

## Electrophilic Heteroaromatic Substitutions: Reactions of 5-X-Substituted Indoles with 4,6-Dinitrobenzofuroxan

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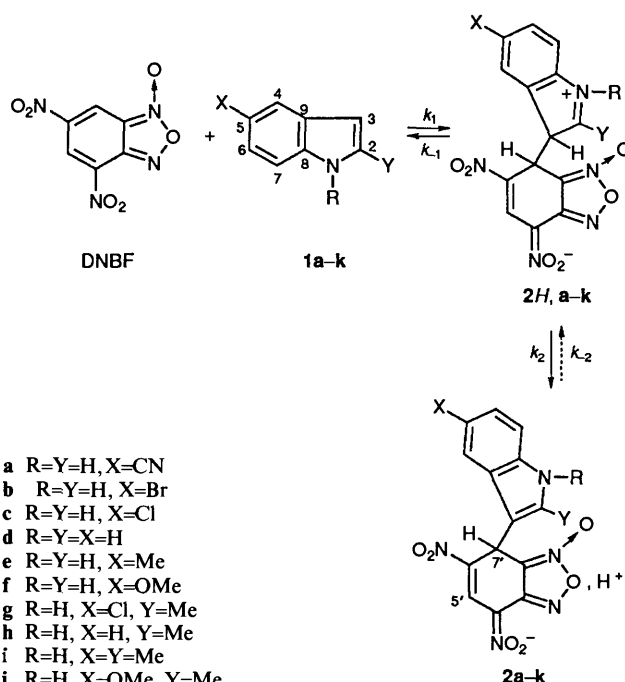
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The S<sub>E</sub>Ar substitutions of a number of 5-X-substituted indoles (**1a-f**), 5-X-substituted 2-methylindoles (**1g-j**) and *N*-methylindole (**1k**) by 4,6-dinitrobenzofuroxan (DNBF) have been kinetically studied in 70–30 (v/v) H<sub>2</sub>O–Me<sub>2</sub>SO, 50–50 (v/v) H<sub>2</sub>O–Me<sub>2</sub>SO, methanol and acetonitrile. The absence of a significant dependence of the rates of reactions on the hydrogen or deuterium labelling at C-3 of the indole ring indicates that electrophilic attack ( $k_1^{\text{DNBF}}$ ) by DNBF at this position is the rate-limiting step of the substitutions. However, the  $k_1^{\text{DNBF}}$  rate constants are strongly sensitive to the solvent polarity, the observed reactivity sequence being 70–30 H<sub>2</sub>O–Me<sub>2</sub>SO > 50–50 H<sub>2</sub>O–Me<sub>2</sub>SO > methanol > acetonitrile. This trend is consistent with a highly dipolar transition state where the development of negative charge in the DNBF moiety is concomitant with that of a partial positive charge on the indole nitrogen. The finding of relatively large negative  $\rho$  values (–3.85) for the Hammett plots  $\log k_1^{\text{DNBF}} = f(\sigma_x^+)$  supports this idea. An interesting result is that the effect of the X substituent on the rates ( $k_1^{\text{DNBF}}$ ) is the same in the four solvents studied and does not depend upon the substitution at C-2 of the indole ring. However, the Brønsted or Hammett lines for the 5-X-2-methylindoles are located about 1.5 log *k* unit below those for the 5-X-indoles in a given solvent, showing that the 2-methyl group causes significant steric hindrance to the approach of DNBF from the adjacent C-3 position. Rates of protiodetritiation of a large number of [3-<sup>3</sup>H]indoles have also been measured in aqueous solution. The data define a unique Brønsted line ( $\beta_{\text{NH}} = 0.65$ ), implying that the 2-substituents do not exert any steric effect on the rates of the exchange process and suggesting that the correlation can be used to estimate unknown p*K*<sub>a</sub> values of indoles with a free 3-position. Comparison of the rates of coupling of indoles with 4,6-dinitrobenzofuroxan with similar data for coupling of these heterocycles with *p*-nitrobenzenediazonium cation reveals that, despite its neutral character, DNBF is the most electrophilic species. DNBF also appears to be a much stronger electrophile than the proton.

Electrophilic aromatic substitution in benzenoid systems has been extensively studied, especially in the case of nitration and halogenation.<sup>1–4</sup> Electrophiles which have been investigated in such processes range widely from the proton to more complex species like benzenediazonium cations.<sup>1,5–7</sup> The latter in particular have yielded valuable information concerning mechanisms, especially the nature of the rate-determining step and the formation of the  $\sigma$ -complex intermediates. In recent years, many studies have concentrated on pyrroles and indoles since these  $\pi$ -excessive heteroaromatics are much stronger carbon bases than simple benzene derivatives and lead to  $\sigma$ -complex intermediates of greater stability.<sup>8–18</sup> Studies reported in this area include direct protonation as well as tritium or deuterium isotopic exchange in acid media, and diazocoupling.

In our laboratories, we have recently discovered that 4,6-dinitrobenzofuroxan (DNBF) and related heteroaromatics act as extremely strong neutral electrophiles in various processes, including addition to weak carbon bases like 1,3,5-trimethoxybenzene, phenols, anilines and related aromatic amines, as well as a number of pyrroles and indoles.<sup>19–25</sup> In the present paper, we report on the results of a kinetic investigation of the reactions of DNBF with a number of 5-X-substituted-indoles (**1a-f**), 5-X-substituted 2-methylindoles (**1g-j**) and *N*-methylindole (**1k**), to give the very stable C-adducts **2a-k** in various solvents according to eqn. (1). This study provides convincing evidence that neutral DNBF is a stronger electrophile than positively charged species like benzenediazonium cations or the proton in electrophilic aromatic substitution processes.

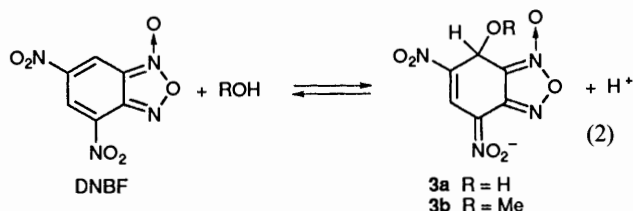


- a R=Y=H, X=CN
- b R=Y=H, X=Br
- c R=Y=H, X=Cl
- d R=Y=X=H
- e R=Y=H, X=Me
- f R=Y=H, X=OMe
- g R=H, X=Cl, Y=Me
- h R=H, X=H, Y=Me
- i R=H, X=Y=Me
- j R=H, X=OMe, Y=Me
- k R=Me, X=Y=H
- l R=X=Me, Y=H
- n R=Y=Me, X=OMe
- o R=X=Y=Me

## Results

Because of the low solubility of **1a-k** in aqueous solution, we have investigated the kinetics of reactions (1) at 25 °C under pseudo-first-order conditions with respect to the indole reagent as the excess component in two aqueous dimethyl sulfoxide mixtures, namely 70–30 and 50–50 (v/v) H<sub>2</sub>O–Me<sub>2</sub>SO and two non-aqueous solvents, namely methanol and acetonitrile.

As previously reported, DNBF has a strong tendency to react according to eqn. (2) in aqueous or methanolic solution.<sup>21</sup> The  $pK_a$ s for the formation of the hydroxy adduct **3a** are equal to 3



and 2.7 at 25 °C in 70–30 and 50–50 (v/v) H<sub>2</sub>O–Me<sub>2</sub>SO, respectively,<sup>21a</sup> while the  $pK_a$  for the formation of the methoxy adduct **3b** is equal to 6.46 at 20 °C in methanol.<sup>21b</sup> To avoid any interference between eqns. (1) and (2), our experiments were conducted at low pH in these solvents. In 70 and 50% aqueous Me<sub>2</sub>SO, 0.2 or 0.1 mol dm<sup>-3</sup> HCl solutions of DNBF ( $\approx 5 \times 10^{-5}$  mol dm<sup>-3</sup>) were mixed with equal volumes of various solutions of **1a-k** ( $10^{-3}$ – $1.5 \times 10^{-2}$  mol dm<sup>-3</sup>) in a stopped-flow apparatus; the final ionic strength was maintained at 0.1 mol dm<sup>-3</sup> by addition of KCl as needed. Similarly,  $2 \times 10^{-3}$  or  $10^{-3}$  mol dm<sup>-3</sup> methanesulfonic acid solutions of DNBF were mixed with the appropriate solutions of **1a-k** in methanol, not correcting, however, for the changes in the final ionic strength. In acetonitrile solutions, neutral DNBF solutions were directly mixed with the indole solutions. In all experiments, only one relaxation time corresponding to the quantitative formation of the adducts **2a-k** ( $\lambda_{\text{max}} \approx 480$  nm) was observed.

Based on eqn. (1), the general expression for the observed first-order rate constant,  $k_{\text{obsd}}$ , for the formation of the adducts **2a-k**, as derived under the assumption that the zwitterions 2H are low concentration ('steady-state') intermediates, is given by:

$$k_{\text{obsd}} = \frac{k_1 k_2}{k_{-1} + k_2} [\mathbf{1a-k}] = k [\mathbf{1a-k}] \quad (3)$$

In accordance with eqn. (3), excellent straight lines with zero intercepts were obtained in all cases when the  $k_{\text{obsd}}$  values were plotted *vs.* the indole concentration, with no evidence for a pH dependence of the rates (Fig. 1). While confirming the absence of reaction (2), the latter result also shows that protonation at C-3 of the indole reagents was not interfering appreciably with the complexation under our experimental conditions.<sup>26</sup> Determination of the second-order rate constant  $k$  from the slopes of the  $k_{\text{obsd}}$  *vs.*  $[\mathbf{1a-k}]$  plots was therefore straightforward in the different solvents studied. The results are summarized in Table 1 which also includes some rate constants  $k$  obtained from experiments conducted under similar experimental conditions with 3-deuterated indoles. The corresponding  $k_{\text{H}}/k_{\text{D}}$  ratios range from  $1.1 \pm 0.1$  (e.g.  $k_{\text{H}}/k_{\text{D}} = 1.00$  for 5-cyanoindole in 70–30 and 50–50 H<sub>2</sub>O–Me<sub>2</sub>SO) to  $1.6 \pm 0.1$  (e.g.  $k_{\text{H}}/k_{\text{D}} = 1.71$  for 5-methoxyindole in acetonitrile).

For completeness and for the purpose of comparison of the electrophilic reactivities of DNBF and the proton, rates of tritium displacement at 25 °C from the 3-position of a number of indoles were measured under pseudo-first-order conditions with respect to the H<sup>+</sup> concentration in various aqueous HCl

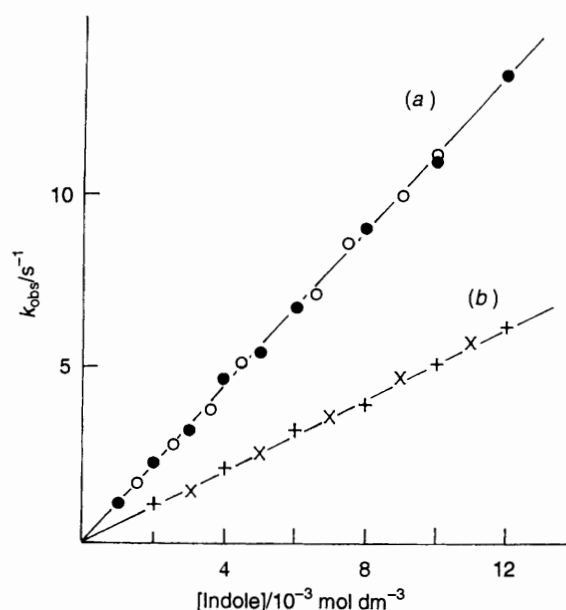
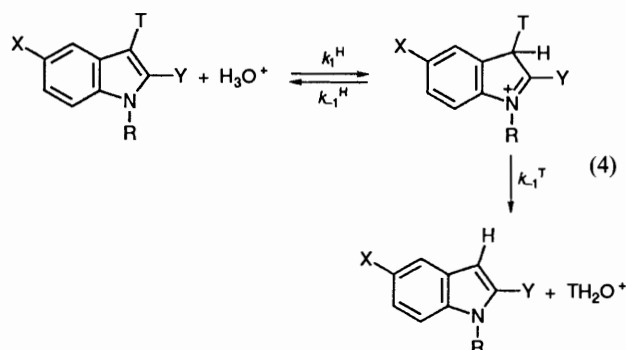


Fig. 1 Influence of indole concentration and pH on the observed first-order rate constant  $k_{\text{obsd}}$  (eqn. 3) for addition of DNBF in 70% H<sub>2</sub>O–30% Me<sub>2</sub>SO {Indole, (a); (●) [H<sup>+</sup>] = 0.10 mol dm<sup>-3</sup>; (○) [H<sup>+</sup>] = 0.05 mol dm<sup>-3</sup>} and methanol {2-methylindole, (b); (×) [H<sup>+</sup>] = 0.001 mol dm<sup>-3</sup>; (+) [H<sup>+</sup>] =  $5 \times 10^{-4}$  mol dm<sup>-3</sup>} ( $T = 25$  °C)

solutions. As previously discussed by various authors,<sup>6–10</sup> such displacements occur as described in eqn. (4) with the observed rate constant,  $k_{\text{obsd}}$ , being given by eqn. (5). Table 2 gives the values of the second-order rate constants,  $k_{\text{exch}}$ , which were readily deduced from the slopes of the linear plots  $k_{\text{obsd}}$  *vs.* [H<sub>3</sub>O<sup>+</sup>] (Fig. 2). It is noteworthy that our  $k_{\text{exch}}$  values for detritiation of indole and 2-methylindole agree satisfactorily with previous determinations by Challis and Long.<sup>7b,8</sup>



$$k_{\text{obsd}} = \frac{k_1^{\text{H}}[\text{H}_3\text{O}^+]}{1 + k_{-1}^{\text{H}}/k_{-1}^{\text{T}}} = k_{\text{exch}}[\text{H}_3\text{O}^+] \quad (5)$$

## Discussion

**General Features.**—The indoles **1a-k** have  $pK_a$  values which range from +0.26 for the most basic derivative, *i.e.* 2,5-dimethylindole, to –6.00 for the less basic compound, *i.e.* 5-cyanoindole.<sup>26</sup> All of these compounds, however, react readily with DNBF, giving quantitatively the  $\sigma$ -adducts **2a-k** which are essentially insensitive to decomposition by strong acids (2 mol dm<sup>-3</sup> H<sub>2</sub>SO<sub>4</sub>). This behaviour emphasizes the extremely high electrophilic character of DNBF which appears capable of reacting with carbon bases of  $pK_a \sim -6$ . For comparison, similar couplings of neutral indoles with 1,3,5-trinitrobenzene

**Table 1** Second-order rate constants  $k (= k_1)$  for DNBF addition to indoles **1a–k** in aqueous Me<sub>2</sub>SO mixtures, methanol and acetonitrile<sup>a</sup>

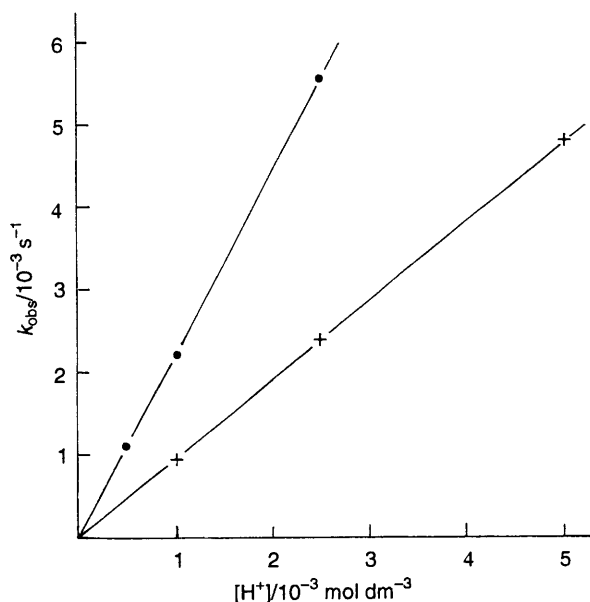
Indole	$pK_a^{H_2O}$	70–30 (v/v) H <sub>2</sub> O–Me <sub>2</sub> SO <sup>b</sup> $k_1/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	50–50 (v/v) H <sub>2</sub> O–Me <sub>2</sub> SO <sup>b</sup> $k_1/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	CH <sub>3</sub> OH $k_1/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	CH <sub>3</sub> CN $k_1/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
5-cyanoindole	<b>1a</b> –6.00 <sup>c</sup>	2.8	1.14	$1.63 \times 10^{-2}$	$3.5 \times 10^{-3}$
	<b>1a–d</b>	2.79	1.13	$1.46 \times 10^{-2}$	$2.38 \times 10^{-3}$
5-bromoindole	<b>1b</b> –4.57, –4.30 <sup>c</sup>	125	46.2	0.885	0.15
5-chloroindole	<b>1c</b> –4.53 <sup>d</sup>	125.5	52	0.975	0.158
indole	<b>1d</b> –3.46 <sup>d</sup>	1 110	555	16	1.96
	<b>1d–d</b>	940	500	11.5	1.20
5-methylindole	<b>1e</b> –3.30 <sup>d</sup>	5 000	2 100	67	9.4
5-methoxyindole	<b>1f</b> –2.90 <sup>c</sup>	5 260	2 613	71	24
	<b>1f–d</b>	4 260	2 140	43	14
5-chloro-2-methylindole	<b>1g</b> –1.30	1 586	880	57	10.8
2-methylindole	<b>1h</b> –0.28 <sup>d</sup>	21 000	9 900	510	99
	<b>1h–d</b>	19 900	9 650		
2,5-dimethylindole	<b>1i</b> +0.26 <sup>d</sup>	94 000	42 400	1 850	250
5-methoxy-2-methylindole	<b>1j</b> +0.13 <sup>e</sup>	81 000	40 500	2 850	322
	<b>1j–d</b>	71 000	34 000	2 400	280
<i>N</i> -methylindole	<b>1k</b> –2.32 <sup>d</sup>	6 980	3 510	29	19.6

<sup>a</sup>  $T = 25^\circ\text{C}$ . <sup>b</sup>  $I = 0.1 \text{ mol dm}^{-3} \text{ KCl}$ . <sup>c</sup> Ref. 8. <sup>d</sup> Ref. 26. <sup>e</sup> See discussion

**Table 2** Second-order rate constants  $k_{\text{exch}}^{H_3O^+}$  for the protidetritiation of various indoles at  $T = 25^\circ\text{C}$  in aqueous solution

Indole	$pK_a^{H_2O}$	$k_{\text{exch}}^{H_3O^+}/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
<b>1p</b> 6-nitroindole	–6.90 <sup>c</sup>	$2.75 \times 10^{-3}$ <sup>a</sup>
<b>1a</b> 5-cyanoindole	–6.00 <sup>a</sup>	$5.27 \times 10^{-3}$ <sup>a</sup>
<b>1d</b> indole	–3.46 <sup>c</sup>	$0.454$ <sup>b</sup> ; $0.50$ <sup>a</sup>
<b>1e</b> 5-methylindole	–3.30 <sup>a</sup>	$0.98$ <sup>b</sup>
<b>1f</b> 5-methoxyindole	–2.90 <sup>a</sup>	$1.14$ <sup>a</sup>
<b>1k</b> <i>N</i> -methylindole	–2.32 <sup>c</sup>	$1.076$ <sup>b</sup>
<b>1l</b> 1,5-dimethylindole	–2.15 <sup>b</sup>	$2.33$ <sup>b</sup>
<b>1m</b> 2- <i>tert</i> -butylindole	–0.80 <sup>a</sup>	$31.90$ <sup>a</sup>
<b>1h</b> 2-methylindole	–0.28 <sup>c</sup>	$35.9$ ; $40.8$ <sup>a</sup>
<b>1i</b> 2,5-dimethylindole	+0.26 <sup>c</sup>	$53.83$ <sup>b</sup>
<b>1j</b> 5-methoxy-2-methylindole	+0.13 <sup>b</sup>	$65.45$ <sup>b</sup>
<b>1n</b> 1,2-dimethyl-5-methoxyindole	+0.25 <sup>b</sup>	$81.28$ <sup>b</sup>
<b>1o</b> 1,2,5-trimethylindole	+0.50 <sup>b</sup>	$118.2$ <sup>b</sup>

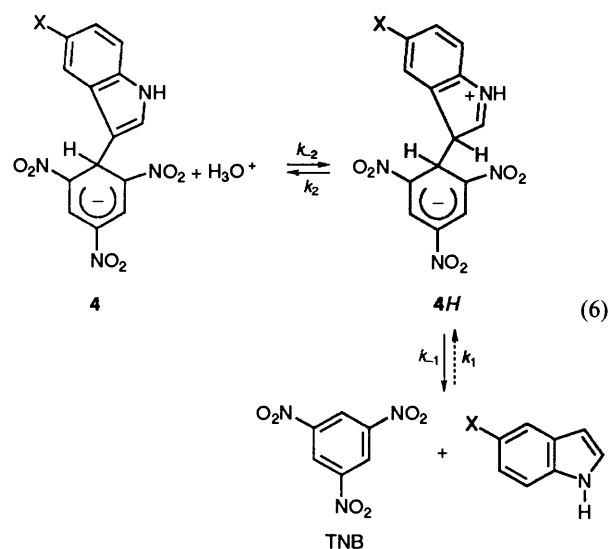
<sup>a</sup> Ref. 8. <sup>b</sup> This work. <sup>c</sup> ref. 26.



**Fig. 2** Influence of the H<sup>+</sup> concentration on the observed first-order rate constant  $k_{\text{obs}}$  [eqn. (5)] for the protidetritiation of 5-methylindole (+) and 1,5-dimethylindole (●) in aqueous solution ( $T = 25^\circ\text{C}$ )

(TNB)—a common reference aromatic electrophile—do not occur, even to a small extent, under the same experimental conditions as those used with DNBF. In these instances, the

presence of a strong base like hydroxide or methoxide ion is required in the solutions to generate equilibrium concentrations of the conjugate strongly basic indolide anions which then add to TNB, giving quantitatively the adducts **4**.<sup>27</sup> Interestingly, these adducts are stable in neutral or basic aqueous or methanolic solutions but they decompose rapidly in media of  $\text{pH} < 5$  with return to the reactants according to eqn. (6) which is simply the reverse of eqn. (1).<sup>28</sup>



Two main factors are probably contributing to the greater ease of formation and stability of the DNBF adducts **2** relative to the TNB analogues **4**. The first is that the negatively charged DNBF moiety in **2** exerts an electron-withdrawing  $-I$  effect which is considerably higher than the one recognized for a trinitrocyclohexadienyl moiety in TNB adducts like **4**.<sup>19,21,29</sup> Accordingly, protonation at the 3-position of the indole ring of **4** to give the indolenium intermediates **4H** is both kinetically ( $k_2$ ) and thermodynamically ( $K_2$ ) highly favoured compared to the same process in **2** to give the zwitterions **2H**. On the other hand, the decomposition of the zwitterionic adducts **4H** via the  $k_{-1}$  step results in the formation of two markedly aromatic compounds, namely TNB and the parent indole, while that of the DNBF analogues **2H** produces only one highly aromatic compound, *i.e.* the parent indole. As pointed out by various authors,<sup>19b,20,30</sup> DNBF is a 10- $\pi$ -electron heteroaromatic

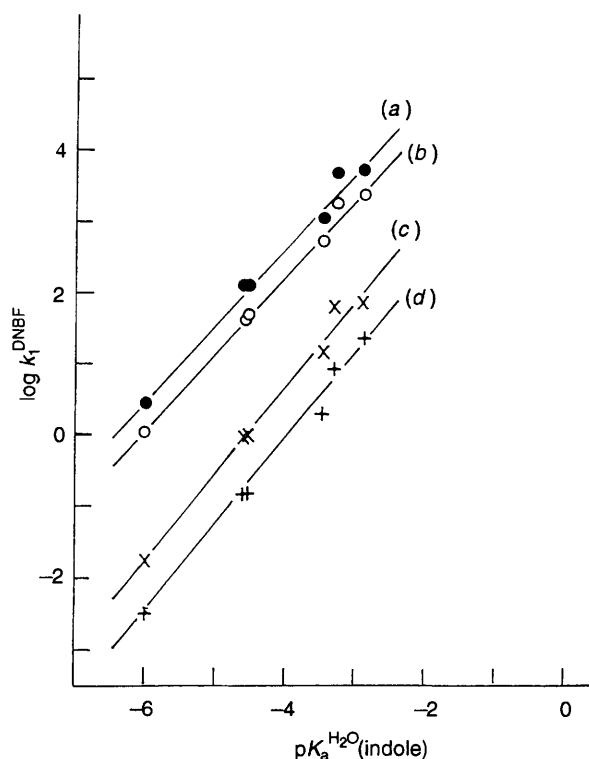


Fig. 3 Effect of the indole basicity on the rates of complexation of DNBF by 5-X-substituted indoles at  $T = 25^\circ\text{C}$  in different solvents: (a) 70–30 (v/v)  $\text{H}_2\text{O}$ – $\text{Me}_2\text{SO}$ ; (b) 50–50 (v/v)  $\text{H}_2\text{O}$ – $\text{Me}_2\text{SO}$ ; (c)  $\text{MeOH}$ ; (d)  $\text{MeCN}$

compound which exhibits a low aromatic character compared to benzenoid derivatives. This difference increases the intrinsic reactivity of DNBF towards a given nucleophile ( $k_1$ ) while reducing the tendency of intermediates like **2H** to rearomatize via the  $k_{-1}$  step.

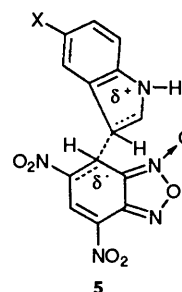
**Isotope Effects: The Nature of the Rate-limiting Step.**—Table 1 reveals that the second-order rate constants  $k$  for formation of the adducts **2** according to eqn. (1) are essentially independent of the hydrogen or deuterium labelling at the 3-position of the parent indoles in 70–30 and 50–50 (v/v)  $\text{H}_2\text{O}$ – $\text{Me}_2\text{SO}$  mixtures. The deuterium isotope effects are negligible ( $k_{\text{H}}/k_{\text{D}} = 1.1 \pm 0.1$ ) with no dependence upon the substrate basicity. This shows that proton elimination from the zwitterion **2H** is rapid in these aqueous solvents and that electrophilic attack by DNBF is the rate-determining step of the formation of the anionic complexes **2**, i.e.  $k = k_1$  in these aqueous solvents.

The situation is not so clearcut in methanol and acetonitrile where the measured kinetic isotope effects are in the ranges 1.11–1.65 and 1.47–1.71, respectively. In addition, the  $k_{\text{H}}/k_{\text{D}}$  ratio shows a slight tendency to increase with increasing the basicity of the indole, e.g. in acetonitrile, we have: 5-CN,  $\text{p}K_{\text{a}} = -6$ ,  $k_{\text{H}}/k_{\text{D}} = 1.47$ ; 5-H,  $\text{p}K_{\text{a}} = -3.5$ ,  $k_{\text{H}}/k_{\text{D}} = 1.63$ ; 5- $\text{OCH}_3$ ,  $\text{p}K_{\text{a}} = -2.9$ ,  $k_{\text{H}}/k_{\text{D}} = 1.71$ . Since the observed kinetic isotope effect combines a secondary effect on the formation of the adduct (probably inverse) and that on the proton transfer step, it is possible that the above sequence reflects some shift towards a rate limiting proton transfer mechanism.\* Assuming  $k = k_1$  in the two solvents leads, however, to Brønsted lines which are essentially parallel to those obtained in the two aqueous mixtures (*vide infra*), suggesting that such a shift must in fact be small. It thus appears that the coupling of DNBF with indoles resembles the majority of aromatic electrophilic substitution

\* We are grateful to a referee for this suggestion.

reactions in which the formation of the Wheland-type intermediates is rate-determining.<sup>1b</sup> In this regard, we note that Jackson and Lynch have recently studied the coupling of indole, *N*-methylindole and 2-methylindole with *p*-nitrobenzenediazonium cation in acetonitrile and found that the initial attack of the electrophile is also rate-limiting.<sup>18</sup>

**Structure–Reactivity Relationships.**—Inspection of Table 1 reveals that the rate constants  $k_1^{\text{DNBF}}$  for DNBF addition to the 5-X-substituted indoles **1a–1f** increase regularly with increasing basicity of the indole. This behaviour is best illustrated by Fig. 3 which shows that four different straight lines are obtained by plotting the  $\log k_1^{\text{DNBF}}$  values measured in the four solvents studied *vs.* the  $\text{p}K_{\text{a}}$  values measured for protonation of the parent indoles in aqueous solution. Interestingly, these lines have nearly identical slopes, indicating that the effect of the X-substituent on the addition process is essentially solvent independent. However, Fig. 3 shows that the rate of complexation of DNBF by a given indole decreases markedly with decreasing the polarity of the solvent, the observed reactivity sequence being 70–30  $\text{H}_2\text{O}$ – $\text{Me}_2\text{SO}$  > 50–50  $\text{H}_2\text{O}$ – $\text{Me}_2\text{SO}$  > methanol > acetonitrile. This behaviour agrees with the fact that the reactions must proceed through a strongly dipolar transition state, namely **5**, which is expected to be



especially stabilized in aqueous solvents.<sup>31</sup> In accordance with structure **5** relatively large negative  $\rho$  values are deduced from the Hammett relationship (not shown) obtained on plotting the  $\log k_1^{\text{DNBF}}$  values *versus* the substituent constants  $\sigma_{\text{p}}(\rho \approx -3.85 \pm 0.1)$ . Such negative values support the development of a significant positive charge on the indole nitrogen in the transition states of the reactions.<sup>32</sup>

Satisfactorily linear Brønsted plots can also be drawn from the rate data for DNBF addition to 5-X-2-methylindoles **1g–1j** in the various solvents studied. As can be seen in Fig. 4, these plots are parallel to, but located about 1.5  $\log k$  unit below, the

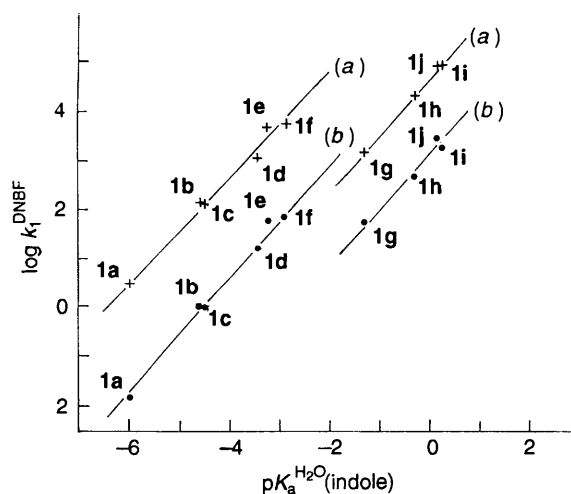
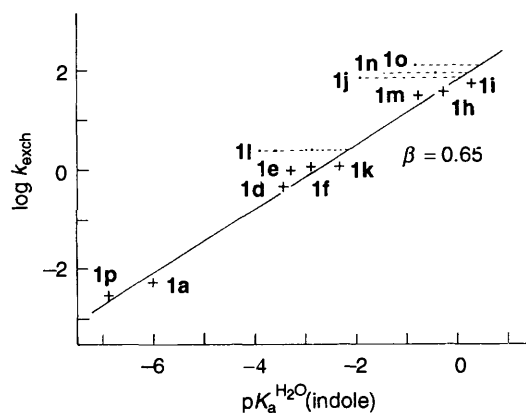


Fig. 4 Effect of the presence of a 2-methyl group on the addition of DNBF to 5-X-substituted indoles in (a) 70–30 (v/v)  $\text{H}_2\text{O}$ – $\text{Me}_2\text{SO}$  and (b) methanol ( $T = 25^\circ\text{C}$ )

**Table 3** Relative electrophilic reactivities of the proton and DNBF towards indoles in aqueous solution<sup>a</sup>

Indole	$pK_a^{H_2O}$	$k_1^{H_3O^+}/dm^3 mol^{-1} s^{-1}$	$k_1^{DNBF}/dm^3 mol^{-1} s^{-1}$	$k_1^{DNBF}/k_1^{H_3O^+}$
5-cyanoindole	-6.00 <sup>d</sup>	0.095	2.8	29.47
indole	-3.46 <sup>e</sup>	8.17; 9	1 110	135.8; 123.3
5-methylindole	-3.30 <sup>e</sup>	17.67	5 000	283
5-methoxyindole	-2.90 <sup>d</sup>	20.5	5 260	256.6
<i>N</i> -methylindole	-2.32 <sup>e</sup>	19.38	≈ 7 000	362
2-methylindole	-0.26 <sup>e</sup>	646; 756	21 000	32.50; 27.8
5-methoxy-2-methylindole	+0.13 <sup>f</sup>	1 178	81 000	68.7
2,5-dimethylindole	+0.26 <sup>e</sup>	969	94 000	97

<sup>a</sup>  $T = 25^\circ C$ . <sup>b</sup> Calculated from the  $k_{exch}$  rate constants by assuming a ratio  $k_1^H/k_1^T$  of 18 (see text). <sup>c</sup>  $k_1^{DNBF}$  values measured in 70–30 (v/v)  $H_2O$ – $Me_2SO$ . <sup>d</sup> Ref. 8. <sup>e</sup> Ref. 26. <sup>f</sup> This work.



**Fig. 5** Effect of the indole basicity on the rates of protidetritiation of  $[3-^3H]$ indoles in aqueous solution ( $T = 25^\circ C$ )

corresponding Brønsted lines for the indoles **1a–f**. It therefore appears that the 5-X substituent exerts a similar electronic influence in both series but that the presence of the methyl group in the position adjacent to the site of electrophilic attack reduces considerably the efficiency of the DNBF addition. This decrease can reasonably be attributed to steric hindrance of the approach of DNBF from the C-3 position of 2-methylindoles.

In contrast with the DNBF reactions, the detritiation reactions of 5-substituted indoles and 5-substituted-2-methylindoles define a unique Brønsted relationship (Fig. 5), indicating that protonation at C-3 of the indole ring is not subject to steric effects from the adjacent 2-methyl group. This behaviour is interesting in itself since the plot of Fig. 5 can be used to estimate (to  $\pm 0.2$  pK units) the unknown  $pK_a^{H_2O}$  values of indoles from protidetritiation rate data, thus avoiding the drawback of acidity function studies in concentrated acid media. On this basis, we have assessed the  $pK_a$  values of 1,5-dimethylindole **1l** ( $pK_a^{H_2O} = -2.15$ ), 5-methoxy-2-methylindole **1j** ( $pK_a^{H_2O} = 0.13$ ), 1,2-dimethyl-5-methoxyindole **1n** ( $pK_a^{H_2O} = 0.25$ ) and 1,2,5-trimethylindole **1o** ( $pK_a^{H_2O} = 0.50$ ).

A noteworthy result is the consistency of our  $\beta_{inH}^{H^+}$  value ( $0.65 \pm 0.04$ ) with that previously determined by Challis and Millar using a more limited set of data ( $0.67$ )<sup>8</sup> and the fact that this value is significantly different from the equivalent Brønsted  $\alpha_{AH}$  exponent ( $0.46$ ) found for exchange of  $[3-^3H]$ indoles by variation of the acid catalyst.<sup>8</sup> Indeed, the difference ( $I = \beta_B - \alpha_{CH} = 0.18$ ) is really too high to be accounted for in terms of experimental errors associated with the determination of the two coefficients and this suggests that the protonation of indoles is characterized by some transition state imbalance of the type commonly encountered in the ionization of carbon acids like nitroalkanes or carbonyl compounds.<sup>33</sup> Interestingly, this behaviour fits that recently observed in the protonation of pyrroles,<sup>11</sup> although more data must be obtained before one

can draw firm conclusions about the generality of imbalance phenomena in aromatic protonation reactions.

**Relative Electrophilic Reactivities of DNBF,  $H^+$  and  $ArN_2^+$  Cations.**—Kinetic studies of the protidetritiation of a number of aromatic and heteroaromatic substrates have shown that the isotope effect ratios  $k_1^H/k_1^T$  are rather insensitive to the structure and basicity of the derivative undergoing the exchange process, an average value of 18 being generally observed.<sup>6–10,34</sup> On this basis, the corresponding second-order rate constants  $k_1^{H_3O^+}$  for protonation at C- $\beta$  of the indoles listed in Table 2 can be readily evaluated from eqn. (5).

The  $k_1^{H_3O^+}$  values thus obtained in aqueous solution are compared in Table 3 with similar data ( $k_1^{DNBF}$ ) for DNBF addition in 70–30 (v/v)  $H_2O$ – $Me_2SO$ . Given that the effect of the  $Me_2SO$  co-solvent is to decrease the rate constants  $k_1^{DNBF}$  relative to those measured in aqueous solution (see Table 1), it is clear that the neutral DNBF molecule behaves as a much stronger electrophile than the positively charged hydronium ion. That the  $k_1^{DNBF}/k_1^{H_3O^+}$  ratio increases markedly on going from 5-cyanoindole (30) to 5-methoxyindole (257) and 5-methylindole (283) or *N*-methylindole (362) reflects the greater sensitivity of the rates of DNBF addition than of the protonation rates to increased basicity of the indole reagent ( $\beta_{inH}^{H^+} = 0.65$ ;  $\beta_{inH}^{DNBF} \approx 1.15$ ). On the other hand, the  $k_1^{DNBF}/k_1^{H_3O^+}$  ratio decreases markedly on going from the 5-X series to the 5-X-2-methyl series, in accord with the idea suggested earlier of the occurrence of steric hindrance to the approach of the bulky DNBF molecule from the  $\beta$ -position of a 2-methyl substituted indole ring.

Available data also allow a comparison to be made of the electrophilic reactivity of DNBF with that of a stronger electrophile than the proton, namely the positively charged *p*-nitrobenzenediazonium cation ( $ArN_2^+$ ). As can be seen in Table 4, the rates of DNBF complexation by indole and *N*-methylindole (at  $25^\circ C$ ) are 1.43 and 3 times faster than the rates of diazocoupling of these compounds by  $ArN_2^+$  (at  $30^\circ C$ ) in acetonitrile, indicating some slightly higher electrophilic character of the neutral molecule in this solvent. Different trends are observed, however, in comparing the behaviour of the two reagents towards 2-methylindole. Then, DNBF becomes the less efficient electrophile in acetonitrile ( $k_1^{DNBF}/k_1^{ArN_2^+} = 0.23$ ) but it is the more efficient reactive species in aqueous solution ( $k_1^{DNBF}/k_1^{ArN_2^+} = 7.7$ ). This reversal may reflect a subtle balance of solvation and steric effects on the reaction in the two solvents. Solvation effects would predominate in aqueous solution, thereby reducing the electrophilicity of the positively charged species compared to the neutral DNBF molecule, whereas they would be of lesser importance in acetonitrile. In this case, steric hindrance to the approach of C-3 would disfavour attack by DNBF to a greater extent than that by  $ArN_2^+$ . Interestingly,  $k_1^{DNBF}/k_1^{ArN_2^+}$  ratios of the order of 10 have also been recently found for pyrrole systems in aqueous solution.<sup>25</sup>

**Table 4** Relative electrophilic reactivities of 4-nitrobenzenediazonium cation and DNBF towards indoles in acetonitrile and aqueous solutions

Indole reagent	$pK_a^{H_2O}$	Solvent	$k_1^{DNBF}/dm^3 mol^{-1} s^{-1}$	$k_1^{ArN_2^+}/dm^3 mol^{-1} s^{-1}$
indole	-3.46 <sup>a</sup>	CH <sub>3</sub> CN	1.96 <sup>b</sup>	1.37 <sup>c</sup>
<i>N</i> -methylindole	-2.32 <sup>a</sup>	CH <sub>3</sub> CN	19.6 <sup>b</sup>	6.50 <sup>c</sup>
2-methylindole	-0.28 <sup>a</sup>	CH <sub>3</sub> CN	99 <sup>b</sup>	435 <sup>c</sup>
		H <sub>2</sub> O	21 000 <sup>b</sup>	2 700 <sup>b</sup>

<sup>a</sup> Ref. 26. <sup>b</sup> This work at  $T = 25^\circ C$  in 70–30 (v/v) H<sub>2</sub>O–Me<sub>2</sub>SO. <sup>c</sup> Ref. 18.

## Experimental

**Materials.**—4,6-Dinitrobenzofuroxan was prepared according to the procedure of Drost: m.p. 172 °C (lit. 172–174.5 °C).<sup>21a,23b,35</sup> The various indoles were commercial products which were purified by recrystallization, sublimation or distillation under vacuum.

Deuteration of **1a**, **1d**, **1f**, **1h** and **1j** was effected by acid and/or base-catalyzed exchange using procedures developed by various authors.<sup>8,11,14,15,18</sup> Details of the preparation of 1,3-dideuterioindole [<sup>2</sup>H<sub>2</sub>]**1d** and 1,3-dideuterio-2-methylindole [<sup>1,3-2</sup>H<sub>2</sub>]**1h** were recently reported.<sup>18,25</sup> 1,3-Dideuterio-5-cyano-, -5-methoxy and -5-methoxy-2-methylindoles ([<sup>1,3-2</sup>H<sub>2</sub>]**1a**, [<sup>1,3-2</sup>H<sub>2</sub>]**1f** and [<sup>1,3-2</sup>H<sub>2</sub>]**1j**) were similarly obtained.<sup>8</sup> Deuterium incorporation at C-3 was in all cases found to be ≥98% on the basis of 250 MHz <sup>1</sup>H NMR spectra (recorded in [<sup>2</sup>H<sub>6</sub>]Me<sub>2</sub>SO on a Bruker AM-250 spectrometer equipped with an ASPECT 3000 computer). Dissolution of the 1,3-dideuterated products in H<sub>2</sub>O–Me<sub>2</sub>SO and methanol solution was found to restore the NMR signals assigned to the NH protons in a few minutes, as expected from the known lability of this hydrogen atom.<sup>8,15</sup> For this reason, the kinetic experiments carried out to measure the effect of the isotopic substitution at C-3 on the rates of complexation by DNBF have been described in referring only to reactions involving 3-deuterio derivatives as the starting materials. In fact, similar rates were obtained whether 1,3-dideuterio or 3-deuterio derivatives were used as starting deuterated substrates.

A number of the [<sup>3-3</sup>H]indoles listed in Table 2 (**1d**, **1e**, **1h**, **1i**, **1j**, **1k**, **1l**, **1n** and **1o**) were prepared using a procedure similar to that described for various pyrroles.<sup>12</sup> However, as noted by Challis and Miller,<sup>8</sup> decomposition occurred readily under acidic conditions and at elevated temperatures. Thus, somewhat milder conditions were found to be necessary.

Typically, the substrate (20 mg) was dissolved in Me<sub>2</sub>SO (10 mm<sup>3</sup>); tritiated water (2 mm<sup>3</sup>, 20 Ci cm<sup>-3</sup>) was added, together with a trace (<1 mm<sup>3</sup>) of 1.10<sup>-3</sup> mol dm<sup>-3</sup> aqueous hydrochloric acid. Mixtures were then maintained in sealed tubes at ca. 50 °C for 6–12 h or left at room temp. for 3–4 days. Aqueous sodium hydrogen carbonate was then added and the tritiated indole was isolated by means of diethyl ether extraction.

Specific activities of 15–20 mCi mmol<sup>-1</sup> were typical. <sup>3</sup>H NMR spectroscopy was used to verify the position of the label and the radiochemical purity of the products. Solutions of the labelled indoles were prepared in [<sup>2</sup>H<sub>6</sub>]Me<sub>2</sub>SO to contain typically 0.5–2 mCi so that <sup>3</sup>H NMR signals could be obtained in a few hours. The <sup>1</sup>H NMR spectra of the tritiated materials showed that no decomposition had occurred during the labelling procedure.

The <sup>3</sup>H NMR spectra showed labelling to have occurred exclusively at the 3-positions of all the substrates. In the case of **1j**, (5-methoxy-2-methylindole), use of the aforementioned tritiation procedure at 50 °C resulted in additional labelling at the 4- and 6-positions, *i.e.* *ortho*- to the methoxy substituent. At room temp. labelling occurred only at the desired 3-position.

Reactions (1) afforded the adducts **2a–k** in their acid form, which were not very stable in air but exchange of the H<sup>+</sup> counterion for a Na<sup>+</sup> cation gave stable salts.<sup>24c</sup> The

preparation and full characterization of the sodium salts of indole (**1d**) and 2-methylindole (**1h**) has been reported elsewhere.<sup>25</sup> The sodium salts of all other adducts have been similarly obtained in 70–80% yields. As with most alkali salts of anionic DNBF  $\sigma$ -adducts isolated so far, the crystals obtained for **2a–k**, Na<sup>+</sup> were not found to melt at  $T < 320^\circ C$ . In addition, attempts to obtain satisfactory elemental analysis of these salts have been unsuccessful. In contrast, dissolution of the salts in [<sup>2</sup>H<sub>6</sub>]Me<sub>2</sub>SO gave NMR spectra identical to those recorded in the *in situ* generation of the acid form of the adducts in this solvent. All visible spectra exhibited a strong absorption maximum at  $\lambda = 480–490$  nm, a wavelength typical for all C-bonded  $\sigma$ -adducts of DNBF in H<sub>2</sub>O–Me<sub>2</sub>SO mixtures.

The <sup>1</sup>H NMR data obtained for the various adducts and the parent indoles in [<sup>2</sup>H<sub>6</sub>]Me<sub>2</sub>SO are summarized in Table 5. The data do not call for much comment since they agree well with the proposed structures.<sup>19,20,27</sup> In accord with previous observations for many DNBF adducts, the chemical shift of the H<sub>5'</sub> proton located between the two NO<sub>2</sub> groups of the negatively charged DNBF moiety appears essentially independent of the nature of the bonded indole structure.<sup>22–24</sup> On the other hand, all H<sub>7'</sub> resonances are typical of DNBF C-adducts, being in the range 5.57–5.77 ppm.<sup>22–24</sup> However, there is a slight but noteworthy shift to low field of this resonance on increasing the electron-withdrawing character of the X substituent in the adducts derived of either the 5-X-substituted or the 5-X-substituted-2-methylindoles.<sup>13</sup> <sup>13</sup>C NMR data have also been collected for 5-X-substituted indoles and related  $\sigma$ -adducts. They are summarized in Table 6 which shows in particular that the substitution of DNBF results in a significant low field shift of the C-3 carbon of the indole moiety. This result is in agreement with the fact that a negatively charged DNBF structure still exerts a notable –I effect.<sup>21a,29</sup>

**Kinetic Measurements.**—Stopped-flow determinations of the rates of reactions (1) were performed on a Durrum-stopped-flow spectrophotometer, the cell compartment of which was maintained at 25 ± 0.3 °C. A conventional Kontron-Uvikon spectrophotometer was also used to follow some of the slowest processes. All kinetic runs were carried out in triplicate under pseudo-first order conditions with a DNBF concentration of ca. 3 × 10<sup>-5</sup> mol dm<sup>-3</sup> and indole concentrations in the range 10<sup>-3</sup>–10<sup>-2</sup> mol dm<sup>-3</sup>. In a given experiment, the rates were found to be reproducible to ±2–3% and to be similar whether the process was followed by monitoring the increase in absorbance at  $\lambda_{max} = 480–490$  nm of the adducts **2a–k** or the decrease in absorbance at  $\lambda_{max} = 415$  nm of the parent DNBF substrate as a function of time. The visible absorption spectra of the final solutions were in all cases identical to those recorded by dissolving samples of the isolated sodium salts of the adducts in the appropriate solvent.

Protidetritiation rates of the [<sup>3-3</sup>H]indoles were measured as described previously for *N*-phenyl-2,5-dimethylpyrroles.<sup>12</sup> The sole modification was that the tritiated indole was added to the aqueous acid as a droplet of a Me<sub>2</sub>SO solution. (This was necessary as the more reactive indoles (**1i**, **1j**, **1n** and **1o**) were found to undergo protidetritiation in aqueous stock solutions.)

**Table 5** <sup>1</sup>H NMR Data for 5-X-substituted indoles **1a–f**, 5-X-substituted-2-methylindoles **1g–j**, N-methylindole **1k** and related DNBF  $\sigma$ -adducts **2a–k** in [<sup>2</sup>H<sub>6</sub>]Me<sub>2</sub>SO<sup>a</sup>

X	Indole	$\delta_{H1}$	$\delta_{H2}$	$\delta_{H3}$	$\delta_{H4}$	$\delta_{H5}$	$\delta_{H6}$	$\delta_{H7}$	$\delta_{H5'}$	$\delta_{H7'}$	$J_{H1-H2}$	$J_{H2-H3}$	$J_{H4-H6}$	$J_{H6-H7}$
CN	<b>1a</b>	11.68	7.57	6.59	8.09		7.43	7.57			3.2	3.2	1.6	8.4
	<b>2a</b>	11.70	7.52		7.90		7.42	7.52	8.72	5.77	2.4		1.5	8.5
Br	<b>1b</b>	11.30	7.40	6.42	7.73		7.18	7.37			2.8	2.8	1.9	8.6
	<b>2b</b>	11.32	7.37		7.50		7.17	7.32	8.70	5.66	2.6		1.8	8.6
Cl	<b>1c</b>	11.28	7.42	6.42	7.58		7.07	7.40			2.6	2.6	2.1	8.6
	<b>2c</b>	11.30	7.39		7.33		7.06	7.35	8.70	5.66	2.5		2.1	8.6
H	<b>1d</b>	11.08	7.33	6.42	—	—	—	—			2.8	2.8	—	—
	<b>2d</b>	11.09	7.35		—	—	—	—	8.71	5.64	2.4		—	—
CH <sub>3</sub>	<b>1e</b>	10.92	7.26	6.31	7.30	2.37	6.89	7.27			2.8	2.8	1.5	8.2
	<b>2e</b>	10.94	7.25		7.07	2.29	6.87	7.22	8.70	5.61	2.4		1.4	8.3
CH <sub>3</sub> O	<b>1f</b>	10.91	7.28	6.34	7.03	3.73	6.73	7.28			3.0	3.0	2.4	8.7
	<b>2f</b>	10.93	7.29		6.73	3.62	6.71	7.23	8.71	5.60	2.3		2.5	8.7
Cl	<b>1g</b>	11.11	2.38	6.11	7.42		6.97	7.26					2.1	8.7
	<b>2g</b>	11.23	2.43		6.98		6.96	7.25	8.71	5.64			2.0	9.0
H	<b>1h</b>	10.88	2.38	6.10	7.39			7.26					—	—
	<b>2h</b>	10.98	2.47		—	—	—	—	8.70	5.61			—	—
CH <sub>3</sub>	<b>1i</b>	10.73	2.35	6.00	7.16	2.33	6.80	7.13					1.5	8.2
	<b>2i</b>	10.83	2.43		6.78	2.34	6.77	7.12	8.70	5.58			1.5	8.7
CH <sub>3</sub> O	<b>1j</b>	10.71	2.35	6.02	6.48	3.72	6.42	7.13					2.4	8.7
	<b>2j</b>	10.81	2.45		6.90	3.56	6.60	7.13	8.71	5.57			2.3	8.7
H	<b>1k</b>	3.78	7.32	6.42	7.55	—	—	7.43					—	—
	<b>2k</b>	3.73	7.37		7.30	—	—	7.37	8.69	5.63			—	—

<sup>a</sup>  $\delta$  in ppm, internal reference Me<sub>4</sub>Si; J in Hertz.**Table 6** <sup>13</sup>C NMR Data for 5-X-substituted indoles **1a–f** and related DNBF  $\sigma$ -adducts **2a–f** in [<sup>2</sup>H<sub>6</sub>]Me<sub>2</sub>SO<sup>a</sup>

X	Indole	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-X	C-5'	C-7'
CN	<b>1a</b>	127.96	102.05		100.98		112.61	137.62	147.43	120.72		
	<b>2a</b>	127.65	111.68	124.02	101.29	124.02	113.42	137.89	125.97	120.97	130.41	30.76
Cl	<b>1c</b>	127.11	100.91		123.45		112.90	134.40	128.86			
	<b>2c</b>	126.96	109.93		123.78		113.64	134.67	129.96		130.17	31.08
H	<b>1d</b>	125.24	101.09		—		111.48	135.98	127.74			
	<b>2d</b>	125.57	109.22		—		112.07	136.29	125.48		130.04	31.63
CH <sub>3</sub>	<b>1e</b>	125.20	100.56		128.02		111.13	134.59	127.19	21.68		
	<b>2e</b>	125.32	109.05		125.88		111.72	134.59	127.41	21.68	129.98	31.41
CH <sub>3</sub> O	<b>1f</b>	125.64	100.88	101.91	153.36	111.15	111.93	131.15	128.10	55.30		
	<b>2f</b>	126.01	109.06	100.37	153.26	110.75	112.66	131.44	125.80	55.12	129.80	30.63

<sup>a</sup>  $\delta$  in ppm, internal reference Me<sub>4</sub>Si; J in Hertz.

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