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Synthesis of calixarene-based ketocyanine fluorophores

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ABSTRACT

Cup-shaped calix[4]arenes bearing one or two ketocyanine fluorophore fragments at the wide rim of the macrocycle are synthesized by condensation of formyl calix[4]arenes with arylmethylene(hetarylmethylene)cyclopentanones in the presence of the ionic liquid, dimethylammonium dimethylcarbamate (DIMCARB) and characterized using UV–vis and fluorescence spectroscopy. Strong positive solvatofluorochromism for the calixarene ketocyanines is observed.

Molecular sensing is a rapidly developing field in science and technology.[1] The key task in construction of efficient chemosensors is the design of sensor systems capable of producing a high-amplitude physical signal upon selective molecular recognition. Among a variety of chemosensory devices, fluorescence systems are commonly considered superior due to their simple construction and extremely high sensitivity.[2] On the other hand, calixarenes are phenol-derived macrocycles that possess a unique cup-shaped molecular cavity and are able to demonstrate high selectivity in the formation of supramolecular host–guest complexes with metal cations, anions, and organic and biomolecules.[3] This ability makes calixarenes an attractive framework for construction of optical sensing systems. A chromo(fluoro)phore electronic system can be conjugated in the sensors with the π-system of the calixarene recognition site.[4] Chromophore-functionalized calixarenes were synthesized and studied previously.[5]

In this Letter, we report the synthesis of calix[4]arenes bearing ketocyanine chromofluorophore groups, the fluorescence of which is highly sensitive to the environment and could provide responses to substrate binding.

To functionalize the macrocyclic backbone with ketocyanine groups, we employed the condensation reaction between the readily available monoformyl or diformyl propoxycalix[4]arenes **1a**,**b**,[6] **c** and α,β-unsaturated cyclopentanones **2a–c**.

All attempts to react calixarenes **1a–c** with cyclopentanones **2a–c**[7] via typical aldol condensation conditions in basic or acidic medium failed. However, aldehydes **1a–c** reacted smoothly with cyclopentanones **2a–c** in the presence of dimethylammonium dimethylcarbamate (DIMCARB)[8] as a co-solvent and catalyst to give (depending on the reagent ratio) calixarenes **3** and **4** possessing one or two ketocyanine moieties in moderate to good yields (Scheme 1). All the reactions were carried out by heating at 45–50 °C in chloroform for 5–11 days. Interestingly, the reaction proceeds stereoselectively with formation of the *E*,*E*-isomer exclusively. In the ^{1}H NMR spectra of compounds **3a–c** recorded in $CDCl_3$, the AB spin system due to the axial and equatorial protons of the $ArCH_2Ar$ methylenes appeared as two doublets at δ 4.33 and δ 4.31 (H_{ax}) and a multiplet at δ 3.41 (H_{eq}) with $^2J_{HH}$ 12.8–13.1 Hz. The chemical shift difference between H_{ax} and H_{eq} of about 0.9 ppm reflects the *cone* conformation of **3a–c** in solution.[9] The protons of the cyclopentanone ring were observed as a broad singlet at δ 3.10. The hydroxy protons appeared as two singlets in the region δ 8.30–8.92. ^{13}C NMR resonances for the carbons of the methylene bridges appeared at δ 31.31–31.48, which reflects the *syn* orientation of the adjacent phenolic rings in the *cone* conformation.[10] The presence of long-range couplings between $H_{a,b}$ and the cyclopentanone ring protons in the COSY-spectrum gave additional insight into the structural features of **3a–c**. The signals of $H_{a,b}$ at δ 7.48 and δ 7.54, which overlap with the doublet due to the aromatic protons at δ 7.52, showed long-range couplings to the cyclopentanone methylene protons while couplings to the *ortho*-protons of the neighbouring benzene rings were not present. It should be

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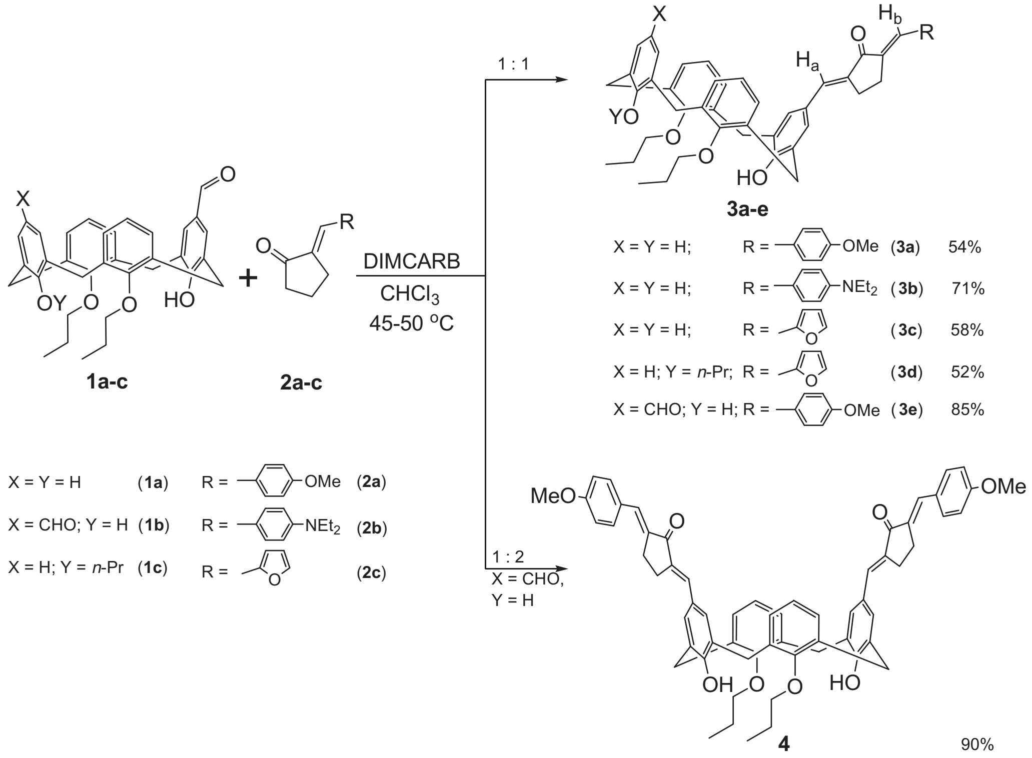


Scheme 1. Synthesis of calixarene-based ketocyanine fluorophores.

noted that the signal for the hydroxy proton of **3d** at δ 5.56 was shifted significantly to a high field compared to **3a–c** which is typical for calixarenes trisubstituted on the narrow rim.[11] The aldehyde proton of **3e** appeared as a sharp singlet at δ 9.79.

The ^1H NMR spectrum of the disubstituted derivative **4** in $CDCl_3$ contained two well-resolved doublets due to the methylene protons at δ 3.45 (H_{eq}) and δ 4.33 (H_{ax}) with coupling constants of 13.1 Hz. This reflects the C_{2v}-symmetry of the *cone*-shaped macrocycle backbone.

Diffraction quality crystals of **3a** and **3d** were grown from chloroform-methanol and ethyl acetate–hexane mixtures, respectively. The X-ray diffraction study showed that both the molecules existed in *E*,*E*-form in the solid state.

Macrocycles **3a** and **3d** adopt a *pinched cone* conformation (Figure 1). The angles between the opposite benzene rings of the macrocycles differ considerably (13.6° and 74.9° for **3a**, 19.2° and 67.0° for **3d**). Conjugation of the aromatic π-system with the ketocyanine fragment is revealed in both compounds **3a** and **3d**.

In order to estimate the influence of the calixarene framework on the absorption and fluorescence properties of **3a–e** and **4**, model compound **5** was synthesized (Scheme 2). The structure of **5** can be considered as that of the isolated fluorophore of **3a**.

The reaction between *para*-hydroxybenzaldehyde and (2*E*)-2-(4-methoxybenzylidene)cyclopentanone (**2a**) was carried out using conditions similar to those employed for **3a–e** and **4** for 5 days and gave (2*E*,5*E*)-2-(4-methoxybenzylidene)-5-(4-hydroxbenzylidene)cyclopentanone (**5**) in 76% yield.

The UV–vis and steady state fluorescence spectra of compounds **3–5** were studied in solvents of different polarities (toluene, chloroform, acetone, DMSO, and MeOH). Relative fluorescence quantum yields were measured using quinine sulfate in 0.1 M H_2SO_4 ($\Phi_f = 57.7\%$) as a reference.[12] Selected spectral data are listed in Table 1.

All the products showing molar extinctions of about 40,000 L mol^{-1}cm^{-1} absorb on the border of the UV and visible regions, and demonstrate green or yellow fluorescence. Only **3b** shows a substantial positive solvatochromism. At the same time all the compounds possess rather strong positive solvatofluorochromism (Table 1 and Figure 2), which for the dye **3b** is comparable with that of known analogs[13] or Prodan,[14] while for other dyes it is 1.5–2 times lower.

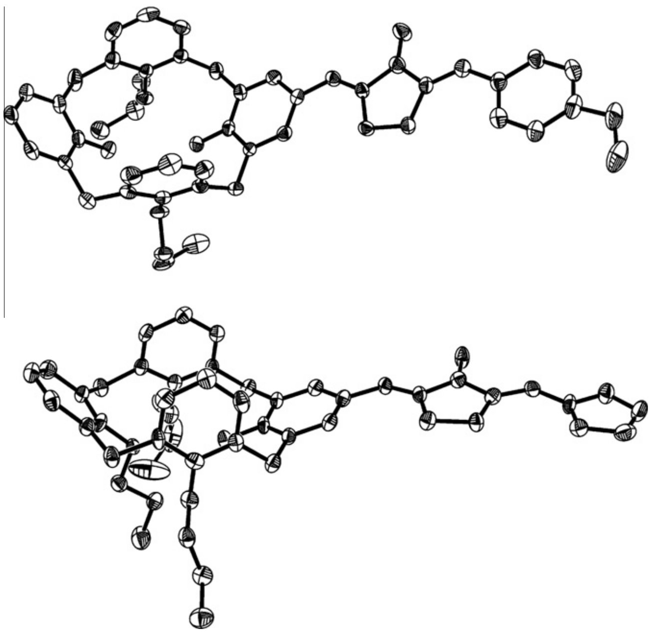
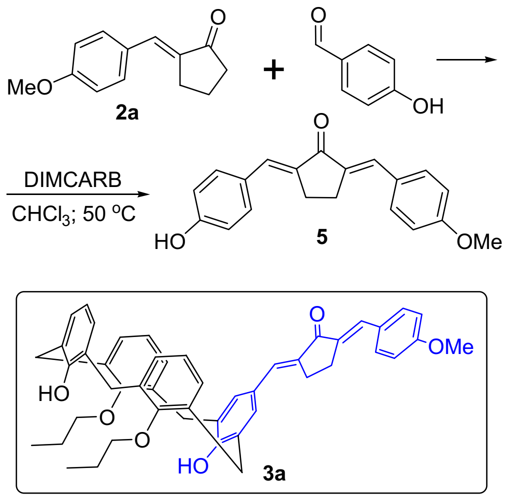


Figure 1. X-ray crystal structures of compounds **3a** (above) and **3d** (below); H-atoms are omitted for clarity. The *E*,*E*-conformations are clearly shown. Thermal ellipsoids are shown at the 50% probability level.

These features provide a regular increase of Stokes' shifts with increasing solvent polarity. The fluorescence quantum yields are relatively low – up to several percent for compound **3b** and about



Scheme 2. Synthesis of the model compound **5**.

Table 1
UV–vis and fluorescent spectral characteristics of compounds **3–5**, measured in $CHCl_3$ and MeOH at 25 °C

Compound	Solvent	λ_{max}^{abs} [a] (nm)	λ_{max}^{fl} [a] (nm)	S^a	Φ_f^a (%)	SS^a (cm^{-1})
3a	$CHCl_3$	403	472	0.378	0.8	3630
	MeOH	402	498		1.3	4800
3b	$CHCl_3$	421	534	1.25	3.4	5030
	DMSO[b]	462	574		4.6	4220
3c	$CHCl_3$	404	484	0.590	1.1	4090
	MeOH	409	528		1.2	5510
3d	$CHCl_3$	401	482	0.560	0.7	4190
	MeOH	406	529		1.5	5730
3e	$CHCl_3$	399	476	0.531	0.3	4050
	MeOH	402	514		0.6	5420
4	$CHCl_3$	402	474	0.510	1.0	3780
	MeOH	403	510		1.3	5210
5	$CHCl_3$	384	462	0.521	0.03	4400
	MeOH	393	497		0.8	5320

[a] λ_{max}^{abs}—absorption maximum; λ_{max}^{fl}—fluorescence maximum; *S*—relative solvatofluorochromism: Δ/Δ_{Prodan} for the pair of solvents used; Φ_f—fluorescence quantum yield; *SS*—Stokes' shift.

[b] DMSO was used as compound **3b** and is almost non-fluorescent in MeOH.

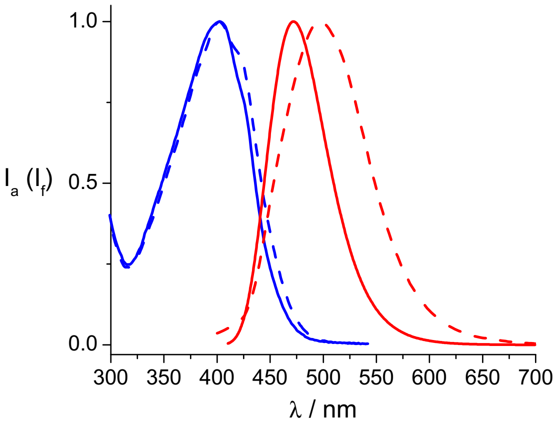


Figure 2. Normalized UV–vis (blue lines) and fluorescent (red lines) spectra of compound **3a** in $CHCl_3$ (solid lines) and MeOH (dashed lines).

one percent for other chromophores. Nevertheless, they are several times higher for calixarene **3a** than for the model compound **5**, showing the spatial influence of the rigid calixarene skeleton on the fluorescence properties.

In summary, this preliminary study of calixarene-based ketocyanines has demonstrated them to be promising materials as new fluorescent chemosensors. The estimated solvatofluorochromism levels and quantum yield values demonstrate clearly the possibility of control of the fluorescence colour and intensity by varying the nature of the analyte bound in the proximity of the fluorophore unit.

X-ray diffraction study. The colourless crystals of **3a** $C_{48}H_{48}O_6$ are monoclinic. At 100 K: $a = 10.0804(7)$, $b = 42.357(2)$, $c = 9.3766(8)$ Å, $\beta = 108.380(9)$, $V = 3799.3(5)$ Å^3, Mr = 720.86, $Z = 4$, space group $P2_1/c$, $d_{calc} = 1.260$ g/cm^3, μ(MoK) = 0.082 mm^{-1}, $F(0\,0\,0) = 1536$. Intensities of 36345 reflections (11012 independent, $R_{int} = 0.160$) were measured on an Xcalibur-3 diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scanning, 2Θmax = 60°).

The colourless crystals of **3d** $C_{48}H_{50}O_6$ are triclinic. At 100 K: $a = 9.9903(5)$, $b = 14.195(1)$, $c = 15.524(1)$ Å, $\alpha = 65.071(7)°$, $\beta = 74.497(5)$, $\gamma = 86.053(5)°$, $V = 1921.3(2)$ Å^3, Mr = 722.88, $Z = 2$, space group $P\bar{1}$, $d_{calc} = 1.250$ g/cm^3, μ (Mo K_α) = 0.081 mm^{-1}, F (0 0 0) = 772. Intensities of 14310 reflections (6748 independent, $R_{int} = 0.084$) were measured on an Xcalibur-3 diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scanning, $2\Theta_{max} = 50°$).

The structures were solved by direct methods using the SHELXTL package.[15] The positions of the hydrogen atoms were located from electron density difference maps and refined using the 'riding' model with $U_{iso} = nU_{eq}$ for the carrier atom ($n = 1.5$ for methyl and hydroxy groups and for the water molecule, and $n = 1.2$ for other hydrogen atoms). Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for non-hydrogen atoms using 10890 (**3a**) and 6650 (**3d**) reflections converged to: $wR_2 = 0.041$ ($R_1 = 0.047$ for 3221 reflections with $F > 4\sigma(F)$, $S = 0.589$) for structure **3a** and $wR_2 = 0.034$ ($R_1 = 0.043$ for 2344 reflections with $F > 4\sigma(F)$, $S = 0.573$) for structure **3d**. The final atomic coordinates, and crystallographic data for molecules **3a** and **3d** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 793141 for **3a** and CCDC 793142 for **3d**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.094.

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