COMMUNICATION

Selective sulfate binding induces helical folding of an indolocarbazole oligomer in solution and solid state†

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Hydrogen bonding to anions drives the helical folding of an indolocarbazole oligomer, thus resulting in an internal cavity with six NHs and two OHs for binding sulfate with high selectivity.

Binding of oxoanions such as sulfates and phosphates by synthetic receptors remains popular given their biological and environmental relevance, but also due to their tetrahedral coordination geometry and ability to accept multiple hydrogen bonds. Sulfate has been shown to form between four and twelve hydrogen bonds with a range of synthetic hosts such as helicates, macrocyles, capsules and catenanes.[1,2]

We have previously shown that indole derivatives can be successfully implemented in macrocyles[3] and foldamers,[4] functioning as efficient receptors for anions. Herein, we expand upon the utility of this modular building block by constructing a functional oligomer **1**. Folding of **1** generates a helical cavity containing eight hydrogen bond donors. ^{1}H NMR and fluorescence studies support helical folding upon anion binding, which for the first time is unambiguously proved by crystal structures of complex **1**·(Bu$_4$N$^+$)$_2$SO$_4$$^{2-}$ (Fig. 1).‡ Moreover, **1** displays high selectivity toward sulfate with a binding strength (K_a) more than two orders of magnitude higher than any other anions studied.

Oligomer **1** was prepared from sequential Sonogashira coupling reactions of monomers synthesized from 4-*tert*-butylaniline (see ESI†). The binding properties of **1** with anions were first investigated by ^{1}H NMR spectroscopy. Upon addition of anions as tetrabutylammonium salts, signals for indole NHs of **1** are downfield shifted in 1:1:8 CD$_3$OH/CD$_2$Cl$_2$/CD$_3$CN, indicative of hydrogen bonding to the anions. For example, in the presence of (Bu$_4$N$^+$)$_2$SO$_4$$^{2-}$ (1 equiv.), the NH signals shift from 9.74, 10.21 and 10.22 ppm to 12.02, 12.35 and 13.57 ppm, respectively (Fig. 2). In addition, the terminal OH resonance shifts from 4.08 to 6.06 ppm, also indicating hydrogen bonding with sulfate. On the other hand, aromatic protons of the stacked terminal arenes (H^b, H^c, H^d, H^e) experience considerable upfield shifts

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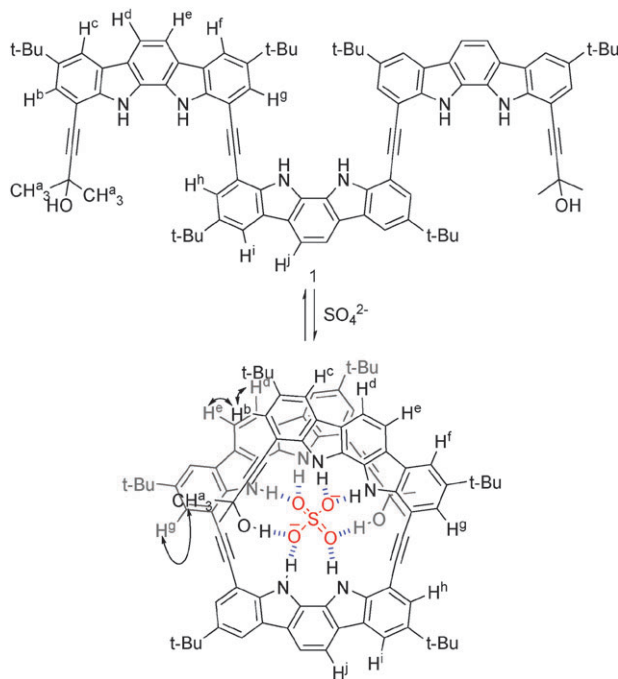

Fig. 1 Indolocarbazole oligomer **1** depicted in unbound (top) and inferred sulfate binding conformation (bottom). Relevant NOEs and hydrogen bonds are also displayed.
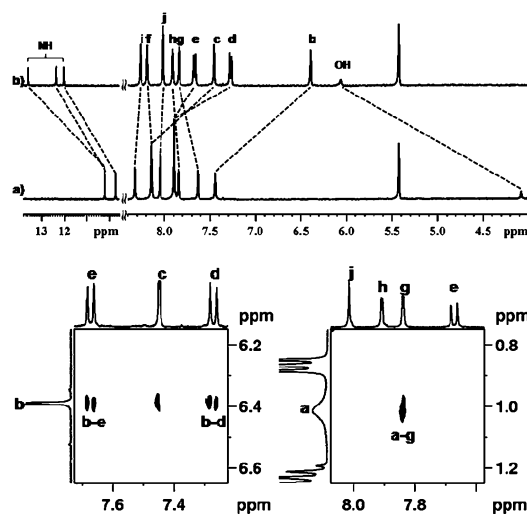

Fig. 2 Top: Partial ^{1}H NMR spectra (400 MHz, 1:1:8 CD$_3$OD/CD$_2$Cl$_2$/CD$_3$CN, 298 K) of: (a) unbound oligomer **1** (0.5 mM) and b) oligomer **1** (0.5 mM) and (Bu$_4$N$^+$)$_2$SO$_4$$^{2-}$ (1 equiv.). Bottom: Partial [1]H–[1]H NOESY spectra (400 MHz, 1:1:8 CD$_3$OD/CD$_2$Cl$_2$/CD$_3$CN, 298 K) of oligomer **1** (3 mM) and (Bu$_4$N$^+$)$_2$SO$_4$$^{2-}$ (2 equiv.) showing relevant NOEs indicative of helical folding.

($\Delta\delta(H^b)$ = −1.05 ppm, $\Delta\delta(H^c)$ = −0.68 ppm, $\Delta\delta(H^d)$ = −0.64 ppm, $\Delta\delta(H^e)$ = −0.22 ppm) due to increased shielding from π-stacking induced by anion binding. These changes saturated upon the addition of approximately 1 equivalent of sulfate (see ESI†). All the other anions showed significantly lower induced changes in the chemical shift of the NH signals compared to sulfate; induced chemical shift changes were less than 1.10 ppm with 1 equivalent of other anions (see ESI†). It should be noted that the OH signal of **1** remains unchanged upon addition of other anions (chloride, bromide, iodide and azide),[5] which is in contrast to the large downfield shift induced by sulfate ($\Delta\delta$ = 1.98 ppm). We believe that the additional OH···O hydrogen bonds are responsible for the high affinity and selectivity towards sulfate (*vide infra*). Job's plot[6a] demonstrates a 1 : 1 binding stoichiometry for all the anions investigated.

The initial results observed by ^{1}H NMR spectra are clarified by [1]H–[1]H NOESY experiments. In the presence of $(Bu_4N^+)_2SO_4^{2-}$, NOE cross-peaks are observed between H^b and non-adjacent protons H^d and H^e as well as between the terminal methyl proton H^a and aromatic proton H^g of the opposite termini (Fig. 2). These correlations can only be observed upon folding, where π-stacking of the terminal segments of the oligomer brings the aforementioned protons within close proximity to each other. Upon binding to the anion, the hydroxyl group is oriented into the helical cavity while each methyl proton H^a is directed above the π-stacked arenes, at a distance close enough to result in an NOE. These observations provide clear evidence for the formation of a helical, folded structure in the presence of a sulfate template.

The highly conjugated backbone of **1** allows for detection and measurement of binding by fluorescence spectroscopy. Helical folding of the aromatic strands often leads to the bathochromic and/or hypochromic shifts of the emission spectra because of the intramolecular excimer formation in the π-stacked complex. The fluorescence spectra of **1** were taken with excitation at 320 nm in 10% v/v MeOH–CH₃CN at room temperature. Under these conditions, **1** shows a distinct emission band with the highest intensity at 413 nm. Titration of **1** with $(Bu_4N^+)_2SO_4^{2-}$ leads to lowering of the emission band intensity (hypochromic) and the red-shifting of the wavelength (bathochromic) by $\Delta\lambda$ = 40 nm. In comparison, dihydrogen phosphate and chloride induce bathochromic shifts of 14 nm and 25 nm, respectively. Futhermore, there is a distinct color change from blue to bluish green of the solution upon addition of 2 equivalents of sulfate (Fig. 3). Association constants (K_a) were determined by nonlinear fitting analyses[6] of the titration curves and the results are summarized in Table 1. While there is clearly a preference for sulfate (K_a = 6.4 × 10⁵ M⁻¹) there seems to be no distinguishing preference between other anions. The binding strengths of dihydrogen phosphate, chloride, bromide, acetate and cyanide are comparable to each other ($K_a \approx$ 10³ M⁻¹).[7]

Slow vapor diffusion of hexanes into a 10% (v/v) CH_2Cl_2–EtOAc solution of **1** and tetrabutylammonium sulfate (1 equiv.) provided single crystals suitable for X-ray diffraction analysis. The crystal structure clearly describes the folded structure of **1**·$(Bu_4N^+)_2SO_4^{2-}$ by aromatic stacking of the terminal arms containing the hydroxyl functionalities and the
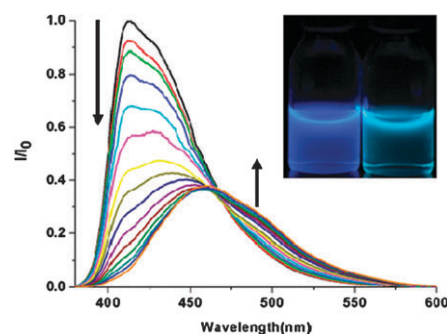

Fig. 3 Fluorescence spectral changes of **1** (1 μM, 10% MeOH–CH₃CN, 298 K) upon addition of $(Bu_4N^+)_2SO_4^{2-}$. Anin complexation induces a color change from blue to bluish-green.

Table 1 Association constants ($K_a \pm 20\%$, M⁻¹) of **1** with anions in 10% v/v CH₃OH / CH₃CN at 298 K

Anion[a]	K_a/M⁻¹	λ_{max}(complex)[c]/nm	$\Delta\lambda_{max}$/nm
SO_4^{2-}	640 000	453	40
$H_2PO_4^-$	3600	427	14
Cl^-	8800	438	25
Br^-	2800	429	16
I^-	<100	428	14
$CH_3CO_2^-$	5700	430	17
CN^-	1600	422	9
N_3^-	790	434	21

[a] Tetrabutylammonium salt. [b] λ_{max} (free) = 413 nm. [c] λ_{max} (complex) determined in the presence of large excess of anions.

subsequent presence of eight total hydrogen bond donors within the helical cavity. The sulfate anion is held by a total of eight hydrogen bonds (6 NH···O and 2 OH···O bonds). We attribute the high binding strength and selectivity for sulfate to arise from the two additional hydrogen bonds from the terminal hydroxyls that point into the binding cavity upon folding. It is of interest to note that the crystal of complex **1**·$(Bu_4N^+)_2SO_4^{2-}$ is a true racemate.[8] In the solid state, individual helices of the complex aggregate to form a higher order architecture in which *M*- and *P*-helices are alternately stacked to afford a racemic compound (Fig. 4). Moreover, tetrabutylammoniums are intercalated in between the aromatic planes of two enantiomeric helices, possibly owing to cation-π bonding interactions with the indolocarbazole surface and/or electrostatic interactions with the cavity bound sulfate ions.

In conclusion, an indolocarbazole foldamer containing NH and OH donor groups has been synthesized. Its efficacy in binding to anions has been demonstrated in solution and in the solid state. The presence of additional hydroxyl OH groups enhances the complementarity of the helical binding cavity of oligomer **1** towards sulfate and is responsible for the high selectivity in binding. This work describes the efficacy of foldamers as selective anion receptors through an induced-fit model, like in proteins and enzymes.
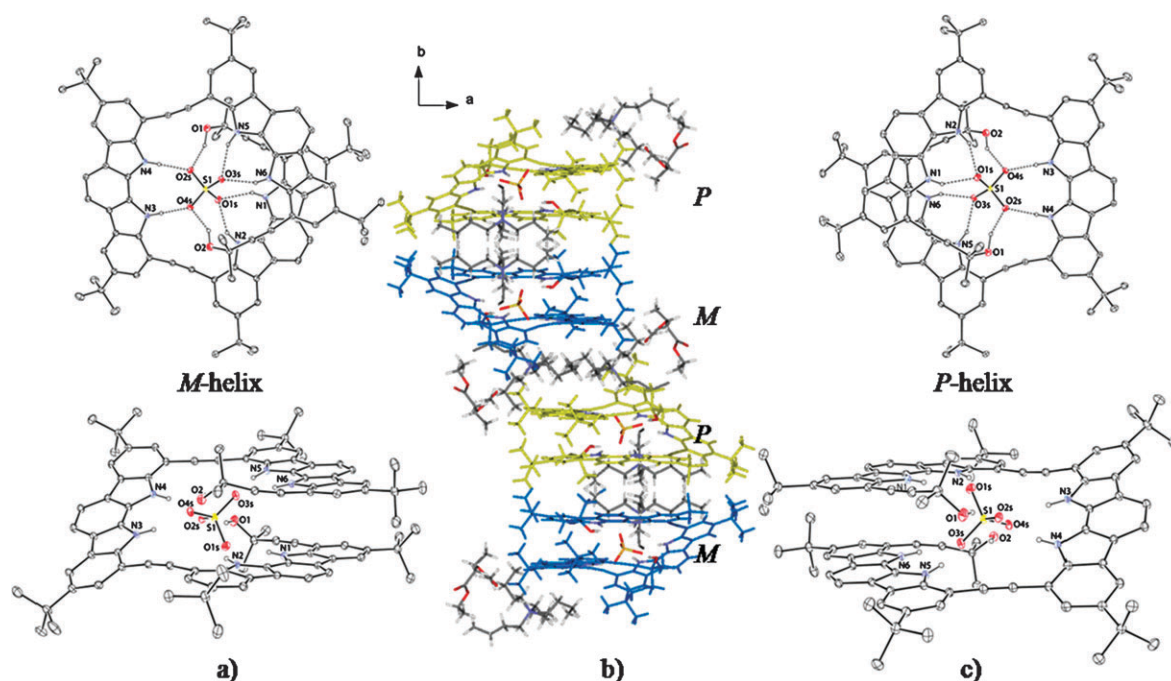
Fig. 4 Crystal structures of complex $\mathbf{1}\cdot(Bu_4N^+)_2SO_4^{2-}$: (a) Top and side views of *M*-helix, (b) the packing structure of $\mathbf{1}\cdot(Bu_4N^+)_2SO_4^{2-}$ showing alternately stacked *P*- and *M*-helices with two sandwiched tetrabutylammoniums, and (c) top and side views of *P*-helix. The dotted lines in the top views of *M*- and *P*-helices represent hydrogen bonds. Displacement ellipsoids in (a) and (c) are scaled to 20% probability level.

Notes and references

‡ Crystal data for [$\mathbf{1}\cdot(Bu_4N^+)_2SO_4^{2-}$]: $C_{136}H_{188}N_8O_{12}S$, fw = 2159.00 g mol^{-1}, monoclinic, space group $P2_1/c$, a = 18.123(4) Å, b = 40.036(8) Å, c = 17.059(3) Å, β = 92.11(3)°, V = 12369(4) Å^3, T = 99(2) K, Z = 4, μ = 0.089 mm^{-1}, 108247 reflections were collected, 30687 were unique [R_{int} = 0.0945]. Refinement of the structure converged at a final R_1 = 0.0829, wR_2 = 0.2193 for 20072 reflections with $I > 2\sigma(I)$; R_1 = 0.1288, wR_2 = 0.2544 for all 30687 reflections. The largest difference peak and hole were 0.881 and − 0.690 e·Å^{-3}, respectively. Details of the crystallographic analyses are provided in the ESI. CCDC 727661.

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