Fluorescence Quenching in 2-(2'-Pyridyl)indoles as a Direct Probe of Host–Guest Binding in Hydrogen-bonded Complexes

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The formation of a cyclic hydrogen-bonded complex between 2-(2'-pyridyl)indoles and amide-containing guests leads to quenching of the host fluorescence which provides a direct and sensitive probe of binding.

There has been considerable recent interest in the investigation of host–guest systems based on hydrogen-bonding interactions. Taking a cue from nature in which these interactions are integral to the structure and function of many vital biomolecules, H-bonding effects are being utilized to construct elaborate two- and three-dimensional assemblies,[1] to sequester a wide variety of substrates,[2] and to design systems potentially capable of self-replication.[3]

The quantitative evaluation of receptor–substrate binding generally focusses on a physical property of the host or guest which varies as a function of the degree to which these two species associate. For neutral organic molecules the most widely employed analytical method is NMR titration. This method has been critically evaluated and several weaknesses have come to light.[4] The concentration range over which measurements can be made is somewhat limited, normally being in the range of 10^{-2} to 10^{-3} mol dm^{-3}. Deuteriochloroform is most often the solvent of choice. Other solvents are less practical from the standpoint of both economy and residual proton signal. Finally, NMR analysis is not amenable to many routine analytical applications and would be inconvenient for use in a continuous sensor.

An attractive alternative to NMR is fluorescence quenching which would allow a broader range of economical solvents, a much lower concentration range, and adaption to routine sensor technology. Although this technique has been applied to tryptophan luminescence in biological systems,[5] it has only recently been used to monitor binding in synthetic host–guest systems. Generally these applications have involved the incorporation of a fluorophore into the host or guest as a reporter of the binding.[6] The involvement of an appended fluorophore raises a new set of problems such as possible involvement of the fluorophore in the binding process. A recent study on a receptor for barbituates containing two pyrene appendages illustrates this point. The system shows monomer and excimer emission, both of which are affected to different degrees and sometimes in opposite directions by different guests.[7]

We are thus prompted to report a simple hydrogen-bonding host system in which the *host itself* is an effective fluorophore and the association phenomenon can be directly assessed by modulation of its emission properties. We have prepared the series of 2-(2'-pyridyl)indoles **1a–1e** by Fischer cyclization of the phenylhydrazones derived from the corresponding pyridyl ketones.[8] These species behave in a manner analogous to the closely related pyrido[3,2-*g*]indoles **2** which we have earlier reported to be excellent receptors for amide-containing substrates, especially ureas.[9] Both **1** and **2** exhibit strong fluorescence in the range 370–420 nm in dichloromethane. Unfortunately 2-substituted derivatives of **2** do not appear to be photostable and repetitive emission scans of a dilute solution show a monotonic decrease in the fluorescence intensity.

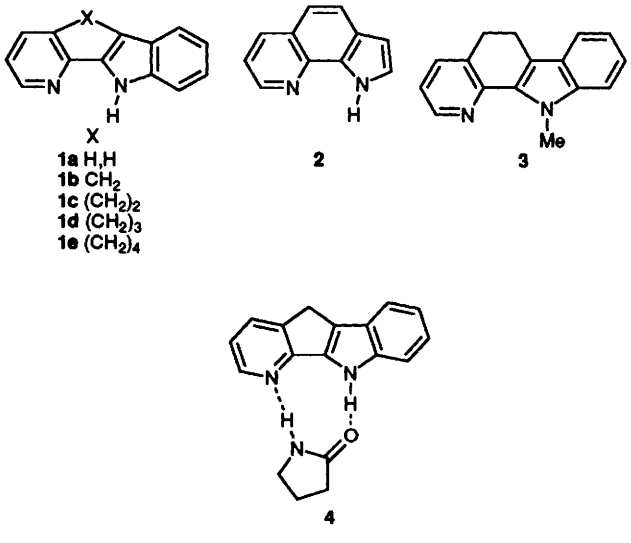
Host **1**, on the other hand, is photostable and the addition of guests capable of forming a cyclic H-bonded complex such as **4** causes strong quenching of the emission.[10] The quenching data for the interaction of **1e** with butyrolactam is shown in Fig. 1 and the association constants for **1a–1e** with *n*-butanol and butyrolactam are collected in Table 1.

When the emission intensities illustrated in Fig. 1 are plotted against butyrolactam concentration saturation behavi-

Table 1 Association constants and estimated dihedral angles for 3,3'-polymethylene-2-(2'-pyridyl)indoles

Host[a]	Bridge (X)	Dihedral Angle[b]/°	K_a(*n*-butanol)/ dm^3 mol^{-1}	K_a(butyrolactam)/ dm^3 mol^{-1}
1a	H, H		10.7	4.6
1b	CH_2	0	16.5	18.8
1c	$(CH_2)_2$	13	12.4	11.0
1d	$(CH_2)_3$	0/41[c]	8.6	4.9
1e	$(CH_2)_4$	52	3.5	3.2

[a] [Host] = 3.4–17.2 × 10^{-7} mol dm^{-3} in CH_2Cl_2; T = 25 °C. [b] Estimated using the programs PC MODEL and MMX from Serena Software, Bloomington, Indiana, USA. [c] Two approximately equal energy minima were located.



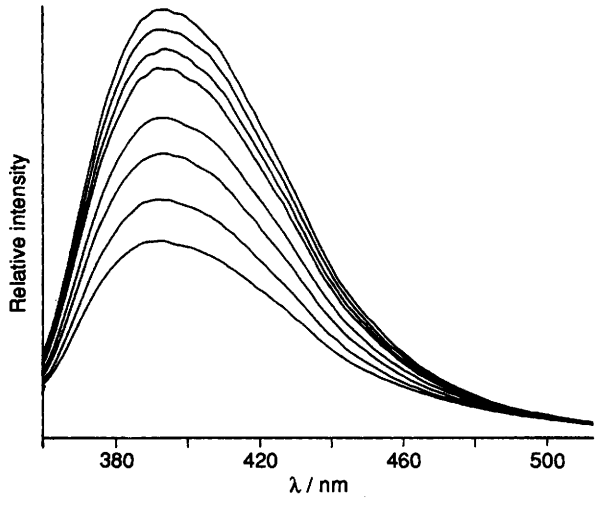


Fig. 1 Emission spectra of **1e** (1.72 × 10^{-6} mol dm^{-3} in CH_2Cl_2) in the presence of increasing amounts of butyrolactam (0–1.0 mol dm^{-3} top to bottom)

our is evidenced and a least-squares analysis of the data according to the method of Horman and Dreux provides a K_a value of 3.2 dm^3 mol^{-1}. Lower homologues of **1e** show stronger binding constants which may be related in an approximately linear fashion to the estimated dihedral angle between the indole and pyridine rings in **1** as governed by the 3,3′-polymethylene bridge. Very similar guest behaviour is evidenced by *n*-butanol which shows binding constants in the range 3.5–16.5 dm^3 mol^{-1}.

The importance of cyclic hydrogen bonding as depicted by structure **4** was tested by treatment of the *N*-methylindole **3** (8×10^{-7} mol dm^{-3}) in dichloromethane with up to 0.17 mol dm^{-3} butyrolactam. This indole is incapable of forming a complex such as **4** and no quenching whatsoever was observed.

It is noteworthy that two minimum energy conformations are located for **1d** with dihedral angles of approximately 0 and 41°. The planar conformation would have a more pinched geometry which would be less favourable for the formation of a cyclic complex similar to **3** and thus we assume that the less planar form makes a more significant contribution to binding.

The monomethylene-bridged host **1b** forms the strongest complex due to its planarity as well as its more open bite. We therefore chose this system to evaluate binding with other simple amide guests including urea itself which showed a K_a = 940 dm^3 mol^{-1}. Owing to its poor solubility in non-polar solvents, a direct measurement of urea binding has not previously been possible. Other related amides were also evaluated with host **1b**: imidazolidone (K_a = 41 dm^3 mol^{-1}), trimethylene urea (K_a = 18 dm^3 mol^{-1}), oxazolidone (K_a = 23 dm^3 mol^{-1}), and barbital (K_a = 170 dm^3 mol^{-1}). These results are consistent with earlier NMR titrations based on binding with a pyridoindole similar to **2**.[11]

It should be noted that this behaviour does not extend to aromatic guests such as phenol. These species are capable of quenching the indole fluorescence *via* bimolecular energy transfer which need not involve host–guest association. Thus the method is limited to guests which do not exhibit electronic overlap with the host.

We are continuing to exploit this very useful method both in terms of substrate specificity and technological application.

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