy sites between these 2D sheets as shown in Fig. 5.

Similar to the situation encountered in the methoxy-substituted crownophane, ethoxy derivative **7** does not exhibit the head-to-tail packing found in **4** and **5**. Moreover, the ethoxy group from one molecule also approaches the convex macrocyclic face of a second molecule. Rather than generating a one dimensional zig-zag pattern, however, the crownophane portion of **7** is rotated with respect to the dangling ethoxy-substituted arene such that intermolecular interactions are propagated in three dimensions. Another important difference between the structures of **6** and **7** concerns the presence of water molecules in the latter material that are firmly imbedded within each macrocyclic cavity (Fig. 6). The water molecules appear to be held within individual crownophane rings via two bifurcated hydrogen bonding interactions to the ethylene oxy moieties. The H···O distances of these interactions range from 2.269 to 2.557 Å. The methyl groups of the ethoxy substituents also approach the encircled water molecules along trajectories consistent with formation of C–H···O hydrogen bonds (H···O distances = 2.618 Å).

Comparison of the solid state structures of the four crownophanes characterized in this study reveal several common features. First, all four derivatives crystallize as inclusion complexes with small molecule solvates (acetone, chloroform, or water). Only in the case of the CHCl$_3$ complex was the included solvent found not to be

associated in some manner with the macrocyclic crowno-phane cavity. It is also notable that in each structure a dangling (i.e., non-cyclophane) phenyl ring approaches the concave face of the crownophane macrocycle. In **4** · acetone and **5** · H$_2$O this interaction is part of an overall centrosymmetric head-to-tail dimerization, while in **6** · (CHCl$_3$)$_{0.5}$ and **7** · H$_2$O this interaction is part of a larger catameric network. Thus, substitution on the dangling arene in these triaroylbenzene derived crownophanes appears to greatly influence solid state self-assembly as incorporation of alkoxy groups disrupts dimer formation. This characteristic may prove important in guiding the design of new solid state composites and inclusion complexes built from triaroylbenzene-based crownophanes. Finally, while alkali metal ions were found to be poor substrates for crown ether-like receptors such as **4** [9], a small molecule such as H$_2$O appears to be comfortably accommodated within the crownophane cavity as observed in the hydrated structure of **7** (Fig. 6). This may indicate that crownophanes **4**–**7** and structurally related analogues are better suited to complex metal ions through second sphere interactions [18]. Studies aimed at probing this issue are underway.

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