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Synthesis and X-ray structures of iodothiacalix[4]arenes

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Abstract—Mono-, di-, and tetraiodothiacalix[4]arenes **13**–**16** have been successfully synthesized for the first time by the Griess reaction of diazonium salts of the corresponding aminothiacalix[4]arenes **4**–**7**. X-ray crystallography reveals that monoiodinated compound **13** adopts a distorted pinched cone conformation, in which the three hydroxy groups and the iodine atom form a pseudocyclic hydrogen bonding. On the other hand, tetraiodinated compound **16** adopts a 1,3-alternate conformation presumably due to the steric hindrance and dipole repulsion between the iodine atoms.

Calix[4]arenes are one of the most popular building blocks in the field of supramolecular chemistry.[1] Among a large number of calixarene derivatives, halogenated ones such as iodine derivatives (e.g., **1**) are especially useful as an intermediate for the elaboration of sophisticated molecular hosts by using various reactions including transmetallations and transition metal-catalyzed coupling reactions. Although a number of papers have dealt with the introduction of halo-substituents into the upper rim of calixarenes (para to the hydroxy group) and their successive transformation into other functional groups,[2] it is quite recent that a calixarene bearing iodo-substituents at the lower rim (**2**) has appeared in the literature for the first time as an accidental by-product of the palladium-catalyzed Sonogashira coupling reaction of 1,3-bistriflate of calix[4]arene.[3,4] This is due to the difficulty of replacing hydroxy groups on the benzene nuclei of calixarenes with other functions by cleaving the aryl-oxygen bond particularly in the case of calixarenes of small ring size.[6] In addition, thiacalixarenes (e.g., **3**), having epithio groups instead of methylene bridges in the conventional calixarenes, often show different reactivity and/or selectivity from those of the methylene-bridged counterparts in the modification reactions and the palladium-catalyzed iodination was found to be inapplicable to 1,3-bistriflate of thiacalix[4]arene **3**. In our continuing efforts to develop novel functions of thiacalixarenes,[7] we have recently succeeded in the synthesis of tetraaminothiacalix[4]arene **4** via a chelation-assisted nucleophilic aromatic substitution (S_NAr) reaction[8] of tetra-*O*-methylsulfinylcalix[4]arene of rtct configuration[9] **8**(rtct) with lithium benzylamide, followed by debenzylation of the resulting tetra(benzylamino)sulfinylcalix[4]arene and successive reduction of the sulfinyl functions.[10] In the solvent extraction experiment, while thiacalixarene **3** can extract soft to intermediate metal ions by cooperative coordination of the bridging sulfur with two neighboring phenolates to the metal center,[11] aminothiacalixarene **4** selectively extracted gold and palladium ions,[12] which are classified as the softest among metal ions. This was attributed to the softer nature of the amino nitrogen than hydroxy oxygen, which realized selective coordination to these softest metal ions. On the other hand, it goes without saying that the amino group is pivotal in aromatic synthesis as it can be easily converted into various functions via diazonium salts.[13] Therefore, aminothiacalixarene **4** does not only present attractive features not attainable by phenol-based calixarenes as a host molecule but is also expected to serve as a useful precursor of highly elaborated synthetic receptors. Herein, we wish to report the first synthesis of iodothiacalixarenes, in which all or a part of the hydroxy groups of thiacalixarene **3** are replaced with iodine atoms, by iodination of diazonium salts prepared from aminothiacalixarenes **4**–**7**.

Keywords: Calixarene; Griess reaction; Amination; Nucleophilic aromatic substitution.

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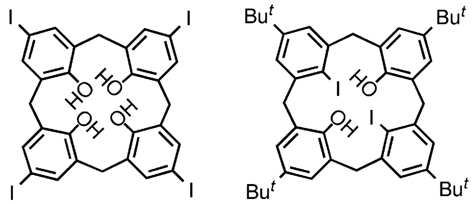

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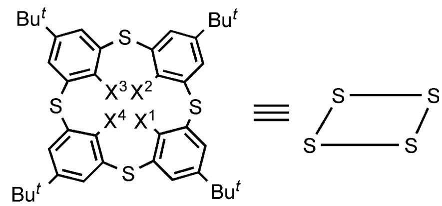
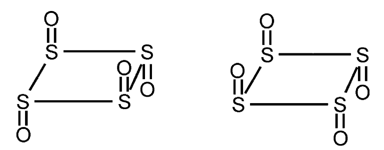


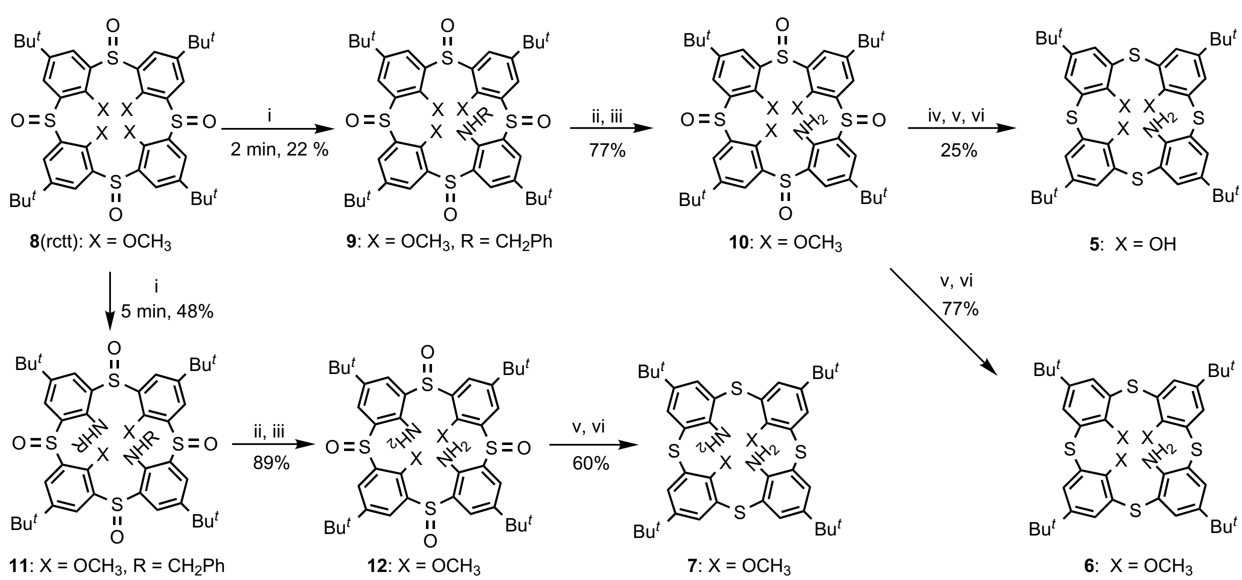
3: $X^{1\text{-}4}$ = OH
4: $X^{1\text{-}4}$ = NH_2
5: X^1 = NH_2, $X^{2\text{-}4}$ = OH
6: X^1 = NH_2, $X^{2\text{-}4}$ = OMe
7: $X^{1,3}$ = NH_2, $X^{2,4}$ = OMe



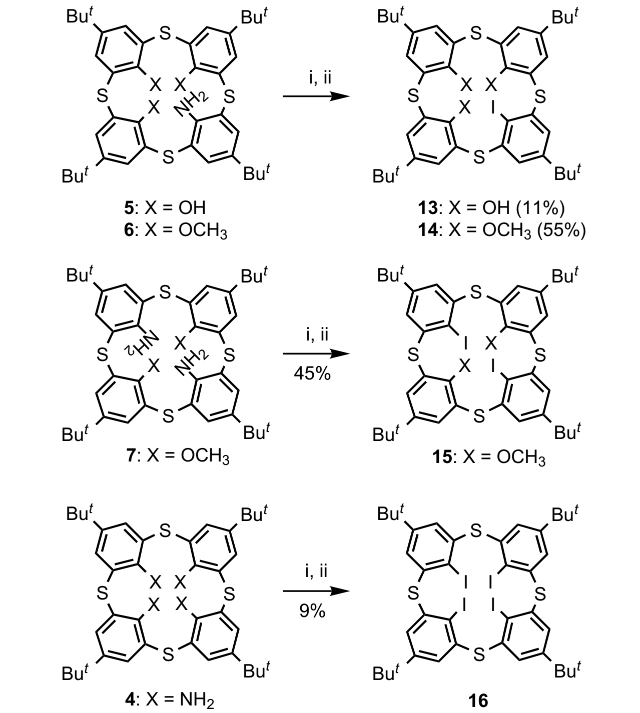
8(rtct): $X^{1\text{-}4}$ = OMe 8(rctt): $X^{1\text{-}4}$ = OMe

Prerequisite tetraaminothiacalixarene **4** was prepared according to our previously reported procedure.[10] We have found that mono- and diaminothiacalixarenes **5**–**7** can also be prepared by a similar procedure by using tetra-*O*-methylsulfinylcalixarene of rctt configuration[9] **8**(rctt) as a starting material (Scheme 1). Thus, the S_NAr reaction of **8**(rctt) with 8.0 mol equiv of lithium benzylamide in THF gave 1,3-diaminosulfinylcalixarene **11** in 48% yield with concomitant formation of a small amount of monoamino counterpart **9**, which was in turn obtained in substantial yield by reducing the reaction time (Scheme 1). On the other hand, no triaminated compound could be prepared by changing the reaction conditions and/or employing the other stereoisomer[9] of compound **8**. Removal of the benzyl moieties (**10**) from **9**[10] followed by demethylation with a sodium thioalkoxide and subsequent reduction of the sulfinyl functions with $LiAlH_4$–$TiCl_4$[14] delivered the desired monoaminothacalixarene **5**.[15] On the other hand, direct reduction of debenzylated compound **10** gave *O*-methyl protected monoamine **6**.[15] *O*-Methyl protected diamine **7** was also obtained from diaminosulfinylcalixarene **11** by applying the same procedure as used for the preparation of monoamine **6**.[15]

Monoamine **5** was diazotized with nitrous acid in acetic acid by stirring the mixture for 4 h to give a clear solution of the diazonium salt, which was treated with KI and I_2 to give monoiodinated compound **13** in 11% yield,[16,17] accompanied by the formation of many unidentified by-products (Scheme 2). The identity of **13** was confirmed by FAB-MS [*m*/*z* 830 (M^+)] and ^1H NMR spectrum, which showed three singlets for the *tert*-butyl protons (9H, 9H, and 18H) and two singlets (each 2H) and two doublets (each 2H) for the aromatic protons, being consistent with a symmetric structure with a σ-plane. Biali and co-workers reported that the thermal dediazoniation of a diazonium salt of monoaminocalix[5]arene afforded a xanthene-type compound by an intramolecular cyclization between the in situ-generated phenyl cation and an adjacent hydroxy group.[5] Such a cyclization could be a cause of reducing the yield in the present iodination. We then tried the reaction of *O*-methyl protected amines **6** and **7**. To our pleasure, they gave the corresponding mono- and diiodinated compounds **14** and **15**,[17] respectively, in good yields. Iodination of compound **4**, having four amino groups to be converted, was difficult but gave tetraiodinated compound **16** in a meaningful yield.[17] It should be noted that this is the first successful synthesis of a calix-type compound in which all the hydroxy groups at the lower rim are replaced with halogen atoms. The ^1H NMR



Scheme 1. Reagents and conditions: (i) $PhCH_2NHLi$, THF, rt; (ii) NBS, BPO, benzene, reflux; (iii) 6 M HCl, benzene, reflux; (iv) NaH, $CH_3(CH_2)_7SH$, THF, reflux; (v) $LiAlH_4$, $TiCl_4$, THF, rt; (vi) Bu_4NF, THF, rt.



Scheme 2. Reagents and conditions: (i) $NaNO_2$, H_2SO_4, CH_3CO_2H, rt; (ii) KI, I_2, rt.

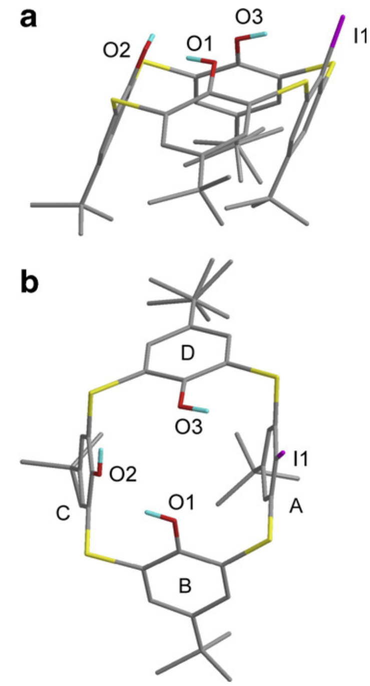


Figure 1. X-ray structure of compound **13**. (a) Side view; (b) top view. Hydrogen atoms except of OH are omitted for clarity.

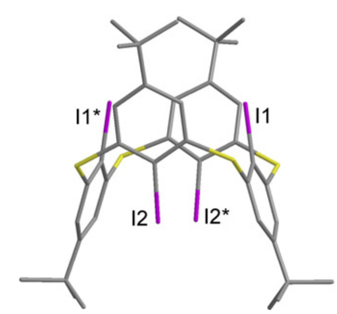


Figure 2. X-ray structure of **16**. Hydrogen atoms and solvent are omitted for clarity.

spectrum of **16** showed one singlet each for the *tert*-butyl and aromatic protons, indicating that the compound adopted either cone or 1,3-alternate conformation. The latter conformation is the same as that in the crystals and more feasible in the solution, considering the steric hindrance and dipole repulsion between the iodine atoms (vide infra).

X-ray crystallographic analyses of compounds **13** and **16** were carried out to examine the influence of the iodine substituent(s) on the conformation of the calixarene framework.[18] Single crystals of **13** and **16** were obtained by slow diffusion of ethanol or hexane to a chloroform solution of each compound. Compound **13** adopted a distorted pinched cone conformation, in which the benzene ring bearing the iodine atom was almost parallel to the facing benzene ring and tilted so as to put the bulky iodine atom outside the macrocycle, the dihedral angles between the facing benzene rings being 3.97(15)° for the A–C pair and 87.83(8)° for the B–D pair, respectively (Fig. 1). No solvent was included in the cavity due to the distorted structure. The conformation was stabilized by a pseudo-cyclic hydrogen bonding among the three hydroxy groups and the iodine atom as evidenced by the interatomic distances between O_1–O_2 (2.828 Å), O_2–O_3 (3.182 Å), O_3–I (3.841 Å), and I–O_1 (4.081 Å) atoms. On the other hand, compound **16** adopted 1,3-alternate conformation with C_2 symmetry, which would be the result of minimizing the dipole moment of the molecule and avoiding the steric hindrance between the iodine atoms (Fig. 2). It is of interest to note here that the trigonal planar geometry of four aromatic carbons bearing an iodine atom was warped outside the macrocycle to place the facing iodine atoms apart from each other, the deviations form the trigonal plane defined by the improper torsion angles being 1.20° for I1, I1* and 1.43° for I2, I2*, respectively.

In conclusion, we have synthesized mono-, di-, and tetraiodothiacalix[4]arenes for the first time by the Griess reaction of diazonium salts of the corresponding aminothiacalix[4]arenes, which could be prepared by using a chelation-assisted S_NAr reaction of tetra-*O*-methylsulfinylcalix[4]arenes with lithium benzylamide as a key step. X-ray crystallographic analyses of two iodinated compounds revealed that their conformations were affected by the bulkiness, electronegativity, and hydrogen-bonding acceptor nature of the iodine atoms. The structural information is potentially useful for a further derivatization of these compounds.

References and notes

1. Reviews: (a) Gutsche, C. D. Calixarenes. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The

Royal Society of Chemistry: Cambridge, 1989; (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713; (c) Gutsche, C. D. Calixarenes Revisited. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998; (d)*Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000; (e) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J. M., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001.

2. For iodination of the upper rim of calixarenes, see: (a) van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639; (b) Arduini, A.; Pochini, A.; Rizzi, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron Lett.* **1990**, *31*, 4653; (c) Timmerman, P.; Verboom, W.; Reinhoudt, D. N.; Arduini, A.; Grandi, S.; Sicuri, A. R.; Pochini, A.; Ungaro, R. *Synthesis* **1994**, 185; (d) Aruduini, A.; McGregor, W. M.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Org. Chem.* **1996**, *61*, 6881; (e) Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 839; (f) Pinkhassiki, E.; Stibor, I.; Casnati, A.; Ungaro, R. *J. Org. Chem.* **1997**, *62*, 8654; (g) Barbour, L. J.; Orr, G. W.; Atwood, J. M. *Chem. Commun.* **1997**, 1439; (h) van Wageningen, A. M. A.; Timmerman, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Chem. Eur. J.* **1997**, *3*, 639; (i) Klenke, B.; Friedrichsen, W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3377.
3. Al-Saraierh, H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 8273.
4. It was also reported that a diazonium salt of monoaminocalix[5]arene on treatment with tetrabutylammonium iodide in chloroform afforded a practically unisolable mixture of monochloro- and monoiodocalix[5]arene. See Ref. 5.
5. Van Gelder, J. M.; Aleksiuk, O.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 8419.
6. For transformation of the hydroxy group of calixarenes into other functions, see: (a) Gibbs, C. G.; Sujeeth, P. K.; Rogers, J. S.; Stanley, G. G.; Krawiec, M.; Watson, W. H.; Gutsche, C. D. *J. Org. Chem.* **1995**, *60*, 8394; (b) Ohseto, F.; Murakami, H.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1992**, *33*, 1217; (c) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 1994.
7. Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291, and references cited therein.
8. For representative examples of the chelation-assisted S_NAr reaction, see: (a) Hattori, T.; Hotta, H.; Suzuki, T.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 613; (b) Hattori, T.; Suzuki, T.; Hayashizaka, N.; Koike, N.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3034; (c) Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis* **1994**, 199; (d) Hattori, T.; Suzuki, M.; Tomita, N.; Takeda, A.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1117; (e) Hattori, T.; Takeda, A.; Suzuki, K.; Koike, N.; Koshiishi, E.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3661; (f) Hattori, T.; Shimazumi, Y.; Goto, H.; Yamabe, O.; Morohashi, N.; Kawai, W.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2099.
9. For stereoisomers of sulfinylcalix[4]arene, see: Morohashi, N.; Katagiri, H.; Iki, N.; Yamane, Y.; Kabuto, C.; Hattori, T.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2324.
10. Katagiri, H.; Iki, N.; Hattori, T.; Kabuto, C.; Miyano, S. *J. Am. Chem. Soc.* **2001**, *123*, 779.
11. Morohashi, N.; Iki, N.; Sugawara, A.; Miyano, S. *Tetrahedron* **2001**, *57*, 5557.
12. Katagiri, H.; Iki, N.; Matsunaga, Y.; Kabuto, C.; Miyano, S. *Chem. Commun.* **2002**, 2080.
13. (a) *The Chemistry of Diazonium and Diazo Groups*; Patai, S. Ed.; Wiley: New York, 1978; (b) Zollinger, H. *Diazo Chemistry I: Aromatic and Heteroaromatic Compounds*; John Wiley & Sons: New York, 1994; (c) Roglans, A.; Quintana, A. P.; Manas, M. M. *Chem. Rev.* **2006**, *106*, 4622.
14. Drabowicz, J.; Mikolajczyk, M. *Synthesis* **1976**, 527.
15. Compound **5**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (s, 9H, $C(CH_3)_3$), 1.23 (s, 9H, $C(CH_3)_3$), 1.23 (s, 18H, $C(CH_3)_3$), 7.60 (d, 2H, $J = 2.5$ Hz, Ar*H*), 7.63 (s, 2H, Ar*H*), 7.65 (s, 2H, Ar*H*), 7.66 (d, 2H, $J = 2.5$ Hz, Ar*H*); FAB MS (*m*/*z*) 719 (M^+). Compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$, 333 K): δ 1.09 (s, 18H, $C(CH_3)_3$), 1.28 (s, 9H, $C(CH_3)_3$), 1.36 (s, 9H, $C(CH_3)_3$), 3.69 (s, 6H, OCH_3), 3.76 (s, 3H, OCH_3), 5.19 (br, 2H, NH_2), 7.26 (d, 2H, $J = 2.4$ Hz, Ar*H*), 7.42 (d, 2H, $J = 2.4$ Hz, Ar*H*), 7.54 (s, 2H, Ar*H*), 7.60 (s, 2H, Ar*H*); FAB MS (*m*/*z*) 761 (M^+). Compound **7**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (s, 18H, $C(CH_3)_3$), 1.29 (s, 18H, $C(CH_3)_3$), 4.03 (s, 6H, OCH_3), 5.61 (br, 4H, NH_2), 7.19 (s, 4H, Ar*H*), 7.59 (s, 4H, Ar*H*); FAB MS (*m*/*z*) 846 (M^+).
16. *Typical procedure for the iodination*: To a solution of amine **6** (100 mg, 0.139 mmol) in acetic acid (10 ml) was added $NaNO_2$ (20.0 mg, 0.290 mmol) in concd sulfuric acid (3 ml) and the mixture was stirred at room temperature. After 4 h, the excess of $NaNO_2$ was decomposed by the addition of urea (15.7 mg, 0.261 mmol). To the mixture was added a mixed solution of KI (348 mg, 2.10 mmol) and I_2 (33.2 mg, 0.131 mmol) in water (7 ml) and the resulting mixture was stirred for a further 12 h. The mixture was quenched with 10% $NaHSO_3$ and extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel with chloroform–hexane (1:2) as an eluent to give iodide **14** (57.1 mg, 55%).
17. Compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.51 (s, 9H, $C(CH_3)_3$), 1.12 (s, 9H, $C(CH_3)_3$), 1.33 (s, 18H, $C(CH_3)_3$), 6.64 (s, 2H, Ar*H*), 7.36 (s, 2H, O*H*), 7.42 (s, 2H, Ar*H*), 7.67 (d, 2H, $J = 2.4$ Hz, Ar*H*), 7.69 (d, 2H, $J = 2.4$ Hz, Ar*H*), 8.44 (br, 1H, O*H*); FAB MS (*m*/*z*) 830 (M^+). Compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$, 333 K): δ 1.19 (br s, 9H, $C(CH_3)_3$), 1.25 (s, 9H, $C(CH_3)_3$), 1.29 (s, 18H, $C(CH_3)_3$), 3.19 (br s, 3H, OCH_3), 3.66 (s, 6H, OCH_3), 7.44 (s, 2H, Ar*H*), 7.47 (d, 2H, $J = 2.5$ Hz, Ar*H*), 7.58 (br s, 2H, Ar*H*), 7.60 (d, 2H, $J = 2.5$ Hz, Ar*H*); FAB MS (*m*/*z*) 872 (M^+). Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 18H, $C(CH_3)_3$), 1.29 (s, 18H, $C(CH_3)_3$), 3.68 (s, 6H, OCH_3), 7.58 (s, 4H, Ar*H*), 7.66 (s, 4H, Ar*H*); FAB MS (*m*/*z*) 968 (M^+). Compound **16**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 36H, $C(CH_3)_3$), 7.90 (s, 8H, Ar*H*); FAB MS (*m*/*z*) 1160 (M^+).
18. Crystallographic data for **13**: $C_{40}H_{47}IO_3S_4$, fw = 830.92, triclinic, $P\bar{1}$, $a = 9.6635(13)$ Å, $b = 10.1568(14)$ Å, $c = 21.158(3)$ Å, $\alpha = 77.237(3)°$, $\beta = 88.701(3)°$, $\gamma = 82.817(3)°$, $V = 2009.4(5)$ Å^3, $Z = 2$, 9175 independent reflections, 7426 reflections were observed ($I > 2\sigma(I)$), $R_1 = 0.0392$, $wR_2 = 0.1041$ (observed), $R_1 = 0.0488$, $wR_2 = 0.1079$ (all data). Crystallographic data for **16**·$CHCl_3$: $C_{41}H_{45}Cl_3I_4S_4$, fw = 1279.96, orthorhombic, *Pbcn*, $a = 15.198(2)$ Å, $b = 22.152(3)$ Å, $c = 13.4696(17)$ Å, $V = 4534.7(10)$ Å^3, $Z = 4$, 5238 independent reflections, 3499 reflections were observed ($I > 2\sigma(I)$), $R_1 = 0.0242$, $wR_2 = 0.0421$ (observed), $R_1 = 0.0444$, $wR_2 = 0.0438$ (all data). Crystallographic data reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 644542 and 644543.