Bile Acid Based Semi-rigid Molecular Tweezers

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The easily constructed bile acid-based semi-rigid molecular tweezer **2** binds guest **8** in chloroform with an association constant of 83 dm^3 mol^{-1}.

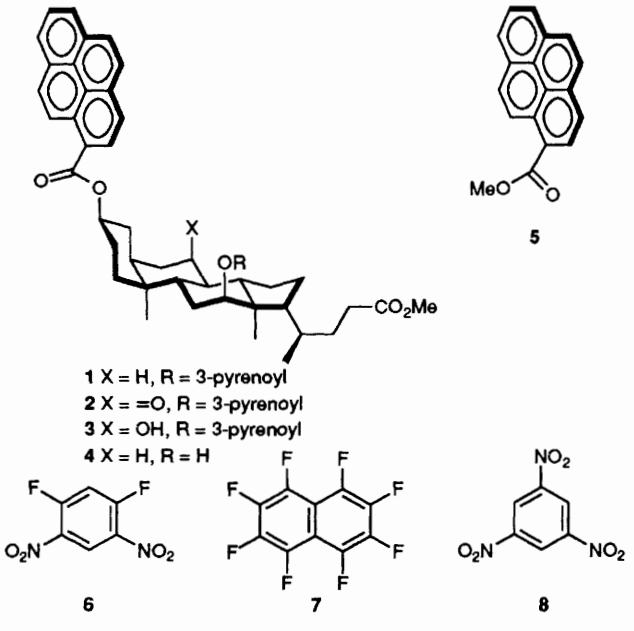
A class of molecular hosts,[1] popularly known as molecular tweezers, have been developed by Whitlock,[2] and by Zimmerman.[3] Whereas the Whitlock tweezers were flexibile, the tweezers synthesized by Zimmerman were much more rigid, and showed exceptionally high association constants with guests such as 9-alkylated adenines. In spite of the success of the Zimmerman approach, variation of the electron density of the aromatic arms presented considerable synthetic effort. We have chosen a modular approach for the construction of semi-rigid systems where 'sticky' arms could be attached to a template through appropriate spacers by a simple reaction.

Bile acids were selected as templates for the construction of new molecular tweezers.[4] Analysis of the PCMODEL† minimized structures of cholic, 7-deoxycholic and 7-ketocholic acids revealed that the hydroxy groups at the 3- and the 12-positions are *ca.* 5.9–6.2 Å apart (O···O distance). The two C–O vectors are, however, not exactly parallel; rather, they diverge away from the steroid. This suggested that the attachment of two large and flat aromatic surfaces to these two hydroxy groups will lead to the formation of a deep cleft thereby generating a new class of molecular tweezers in which structural variations could be accomplished in a straightforward manner. Many relative orientations of the two aromatic units are possible, but preliminary MACROMODEL calculations‡ indicated the existence of a family of low energy conformers in which two covalently attached pyrene units were approximately parallel. In addition to the cleft, the presence of the 7-hydroxy group in cholic acid offers attractive possibilities for further manipulations such as the linking of additional binding or catalytic groups.

Methyl deoxycholate was converted in one step to compound **1** by acylation with pyrene-3-carboxylic acid chloride.§ Compound **2** was prepared by acylating methyl 7-ketocholate. Compound **3** was conveniently obtained by a simple $NaBH_4$ reduction of **2**. Compound **4** was also prepared as a control. Binding studies with **1–3** in $CDCl_3$ were carried out by NMR titration.[5] We found that only electron deficient aromatics, such as **6**, **7** and **8**, bind to these hosts. A variety of other electroneutral or electron rich aromatics showed no binding. A control experiment using 1 equiv. each of **4** and **5** indicated that there was no significant binding, thereby confirming that the two pyrene rings in compounds **1–3** were acting synergistically. Analysis of the difference spectrum of **2** with **8** showed a weak tailing absorption beyond 400 nm indicating a charge transfer band.

The association constants are listed in Table 1, along with calculated O(3)···O(7) distances for parent steroids. It appears that the association constants for compounds **7** and **8** with hosts **1–3** show a trend when compared with the calculated distances between the two oxygen atoms. We believe that this is the *first* receptor system where a subtle change in the distance of separation of the two binding surfaces has been achieved through a remote substituent effect.

UV–VIS spectroscopic studies on compounds **1–5** indicated that the the two pyrene moieties of compounds **1–3** do not



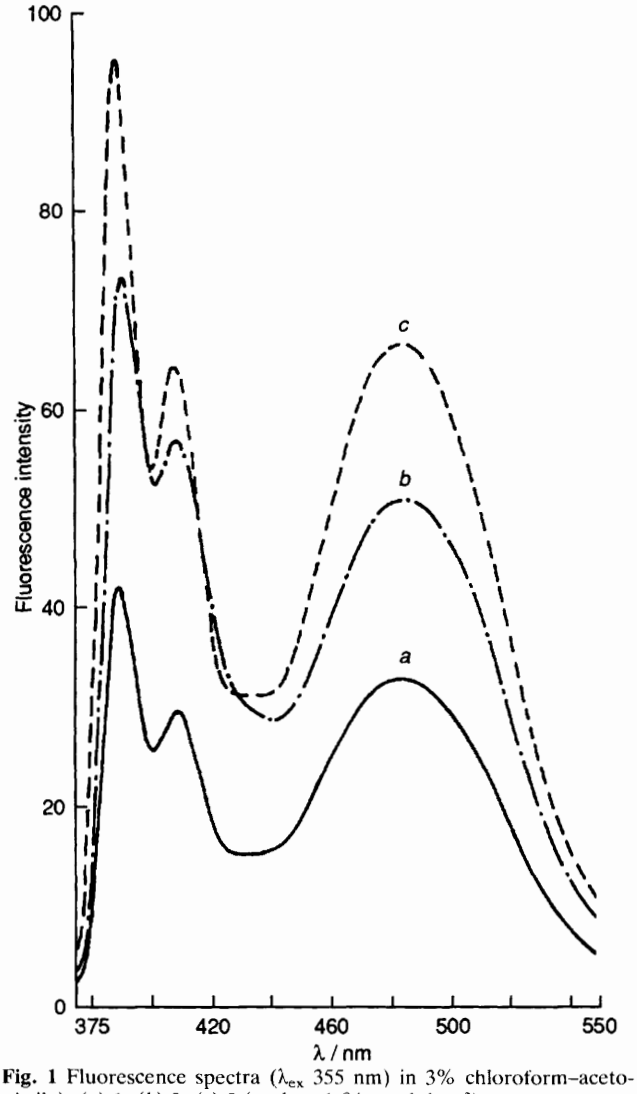


Fig. 1 Fluorescence spectra (λ_{ex} 355 nm) in 3% chloroform–acetonitrile): (*a*) **1**, (*b*) **2**, (*c*) **3** (each at 1.04 μmol dm^{-3})

interact in the ground state. However, the emission behaviour of compounds **1–3** are rather different when compared to that of **4** and **5**. The most remarkable feature is the presence of a strong intramolecular excimer emission (Fig. 1). A control experiment using 1 equiv. each of **4** and **5** showed no excimer emission (Fig. 2). It is noteworthy that the fluorescence spectrum of **1** in the presence of guest **7** showed an *increase* in the monomer emission, as well as quenching of the guest fluorescence (Fig. 3). Under identical conditions the control experiment showed quenching, but no significant change in the fluorescence intensity of the pyrene units (Fig. 4).

Geometric feasibility towards the formation of an intramolecular excimer is supported by INSIGHTII calculations, which shows that in one of the low energy conformations (Fig. 5) the Van der Waals surfaces of the two pyrene rings are almost in contact.

Table 1 Association constants in $CDCl_3$ at 25 °C

	K_a/dm^3 mol^{-1}			
Host	**8**	**7**	**6**	O(3)···O(12)/Å
2	83	19	8	6.08
1	65	15	7	6.15
3	47	11	6	6.22

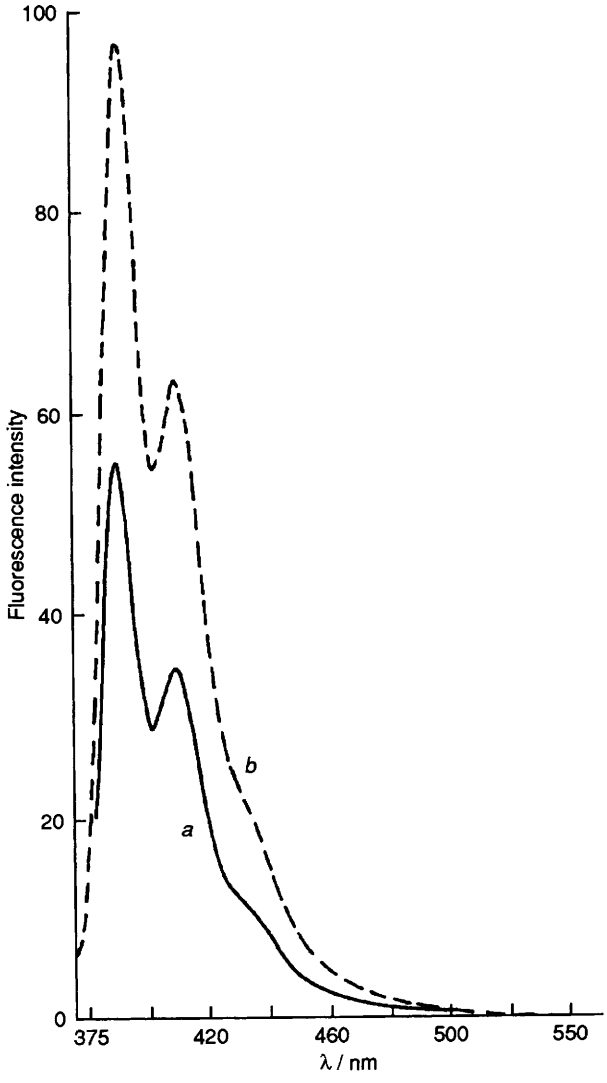


Fig. 2 Fluorescence spectra (λ_{ex} 355 nm) in 3% chloroform–acetonitrile: (*a*) 1.04 μ mol dm^{-3} **4**; (*b*) **4** plus **5** (each at 1.04 μmol dm^{-3})

It should be possible to transform these novel bile acid based molecular tweezers into more effective complexing agents through the incorporation of an additional binding site attached to C-7 of compound **3**. The chiral surface of the

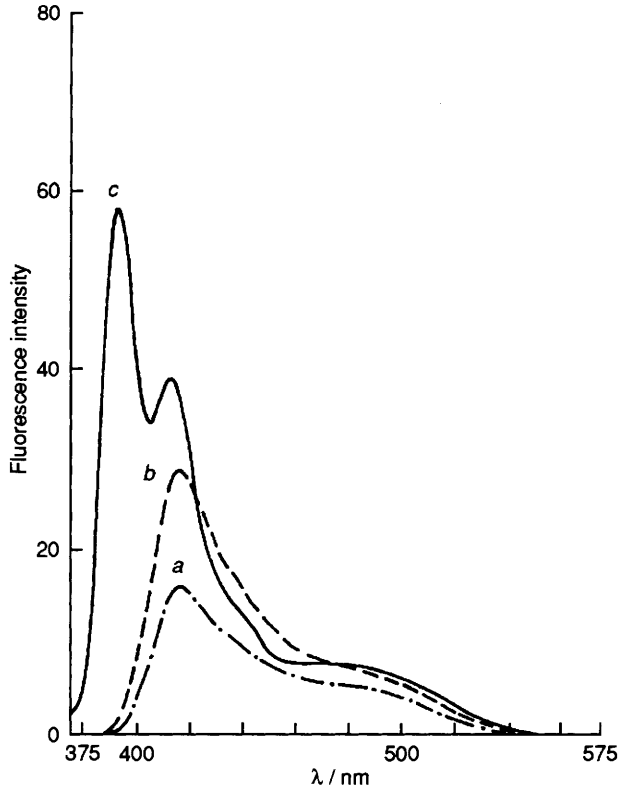


Fig. 3 Fluorescence spectra (λ_{ex} 355 nm) in chloroform: (*a*) 0.67 mmol dm^{-3} **1**; (*b*) 0.67 mmol dm^{-3} **1** with 33 mmol dm^{-3} **7**; (*c*) 33 mmol dm^{-3} **7**

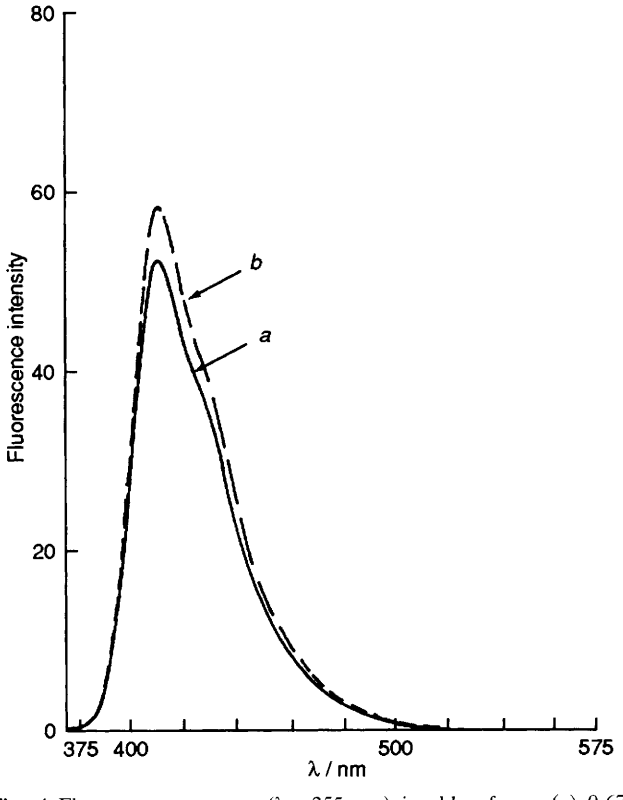


Fig. 4 Fluorescence spectra (λ_{ex} 355 nm) in chloroform: (*a*) 0.67 mmol dm^{-3} each of **4** and **5**, (*b*) 0.67 mmol dm^{-3} each of **4** and **5** plus 33 mmol dm^{-3} of **7**

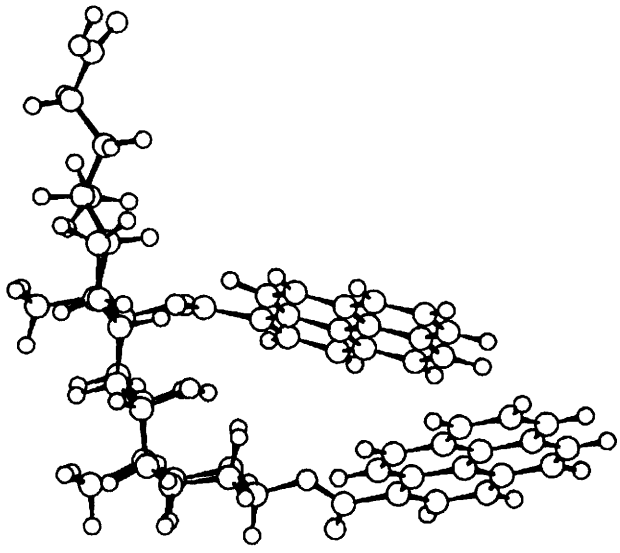


Fig. 5 INSIGHTII minimized structure of compound **3** (in the free acid form) is shown in ball and stick representation. The VA09A forcefield in the DISCOVER module was used for the minimization.

steroid could also be utilized for enantioselective recognition. Moreover, the coupling of these molecular tweezers to polymeric supports[6] through the sidechain, or, modifying the sidechain to impart partial water solubility would lead to receptors capable of taking advantage of the hydrophobic interaction as well for binding. Many of these possibilities, as well as growing single crystals of host–guest complexes are now being examined in our laboratory, and the results of these investigations will be reported in due course.

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Footnotes

† PCMODEL is available from Serena Software, Bloomington, USA.

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§ *Representative procedure and data* for **1**: A mixture of methyl 7-deoxycholate (0.40 g), CaH_2 (0.124 g), $Bu^n_4N^+I^-$ (0.055 g) and 3-pyrenoyl chloride (0.573 g) in dry toluene (5 ml) was refluxed for 24 h. Aqueous workup followed by purification by column chromatography afforded **1** in 86% yield (0.73 g). Mp 183–184 °C; $[\alpha]_D^{21}$ = +137 (*c* 1.90 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, $SiMe_4$): δ 9.12 (d, 1H, *J* = 9.4 Hz), 8.95 (d, 1H, *J* = 9.4 Hz), 8.580 (d, 1H *J* = 8.0 Hz), 8.20 (t, 2H, *J* = 4.4 Hz), 8.14 (d, 1H, *J* = 7.5 Hz), 8.12 (d, 1H, *J* = 6.9 Hz), 8.07 (d, 1H, *J* = 8.07 Hz), 8.04 (d, 1H, *J* = 8.1 Hz), 7.97 (d, 2H, *J* = 4.8 Hz), 7.89 (t, 2H, *J* = 8.8 Hz), 7.81 (d, 1H, *J* = 9.4 Hz), 7.75 (d, 1H, *J* = 7.5 Hz), 7.68 (d, 1H, *J* = 8.9 Hz), 7.60 (t, 1H, *J* = 7.6 Hz), 7.47 (d, 1H, *J* = 8.1 Hz), 5.63 (s, 1H, 12-H), 5.15 (m, 1H, 3-H), 3.61 (s, 3H, OMe), 2.43–1.14 (m, steroidal CH and CH_2), 1.07 (s, 3H, 18-H), 0.997 (d, 3H, *J* = 6.5 Hz, 21-H), 0.945 (s, 3H, 18-H); UV/VIS (6% $CHCl_3$–Me_3CN): λ_{max} (log ε): 349 (4.63), 279 (4.70), 243 (4.93); HRMS: Found *m/z* 862.4226; calc. for $C_{59}H_{58}O_6$, 862.4233.

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5 R. S. Macomber, *J. Chem. Educ.*, 1993, **69**, 375. The program shown in Table 2 of this paper has some typographical errors.

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