Novel and unexpected one-pot synthesis of 7,7-dioxo-14-oxa-7λ^6-thiadibenzo[*a,j*]anthracene-2,12-disulfonic acid from α-tetralone

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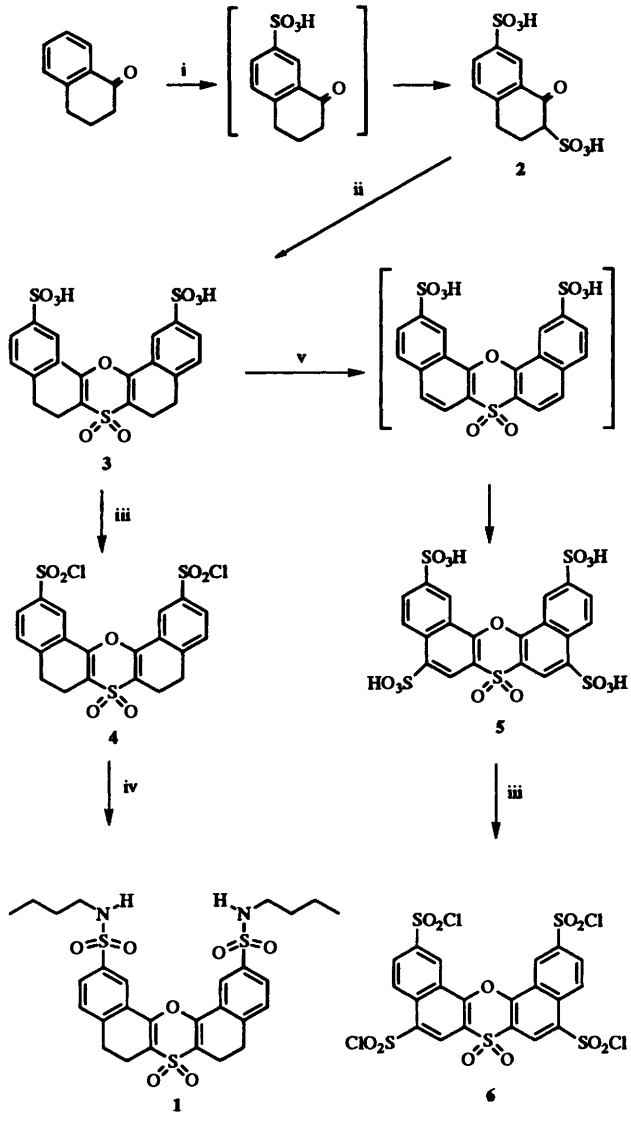
7,7-dioxo-14-oxa-7λ^6-thiadibenzo[*a,j*]anthracene-2,12-disulfonic acid is synthesized from α-tetralone and fuming sulfuric acid. By prolonged treatment, other related polysulfonated compounds are obtained. The course of the reaction has been followed by isolation or detection of intermediates.

An unexpected and quite remarkable reaction is described, which generates a complex structure in one step from a single starting material. This reaction represents an interesting method for the preparation of a class of compounds that are potentially useful as receptors for use in host–guest chemistry. The product's rigid framework, with versatile groups in adequate convergent functionalized positions, is suitable for binding guest molecules.

The starting material is α-tetralone, which when treated with fuming sulfuric acid at 100 °C, through autocondensation of intermediate sulfonated compounds, produces the 7,7-dioxo-5,6,8,9-tetrahydro-14-oxa-7λ^6-thiadibenzo[*a,j*]anthracene structure. By heating at 110 °C, polysulfonated compounds are obtained. Progressive deactivation of the aromatic rings accounts for the tolerance to drastic conditions.

Treatment of α-tetralone with an excess of fuming sulfuric acid for 10 min at room temperature leads to an aromatic monosulfonate compound. This is detected by ^{1}H NMR since it shows a *meta*-coupled proton resonance at δ 8.35 together with other signals overlapping those of the starting material. A longer reaction time under these conditions produces mixtures of products. However, by heating α-tetralone at 100 °C for 15 min, a disulfonate compound, **2**, is isolated. The ^{1}H NMR shows the monosulfonate aromatic ring, and a triplet at δ 4.12 (*J* 5.4 Hz) which is the resonance of a proton geminal to a sulfonic acid group and α to the ketone function.[1] The multiplicity of the signal is in agreement with an axial arrangement between the α-ketone and the sulfonyl group, because otherwise this proton would appear as a double doublet with very different coupling constants. These findings are in concordance with those obtained in molecular modelling studies. Indeed, using COSMIC[2] force field for minimization and Charge-2[3] to compute partial charges, the conformer with the sulfonic group in the axial disposition is 2.3 kcal mol^{-1} more stable than the one with this moiety in the equatorial arrangement.†

When the reaction mixture was kept for 4–5 hours at 100 °C, compound **3** was obtained as the only product. The spectroscopic data are in agreement with this structure. The butylsulfonamide derivative **1** was prepared to ensure that the correct structure had been assigned. Treatment of compound **3** with chlorosulfonic acid at room temperature yielded the chloride **4**, which has an IR absorption at ν_{max} 1650 cm^{-1}. The addition of butylamine to compound **4** produced a compound which, after crystallization from chloroform, appeared as colourless crystals with mp 216 °C in 55% total yield from α-tetralone. This compound, identified as **1**, shows a molecular peak $(M + 1)^+$ at *m/z* 607.2231 in its FAB-HRMS,



Scheme 1 *Reagents and conditions:* i, H_2SO_4 (f), 100 °C, 15 min; ii, 100 °C, 4 h; iii, HSO_3Cl, room temp; iv, $BuNH_2$; v, 110 °C, 2 h

corresponding to a molecular formula of $C_{28}H_{34}O_7N_2S_3$, in agreement with the elemental analysis. No carbonyl group absorptions are observed in the IR spectra of compounds **1**, **3** and **4**.

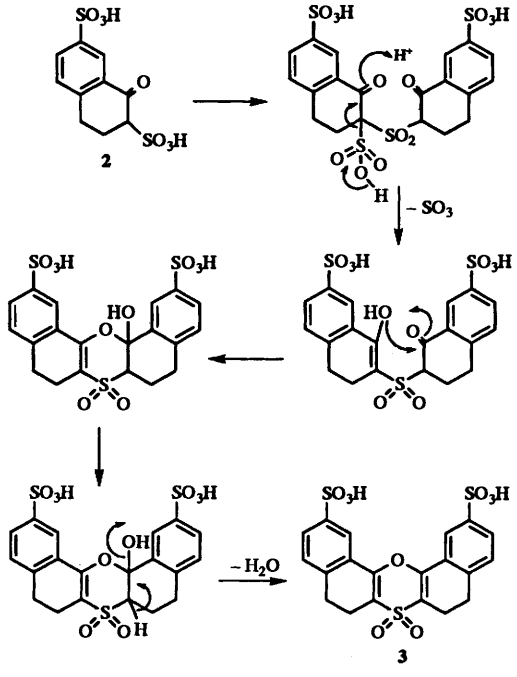
The ^{1}H NMR spectrum of **1** exhibits signals of a trisubstituted monosulfonated aromatic ring (δ 7.39, 7.81 and

† 1 cal = 4.184 J.

8.24), a butylamide moiety, and two coupled methylenes at δ 3.12 and 2.98. In the ^{13}C NMR, apart from the carbons of the butylamide chain, ten different signals were observed, corresponding to the carbons of the original framework of tetralone. Three of them are aromatic methines (δ 129.1, 128.7 and 122.2), another two are aliphatic methylenes (δ 26.5 and 16.7) and a further three correspond to substituted aromatic carbons. The remaining carbons have a tetrasubstituted double bond, attached to a sulfone or ether group; the carbon at δ 113.2 is shielded by the oxygen in the β position and the other is strongly deshielded (δ 147.3) by the α-oxygen and conjugation with the sulfone group. These data allow to propose the structure depicted for **1** in Scheme 1.

When heating in fuming sulfuric acid was continued for a further 1 h at 110 °C, the spectroscopic data revealed the transformation of the methylene groups (δ 3.14 and 2.95) into two double bonds (δ 7.60 and 7.95, 4 H, **AB**, *J* 7.4 Hz), probably due to SO_3 oxidation. (Scheme 1).[4] However, this compound can only be observed as an intermediate because it is readily sulfonated under the reaction conditions; accordingly, the isolated product was the tetrasulfonic acid **5**. Treatment of this with chlorosulfonic acid under the above-mentioned conditions gave the acid chloride **6**, which was characterized.

From these observations a reaction mechanism is postulated (Scheme 2). This comprises, as the first step, the formation of



Scheme 2 Proposed mechanism of the formation of **3** from **2**

the disulfonic acid **2**, one sulfonic group in the aromatic ring and the other α to the carbonyl group. The key step in this reaction is the formation of compound **3**, which must arise from a new sulfonation α to the ketone by the sulfone group of another molecule of **2**, taking into account the fact that only ketone **2** is present in the ^1H NMR spectra at this stage in the reaction. Although the sulfonation of **2** could be reversible, the process would be directed by irreversible formation of the final product **3** by elimination of SO_3, intramolecular cyclization and dehydration in the acidic medium.

The title framework is interesting for molecular recognition purposes because it has a preorganized and rigid structure with a U shape[5] and versatile functional groups which can form hydrogen bonds to bind suitable substrates. We are currently developing receptors with similar structural characteristics.[6] A

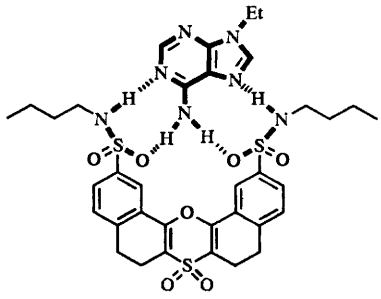


Fig. 1 Proposed structure of the complex of **1** and 9-ethyladenine

preliminary study of the affinity of receptor **1** for 9-ethyl adenine in non polar solvents gave K_s 50 dm^3 mol^{-1} ($CDCl_3$, 298 K). Watson–Crick type hydrogen bonds are probably strong in the complex; however, Hoogsteen type hydrogen bonds are weak (Fig. 1) because they have non linear geometry. This affinity is small in comparison with the large association constants described for other systems.[7] However, the association is promising in view of the poor hydrogen bonding ability of oxygen in the sulfone group and the absence of stacking interactions. We are currently investigating the use of derivatives with this framework for molecular recognition and will report on the results in due course.

Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer (200 MHz and 50.3 MHz) in D_2O (trimethylsilyl [2,2,3,3-$^2H_4$]propionate, TPS as internal standard) or [$^2H_6$]DMSO or $CDCl_3$ [tetramethylsilane (TMS) as internal standard] solutions. Chemical shifts (δ) are reported in ppm and *J* values in Hz. IR spectra were determined on a Beckman 33-IR spectrophotometer. Mass spectra were measured on a VG ANTOSPEC spectrometer. Elemental analyses were carried out using a Perkin-Elmer 240 B Analyser. Sample preparation and evaluation of binding titrations were performed as previously described.[6a]

General procedure

α-Tetralone (1,2,3,4-tetrahydronaphthalen-1-one) (2 g) was added with stirring to fuming sulfuric acid (7 cm^3) cooled to 0 °C and then the mixture was heated at 100 °C for 15 min. An aliquot was added to saturated aqueous sodium chloride affording 1-oxo-1,2,3,4-tetrahydronaphthalene-2,7-disulfonic acid **2** as the disodium salt. A second aliquot was taken after the reaction had been heated at 100 °C for 4–5 h and added to saturated aqueous sodium chloride. The disodium salt of 7,7-dioxo-5,6,8,9-tetrahydro-14-oxa-7λ^6-thiadibenzo[*a*,*j*]-anthracene-2,12-disulfonic acid **3** precipitated from the reaction mixture and was isolated. Further fuming sulfuric acid (2 cm^3) was added to the remaining reaction mixture and heating was continued for 2 h at 110 °C. A further aliquot was removed and the sodium salt of 7,7-dioxo-14-oxa-7λ^6- thiadibenzo[*a*,*j*]-anthracene-2,5,9,12-tetrasulfonic acid **5** was obtained by precipitation under the conditions described above. The reaction mixture was then cooled to room temperature, treated with chlorosulfonic acid (4 cm^3) and left to stand overnight. The solution was then added dropwise to a vigorously stirred mixture of ethyl acetate and ice. The organic layer was separated and dried over Na_2SO_4 and then the solvent was removed to give 7,7-dioxo-14-oxa-7λ^6-thiadibenzo[*a*,*j*]anthracene-2,5,9,12-tetrasulfonyl tetrachloride **6**.

Compound **2**: $\delta_H(D_2O)$ 2.50–2.65 (2 H, m), 3.00 (1 H, tt, *J* 16.4, 5.4), 3.40 (1 H, dt, *J* 16.4, 5.4), 4.12 (1 H, t, *J* 5.4), 7.50

(1 H, d, *J* 8.0), 7.95 (1 H, dd, *J* 8.0, 2.1) and 8.34 (1 H, d, *J* 2.1).

Compound **3**: $\delta_H(D_2O)$ 2.78 (4 H, t, *J* 7.4), 3.05 (4 H, t, *J* 7.4), 7.40 (2 H, d, *J* 7.8), 7.79 (2 H, dd, *J* 7.8, 2.1) and 8.25 (2 H, d, *J* 2.1).

Compound **5**: $\delta_H(D_2O)$ 8.25 (2 H, dd, *J* 8.0, 2.0), 8.47 (2 H, s), 8.80 (2 H, d, *J* 8.0), and 9.00 (2 H, d, *J* 2.0).

Compound **6**: $\delta_H([^2H_6]DMSO)$ 7.24 (2 H, d, *J* 8.8), 8.06 (2 H, s), 8.46 (2 H, s) and 8.61 (2 H, d, *J* 8.8); $\delta_C([^2H_6]DMSO)$ 119.70 (2 C, d), 121.91 (2 C, s), 124.01 (2 C, s), 124.78 (4 C, d), 126.88 (2 C, d), 130.56 (2 C, s), 133.57 (2 C, s), 143.90 (2 C, s) and 150.98 (2 C, s).

7,7-Dioxo-5,6,8,9-tetrahydro-14-oxa-7λ⁶- thiadibenzo[*a*,*j*]-anthracene-2,12-disulfonyl dichloride 4

α-Tetralone (2 g) was treated as above to give compound **3**. The solution of compound **3** was cooled to room temperature and chlorosulfonic acid (4 cm_3) was added to it. The reaction mixture was left to stand overnight and then added dropwise to a vigorously stirred CH_2Cl_2–H_2O mixture. The organic layer was separated, dried over Na_2SO_4 and then the solvent was removed to give the title compound **4**, mp 208 °C (decomp.); ν_{max}/cm^{-1} 1651, 1593, 1462, 1377, 1314, 1283, 1177 and 1138; $\delta_H([^2H_6]DMSO)$ 2.76 (4 H, t, *J* 7.8), 2.99 (4 H, t, *J* 4.5), 7.37 (2 H, d, *J* 7.8), 7.71 (2-H, dd, *J* 7.6, 1.3) and 8.0 (2 H, s); $\delta_C([^2H_6]DMSO)$ 148.32 (2 C, s), 146.66 (2 C, s), 137.74 (2 C, s), 128.13 (2 C, d), 126.20 (2 C, s), 120.28 (2 C, d), 112.36 (2 C, d), 26.03 (2 C. t) and 16.60 (2 C, t).

N,*N*-Dibutyl-7,7-dioxo-5,6,8,9-tetrahydro-14-oxa-7λ⁶-thiadibenzo[*a*,*j*]anthracene-2,12-disulfonamide 1

An excess of butylamine was added to a solution of the above dichloride **4** in ethyl acetate and the solution was stirred for 30 min until the starting material had disappeared (TLC). The excess of butylamine was distilled off at reduced pressure and the residue crystallized in chloroform, yielding the title compound **1** (55% from α-tetralone) as colourless crystals, mp 216 °C (Found: C, 55.4; H, 5.6; N, 4.6. $C_{28}H_{34}N_7O_2S_3$ requires: C, 55.43; H, 5.65; N, 4.62%); $\delta_H(CDCl_3)$ 0.86 (6 H, t, *J* 7.4), 1.26–1.37 (4 H, m), 1.49–1.56 (4 H, m), 2.94–3.04 (8 H, m), 3.10–3.15 (4 H, brt), 5.13 (2 H, NH), 7.39 (2 H, d, *J* 7.8), 7.81 (2 H, dd, *J* 7.8, 2) and 8.24 (2 H, d, *J* 2); $\delta_C(CDCl_3)$ 13.4 (2 C, q), 16.7 (2 C, t), 19.5 (2 C, t), 26.5 (2 C, t), 31.7 (2 C, t), 43.1 (2 C, t), 113.2 (2 C, s), 122.2 (2 C, d), 127.6 (2 C, s), 128.7 (2 C, d), 129.1 (2 C, d), 139.9 (2 C, s), 140.8 (2 C, s) and 147.3 (2 C, s).

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