Reactions of thiacalix[4]arene 1,3-bistriflate: formation of thiacalix[2]phenoxathiins—structural and complexation studies†

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Reaction of the 1,3-bistriflate of thiacalix[4]arene **2** under various conditions including typical Sonogashira and other basic conditions with CuI, afforded a mixture of hydrolysis and rearrangement products including a bis(phenoxathiin) **3** reported also by Hattori and co-workers. An unprecedented displacement of a narrow-rim triflate by a hydrogen atom to form a new *partial cone* thiacalixarene **2i** is reported as are five new X-ray crystal structures. The de-*tert*-butylated analogue **3a** was synthesized from **3** and their complexation properties with Ag^{+} and Hg^{2+} are also reported.

Introduction

The recent reports by Hattori and co-workers[1,2] on their reactions with the 1,3-bistriflates **1** and **2** of *p*-*tert*-butylcalix[4]-arene (**1a**) and *p*-*tert*-butylthiacalix[4]arene (**2a**), respectively (Fig. 1), and also the report of Parola and co-workers,[3] prompts us to report on our own findings with these related compounds.[4]

It is, of course, well-documented that there continues to be intensive research being conducted in which calix[*n*]arenes play an integral part, since among other properties, these compounds serve as very useful scaffolds for further modifications and investigations.[5] Included in this increasingly large and diverse family of compounds and their derivatives is a relatively less well-studied class of heteroatom-bridged calixarenes,[6] the best known of which are the thiacalix[*n*]arenes.[7] The majority of functionalized derivatives of both types of calix[4]-arenes, **1a** or thiacalix[4]arenes **2a** have involved their wide (or "upper") rims, but work involving narrow- (or "lower"-) rim functionalization has, to date, been rather limited, and for the most part have involved mostly *O*-alkylation. Recently however, the Sonogashira[8] reaction has been successfully employed with **1** to afford various 1,3-bis(arylethynyl)-calix[4]arenes such as *e.g.* **1b** (Scheme 1).[9] These findings were in contrast to the attempted similar direct metal-assisted functionalization of **1** under either Suzuki–Miyaura[10] and/or Stille[11] conditions which had previously been reported to have failed.[12] Several other approaches to displacement of the narrow-rim oxygen functionality have been reported, but these approaches have involved indirect approaches, and in general

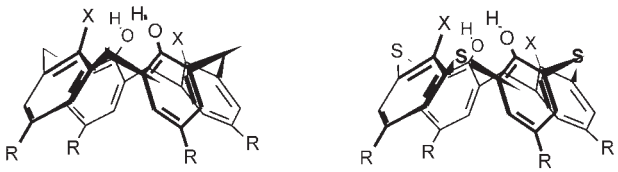
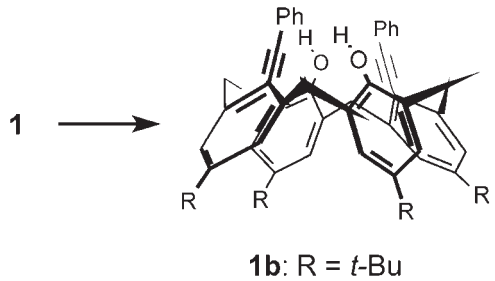


Fig. 1

were conducted mainly with the methano-bridged calixarenes such as **1a**.[13]

Miyano and co-workers[14] however, successfully synthesized the lower-rim tetraamino derivative of thiacalix[4]arene **2b** (Fig. 2) *via* an indirect route, but more recently, Hattori and co-workers[1] reported a direct Ullmann-type conversion of **2** and also of **1**, to the corresponding monobenzylamino thiacalix[4]-arene derivatives **2c** and **1c**, respectively. They also reported that the 1,3-bistriflate of *p*-*tert*-butylthiacalix[4]arene **2** underwent intramolecular rearrangements under various reaction conditions (see below), and also formed a new macrocyclic compound, a bis(phenoxathiin) or "thiacalix[2]phenoxathiin" **3** (Fig. 3).[1,2] Desroches, Parola and co-workers[3] were able to effect substitution of the narrow-rim hydroxyls of tetra-*p*-*tert*-butylthiacalix[4]arene itself *via* thermally-induced Newman–Kwart rearrangement reactions of the precursor tetra-*O*-thiacarbamoyl derivatives **4** and **4a**, but these reactions led directly



Scheme 1

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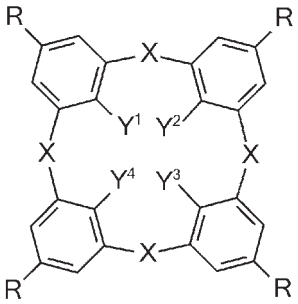


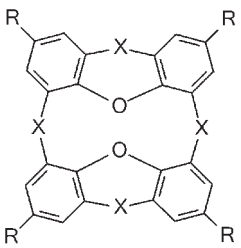
	X	R	Y^1	Y^2	Y^3	Y^4
1c	CH_2	*t*-Bu	$NHCH_2Ph$	OH	OH	OH
2b	S	*t*-Bu	NH_2	NH_2	NH_2	NH_2
2c	S	*t*-Bu	$NHCH_2Ph$	OH	OH	OH
2d	S	*t*-Bu	NH_2	OH	OH	OH
2e	S	*t*-Bu	C≡CPh	OH	C≡CPh	OH
2f	S	*t*-Bu	OTf	OH	OH	OH
2g	S	*t*-Bu	OTf	OTf	OH	OH
2h	S	*t*-Bu	OTf	OH	OH	H
2i	S	*t*-Bu	OPr	OPr	OPr	OPr
4	S	*t*-Bu	$Y^1 = Y^2 = Y^3 = Y^4 = OCSN(CH_3)_2$			
4a	S	H	$Y^1 = Y^2 = Y^3 = Y^4 = OCSN(CH_3)_2$			

Fig. 2

to the formation of the novel analogues of **3**, namely, thiacalix[2]thianthrenes **5** and **5a**, respectively (Fig. 3).

In connection with our own work, we were interested in extending our previous findings with the Sonogashira reaction[8,9] to the 1,3-bistriflate of thiacalix[4]arene (**2**), in order to study both the potential non-linear optical and also the complexation properties of suitably-designed narrow-rim arylethynyl derivatives of thiacalix[4]arene itself, such as **2e**. Although we have thus far failed to synthesize **2e** or other narrow-rim ethynyl derivatives using this approach, we herein report our recent findings[4] which complement in some instances those disclosed coincidentally in those recent publications of Hattori and co-workers[1,2] and also that of Desroches, Parola and co-workers[3]

The same Sonogashira-type reaction conditions, (CuI, DBU and phenylacetylene in anhydrous degassed toluene) which we had successfully used with 1,3-bistriflate **1** to afford the corresponding 1,3-bis(phenylethynyl)calix[4]arene (**1b**) were therefore employed with *p-tert*-butylthiacalix[4]arene-1,3-bistriflate (**2**). However, with **2** these conditions afforded none of the desired corresponding phenylethynyl substituted product **2e**. Instead, monotriflate **2f** (11%); 1,2-bistriflate **2g** (8%), and the bis(phenoxathiin) **3** (60%) as the major product were isolated (Table 1, entry 1).[15]



	X	Y	R
3	S	O	*t*-Bu
3a	S	O	H
5	S	S	*t*-Bu
5a	S	S	H
6	CH_2	O	*t*-Bu

Fig. 3

The structure of **3** which crystallized from benzene was confirmed by single-crystal X-ray crystallography (Fig. 4).[16] Subsequently, this structure proved to be virtually identical to that reported by Hattori and co-workers,[1] except that our structure contained a single molecule of benzene in the unit cell. Hattori's crystal, on the other hand was derived from CH_2Cl_2–CH_3CN, resulting in differences in the crystal packing. The molecule of benzene in our case, as can be seen, is not within the "cavity" of the macrocycle and is therefore not a true inclusion complex.

The corresponding C–S–C and C–O–C bond angles which are parts of each of the phenoxathiin moieties in our X-ray structure of **3**, are nevertheless comparable with those of Hattori's: 97.28 and 114.72°; and 97.60 and 115.89° as compared with those in Hattori's structure of 97.51 and 116.17°; and 97.88 and 115.95°, respectively. The C–S–C bond angles which incorporate the two sulfur atoms connecting the two phenoxathiins in our structure are 98.02 and 100.49° as compared with the values of 98.29 and 100.92°, respectively, in Hattori's structure.

The X-ray crystal structure of monotriflate **2f** which has now been obtained for the first time, shows it to be in a "skewed" *pinched-cone* conformation in which the aromatic ring which bears the triflate group is angled inwards toward the distal phenolic ring.[17] The opposing C–S–C bond angles were 98.57 and 98.04°; and 106.14° and 101.90°, respectively (Fig. 5).

We were also able to solve the X-ray crystal structure of 1,2-bistriflate, **2g** which revealed that there are two molecules in the unit cell. Each of the two molecules are in *pinched-cone* conformations and are oriented in opposite directions to each other (Fig. 6).[18] Hattori's group has also reported the formation of **2g** produced by the intramolecular rearrangement of the precursor, **2a** under several basic conditions.[2] Previously, we[10b] and others[12a] had reported similar intramolecular rearrangement of **1**, the analogous 1,3-bistriflate of *p-tert*-butylcalix[4]arene under various Pd-catalysed reaction conditions.

In our hands, different reaction conditions were tried (Table 1) and only those shown in entries 1–5 afforded any of **3**. As can be seen from entries 2 and 3, phenoxathiin **3** was also formed in the absence of added CuI as was found by Hattori and co-workers.[2] However, in general, higher yields of **3** were obtained when catalytic amounts (10 mol%) of Pd(II) were employed (entries 1, 3 and 5). When triethylamine was used as both the base and as the solvent, with Pd(II),[19] (entry 5) **3** was also formed, albeit in lower yield (28%) than when toluene and DBU were used. With Pd(0) and DBU, both with and without added CuI, small amounts of **3** (8%) were formed, along with **2g** (entries 7 and 8). No new product formation was observed when only CuI and Pd(II) together were used without any DBU, and only unreacted starting material was recovered (entry 6). Buchwald's conditions[20] using Pd(II) in acetonitrile

Table 1 Some experimental conditions employed with 1,3-bistriflate **2**

Entry	CuI/mol eq.	Base (mol eq.)	Pd cat. (mol %)	Solvent	*t*/h, temp.	Yield[a] (%) **2f**	**2g**	**3**
1	5	DBU (4.4)	$PdCl_2(PPh_3)_2$ (10)	Toluene	24, reflux	11	8	60
2	—	DBU (4.4)	—	Toluene	15, reflux	n.d.	89	8
3	—	DBU (4.4)	$PdCl_2(PPh_3)_2$ (10)	Toluene	15, reflux	n.d.	81	13
4	5	DBU (4.4)	—	Toluene	15, reflux	n.d.	86	8
5	0.1	Et_3N	$PdCl_2(PPh_3)_2$ (5)	Et_3N	24, 40 °C	30	40	28
6	5	Et_3N	$PdCl_2(PPh_3)_2$ (10)	Toluene	15, reflux	n.d.	n.d.	n.d.
7	5	DBU (4.4)	$Pd(PPh_3)_4$ (10)	Toluene	15, reflux	n.d.	84	8
8	—	DBU (4.4)	$Pd(PPh_3)_4$ (10)	Toluene	15, reflux	6	80	8
9	—	Cs_2CO_3(5)	$PdCl_2(PPh_3)_2$ (5)	CH_3CN	10, reflux	n.d.	n.d.	n.d.

[a] Note: In entry 6 only unreacted starting material **2** was recovered. In entry 9 only **2a** was obtained. n.d. = not detected.

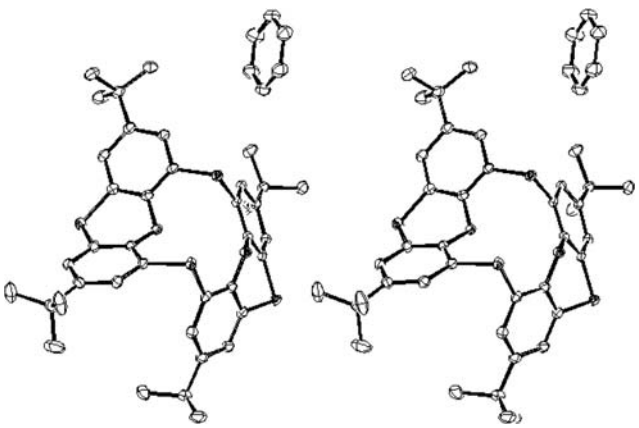


Fig. 4 X-Ray crystal structure stereoview of **3** with a benzene molecule in the unit cell.

with Cs_2CO_3 only afforded the product of hydrolysis of **2**, namely, thiacalix[4]arene (**2a**) itself (entry 9).

When **2** was reacted with only 1 molar equivalent of CuI and 4.4 mol equivalents of DBU and 10 mol% of $PdCl_2(PPh_3)_2$ in toluene, in addition to compounds **2f**, **2g** and **3** (isolated in 40, 7 and 28% yields, respectively), an unexpected and unprecedented new product, **2h** was obtained in 10% yield.[21] The X-ray structure of this new product **2h** (Fig. 7) shows it to exist in a *partial-cone* conformation and confirmed that one of the triflate groups has been replaced by a hydrogen atom.[22] The phenyl ring which bears the triflate group is angled inwards toward the distal ring, and the intra-annular hydrogen appears at δ 6.92 ppm in the ^{1}H NMR spectrum. It is not certain as yet how this unusual hydrogen displacement of a triflate has occurred and experiments are underway in order to potentially exploit this new finding.

Molecular mechanics (MM) modeling[23] suggested that the bowl-shaped phenoxathiin **3** could be capable of complexation with C_{60} and/or C_{70}. However, none of the conditions which were tried provided any supporting evidence for this. One possible reason for this lack of experimentally demonstrable complexation ability is suggested by the two structures shown in Fig. 8. Fig. 8(a) is the MM computer-generated structure of the hypothetical **3**:C_{60} complex; and Fig. 8(b) is that of the complex of C_{60} with tetra-*tert*-butylcalix[4]naphthalene (**7**), a molecule with which we have conducted extensive studies[24] of its experimentally demonstrable complexation behaviour with C_{60}. We hypothesize that in the case of **3**, a C_{60} molecule is not as deeply embedded, or as tightly embraced, by this host molecule, as can readily be seen, in comparison with the deeper, basket-shaped calixnaphthalene **7**. Another factor could be that the barrier to conformational interconversion in the case of **3** is smaller than that in **7**, in which the narrow-rim hydroxyl groups are hydrogen-bonded to one another thus allowing for a greater degree of pre-organization for effective complexation with a C_{60} molecule.

Since the anticipated complexation of **3** with C_{60} and C_{70} could not be realized, experiments were therefore conducted in

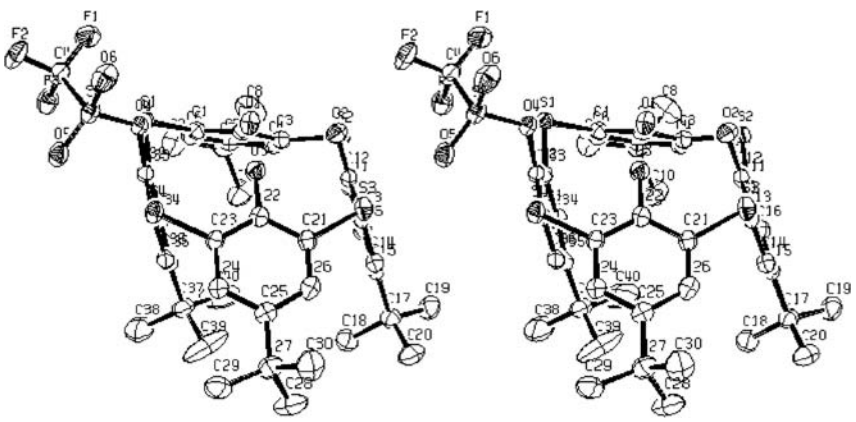


Fig. 5 X-Ray crystal structure stereoview of monotriflate **2f**.

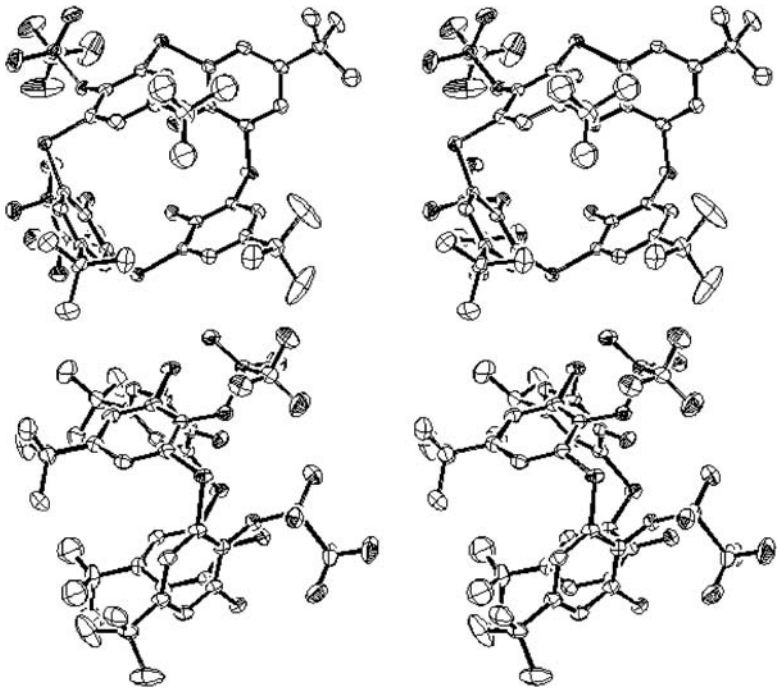


Fig. 6 X-Ray crystal structure stereoview of 1,2-bistriflate **2g** showing the orientation of the two molecules in the unit cell. The hydrogen atoms and the solvent molecule ($CHCl_3$) have been removed for clarity.

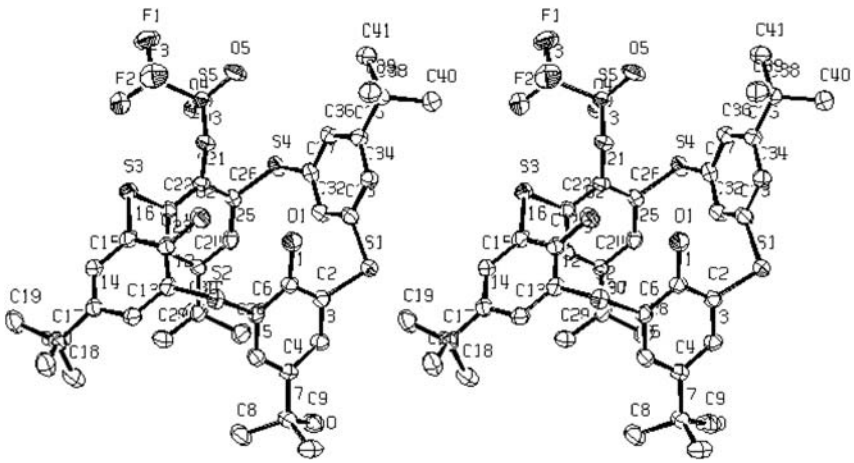


Fig. 7 X-Ray crystal structure stereoview of **2h**.

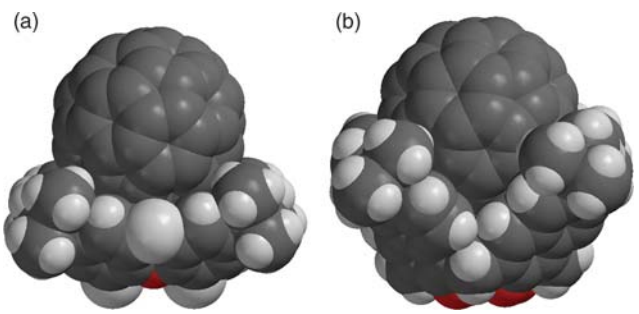


Fig. 8 MM computer-generated hypothetical structures of supramolecular complexes of C_{60} with (a) phenoxathiin **3** and (b) tetra-*tert*-butylcalix[4]naphthalene (**7**).

order to produce new derivatives of **3** containing different *wide*-rim ethynyl substituents instead of the *tert*-butyl groups, which in principle could be installed *via* Sonogashira coupling reactions as demonstrated in 2003 by Parola and co-workers with tetra-*O*-propylthiacalix[4]arene (**2i**).[19] The pre-requisite removal of the *tert*-butyl groups from **3** as a first step towards this goal was achieved using the $AlCl_3$-phenol protocol described by Hosseini and co-workers[25] The desired de-*tert*-butylated bis(phenoxathiin) **3a** was obtained in 26% yield[26] and its X-ray structure (Fig. 9) revealed it to be quite different to that of Desroches and Parola's comparable "thiacalix[2]thianthrene" **5a**.

This X-ray structure of **3a** reveals that there is a pair of interlocked "L-shaped" molecules of in the unit cell.[27] The planes of each of the phenoxathiin units of one of these molecules are anti-parallel to the corresponding phenoxathiin

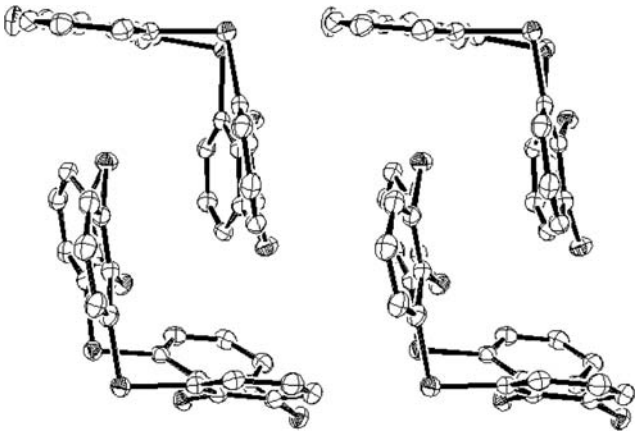


Fig. 9 X-Ray crystal structure stereoview of de-*tert*-butylated bis(phenoxathiin) **3a**.

units of its partner molecule. Each of the C–S–C bond angles which incorporate the sulfur atoms connecting the pair of phenoxathiins in each molecule are 100.76 and 100.15°; and 99.70 and 98.82°, respectively. These particular angles are not much different than the corresponding ones seen in either Hattori's, or our compound **3**. However, significant differences are clearly evident in the C–S–C and C–O–C bond angles for each of the phenoxathiin moieties of each molecule of **3a** in the unit cell when compared with those of **3**. In **3a** these angles are respectively, 97.73 and 117.17°; and 99.21 and 118.3°; and for the second molecule the respective angles are 99.81 and 120.32°; and 101.01 and 122.9°. The three fused rings of the phenoxathiin moiety having the largest C–O–C angle is nearly co-planar when compared with those in the other phenoxathiin in the unit cell.

MM modeling of **3a** suggested that, as in the case of **3**, it could potentially also be capable of complexation with C_{60} and/or C_{70}, but again no evidence for any such complexation could be observed with **3a** either, presumably for the same reasons as were presented above. Nonetheless, as would be expected, both **3** and **3a** form 1 : 1 complexes with Ag^+ with apparent binding K_{assoc} values of 2200 ± 200 and 630 ± 50 as determined by ^{1}H NMR spectroscopy,[28] using a mixture of 1 : 9 CD_3CN–$CDCl_3$ (v/v) as the solvent. To avoid any solvent effect, all host and guest solutions were prepared using the same solvent mixture. Upon addition of aliquots of solutions of Ag^+ ($\sim 6 \times 10^{-2}$ M) to the host solutions of **3** or **3a** ($\sim 7 \times 10^{-4}$ M), the ^{1}H NMR spectra showed clear induced changes in the chemical shifts of all of the host signals. With [guest] : [host] ratios $\geq$ 10 : 1, the observed chemical shifts leveled off very rapidly, so instead, the complexation studies were conducted at lower ratios, ranging from 0.5 to 9.0. In these ranges, addition of Ag^+ solutions to the host solutions, resulted in shifts of all of the host signals to lower fields. The mole ratio plots, in both cases indicated the formation of 1 : 1 host–guest complexes with Ag^+ in the concentration ranges which were studied. For the non-linear curve fitting plots a 1 : 1 binding isotherm as described by Connors[29] was employed.

Binding studies with several Hg^{2+} salts with **3** and **3a** were conducted in a similar manner and in the same solvent system (1 : 9 CDCN–$CDCl_3$) as was used in the Ag^+ in preliminary experiments. The most reproducible results however were obtained using $Hg(ClO_4)_2$, although only relatively small complexation-induced chemical shifts could be discerned in the titration experiments. Since the relatively low solubility of $Hg(ClO_4)_2$ limited our ability to accurately determine K_{assoc} values in this solvent system a different solvent system (1.5 : 9 CD_3OD–$CDCl_3$) in which the solubility was higher ($\sim 3 \times 10^{-2}$ M), was therefore employed, in both cases. Both macrocycles revealed similar 1 : 1 binding with Hg^{2+} with K_{assoc} values of 540 ± 75 for **3** and 475 ± 36 for **3a**. We are unable at present to account for this apparent lack of significant difference between the binding constant values seen for **3** and **3a** in the case of Hg^{2+} as compared with that which was seen in the case of the Ag^+ binding, although the nature of the different counter-ions may be a factor. It should be noted however, that no significant differences were also noted when $Hg(OCOCF_3)_2$ was employed in preliminary experiments which as indicted above, were limited by the low solubility of this and other Hg^{2+} salts.

In conclusion, we have shown that bisphenoxathiins **3** and **3a** can be formed by most probably, a Ullmann-type mechanism[2] from the corresponding 1,3-bistriflates of thiacalix[4]-arene. Five new X-ray structures are presented herein. Three of these structures are for compounds **2f**, **2g** and **3** previously reported as having been synthesized by different procedures; one is of a new thiacalix[4]arene derivative **2h** produced in a Pd-catalysed reaction, and the fifth structure is that of **3a**, a de-*tert*-butylated bisphenoxathiin reported herein for the first time. Both **3** and **3a** were capable of 1 : 1 binding with Ag^+ and Hg^{2+} although higher binding constants were observed with the *tert*-butylated bisphenoxathiin **3** than its *de-tert*-butylated analogue **3a** with Ag^+, and in general, in both cases with Hg^{2+}.

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15 Conditions employed for the reactions summarized in Table 1. *Entry 1 (reaction of* **2** *with Pd–CuI–DBU)*: To a stirred mixture of $PdCl_2(PPh_3)_2$ (8.0 mg, 0.011 mmol), CuI (100 mg, 0.53 mmol), and **2** (110 mg, 0.11 mmol) in dry, degassed toluene (30 mL) at reflux temperature was added DBU (70 mg, 0.46 mmol). The mixture was heated, with stirring, under Ar for a further 24 h at the reflux temperature. After cooling to rt, the solvent was evaporated and the resulting crude product was dissolved in CH_2Cl_2 (40 mL), washed with aqueous saturated NH_4Cl (15 mL) and then with water (20 mL). The CH_2Cl_2 extract was dried ($MgSO_4$), filtered, and the solvent was removed, to afford a crude product which was purified by preparative thin-layer chromatography (CH_2Cl_2–hexanes 3 : 7) to afford *bisphenoxathiin* **3** (45 mg, 60%): mp 376–378 °C (lit.[1] 282–284 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, J = 1.5 Hz, 4H), 7.12 (d, J = 2.0 Hz, 4H), 1.262 (s, 36H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.95, 148.20, 133.14, 125.11, 122.41, 34.67, 31.40; MS (APCI$^+$) m/z 685.3 (M^+), calc. for $C_{40}H_{44}O_2S_4$: 684.2; *1,2-bistriflate* **2g** (7.0 mg, 8%): mp 234–236 °C (lit.[2] 236–237 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (br, s, 3H), δ 7.56 (d, J = 2.5, 2H), 7.54 (d, J = 2.0, 2H), 7.38 (d, J = 2.0, 2H), 7.25 (d, J = 2.5, 2H) 1.23 (s, 18H), 0.99 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.19, 151.67, 147.34, 144.10, 135.67, 135.29, 134.45, 134.39, 132.65, 129.49, 120.59, 120.42, 34.74, 34.40, 31.44, 31.05; MS (APCI$^-$) m/z 983.1, calc. for $C_{42}H_{46}F_6O_8S_6$: 984.1; *monotriflate* **2f** (10.5 mg, 11%): mp 270–273 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 3.0, 2H), 7.69 (d, J = 2.5, 2H), 7.50 (s, 2H), 7.08 (s, 2H), 1.31 (s, 18H), 1.16 (s, 9H), 0.80 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.77, 155.66, 151.74, 147.48, 144.50, 144.07, 136.30, 135.64, 135.37, 133.19, 129.99, 121.31, 121.19, 120.19, 34.53, 34.46, 34.36, 31.61, 31.38, 30.67; MS (APCI$^-$) m/z 851.1, calc. for $C_{41}H_{47}F_3O_6S_5$: 852.2. *Entry 2 (reaction of* **2** *with DBU)*: A solution of DBU (35 mg, 0.46 mmol) and **2** (55 mg, 0.056 mmol) in dry degassed toluene (15 mL) under Ar was stirred at the reflux temperature for 15 h. After cooling to rt, the solvent was evaporated, the resulting crude product was dissolved in CH_2Cl_2 (25 mL) and washed with aqueous 10% HCl (15 mL). The CH_2Cl_2 extract was dried ($MgSO_4$), filtered and the solvent was removed. The crude product was purified by preparative thin-layer chromatography using CH_2Cl_2–hexanes (3 : 7) to afford in increasing polarity: **2g** (49 mg, 89%), and **3** (3 mg, 8%). *Entry 3 (reaction of* **2** *with* $PdCl_2(PPh_3)_2$*-DBU)*: To a stirred mixture of $PdCl_2(PPh_3)_2$ (4.0 mg, 0.0055 mmol) and **2** (55 mg, 0.055 mmol) in dry, degassed toluene (30 mL) at the reflux temperature, was added DBU (35 mg, 0.23 mmol). The reaction mixture was heated with stirring, under Ar, for a further 15 h at the reflux temperature. After cooling to rt, the solvent was evaporated the resulting crude product was dissolved in CH_2Cl_2 (20 mL) and washed successively with aqueous 10% HCl (15 mL) and water (20 mL). The CH_2Cl_2 extract was dried ($MgSO_4$) and filtered and the solvent was removed to give a crude product which was purified by preparative thin-layer chromatography using CH_2Cl_2–hexanes (3 : 7) to afford in order of increasing polarity: **2g** (45 mg, 81%) and **3** (5 mg, 13%): mp 376–378 °C. *Entry 4 (reaction of* **2** *with CuI and DBU)*: To a stirred mixture of CuI (50 mg, 0.27 mmol), and **2** (55 mg, 0.055 mmol) in dry, degassed toluene (20 mL) at the reflux temperature was added DBU (35 mg, 0.23 mmol). The reaction mixture was heated with stirring, under Ar, for a further 15 h at the reflux temperature. After cooling to rt, the solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (40 mL) and washed with aqueous saturated NH_4Cl (15 mL) and with water (20 mL). The CH_2Cl_2 extracts was dried ($MgSO_4$), filtered and the solvent was evaporated on a rotary evaporator to give the crude product which was purified by preparative thin-layer chromatography using CH_2Cl_2–hexanes (3 : 7) to afford in order of increasing polarity: **2** (47.5 mg, 86%) and **3** (3 mg, 8%).
16 *Crystallographic data* for **3**: $C_{46}H_{50}O_2S_4$, M_r = 763.14, $P2_1$ (no. 4), a = 13.5552(9), b = 0.8734(6), c = 14.9307(10) Å, β = 111.6526(14)°; V = 2045.4(2) Å^3, Z = 2, D_c = 1.239 g cm^{-3}. Data was collected at a temperature of −160 ± 1 °C to a maximum 2θ value of 61.5°. A total of 19 278 reflections were collected, 9291 were unique (R_{int} = 0.017). The data was processed using CrystalClear (Rigaku). No. of variables = 470; reflection/parameter ratio = 19.77; R_1 ($I > 2.00\sigma(I)$) = 0.0388; R (all reflections) = 0.0391; wR_2 (all reflections) = 0.1034. GoF = 1.038.
17 *Crystallographic data* for **2f**: $C_{41}H_{47}F_3O_6S_5$, M_r = 853.11, $P2_1/c$ (no. 14), a = 12.490(3), b = 16.513(2), c = 21.792(4) Å, β = 104.682(5)°; V = 4347.6(14) Å^3, Z = 4, D_c = 1.303 g cm^{-3}. The data was collected at a temperature of −160 ± 1 °C to a maximum 2θ value of 61.5°. 46 060 reflections were collected, 8526 were unique (R_{int} = 0.069). The data was collected and processed using CrystalClear (Rigaku). No. of variables = 497; reflection/parameter ratio = 17.15; R_1 ($I > 2.00\sigma(I)$) = 0.0695; R (all reflections) = 0.0760; wR_2 (all reflections) = 0.1976. GoF = 1.079.
18 *Crystallographic data* for **2g**: $C_{42.35}H_{46.35}F_6O_8S_6Cl_{1.05}$, M_r = 1026.95, primitive triclinic cell, $P\bar{1}$ (no. 2) a = 13.1289(15), b = 19.649(3), c = 22.054(3) Å, α = 110.835(2), β = 98.5680(18), γ = 104.8480(17)°, V = 4954.7(11) Å^3, Z = 4, D_c = 1.377 g cm^{-3}. The data was collected at a temperature of −160 ± 1 °C to a maximum 2θ value of 61.5°. 42 658 reflections were collected, 20 234 were unique (R_{int} = 0.032). The data was collected and processed using CrystalClear (Rigaku). No. of variables = 1117; reflection/parameter ratio = 18.20; R_1 ($I > 2.00\sigma(I)$) = 0.0862; R (all reflections) = 0.0944; wR_2 (all reflections) = 0. 2550. GoF = 1.065.
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20 D. Gelman and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2003, **42**, 5993–5996.
21 *Synthesis of* **2h**. DBU (70 mg, 0.46 mmol) was added to a stirred mixture of $PdCl_2(PPh_3)_2$ (8.0 mg, 0.011 mmol), CuI (20.0 mg, 0.11 mmol), and **2** (110 mg, 0.11 mmol) in dry-degassed toluene (30 mL) under argon. The reaction mixture was stirred for a further 24 h at reflux. Removal of the volatiles on a rotary evaporator gave the crude product which was dissolved in CH_2Cl_2 (40 mL) and washed with aqueous saturated NH_4Cl (15 mL) and with H_2O (20 mL). The CH_2Cl_2 extract was dried ($MgSO_4$) and the solvent was removed under vacuum to give the crude product which was purified by PLC (CH_2Cl_2–hexane: 1 : 1) to give the following compounds: **3** (21.5 mg, 28% yield), **2f** (37.5 mg, 40% yield), **2g** (8.0 mg, 7.0% yield) and **2h**: (8.5 mg, 9%): mp 260–261 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (s, 1H), 7.64 (s, 1H), 7.63 (s, 1H), 7.61 (s, 1H), 7.41 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 7.24 (s, 1H), 6.92 (s, 1H), 6.14 (s, 2H), 1.32 (s, 4H), 1.31 (s, 4H), 1.21 (s, 4H),

1.18 (s, 4H); ^{13}C NMR ($CDCl_3$, 500 MHz) 155.25, 155.16, 153.15, 151.40, 147,83, 145.16, 143.70, 138.14, 137.31, 137.09, 135.60, 135.45, 134.15, 134.01, 133.98, 130.01, 128.85, 126.90, 126.20, 125.03, 121.11, 120.03, 117.51, 116.98, 35.14, 34.87, 34.43, 34.33, 31.79, 31.51, 31.39, 31.31; MS (APCI$^-$) m/z (M − H) 835.2, calc. for $C_{41}H_{47}F_3O_5S_5$ 835.2.

22 *Crystallographic data* for **2i**: M_r = 837.11, triclinic, $P\bar{1}$ (no. 2), a = 10.9907(13), b = 14.3416(11), c = 15.5658(8) Å, α = 61.816(9), β = 75.573(13), γ = 81.851(13)°, V = 2093.6(3) Å^3, Z = 2, D_c = 1.328 g cm^{-3}. The data was collected at a temperature of −135 ± 1 °C to a maximum 2θ value of 61.7°. 20 163 reflections were collected, 8573 (R_{int} = 0.064) were unique. The data was collected and processed using CrystalClear (Rigaku). No. variables = 488; reflection/parameter ratio = 17.57; R_1 ($I > 2.00\sigma(I)$) = 0.0865; R (all reflections) = 0.0973; wR_2 (all reflections) = 0.2403. GoF = 1.106.

23 Molecular mechanics calculations were conducted using *Spartan'06 for Windows* by Wavefunction, Inc., USA.

24 See *e.g.* P. E. Georghiou, A. H. Tran, S. S. Stroud and D. W. Thompson, *Tetrahedron*, 2006, **62**, 2036–2044, and references therein.

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26 *Synthesis of* **3a**. To a solution of **3** (190 mg, 0.28 mmol) in dry, degassed toluene (5 ml) under Ar, were added phenol (270 mg, 2.8 mmol) and $AlCl_3$ (1.5 mg, 11 mmol), and the mixture was heated at the reflux temperature for 8 days. After cooling to rt, the resulting dark solution was poured into aqueous 10% HCl (10 ml). The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 × 50 ml). The organic layers were separated, dried ($MgSO_4$), filtered and evaporated on a rotary evaporator. The resulting black oil was treated with hexane to afford a precipitate which was purified by column chromatography on silica gel using CH_2Cl_2–hexanes (1 : 9). The major product was crystallized from $CHCl_3$–hexanes to afford **3a** (34 mg, 26%), mp 265–267 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (d, J = 7.0, 4H), 7.14 (d, J = 6.5, 4H), 7.02 (t, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.42, 136.13, 128.29, 125.84, 125.27, 123.51; MS (APCI$^-$) m/z 461.0, calc. for $C_{24}H_{12}O_2S_4$: 460.0.

27 *Crystallographic data* for **3a**: $C_{24}H_{12}O_2S_4$, M_r = 460.60, monoclinic, $P2_1/c$ (no. 14), a = 17.027(4), b = 10.3137(18), c = 24.212(5) Å, β = 117.240(6)°, V = 3780.3(13) Å^3, Z = 8, D_c = 1.618 g cm^{-3}. The data were collected at a temperature of −160 ± 1 °C to a maximum 2θ value of 61.5°. 42 852 reflections were collected, 7814 (R_{int} = 0.049), equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku). No. variables = 542, reflection/parameter ratio = 14.42, R_1 ($I > 2.00\sigma(I)$) = 0.0519, R (all reflections) = 0.0544, wR_2 (all reflections) = 0.1251. GoF = 1.176.

28 L. Fielding, *Tetrahedron*, 2000, **56**, 6151–6170.

29 (*a*) K. A. Connors, *Binding Constants*, Wiley, New York, 1987; (*b*) association constants were calculated using non-linear curve fitting using the program ORIGINPro 7.5 from OriginLab Corporation, or with Excel for simple linear regression analysis.

