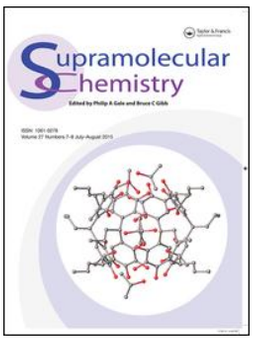

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ARTICLE

New oxacalix[4]arene carboxylate detects viologen in protic media

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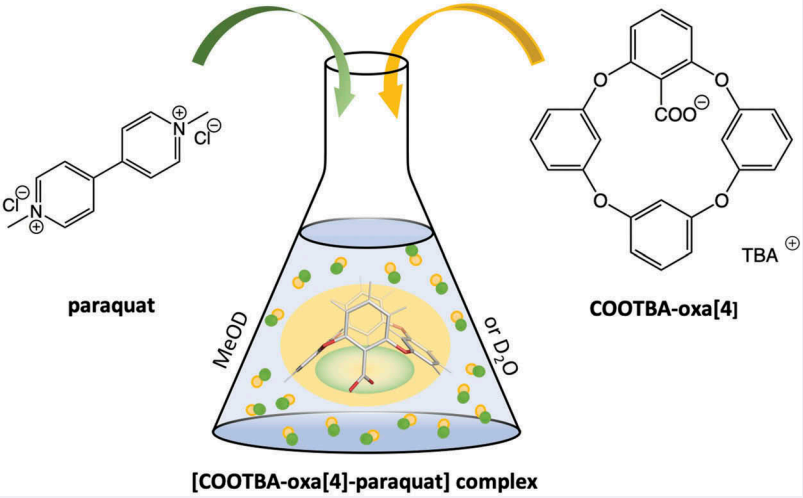
ABSTRACT

We demonstrate that Ullman fragment-coupling can be used to synthesise an oxacalix[4]arene monocarboxylic acid, which provides easy access to its water-soluble carboxylato derivatives. Crystallographic and computational data suggest that the new carboxyl-substituted oxacalix[4]arene adopts a 1,3-alternate conformation both in the solid-state and in methanol solution. Its water-soluble tetrabutylammonium derivate can detect the herbicide paraquat at neutral pH in aqueous media (K_a = 111 ± 3 M^{-1}) and in methanol (K_a = 2020 ± 70 M^{-1}).



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KEYWORDS
Oxacalix[4]arene carboxylate; herbicide sensing; 1,3-alternate conformation

Introduction

Oxacalix[*n*]arenes, the oxygen-bridged heterocalixaromatics, are macrocyclic host compounds that provide unique cavity sizes and shapes and capability for hydrogen bonding and π – π interactions (1, 2). Nevertheless, this class of aromatic macrocycles has been significantly less explored compared to its carbon-bridged analogues, *e.g.* calix[*n*]arenes (3, 4), resorcin[*n*]arenes (5–8) and pillar[*n*]arenes (9–12).

Encapsulation of bipyridinium derivatives, including the harmful herbicide molecule paraquat, has seen much interest in supramolecular chemistry with the aim of reducing their toxicity through the development of viologen targeted chemosensors (13). As such, it has been shown that carboxyl-decorated biphen[4]arene (14) as well as pillar[6]arene (15) can be used in complexation with cationic guest species, including the detection of harmful molecules by encapsulating them through non-covalent interactions (16, 17). This can potentially lead to applications in the treatment of toxicant poisoning by forming stable host-guest complexes with the toxic guest molecule (18). Additional examples of molecular recognition studies of toxicants in water include different-sized S_x-corona[*n*](het)arenes as host compounds (19, 20). To the best of our knowledge, only one example of an oxacalix[*n*]arene, a polycationic tetraammonium macrocycle, that is able to complex with paraquat ($[(C_6H_7N)_2]Cl_2$) in acidic aqueous media (21, 22) has been reported previously.

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Supplemental data for this article can be accessed here.

In general, S- and O-bridged [1$_n$]metacyclophanes, as electron-rich heterocalixaromatic macrocycles, have similar affinities towards cations (23–25), while NH-bridged azacalix[*n*]arenes (26) and triazine-containing oxacalix[*n*]arenes (27–29), have been employed mainly in anion recognition studies and complexation studies with neutral aromatic compounds such as C_{60} fullerene (25, 30). Studies of oxacalix[4]arene complexation with cations have focused on complexation properties with metal cations by oxacalix[4]crowns (31, 32) and ferrocene and the ferrocenium cation complexes with nitro-substituted oxacalix[4]arenes (K_a = 87 M^{-1} in CH_2Cl_2) (33), however, complexation in polar protic solvents remains quite unexplored due to the solubility of the oxacalix[*n*]arene macrocycles. As a scarce example, the aforementioned polycationic oxacalix[4]arene can bind paraquat (21) and neutral aromatic guest molecules (22) in acidic aqueous media with association constant values of K_a = 253 M^{-1} and K_a = 44 M^{-1}, respectively. In comparison, however, Wang and co-workers have shown that S-bridged heterocalixaromatics can bind aromatic dicationic guests (19, 20) with association constants in the range of 10^3–10^5. Therefore, the development of oxacalix[*n*]arene chemosensors that can strongly interact with cationic guest species in polar protic solvents is of great importance for utilising oxacalix[*n*]arenes in paraquat detection. Overcoming the weak complexation and solubility limitations of oxacalix[*n*]arenes by decorating their homooxacalix[*n*]arene core could pave the way towards discovering the full potential of using these host molecules as selective chemosensors.

Results and discussion

Herein, we report the synthesis of an oxacalix[4]arene carboxylic acid **1a**, according to a copper(I) and iron(III) catalysed Ullman fragment-coupling protocol (34, 35) and convert the macrocycle to its anionic tetrabutylammonium derivative **1b**, shown in Figure 1(a). The **1a** macrocycle adopts a 1,3-alternate conformation in methanol solution, similarly to its solid-state structure, and we further determine that **1b** can bind dicationic paraquat in methanol and at neutral, including physiological, pH conditions in aqueous media.

Synthesis

The three-step fragment-coupling synthesis procedure that we have explored to prepare unsubstituted oxacalix[*n*]arene (*n* = 4 and 8), previously (34, 35), resulted in **1a** in 14% yield. Details regarding the yield of the macrocycle are brought in ESI, pp. S3. **1a** could be converted to water-soluble **1b** by treatment with aqueous tetrabutylammonium hydroxide solution. The macrocycles' structures were confirmed by NMR, ESI-HRMS and single-crystal X-ray diffraction.

Binding studies

In our work, we show that **1b** binds paraquat in protic media. Firstly, we performed ^{1}H NMR titration experiments in methanol (see ESI, Fig. S8), whereby we determined the binding strength to be 2020 ± 70 M^{-1} for this host-guest system [Figure 1(b)]. The fits to the titration data were obtained using a 1:1 binding isotherm in the open-source online fitting tool Bindfit (36). In comparison to previous studies that investigate oxacalix[4]arene macrocycles complexation with organic cations (21), the determined K_a value for the [**1b**-paraquat] complex in methanol is an order of magnitude larger. Secondly, we tested the ability of **1b** macrocycle to bind paraquat in aqueous solution (see ESI, Fig. S10). The observed K_a

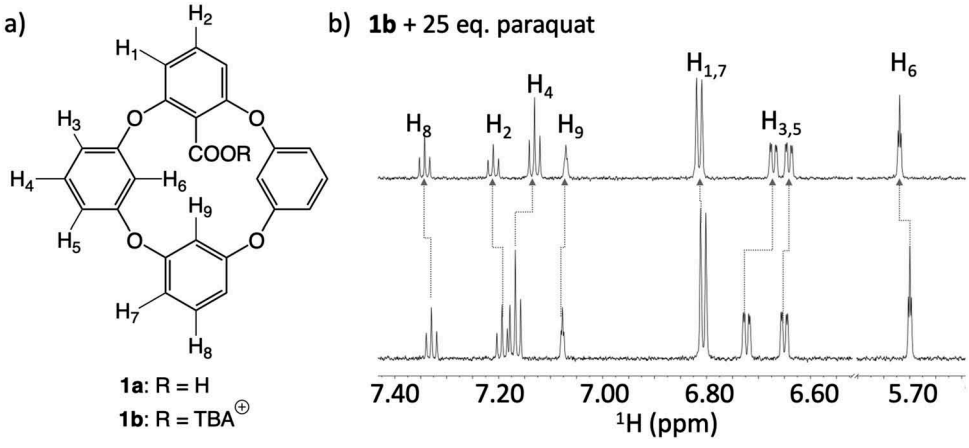

Figure 1. (a) Structures and designation of proton positions of the synthesised macrocycles **1a** and **1b** and (b) ^{1}H NMR spectra of [**1b**-paraquat] complex (top spectrum) and the native **1b** (bottom spectrum) in methanol-d_4 at 298 K.

value was 111 ± 3 M^{-1} for this host-guest complex. The affinity of **1b** for paraquat in aqueous media is comparable to the aforementioned polycationic oxacalix[4]arene (21, 22). It is noteworthy that paraquat detection in aqueous media occurred at neutral pH values, which might be important for detection of paraquat in biological fluids. Moreover, much attention has been attributed to paraquat poisoning by government organisations due to its toxicity, nevertheless, no treatment methodologies with convincing efficiency currently exist (37, 38). This manifests in the need for new paraquat chemosensors that can trap the toxicant in a stable host-guest complex in cases of paraquat poisoning.

Subsequently, we studied the conformation of the **1a** macrocycle in solution and solid-state. The macrocycle **1a** adopts a 1,3-alternate saddle-shape conformation in the solid phase, similarly to the unsubstituted oxacalix[4]arene reported previously (35). However, owing to the strong hydrogen-bonding ability of the carboxylic acid groups, the packing of the **1a** chloroform solvate is directed largely by electrostatic interactions, in contrast to the predominantly dispersion-directed packing of the unsubstituted oxacalixarenes (35). Whole-molecule energy framework analysis (see ESI, pp. S7-S9) using the CrystalExplorer software (39) revealed that the strongest contribution to framework stability comes from the hydrogen bonds between the carboxylic acid groups of two molecules of **1a**, d(O–H···O) = 1.76 ± 0.03 Å, which form the dimeric motif (Figure 2). Weak C–H···O hydrogen bonds and aromatic–aromatic interactions, that mainly contribute to the dispersion term, stabilise the side-to-side stacking of the macrocycles into sheets parallel to the ab-plane of the unit cell (Figure 2). Co-crystallised chloroform molecules are arranged between these sheets, potentially contributing to the observed rapid drying of the crystals when exposed to air.

The NMR spectra of the asymmetric **1a** macrocycle are valuable for providing information regarding its conformation in solution. It was suggested by Lehmann that oxacalix[4]arenes that contain two ortho-connected monomers adopt a saddle (now known as the 1,3-alternate) conformation in solution (40). Lehmann rationalised this based on the very upfield shifts of the inner aromatic protons (5.67 ppm) that relates to their relative position with respect to the anisotropic shielding cones of the adjacent aromatic monomers. In 2005, Katz et al. proposed nitro-substituted oxacalix[4]arenes to adopt the 1,3-saddle conformation, partly to maintain conjugation between the aromatic moieties (41). The experimental difference between the chemical shifts of the **1a** H_6 and H_9 protons that point towards the core of the macrocycle is 1.04 ppm (the protons give signals at 5.66 ppm vs 6.70 ppm, respectively) (40). To gain insight into the conformation of **1a** in solution, we carried out quantum-chemical calculations of the respective structural parameters and corresponding ^{1}H and 13C NMR chemical shifts in methanol. Firstly, we optimised the solution-state geometry of the structure that showed a noticeable resemblance to the conformation of **1a** in the crystal structure (Figure S13).

Subsequently, the ^{1}H NMR chemical shifts were calculated at B3LYP GIAO and MN12-SX CSGT level of theory and the ^{13}C NMR chemical shifts at B3LYP CSGT and lc-TPSS GIAO level of theory (see ESI, pp. S16-S28). The

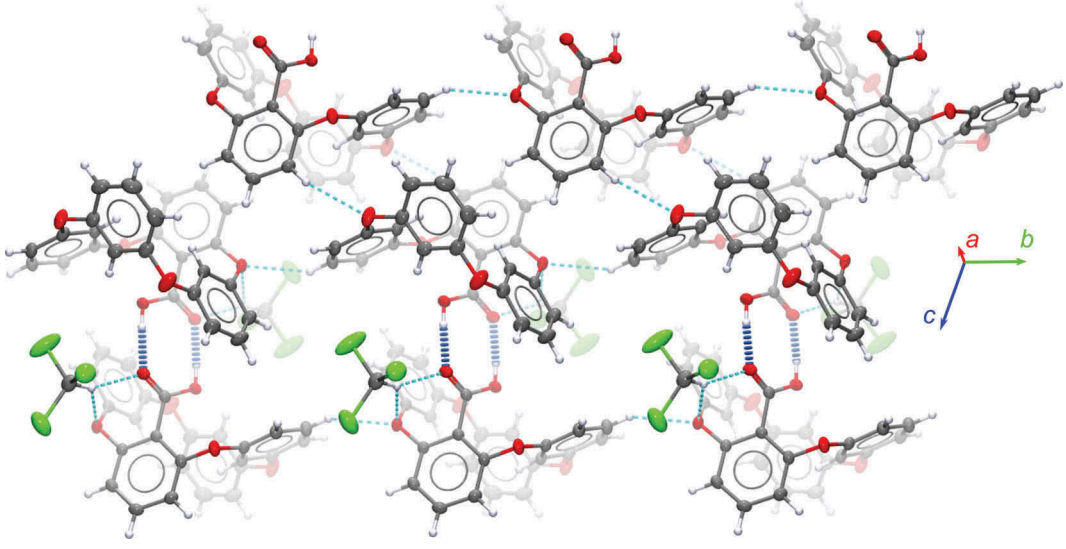

Figure 2. (colour online) Single-crystal XRD structure of 1a showing the hydrogen-bonded dimers (interactions shown with dark blue dotted lines) and the side-to-side stacking of the macrocycles in the ab-plane of the unit cell of 1a with the co-crystallised chloroform molecules.Crystallographic and computational data.

calculated chemical shifts are in good agreement with the experimental data. In particular, the experimental difference between the chemical shifts of the H_6 and H_9 protons is replicated in the calculations [Figure 3(a, b)]. Analogously to previous studies, this likely arises from the position of these protons with respect to the anisotropic shielding cones of the adjacent aromatic monomers [Figure 3(a)]. It is worth noting that when the adjacent aromatic groups were omitted in calculations, the H_6 proton resonances shifted considerably downfield, which is further discussed in the ESI. This finding and the agreement of experimental and calculated geometries suggest the solution-state conformation of **1a** in methanol to resemble the 1,3-alternate conformation of the solid-state. We hypothesise that the 1,3-alternate conformation is prerequisite for the strong binding in protic solvents discussed above, where two aromatic monomers and the carboxyl group of the third monomer form a defined binding cavity for a cationic guest molecule.

Conclusion

We have synthesised a new oxacalix[4]arene macrocycle **1a**, which in its anionic form is able to bind with the cationic aromatic guest paraquat in methanol and aqueous media at neutral pH. The high binding affinity in methanol holds potential to contribute to the development of chemosensors that can selectively detect paraquat, *e.g.* in drinking water, and thereby aid to reduce its harmful effects. To the best of our knowledge, the K_a value in methanol is the largest reported between an organic cation and oxacalix[4]arene macrocycle to date. The strong binding of an aromatic cationic guest in protic media could arise from the static 1,3-alternate conformation in methanol, which creates a defined binding pocket, surrounded by two aromatic moieties and the carboxylate group.

^{1}H NMR titration

The association constant values for [**1b**-paraquat] complexes were determined from methanol-d_4 and D_2O. All the solutions were prepared using Hamilton® Gastight syringes and samples were weighed on a Sartorius microbalance with an accuracy of 15 µg. **1b** stock solutions (0.2 mM) were added to a vial containing paraquat to keep the concentration of the macrocycle fixed throughout the titration experiment. Small aliquots from the paraquat stock solution were added increasingly (from 0 to 160–240 µl) to the NMR tube containing 600 µl of the **1b** stock solution. After every addition, the sample was thoroughly shaken using vortex and measured quantitatively, collecting 8 scans with relaxation delay set to 15 s and acquisition time set to 2.4 s. The changes in H_4 and H_6 proton shifts were monitored and after the addition of paraquat the followed protons shifted upfield with an exception of H_6 in methanol. No remarkable changes in chemical shifts of the guest were observed. The K_a values were determined using nonlinear regression analysis. For the fitting of the binding data the 1:1 binding isotherm of BindFit was used (freely

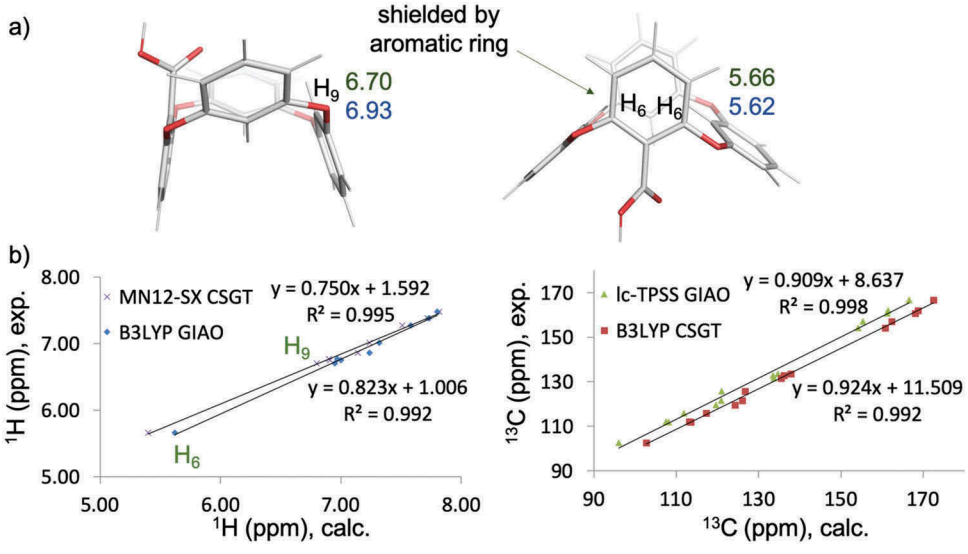

Figure 3. (colour online) (a) The positions of H_6 and H_9 protons with respect to the adjacent aromatic rings and their respective calculated and experimental chemical shifts. Numbers in green and blue denote experimental NMR chemical shifts and calculated chemical shifts (B3LYP/GIAO) in ppm, respectively, and (b) correlation between experimental and calculated ^{1}H and ^{13}C NMR chemical shifts for **1a** in methanol.

available at http://supramolecular.org). Herein, the given standard error depicts error coming from curve fit calculations. In aqueous media, the last titration point, with 23.7 eq of paraquat used as a guest, resulted in 66% of host-guest complex formation. See ESI, pp. S10-S14 for further details.

X-ray crystallography

Single crystals of **1a** were obtained by slow evaporation from chloroform. The small colourless crystals were found to be the chloroform solvate of **1a**, crystallised in the space group *P*-1 (Figure S5). Single crystal X-ray diffraction data was collected on a Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system, at T = 123.0 (1) K using monochromatic Cu-*Ka* radiation (1.54178Å) from a MicroMax^{TM}-003 sealed tube microfocus X-ray source. The strategy of data collection was calculated using Rigaku *CollectionStrategy* (42), *CrysAlisPro* (43) was used for data reduction and empirical absorption correction using spherical harmonics implemented in *SCALE3 ABSPACK* scaling algorithm (44). The structure was solved using *SHELXT* (45) and refined by full-matrix least-squares method against F^2 with *SHELXL-2016* (46) through *OLEX2* (47) program package. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Hydrogen atoms on carbons were treated as riding on their parent atoms, with U_{iso}(H) = 1.2U_{iso}(C) for CH. The hydrogen atom of the carboxylic acid group was located from the Fourier difference map and refined freely (U_{iso}(H) = 0.0531). The figures were drawn using the programs Mercury CSD 3.10 (48) and POV-Ray 3.7 (49).

Computational data

The crystal structure of **1a** was optimised at B3LYP (50, 51)/6–311 + G(2d,p) (52, 53) level of theory and vibrational normal mode analysis was carried out to confirm the absence of imaginary eigenvalues. The effects of solvation were included in the framework of IEF-PCM (54, 55) dielectric continuum model representing methanol environment for all calculations. Another true minimum confirmation was obtained by 180 degrees rotation of the COOH group while the core of macrocycle remained intact. These two structures, being very close in total energy and resembling the overall appearance of the parent crystal structure, represent the whole conformational space of **1a** in methanol. Nuclear magnetic shielding tensors in gauge-independent atomic orbitals (GIAO) (56–60) and continuous set of gauge transformations (CSGT) (60–62) representations were calculated at B3LYP/6–311 + G(2d,p) level of theory for both hydrogen and carbon atoms. Additionally, MN12-SX (63)/cc-pVTZ (64) and lc-TPSSTPSS (65, 66)/cc-pVTZ methods were used for calculations of magnetic shieldings of hydrogens and carbons, respectively. Magnetic shieldings were converted to chemical shifts using TMS at B3LYP/6–311 + G (2d,p) GIAO level as a reference. The calculations were carried out using Gaussian 09 (67) and Gaussian 16 (68) software suites while GaussView package was used for analysing computational NMR data.

Disclosure statement

No potential conflict of interest was reported by the authors.

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