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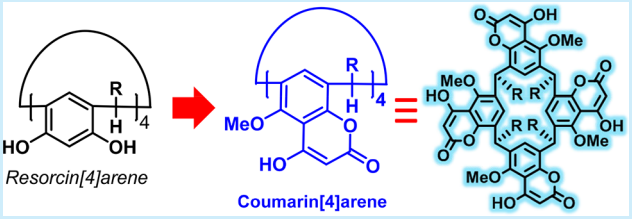
Coumarin[4]arene: A Fluorescent Macrocycle

Pawan Kumar and Parthasarathy Venkatakrishnan*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, Tamil Nadu, India

Supporting Information

ABSTRACT: The pyranone functionalization of the upper rim of resorcinarene to provide the coumarin macrocycle called "coumarin[4]arene", possessing visible fluorescence and conformationally flexible behavior suitable for molecular recognition, has been successfully synthesized and characterized.



Macrocycles (e.g., *m*-cyclophanes) are an important class of organic compounds that play pivotal roles in supramolecular chemistry.[1] Such synthetic macrocyclic hosts/receptors generally display a unique molecular structure and interesting conformational behavior, which indeed facilitate their application in various fields, starting from materials science to molecular device.[1] Most of the macrocyclic skeletons achieved to date were either composed of benzene units, as in calixarenes,[2] resorcinarenes,[3] pillararenes, and biphen[n]-arenes,[4] cyclotriveratrylenes,[5] etc., or of heterocycle units, as in calixpyrroles,[6] caliximidazoliums,[7] etc. (Figure 1). These

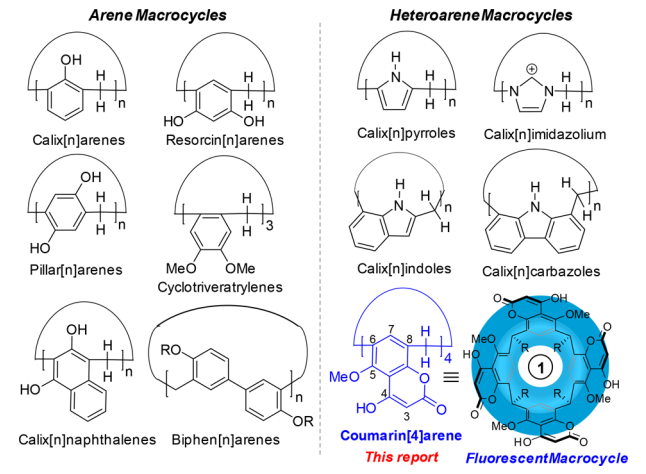


Figure 1. Structures of some literature-reported macrocycles and coumarin[4]arene of this report.

macrocyclic structures were readily synthesized, and they exhibited excellent host−guest and sensing properties. However, macrocycles comprising bicyclic arenes, such as calixnaphthalenes[8] and calixindoles,[9] are rare and have not attracted considerable attention as their syntheses usually involve tedious multistep reactions, and the resultant macrocycles often exhibit poor host−guest behavior and discouraging photophysical characteristics.

To bridge this gap, we thought if the arenes in calix[*n*]arenes are replaced by a bicyclic fluorescent heteroarene the macrocycle would advantageously enjoy (i) a larger π-system with deepened or widened cavity for effective capturing of guests, (ii) a dissymmetric skeleton with interesting built-in stereochemical features for chirality, (iii) better optical (chromophoric/fluorophoric) characteristics enabling inexpensive optical means of sensing possible, and (iv) the ability to form fluorescent molecular capsules via complementary multipoint interactions, etc. The aesthetic simplicity, easy synthesis and rich chemistry,[10] promising photophysical characteristics,[11] excellent bioavailability, structure-based activity, and proven therapeutic potential[12] have compelled us to choose coumarins in macrocycles for our work. While coumarin units are attached either onto the upper or lower rim of the macrocycle,[13] macrocycles composed of coumarin units are yet unexplored.

In continuation of our interest in coumarin-based skeletons,[14] we herein report the synthesis, structure, conformational flexibility, photophysical properties, and potential for host−guest behavior of a new family of macrocycles, i.e., coumarin[4]arenes, where 4-hydroxycoumarins are linked via methine bridges connecting their 6- and 8-positions (Figure 1). Coumarin[4]arene is accomplished by a two-step protocol in good yields using readily available reagents. It is conformationally flexible in solution, exists in boat conformation in solid, exhibits visible fluorescence in solution, and reveals interesting guest-binding properties.

Our pursuit toward the designed macrocyclic scaffold **1** initiated with the synthesis of parent macrocycle, i.e., *C*-isobutyltetramethoxy resorcinarene (**1a**, Figure 2), in good yields (ca. 78%) by modifying the macrocyclization procedure reported earlier.[15] The ^{1}H and ^{13}C NMR spectra (showing one set of averaged signals for **1a** in $CDCl_3$) and ESI-HRMS data suggested a C_4 symmetry for **1a**, which is further confirmed by single-crystal X-ray analysis (Figure 2; see Figures S1−S5 for

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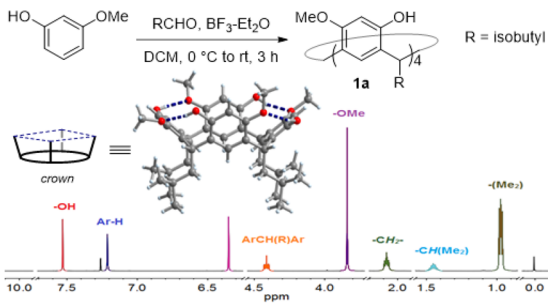

Figure 2. Synthesis of tetramethoxyresorcin[4]arene, **1a**. ^{1}H NMR spectrum of **1a** in $CDCl_3$ as well as its single-crystal X-ray structure revealing crown conformation stabilized via four intramolecular O−H···O hydrogen bonds (shown by dotted lines).

details). As expected, it is evident that the intramolecular hydrogen bonding ($d_{O-H\cdots O}$ = 1.961−2.125 Å; $\theta_{O-H\cdots O}$ = 151.31−175.62°) present between −OMe and −OH groups promotes crown conformation of the macrocycle **1a** in both solution and solid states.[15b] A careful analysis of the X-ray structure of **1a** revealed the presence of both the *P* and *M* enantiomers in the crystal lattice.[15a] The unidirectional arrangement of −OH groups in the enantiomers of **1a** leads to an inherent chirality[16] (see Figures S4 and S5) and also provides a convenient platform for structural elaboration.

Thus, pyranoannulation of **1a** to achieve coumarin[4]arene **1** was targeted by utilizing the available phenolic −OH group via well-known classical methods. These include Shah's method[17] of annulation with malonic acid using $POCl_3/ZnCl_2$ and α-acetylation followed by treatment with diethyl carbonate in the presence of base.[18] Both attempts did not yield the desired product but led to the decomposition of the macrocyclic scaffold **1a** as revealed by the ^{1}H NMR spectrum (Figure S6). As evidenced, introduction of certain functional groups into a preformed macrocyclic scaffold or tailoring the macrocyle into a different core have always been challenging.[19] Hence, we adapted a relatively milder two-step approach. This involves the treatment of Meldrum's acid and Eaton's reagent[20] with *C*-isobutyl tetramethoxyresorcinarene **1a** to provide **1** in good yields (84%, Figure 3).

The isolated coumarin macrocycle **1** was thoroughly characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, and ESI-HRMS techniques (Figures S8−S13). Careful examination of the ^{1}H NMR spectrum of **1** (Figure 3) in $CDCl_3$ solution revealed a triplet at 4.85 ppm for the macrocyclic bridging −C*H*, and three singlets at 3.97, 5.71, and 6.87 ppm for

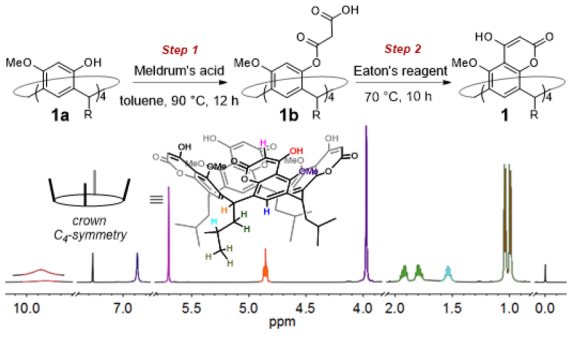

Figure 3. Synthesis of *C*-isobutyl coumarin[4]arene, **1**, from **1a**. ^{1}H NMR spectrum of **1** in $CDCl_3$ at 25 °C showing C_{4v}-averaged signals (structure and the proton resonances are shown).

−OCH_3 proton, coumarin −C_3H proton, and aromatic −C*H* proton, respectively, besides a broad singlet at 9.83 ppm for the −O*H* group pointing to a C_4-symmetric conformation in solution. In addition, ^{13}C NMR signals at 165.3 (C═O) and 161.8 ppm (C−O) and the IR stretching frequency at 1654 cm^{-1} (C═O) as well as 3275 cm^{-1} (O−H) ascertain the annulation of a 4-hydroxypyranone unit to the *C*-isobutyl tetramethoxyresorcinarene. In addition, the ESI-HR mass spectrum of **1** also shows an *m*/*z* peak at 1063.4100 corresponding to [M + Na]$^+$. Thus, HRMS data coupled with IR and NMR data precisely authenticate that the resultant product is a tetrameric coumarin macrocycle, i.e., coumarin[4]-arene **1**, as desired.

Fortunately, single crystals suitable for X-ray crystallography were obtained by vapor diffusion of diethyl ether into the DCM solution of **1** at low temperature (ca. 4 °C). X-ray crystal structure analysis of coumarin[4]arene **1** (space group: *C*2/*c*) confirms the boat shape (C_{2v} symmetry, Figure 4) in solid state,

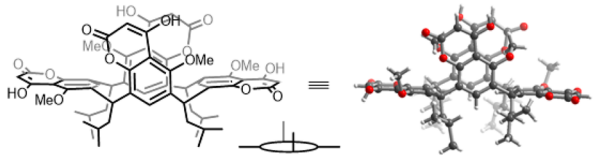

Figure 4. X-ray molecular structure of **1** showing the boat conformation in the solid state.

in contrast to that in solution. In the boat conformation of **1**, coumarin units that are in 1,2-relation are near perpendicular (angle between mean planes: 88.8°) to each other, whereas the coplanar as well as parallel ones in 1,3-relation are separated by a distance of 5.28 and 4.87 Å, respectively. Notably, a considerable deviation in the tetrahedral angle at the bridging methine carbons highlights a significant strain in the macrocycle **1**. Similar to **1a**, both of the enantiomers were witnessed in the crystal lattice of **1** (Figure S14) as expected. Further inspection of the molecular packing diagram reveals that coumarins facing each other participate in O−H···O═C hydrogen bonding interactions to form a shifted-type pillared dimeric assembly. These dimers further self-assemble via weak C−H···O═C interactions in a centrosymmetric fashion through the coplanar coumarins to form a 2D network. Each part of this 2D network is layered by the hydrophobic isobutyl chains via weak van der Waals interactions (see Figures S15−S18). Interestingly, viewing along the "diagonal" of the unit cell, one notices a tubular-type assembly where −OMe groups occupy the interior positions. The reason as to why **1** exists in boat conformation in the crystalline state may be reasoned from the dominant intermolecular interactions or strong close packing effects or interactions induced by the guest solvent molecules or absence of intramolecular H-bonding interactions, as observed in some cases earlier.[21] Generally, boat conformation is noticed in resorcinarenes with short alkyl chains due to efficient close packing, as resorcinarenes with long alkyl chains become organized into lipid-like bilayers facilitating crown conformation.[22]

The ^{1}H NMR spectrum was recorded (at 25 °C) for **1** in solvents of varying polarity, to understand solvent effects on conformational behavior, displayed no signal broadening or splitting or shifting in $CDCl_3/CD_2Cl_2$ but appreciable chemical shift changes for the proton signals in acetone-d_6/DMSO-d_6 (see Figure S19). Clearly, the C_4-O*H* peak of the coumarin unit

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appeared broad at ca. 9.83 ppm in the nonpolar solvent $CDCl_3$ and emerged as a sharp signal at 12.19 ppm in the H-bond competing polar solvent DMSO-d_6 with a downfield shift of ca. 2.36 ppm. Using these chemical shift differences, the Abraham solute H-bond acidity parameter (A) calculated was 0.32, which signifies weak intramolecular H-bonding at C_4-O*H*.[23] Besides, notable shift (ca. 0.57 ppm) in the case of the −O*Me* proton signal, slight shifts in bridging methine (−0.034 ppm), C_3-*H* and of Ar-*H* signals probably suggest solvation by DMSO.[24] Similar changes in ^{1}H NMR chemical shifts were also witnessed in acetone-d_6, but to a lesser extent. These experiments highlight that macrocycle **1** displays C_4-symmetric conformation independent of the solvent. However, this observation could as well be a result of rapidly interconverting two boat conformers or the coexistence of other co-conformers in solution.[25]

To understand the conformational flexibility of skeleton **1** and to trace its boat/other conformers in solution, we carried out VT-NMR (+25 °C to −90 °C) experiments in CD_2Cl_2 (Figure 5). As may be inferred, proton signals broaden below

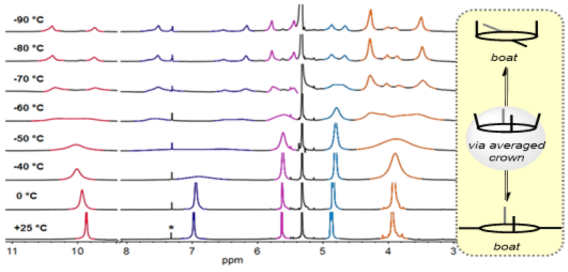

Figure 5. Variable-temperature ^{1}H NMR spectra of **1** in CD_2Cl_2 (left) revealing slow boat-to-boat interconversion equilibrium via averaged crown conformation, shown diagrammatically (right).

0 °C and split below −50 °C. Notably, signals corresponding to C_4-O*H*/C_3-*H*/C_5-O*Me*/C_7-*H* split into two, which emphasizes the slow conformation interconversion between the two boat conformers (less symmetric, C_{2v}) of **1** via the averaged crown conformation. The above observation at low temperatures is consistent with earlier reports.[25] Such a conformational flexibility is the key property desired for host−guest chemistry. Noteworthy is that the ^{1}H NMR experiments at 105 °C in DMSO-d_6 revealed negligible changes in the chemical shift of the protons of **1** (Figure S20).[26] This points to the fact that the barrier for annulus inversion is considerably high for **1**.[27]

The preliminary guest binding potential of flexible **1** was evaluated by DOSY NMR measurements (Figure S26) as well as ^{1}H NMR titrations (Figure 6) with benzyltrimethylammonium chloride (**2**).[4b,28] The diffusion coefficients (D) measured for the host **1** (4.09×10^{-10} m^2s^{-1}) as well as guest **2** (4.32×10^{-10} m^2s^{-1}) in the complex were nearly identical, dictating possibly an inclusion complex.[29] Further, the protons of the phenyl ring, $-^+NMe_3$ and $-CH_2-$ of **2** exhibiting upfield shifts as a result of inclusion-induced shielding effects plus the Job's plot indicated the formation of a 2:1 inclusion complex (Figures S28−31; $K_{21} = 63620 \pm 8.64$ M^{-1})[30] as confirmed by ESI-HRMS. As a consequence, the proton signals for −O*H*, $-C_3H$ of the host are also deshielded, while −OMe is slightly upfield shifted due to interactions with the cationic guest. Similar studies with benzyltriethylammonium chloride (**3**) revealed a substantial decrease in the binding affinity (Figures S32−35; $K_{21} = 2170 \pm 2.85$ M^{-1}) probably due to larger alkyl

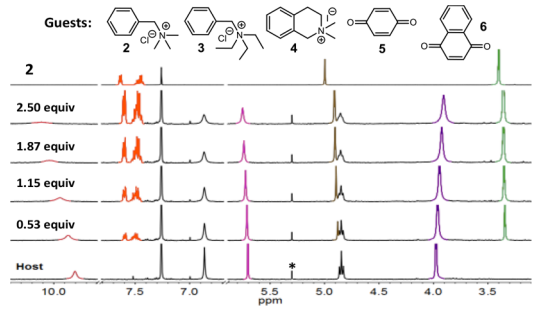

Figure 6. Guests **2**−**6** used for study (top). Partial ^{1}H NMR spectra (bottom) of host (**1**, 2×10^{-3} M) upon addition of **2** in $CDCl_3$; * denotes residual solvent of crystallization, CH_2Cl_2.

chains. In contrast, cationic and less flexible (**4**) and neutral and H-bond acceptor guests (**5**/**6**) did not show any binding, perhaps because of their poor complexation ability (Figures S36−38).

As coumarins and their derivatives are excellent fluorophores,[31] the UV/vis absorption and fluorescence spectra of **1** (Figure 7) were examined in dilute solutions (ca. 10 μM) of

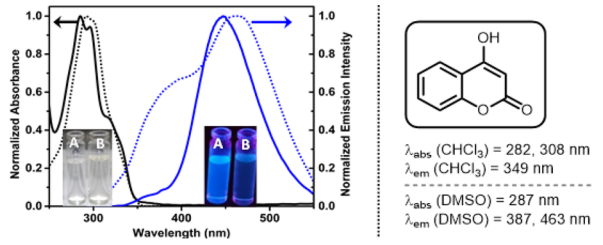

Figure 7. UV−vis absorption (black) and PL (blue) spectrum of **1** in $CHCl_3$ (solid line) and DMSO (dotted line) at 25 °C. Photographs of solutions of macrocycle **1** in $CHCl_3$ (A) and DMSO (B) under room light (left) and under UV light λ_{ex} = 365 nm (right). For comparison, λ_{max} values of 4-hydroxycoumarin are provided.

Table 1. Optical Properties of 1a and 1

		λ_{max} (nm)		
sample	solvent	abs	em[a]	Φ[b]
1a	$CHCl_3$	285	412	na
1	$CHCl_3$	285, 297, 315	447	0.16
	DMSO	292	397, 460	0.091

[a] λ_{ex} = 310 nm. [b] Using Φ_{DPA} = 0.90 in cyclohexane (λ_{ex} = 310 nm) as the standard. na = not available.

$CHCl_3$ and DMSO (Table 1). The UV−vis absorption spectrum of **1** in chloroform solution exhibited an absorption maximum at 285 nm ($\varepsilon = 4.22 \times 10^4$ M^{-1} cm^{-1}) and a nearby second absorption band at 297 nm ($\varepsilon = 3.99 \times 10^4$ M^{-1} cm^{-1}) and a broad shoulder at 315 nm ($\varepsilon = 1.81 \times 10^4$ M^{-1} cm^{-1}). While the absorption maxima of **1** are slightly red-shifted (ca. 7 nm), the broad low energy shoulder band is not vivid in DMSO. The observed differences in spectral characteristics may arise from the excitonic splitting due to the C_{4v} conformation of **1** in non hydrogen bonding solvents.[32] Excitation of **1** (in $CHCl_3$) at all three wavelengths revealed a broad emission band from 340−560 nm with an emission maximum at λ_{em} = 447 nm (Figure 7). In contrast, the emission spectrum of **1** in

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DMSO displayed a much broader emission (300−580 nm) with a red-shifted (ca. 18 nm) emission maximum at λ_{em} = 460 nm, besides a high energy emission band at around 397 nm. Both the absorption and emission maximum of **1** is red-shifted when compared to those of simple 4-hydroxycoumarin, 7-methoxy-4-hydroxycoumarin,[33] precursor macrocycle **1a** (Table 1) and calix[4]naphthalene.[8] This indicates that the visible blue emission arises from the coumarin unit of the macrocycle **1**; the role of heteroaromatic pyranone unit is clearly evident. The visible blue emission from **1** in solution can be attributed to a large Stokes shift of 132−168 nm. Notably, fluorescent dyes with large Stokes shifts are excellent candidates for super-resolution optical microscopy.[34] The photoluminescence (PL) quantum yields (Φ) of **1** measured in polar aprotic solvents, such as chloroform and DMSO, are 0.16 and 0.09, respectively, which is far higher than the simple 7-methoxy-4-hydroxy- and 4-methylcoumarins.[33] The decrement of the fluorescence quantum yield in DMSO compared to $CHCl_3$ may presumably be attributed to a facile nonradiative pathway. To the best of our knowledge, an inherently fluorescent bicyclic heteroaromatic (6-mem.) macrocycle by incorporating a pyran-2-one unit to the resorcinarene core (as **1**) is heretofore unreported.

In conclusion, we have demonstrated a mild synthesis of a new family of fluorescent bicyclic heteroaromatic macrocyclic scaffold, called "coumarin[4]arene", in very good yields. It is found that coumarinarene exists in averaged crown conformation in solution and boat conformation in solid states. While conformational flexibility of the skeleton is revealed by VT-NMR studies, its guest binding potential is proven by ^{1}H NMR titrations. Interestingly, the cyclic arrangement of coumarins in these skeletons promote bright visible luminescence in solution with appreciable PL quantum yields. Such luminescent coumarin macrocycles may lead to potential application in host−guest chemistry, sensing, organic electronics, etc. At present, efforts are in progress to improve the fluorescence properties and to investigate the host−guest and sensing behavior of this macrocyclic skeleton.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b04045.

Synthetic details, NMR, ESI-HRMS scans, details of DOSY, ^{1}H NMR titrations, X-ray packing diagrams, etc. (PDF)

Accession Codes

CCDC 1813284−1813285 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pvenkat@iitm.ac.in.

ORCID

Parthasarathy Venkatakrishnan: 0000-0002-0895-2861

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. S. Sankararaman on the occasion of his 60th birthday.

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