The effects of cyclic terminal groups in di- and tri-arylmethane dyes. Part 2.[1] Steric and electronic effects in derivatives of Victoria Blue

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The effects of *N*-alkyl and heterocycloalkyl substituents on the light absorption properties of a range of novel dyes based on the 1-naphthyl analogue of Crystal Violet, Victoria Blue, have been investigated. Interaction between the *N*-terminal group and the *peri*-hydrogen atom on the naphthyl residue can result in deconjugation of the former, whereupon the dyes exhibit Malachite Green character. Such steric influences are correlated with ^{1}H NMR data.

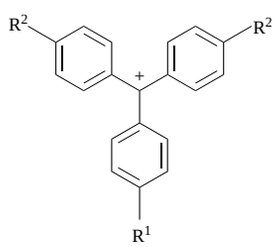
Introduction

Steric congestion associated with the *ortho*-hydrogen atoms in triphenylmethane (TPM) dyes **1** prevents coplanarity of the system and molecular models and X-ray studies[2] indicate that the structure resembles a three-bladed propeller. The planes of the phenyl rings are twisted *ca.* 30 ° out of the plane defined by the central carbon atom and its three bonds.

The response of the TPM system **1** to the electronic and steric effects of substituents has been thoroughly investigated[3–6] and Dewar[7] and Griffiths[8] have offered theoretical explanations for the resulting spectral changes.

It is known[9] that alkylation of the terminal amino groups in TPM dyes causes a red shift and increase in intensity of the *x*-band as a result of increasing the electron donating power of the substituents and in accord with Dewar's rules.[7] We have reported[1,10] that shifts in λ_{max} (*x*) arising from the incorporation of cyclic terminal amino groups in TPM dyes result mainly from inductive effects, though ring size and shape influence basicity and hence the stabilisation of the dye cation, and thus also have a bearing on the spectral parameters. These different effects are also apparent in the spectral and acid–base behaviour of the 4-aminoazobenzene dyes.[11]

Since stabilisation of the cationic dye is clearly influenced by conjugative effects, various attempts have been made to extend the conjugation in Crystal Violet (CV) **1** ($R^1 = R^2 = NMe_2$) through more than one benzene ring,[12] notably in the biphenyl[13] and fluorene[14] analogues of CV, but in both cases the transmission of mesomeric effects is considerably reduced. However, terminal nitrogen atoms attached to longitudinally conjugated naphthalene moieties (2,6-linked) conjugate to a greater extent[15] and lead to a red shift and an increase in intensity of the *y*-band. In the case of the transversely conjugated naphthalene derivatives (1,4-linked), electronic effects are dominated by steric features.[16] Thus, the spectral response is a red shift and increase in ε_{max} of the *x*-band, whilst the *y*-band is red shifted but reduced in intensity, behaviour indicative of enforced rotation about the *y*-axis caused by crowding about the central carbon atom. There has been much interest in compounds based on this last system and Victoria Blue (VB) derivatives **2** ($R^1 = R^2 = NMe_2$) were first patented in the late nineteenth century because of their value for colouring paper, silk and wool in bright shades of blue and purple–red.[17] More recently, they have found use as biological stains for elastic fibres, insulin and plant cells.[18] Most of the commercially-available VB dyes have in common the 1-naphthyl-1,1-diphenylmethane skeleton with a dialkylamino functionality on the phenyl rings, whilst the naphthyl moiety normally has a secondary alkyl- or aryl-amino group. In our present work on the development of photosensitizers, we were interested to ascertain the effects of amino auxochromes on the photoactivity of the VB system in the biological milieu. We now report the results of our investigation into the effects of variations in the auxochrome structure on the spectral parameters of the dyes.



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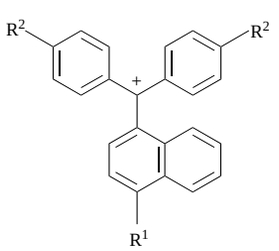

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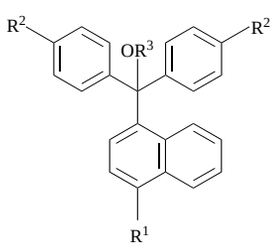

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Discussion

Several routes are available for the synthesis of derivatives of VB **2**, usually based on methods established in the simpler di- and tri-phenylmethane series of dyes. The published route to the VB analogue **3** ($R^3 = H$) of CV base starting from *N*,*N*-dimethyl-1-naphthylamine[16] leads to impure tertiary alcohol which has to be converted into the methyl ether **3** ($R^3 = Me$) *via* the dye perchlorate in order to achieve the purity required for spectral analysis. The overall yield was reported to be of the order of 15%.

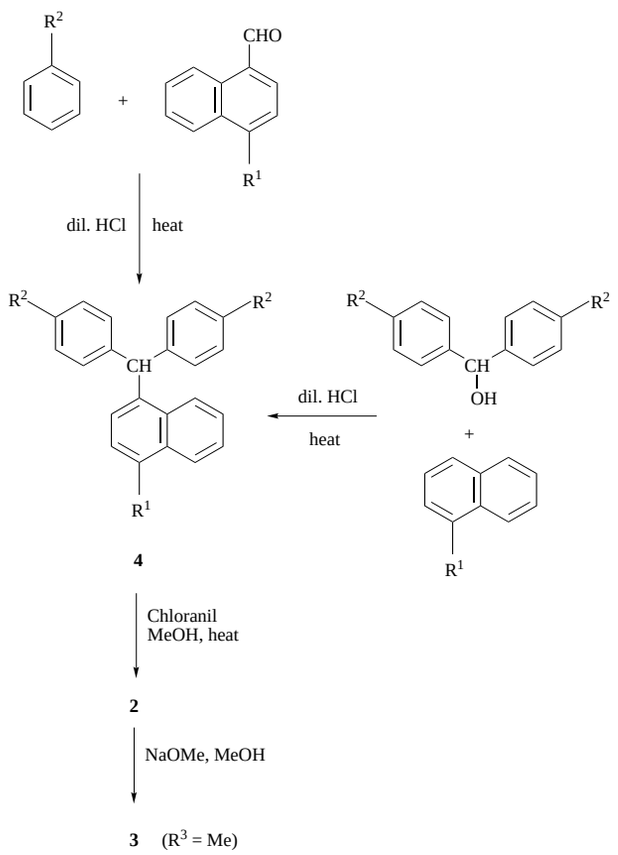
The selective *para*-bromination of *N*,*N*-dimethyl-1-naphthylamine was achieved using 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one[19] and 4-bromo-*N*,*N*-dimethyl-1-naphthylamine was also obtained by the methylation of 4-bromo-1-naphthylamine with trimethyl phosphate.[20] This bromo compound undergoes a fast and complete metal–halogen exchange when treated with BuLi at 0 °C in either diethyl ether or THF; the use of the TMEDA/BuLi complex[21] is unnecessary.

Only a partial reaction occurred when Michler's ketone was treated with the naphthyllithium compound in ether at room

temperature for 1 h, the normal conditions for the synthesis of triphenylmethane dye bases. Optimisation of the process showed that a four-fold molar excess of the lithium reagent and 2 days in refluxing ether are required to achieve the best conversion into the tertiary alcohol. However, separation of the product from unreacted ketone by crystallisation or chromatography was difficult and conversion into the methyl ether (28% overall yield) was still necessary.

A combination of steric and electronic factors is probably the reason for this incomplete reaction. Given that phenyllithium is known to react readily with Michler's ketone, it is likely that in the present work the attacking species has restricted access to the carbonyl group as a result of its own steric bulk. In addition, electronic considerations are against a complete, fast reaction. Competition studies have demonstrated that Michler's ketone is less reactive towards organolithium reagents than benzophenone because of the reduced electrophilic character of its carbonyl group.[22] This finding is confirmed by the observation that 4-dimethylaminophenyllithium reacts satisfactorily with 4-dimethylaminophenyl 1-naphthyl ketone but not with 1-dimethylamino-4-(4-dimethylaminobenzoyl)naphthalene.[16]

An alternative approach to the VB dye is based on the synthesis of triphenylmethanes *via* the reaction of *N*,*N*-dimethylaniline with benzaldehydes,[4] but the synthesis of derivatives of 4-amino-1-naphthaldehyde is difficult. Since only the 4-dimethylamino compound is commercially available, the acid-catalysed condensation of *N*,*N*-dimethyl-1-naphthylamine with Michler's hydrol was investigated (Scheme 1).



Scheme 1 Synthesis of leuco bases of VB dyes and their conversion to the dye cations and methyl ethers

Different acidic media have been employed in the literature to effect similar condensations[4,5,23–25] In all cases, a large excess of the aromatic amine was employed which often resulted in tedious work-ups. Leuco bases show little tendency to solidify when contaminated and since removal of the naphthylamine was likely to prove difficult, the use of an excess of the amine was avoided. A clean condensation occurred in the presence of dilute HCl even when only a slight excess of the amine was used. After a 12 h reflux, basification precipitated **4a** as a solid which was readily purified by crystallisation.

The leuco base **4a** was converted into the dye cation **2** by oxidation with chloranil in refluxing methanol (Scheme 1).[26] The free dye cation was then precipitated as the chloride salt by filtration of the reaction mixture into brine. Unfortunately, the usual method of purification, the precipitation of the salt from an acetone solution by the addition of diethyl ether, proved ineffective. Impure material was also obtained on recrystallisation of the dye salt from acetonitrile. However, a small quantity of this salt was purified by elution from silica gel using water–ethanol–butan-1-ol (10 : 10 : 80) as the mobile phase.

Methyl ethers **3** (R^3 = Me) are stable solids which are readily purified by recrystallisation and which, like the tertiary alcohols **3** (R^3 = H), can be quantitatively converted into the dye cation **2** by dissolution in acetic acid. They are therefore often used in spectroscopic studies. Hence, a methanolic solution of the dye chloride was converted into the methyl ether **3** ($R^1 = R^2 = NMe_2$, R^3 = Me) by treatment with freshly prepared sodium methoxide (Scheme 1).

Since this route uses relatively small quantities of the naphthylamine, gives higher yields than the tertiary alcohol route and offers advantages in work-up, especially for larger scale syntheses, it was chosen for the synthesis of the VB derivatives **3a**–**f** (Table 1). Benzhydrols themselves are usually prepared by reduction of the corresponding benzophenones or less frequently by oxidation of the related diphenylmethanes.[27] Both Michler's ketone and its bis(diethylamino) analogue are commercially available, whilst benzophenones bearing cyclic terminal amino groups may be synthesised from 4,4′-difluorobenzophenone or the corresponding dichloro compound *via* nucleophilic displacement.[1,28]

The ease with which a 4,4′-diaminobenzophenone is reduced to the corresponding alcohol was found to be dependent on the nature of the amino group. For example, Michler's ketone was reduced within a couple of hours by $NaBH_4$ in ethanol, whereas the bis(diethylamino) analogue needed 24 h and a much larger amount of borohydride to achieve reduction in refluxing propan-2-ol. This method of reduction is somewhat unreliable, giving quite variable yields, and can be difficult to monitor because the ketone and its product often have similar R_F values on TLC and some of the hydrols fail to give the characteristic intense blue colour on treatment with acids. Nevertheless, it was possible to reduce all the ketones synthesised in the present work to the corresponding benzhydrols with $NaBH_4$, though not always in good yield. However, the use of sodium bis-(2-methoxyethoxy)aluminium hydride (Red-al) to reduce the pyrrolidino and morpholino analogues of Michler's ketone, in a modification of the published procedure,[29] gave excellent yields of the alcohols, though the benzhydrol derived from the diethylamino analogue was found to be contaminated with significant amounts of the diphenylmethane. Such direct hydrogenolysis is not uncommon in 4-aminoaryl ketones.[30]

Although the leuco synthesis described above was generally successful yielding the leuco bases **4a**–**g** (Table 1), the condensation between *N*,*N*-dimethyl-1-naphthylamine and 4,4′-dipyrrolidinobenzhydrol gave very impure material from which the leuco compound could not be isolated, despite using various techniques. The leuco base **4h** was therefore prepared from 1-phenylpyrrolidine[31] and 4-dimethylamino-1-naphthaldehyde in dilute HCl and converted into the methyl ether in the usual manner. 4-Dimethylamino-1-naphthaldehyde proved difficult to make. The Vilsmeier reaction, which gives excellent yields of 4-dimethylaminobenzaldehyde from *N*,*N*-dimethylaniline,[32] is not as straightforward with the naphthylamine, which reacts to give a mixture of the desired product and some 2,4-diformylated material. 4-Dimethylamino-1-naphthaldehyde was preferably made, and in a good yield, by metallation of 4-bromo-*N*,*N*-dimethyl-1-naphthylamine followed by addition of

Table 1 Preparative and analytical data for derivatives of VB leuco bases and methyl ethers

						Found (%)				Required (%)		
	R^1	R^2	Solvent	Mp/°C	Yield (%)	C	H	N	Formula	C	H	N
4a	Me_2N	Me_2N	*d*	116–117	60	82.1	7.9	9.9	$C_{29}H_{33}N_3$	82.2	7.9	9.9
4b	Me_2N	Et_2N	*d*	111–112	67	82.7	8.8	8.7	$C_{33}H_{41}N_3$	82.6	8.6	8.8
4c	Me_2N	Pip[a]	*d*	131 decomp.	60	83.4	8.2	8.2	$C_{35}H_{41}N_3$	83.4	8.2	8.3
4d	Me_2N	Morph[b]	*e*	213–214	50	77.9	7.4	8.3	$C_{33}H_{37}N_3O_2$	78.1	7.4	8.3
4e	Pyrrol[c]	Me_2N	*d*	170–171.5	56	82.8	8.0	9.4	$C_{31}H_{35}N_3$	82.8	8.0	9.4
4f	Pip[a]	Me_2N	*d*	210–211	28	83.0	8.2	9.2	$C_{32}H_{37}N_3$	82.9	8.0	9.1
4g	Morph[b]	Me_2N	*d*	201–203	28	80.0	7.6	9.0	$C_{31}H_{35}N_3O$	80.0	7.6	9.0
4h	Me_2N	Pyrrol[c]	*f*	185 decomp.	40	83.1	7.7	8.9	$C_{33}H_{37}N_3$	83.3	7.8	8.8
4i	MeO	Me_2N	*e*	192–194	12	82.0	7.4	6.8	$C_{28}H_{30}N_2O$	81.9	7.4	6.8
4j	Et_2N	Me_2N	—	oil	28	*h*						
3a	Me_2N	Me_2N	*d*	151–153[g]	70							
3b	Me_2N	Et_2N	*d*	156 decomp.	75	80.3	8.7	8.1	$C_{34}H_{43}N_3O$	80.1	8.5	8.2
3c	Me_2N	Pip[a]	*d*	151 decomp.	65	81.1	8.2	7.7	$C_{36}H_{43}N_3O$	81.0	8.1	7.8
3d	Me_2N	Morph[b]	*d*	159 decomp.	58	75.9	7.3	7.7	$C_{34}H_{39}N_3O_3$	75.9	7.3	7.8
3e	Pyrrol[c]	Me_2N	*d*	133 decomp.	68	80.8	7.7	8.7	$C_{32}H_{37}N_3O$	80.2	7.8	8.8
3f	Pip[a]	Me_2N	*d*	131 decomp.	65	80.1	7.9	8.4	$C_{33}H_{39}N_3O$	80.3	8.0	8.5
3g	Morph[b]	Me_2N	*d*	159 decomp.	72	77.4	7.7	8.3	$C_{32}H_{37}N_3O_2$	77.6	7.5	8.5
3h	Me_2N	Pyrrol[c]	*d*	144 decomp.	67	80.7	8.0	8.2	$C_{34}H_{39}N_3O$	80.7	7.8	8.3
3i	MeO	Me_2N	*d*	156 decomp.	69	79.2	7.5	6.4	$C_{29}H_{32}N_2O_2$	79.1	7.3	6.4
3j	Et_2N	Me_2N	*d*	131 decomp.	71	79.7	8.4	8.6	$C_{32}H_{39}N_3O$	79.8	8.2	8.7
3k	EtNH	Me_2N	*d*	127 decomp.	31	79.7	8.0	9.2	$C_{30}H_{35}N_3O$	79.4	7.8	9.3

[a] Piperidino. [b] Morpholino. [c] Pyrrolidino. [d] Ethyl acetate–hexane. [e] Acetone. [f] *tert*-Butyl ether. [g] Lit.,[17] mp 152–153 °C. [h] **4j** could not be crystallised, *m*/*z* 452 (M^+).

Table 2 Absorption bands for derivatives of VB in acetic acid

	Compound		98% AcOH		10% AcOH			
	R^1	R^2	λ_{max}/nm	$10^{-4}\,\varepsilon_{max}$	$\lambda_{max}(x)$/nm	$10^{-4}\varepsilon_{max}$	$\lambda_{max}(y)$/nm	$10^{-4}\varepsilon_{max}$
2a	Me_2N	Me_2N	621.5	9.4	632	9.0	424	1.0
2b	Me_2N	Et_2N	627	10.7	640	8.8	424	1.2
2c	Me_2N	Pip[a]	634	9.95	648	8.1[d]	426	1.5[d]
2d	Me_2N	Morph[b]	629.5	6.8	632	6.8	434	0.75
2e	Pyrrol[c]	Me_2N	577/639	6.7 (both)	632	7.9	424	0.75
2f	Pip[a]	Me_2N	622	10.15	632	9.35	426	1.1
2g	Morph[b]	Me_2N	623	10.8	624	9.75	—	—
2h	Me_2N	Pyrrol[c]	629	10.25	640	10.9	422	1.95
2j	Et_2N	Me_2N	624.5	9.7	635	9.8	424	1.25

[a] Piperidino. [b] Morpholino. [c] Pyrrolidino. [d] Spectrum measured in 40% acetic acid.

N-formylpiperidine[33] and subsequent hydrolysis. In the ^{1}H NMR spectrum, the strong electron-withdrawing effect of the formyl group, which itself gives a sharp singlet at 10.2 ppm, results in a general downfield shift of the signals of the protons present on the same ring. The *peri*-proton, H-5, is also strongly deshielded, but the other protons are essentially unaffected, illustrating the difficulty with which electronic effects created on one ring can be transmitted to the other in naphthalene derivatives.

In common with many triphenylmethane dyes and depending on auxochromic character, the VB dyes can exhibit two main absorption bands in the visible region of the spectrum corresponding to transitions along the *x*- and *y*-axes of the molecules, the *y*-band being the weaker transition and occurring at shorter wavelengths, typically *ca*. 400 nm. The $\lambda_{max}(x)$ values for these dyes occur at *ca*. 620 nm in 98% acetic acid, with absorption coefficients of the order of 10^5 dm^3 mol^{-1} cm^{-1} (Table 2). The interpretation of the absorption spectra of this series of compounds is facilitated by comparison with earlier work on related analogues of CV.[1]

Any increase in the electron-donating power of the terminal amino groups favours the NBMO $\longrightarrow \pi^*$ transition responsible for the main absorption and this causes a red shift of the *x*-band. This is the case when *para*-rosaniline **1** ($R^1 = R^2 = NH_2$), λ_{max} = 546 nm, is methylated to give CV **1** ($R^1 = R^2 = NMe_2$), λ_{max} = 589 nm. Increasing the length of the *N*-alkyl chains has a similar effect.[1,28] Introduction of cyclic *N*-terminal groups also influences the spectral parameters and the λ_{max} values of the symmetrical Violet and Green dyes **1** increase in the order $R^2 = NMe_2$ < morpholine ~ pyrrolidine ≤ NEt_2 < piperidine.[1]

From a strictly electronic point of view, the ε_{max} values of structurally symmetrical triarylmethane dyes should increase with increasing electron-donating ability of the terminal amino groups and so follow the trend exhibited by the λ_{max} values. This is found not to be the case, especially for the less stable Green dyes. These dissimilarities can be accounted for in terms of steric interactions between the terminal amino groups and the phenyl rings to which they are attached.[34,35] Relief of steric strain by twisting about the nitrogen–phenyl bond results in a reduced interaction of the nitrogen lone pair with the π-system of the benzene ring. A comparison of the ε_{max} values of the above derivatives of **1** gives a different order of electron donating potential for the tertiary amino groups, *viz*.

$$\text{morpholine} < \text{piperidine} \leqslant NMe_2 < \text{pyrrolidine} < NEt_2$$

This donor order matches almost perfectly those obtained from ^{13}C NMR[36] and ^{1}H NMR[37] studies of relevant derivatives of aniline, though the latter work did not include *N*,*N*-diethylaniline, whilst the former suggested that a pyrrolidino substituent is a marginally better donor than the diethylamino group. A similar order can be derived from the pK_a values of the aniline derivatives, although it should be borne in mind that the measured pK_a value of *N*,*N*-diethylaniline is anomalously

Table 3 λ_{max} values for unsymmetrically substituted CV analogues (**1a**, R^2 = pyrrolidino)

R^1 in **1a**	Morpholino	Piperidino	NMe_2	NEt_2
λ_{max}/nm	602.5	597.5	594.5	594

high[36] and also that inductive electron-withdrawal by the oxygen atom is responsible for the low pK_a of 4-phenylmorpholine.

Taking the donor order obtained from the λ_{max} values of structurally symmetrical Violet and Green dyes as a basis, the λ_{max} value of structurally unsymmetrical Pyrrolidine Violet dyes **1** (R^2 = pyrrolidino) should increase in the sequence $R^1 = NMe_2 < NEt_2 \leqslant$ morpholine < piperidine, a fact which is not observed. The data in Table 3 indicate decreases in λ_{max} which follow the increase in electron-donating power of the amino group as given by the literature and by this work. This situation is very similar to that encountered when the electron-releasing ability of phenyl substituents is increased in Malachite Green. In that respect, it may be recalled that the absorption of CV is now considered to arise from two overlapping transitions polarised at right angles and in the same plane.[38,39] Considering steric effects only, it has been suggested that one transition should remain unaffected by a single substitution, thus rendering the change in excitation energy dependent only on the lowering of the LUMO.[5]

It is possible to use a similar approach and to consider unsymmetrical derivatives of CV as 4-substituted Malachite Green dyes in which the *x*-band corresponds to the transition which takes place between the two strongest electron-releasing groups. Accordingly, the third substituent can only influence the λ_{max} according to its electron-donating ability, any increase of which causes a hypsochromic shift. It is well known that the π-electron density is not uniformly shared in cyanine dyes which contain two markedly different donor groups.[40]

With the exception of the pyrrolidinonaphthyl analogue **2e**, all of the absorption spectra of the VB derivatives consist of a single intense band in the range 620–640 nm (Table 2), generally at 30 nm longer wavelength than the values observed for their CV counterparts. The λ_{max} value measured for **2a** (621.5 nm) is slightly lower than that reported in the literature (623 nm).[16]

The reasons behind this red shift are difficult to ascribe to any one factor, since although a bathochromic shift should be produced by the extension of the chromophoric system provided by the naphthyl ring,[40] a similar shift has also been shown to result from *ortho*- and *meta*-crowding of one of the rings of CV.[6,24] The presence of a single band is usually considered a good indication of the involvement of all terminal amino groups in the resonance system, although PPP-MO calculations, using the parameters determined for Malachite Green (*i.e.* both dimethylamino groups are equally involved), predict a slight splitting of the two transitions of **2a** with a bathochromic shift of the band associated with the naphthyl–phenyl axis.[38]

Such a splitting is not observed in the present series except for **2e** and the λ_{max} of **2a** is significantly lower than that predicted by calculations. The shape of the absorption band of **2a**, a single band with an inflexion on the blue side, similar to that of unsymmetrical Violet dyes, implies that one of the rings does not share in the charge delocalisation system as much as the other two, which therefore dictate the λ_{max} value. Steric considerations suggest that the naphthyl ring will be the least active component of this alternant hydrocarbon analogue.

To confirm this proposal, the spectra of the dyes were measured in acetic acid containing increasing amounts of water (Table 2). As the acidity of the solvent increases, the amino group which is least involved in conjugation is protonated as the most basic site. The dication so produced gives a Malachite Green type of spectrum in which the *x*-band is slightly shifted to the red as a consequence of the electron-withdrawing effect of the new quaternary ammonium substituent.

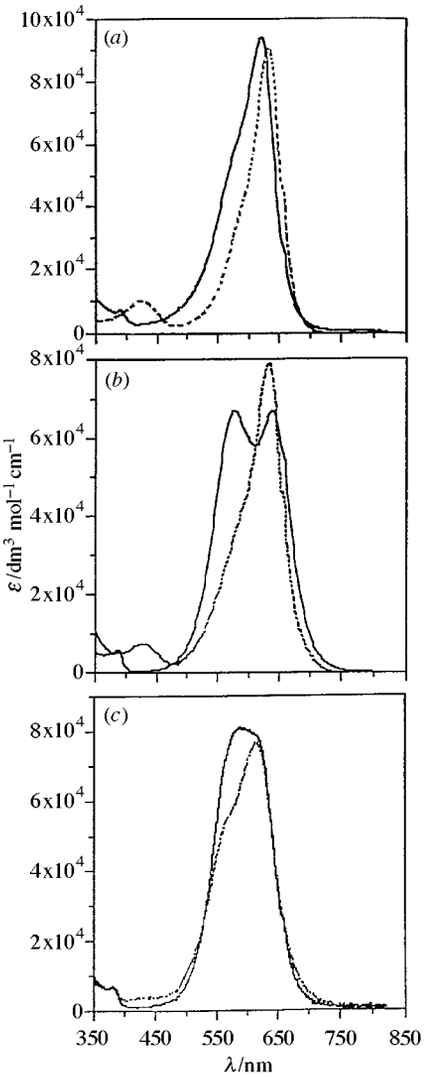


Fig. 1 Absorption spectra of VB dyes in 98% acetic acid (—) and 10% acetic acid (.....)

In general, strongly electron-releasing groups remained unprotonated, unless hindered, but dyes containing a piperidino substituent were readily converted into the dication.[2] There were exceptions, since morpholino groups were not protonated, whilst the efficiently electron-releasing diethylamino group responded anomalously to increases in acidity. This contrasting behaviour can be related to the respectively low and high pK_a values of the corresponding aniline derivatives.

The absorption spectrum of **2a** in 10% acetic acid is quite different from that obtained in 98% acetic acid [Fig. 1 (*a*)]. The first band shows a bathochromic shift of 10.5 nm along with a slight decrease in its extinction coefficient. A second band appears at 424 nm ($\varepsilon_{max} = 10^4$ dm^3 mol^{-1} cm^{-1}), indicating the presence of a dication. This finding confirms the unequal participation of the three dimethylamino groups in the resonance system since CV itself is not protonated under the same conditions.[1] In addition, the spectrum of the dication of **2a** is very similar to that of the symmetrical 1-naphthyl derivative of Malachite Green **1** (R^1 = H, $R^2 = NMe_2$). It follows that the dication derived from **2a** arises from protonation of the aminonaphthyl group and that it is the 4-dimethylamino-1-naphthyl ring which is the less-conjugated moiety. This result is consistent with the behaviour of other *ortho*-substituted analogues of CV[6] and indicates that the steric demands are sufficient to promote protonation of the dimethylamino group in other derivatives of the series, even when poorer donors such as morpholino or piperidino groups are present on the phenyl rings. The low ε_{max} of morpholinophenyl derivative **2d** is, how-

ever, a good sign of a reduced stability of the cation. The piperidino substituents are indeed poor donor groups and, if a fairly good approximation of the spectrum of the dication of **2c** is obtained in 40% acetic acid, any further increase in the acidity of the solvent produces an increased amount of the trication. It is likely that the spectrum of **2c** in 10% acetic acid is that of a mixture of the di- and tri-cations.

The deconjugation of the naphthyl ring is due to a combination of crowding about the central carbon atom and hindrance of the terminal tertiary amino group caused by the *peri*-proton of the naphthyl ring.[3] The extent of the latter effect is difficult to assess because, although *peri*-interactions in 1-naphthalene derivatives are well documented,[41] little appears to be known about tertiary derivatives of 1-naphthylamine. However, steric inhibition of resonance due to the *peri*-proton has been proposed to account for the higher basicity of *N*,*N*-dimethyl-1-naphthylamine compared to that of *N*,*N*-dimethyl-2-naphthylamine.[42]

An indication of the significance of the *peri*-effect in the 1-naphthyl moiety of VB dyes follows from the spectrum of the 4-methoxy derivative **2i**, in which the methoxy group can orient itself to minimise *peri*-interaction.[43] The *x*-band of the 1-naphthyl analogue of Malachite Green ($\lambda_{max} = 630$ nm) exhibits a hypsochromic shift on introduction of a 4-methoxy group ($\lambda_{max} = 620$ nm).[16] This shift is expected, given the electron-releasing effect of the methoxy group, and is of similar magnitude to that observed between Malachite Green [$\lambda_{max}(x) = 621$ nm] and its 4-methoxy derivative [$\lambda_{max}(x) = 608$ nm].[4] However, whilst the replacement of the 4-methoxy group in the Malachite Green derivative by a piperidino substituent results in a further blue shift (17 nm),[1] a small bathochromic shift of 2 nm is observed between the corresponding VB analogues **2i** and **2f**, respectively. The electron-donor effect of the piperidine moiety is negated, demonstrating the importance of *peri*-hindrance and its profound effect on the absorption spectra of VB dyes.

Following the donor order established earlier, the *N*,*N*-diethylnaphthylamine derivative **2j** would be expected to absorb at a shorter wavelength than the dyes having dimethylamino **2a**, piperidino **2f** and morpholino **2g** substitution on the naphthalene unit. In fact, the λ_{max} values of these dyes are found to increase in the order: **2a** = **2f** < **2g** < **2j** (Table 2). This infers that a diethylamino group in the 4-position of a naphthyl ring is a poorer donor than the other groups considered in this series.

Molecular models indicate that the steric clash between the alkyl chains of the amino group and the *peri*-proton of the naphthyl ring is marginally greater for the flexible diethylamino group than for the six-membered heterocyclic substituents which appear more able to accommodate the strain. The planar five-membered pyrrolidino ring is the substituent least affected by the *peri*-proton. Consequently, the pyrrolidino substituent conjugates more effectively with the naphthalene ring than do the other tertiary amino groups. Nevertheless, the visible absorption spectrum of **2e** in 10% acetic acid shows that the pyrrolidino substituent does undergo protonation.

A different situation occurs in 98% acetic acid [Fig. 1 (*b*)]. The absorption spectrum displays two bands of equal intensity ($\varepsilon_{max} = 6.7 \times 10^4$ dm^3 mol^{-1} cm^{-1}) at 577 and 639 nm. It is therefore possible, assuming that despite *peri*-interaction the pyrrolidino group remains a reasonably good donor, to consider **2e** as a system electronically closer to the unsymmetrical naphthyl analogue of Malachite Green than to **2a**. The band at 639 nm would then be caused by the transition which takes place along the naphthyl–phenyl axis, the combined effects of steric crowding about the central carbon atom and extended conjugation being responsible for the significant bathochromic shift observed. Accordingly, the transition existing along the phenyl–phenyl axis would give rise to the second band at 577 nm. It may be recalled that such a splitting of the two degenerate transitions was predicted by PPP-MO treatments of **2a** in which the parameters determined for Malachite Green were used. The calculated λ_{max} value for the transition along the phenyl–phenyl axis is 580 nm.[38]

Table 4 ^{1}H NMR chemical shifts of 2-H in some 1-substituted naphthalenes in $CDCl_3$

1-Substituent	δ_{H2}
NH_2	6.79
NHEt	6.50
NMe_2	7.10
NEt_2	7.16
Pyrrolidino	7.02
Piperidino	7.10
Morpholino	7.10
OMe	6.74

This interpretation is supported by the absorption spectrum in 98% acetic acid of **2k**, marketed as Victoria Blue R, which contains a secondary ethylamino group on the naphthalene moiety [Fig. 1 (*c*)]. Molecular models indicate that the ethylamino group can adopt a conformation free of any *peri*-interaction and is therefore able to exert its electron-donating capability to the full. The spectrum shows signs of band splitting with a very broad band of reduced intensity, the extinction coefficient remaining in the 76 000–81 000 dm^3 mol^{-1} cm^{-1} range between 575 and 622 nm [Fig. 1(*c*)]. The absence of band splitting as pronounced as that of **2e** may be a consequence of the weaker electron-donating ability of secondary amino groups. Victoria Blue R does not show any sign of protonation in 10% acetic acid, which is consistent with the absence of steric hindrance for all the amino substituents [Fig. 1 (*c*)]. The modification of the shape of the absorption spectrum has been attributed to variations in solvent–solute interactions which provoke a degree of asymmetry in the dye molecules.[44]

^{1}H NMR spectroscopy has been shown to give a good measure of the donor strengths of various phenyl-substituted tertiary amino groups[36] and it was therefore of interest to use it in the more complex case of 1-naphthylamines.

The ^{1}H NMR spectra of 1-substituted naphthalene derivatives can be quite complex. However, the most upfield signal in the aromatic region, a double doublet, is always well-resolved when electron-releasing substituents are present and has been assigned to the proton at the 2-position of the naphthyl ring.[43,45] The chemical shifts of the H-2 protons of some relevant naphthalene derivatives are reported in Table 4.

An increase in the electron-releasing power of the substituent should cause further shielding of the *ortho*-proton with a corresponding upfield shift of the signal. This is observed when 1-naphthylamine is alkylated to give *N*-ethyl-1-naphthylamine. The *peri*-effect causes a relative deshielding of the α-proton in tertiary derivatives. The extent of the downfield shift between secondary and tertiary naphthylamines reflects the importance of the deconjugation of the amino groups of the latter.

^{1}H NMR spectroscopy confirms that the diethylamino group suffers a larger steric strain, as already indicated by molecular models and visible absorption spectra. It also demonstrates that primary and secondary amino substituents, as well as the methoxy group, can avoid *peri*-hindrance and conjugate effectively with the aromatic ring. The signal of the *peri*-proton (H-8) is accordingly shifted downfield by tertiary amino substituents and it appears at 7.85 ppm for 1-naphthylamine and *N*-ethyl-1-naphthylamine and at 8.35 ppm for the *N*,*N*-diethyl derivative.

The aromatic proton *ortho* to the pyrrolidino ring displays a slightly more upfield signal than that of other tertiary amino substituents and this confirms the less demanding steric requirements of this planar five-membered ring. A larger upfield shift might have been expected since the visible absorption spectra suggest that **2e** is electronically closer to Victoria

Blue R than to the other tertiary amino dyes. However, it must be pointed out that the ^{1}H chemical shift shown here reflects the donor potential of a group towards an uncharged π-system in the ground state and not the ability of the substituent to stabilise a positive charge. The pyrrolidino ring may therefore be a better donor when part of the charge delocalisation system of **2e** than the ^{1}H NMR spectrum of 1-(1-naphthyl)pyrrolidine indicates. Indeed, it has been suggested that five-membered rings are stabilised by an *exo*-double bond.[46]

Experimental

All visible spectra were measured on a Hewlett-Packard 8452A diode array spectrophotometer using 10^{-5} M solutions of the tertiary alcohols or methyl ethers in glacial acetic acid containing 2% of water. This solvent system was chosen to allow comparison with earlier work[1] and because its acidity is sufficient to promote the complete formation of the dye cation while minimising the possibility of forming other species such as dications.[24] The use of acetic acid also has the advantage of giving easy access to a wide range of solutions of different acid strengths as the addition of water promotes the ionisation of the acid. The dyes were found to obey Beer's law in the concentration range 1–2.5 × 10^{-5} M, a range in which the maximum absorbance was kept between 0.5 and 0.9. The visible spectra were measured immediately and redetermined after 1 h and 48 h to ensure constant values of ε_{max}.

Mps are uncorrected. NMR spectra were recorded on a Bruker WM250 instrument for $CDCl_3$ solutions. Distillations were performed using a bulb-to-bulb (Kügelrohr) apparatus (Büchi GKR-50 glass tube oven) and all boiling points quoted relate to the oven temperature at which distillation commenced. Flash chromatography was performed on silica gel (Sorbsil C60, MPD 60 Å, 40–60 microns) according to the published procedure.[47]

1-Naphthylamines

The 1-naphthylamines were synthesised as described[48] and analogues of Michler's hydrol were obtained by reduction of the corresponding benzophenones.[1]

4-Bromo-*N*,*N*-dimethyl-1-naphthylamine. (a) A solution of *N*,*N*-dimethyl-1-naphthylamine (58 mmol) in dichloromethane (200 cm^3) cooled to −10 °C was treated with small portions of 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (58 mmol) such that the temperature of the solution was maintained below 0 °C. The solution was stirred at room temperature for 45 min and then washed with aqueous sodium hydroxide (3 × 50 cm^3, 2 M) and brine (100 cm^3) and then dried (Na_2SO_4). Removal of the solvent gave a brown oil which was distilled to afford the product (97%), bp 130 °C/0.9 mmHg, as a clear yellow oil. δ_H 2.88 [6 H, s, $N(CH_3)_2$], 6.92 (1 H, d, 2-H), 7.52–7.59 (2 H, m, 6-H and 7-H), 7.67 (1 H, dd, 3-H) and 8.24 (2 H, m, 5-H and 8-H); *m*/*z* 250 (M^+).

(b) A stirred mixture of 4-bromo-1-naphthylamine (45 mmol) and trimethyl phosphate (89 mmol) was heated at 180 °C for 5 h. The cooled mixture was heated under reflux with aqueous sodium hydroxide (250 cm^3, 2 M) for 1.5 h, cooled and extracted with diethyl ether (3 × 150 cm^3). The residue obtained from the combined, dried (Na_2SO_4) and evaporated extracts was refluxed for 20 min with a mixture of glacial acetic acid and acetic anhydride (20 cm^3, 1 : 1) . The cooled solution was poured into water (300 cm^3) and stirred for 1 h. The crude oil which separated was collected, dried and distilled to yield 4-bromo-*N*,*N*-dimethyl-1-naphthylamine (45%) identical with that prepared in (a) above.

4-Dimethylamino-1-naphthaldehyde. A solution of 4-bromo-*N*,*N*-dimethyl-1-naphthylamine (27 mmol) in dry diethyl ether (40 cm^3) was cooled to −15 °C. Butyllithium (12.4 cm^3 of a 2.3 M solution in hexanes) was added dropwise over 25 min, the temperature being kept below −10 °C during the addition. The mixture was stirred at −10 °C for 10 min and at room temperature for a further 45 min before being cooled to 0 °C. *N*-Formylpiperidine (29 mmol) was added in one portion and the resulting slurry was stirred at room temperature for 30 min before being dissolved in aqueous hydrochloric acid (10 cm^3, 1 M). The solution was neutralised with dilute aqueous sodium hydroxide and the two layers were separated. The aqueous layer was extracted three times with diethyl ether and the combined ethereal fractions were washed with water and brine, dried (Na_2SO_4) and the solvent evaporated to yield a dark yellow oil. Elution from silica with 20% ethyl acetate in hexane afforded the title compound as a yellow oil (69%) which slowly solidified on standing, mp 43.5 °C (lit.,[49] gives mp 43–44 °C).

General method for the preparation of leuco bases 4

A blue solution of the benzhydrol (15 mmol) in aqueous hydrochloric acid (50 cm^3, 2 M) was treated with *N*,*N*-dimethyl-1-naphthylamine (16 mmol) and then refluxed for 16 h. The reaction mixture was cooled and slowly basified with ice-cold aqueous sodium hydroxide (60 cm^3, 2 M). The precipitate was collected, washed with water and dried. Recrystallisation from ethyl acetate and hexane afforded the leuco compound.

Yields, mps and microanalytical data for the leuco bases prepared in this manner are given in Table 1.

(4-Dimethylamino-1-naphthyl)bis(4-pyrrolidinophenyl)-methane 4h. A mixture of 4-dimethylamino-1-naphthaldehyde (2 mmol), 1-phenylpyrrolidine (4 mmol) and aqueous HCl (20 cm^3, 2 M) was refluxed for 20 h. The cooled mixture was basified and the precipitate was collected, washed with water, dried and eluted from silica gel (10% ethyl acetate in hexane). Recrystallisation from *tert*-butyl methyl ether gave the title compound **4h** (40%), mp 185–187 °C as colourless microcrystals (Found: C, 83.1; H, 7.7; N, 8.9%. $C_{33}H_{37}N_3$ requires C, 83.3; H, 7.8; N, 8.8%).

(4-Methoxy-1-naphthyl)bis(4-dimethylaminophenyl)methane 4i. A mixture of 4-methoxy-1-naphthaldehyde (11 mmol), *N*,*N*-dimethylaniline (50 mmol) and aqueous HCl (40 cm^3, 4 M) was refluxed in ethanol for 5 days. The cooled reaction mixture was washed with dichloromethane (2 × 50 cm^3) and the aqueous layer was basified. After extraction with diethyl ether (2 × 150 cm^3), the combined organic layers were washed with water (100 cm^3) and brine (80 cm^3) and dried (Na_2SO_4). The solvent was removed and the resulting thick oil was triturated with cold acetone (10 cm^3). The resulting solid was recrystallised twice from acetone to afford the leuco base **4i** (12%), mp 192–194 °C as colourless micro-crystals (Found: C, 82.0; H, 7.4; N, 6.8%. $C_{28}H_{30}N_2O$ requires C, 81.9; H, 7.4; N, 6.8%).

General method for the preparation of methyl ethers 3

A solution of the leuco base (5 mmol) in methanol (60 cm^3) was boiled with chloranil (5 mmol) for 6 h. The cooled blue solution was filtered into brine (500 cm^3) and the mixture was left overnight. The chloride which separated was collected, washed with water, dried and washed with diethyl ether (5 x 50 cm^3). The salt was dissolved in methanol (60 cm^3) and a solution of sodium methoxide in methanol (1 M) was added dropwise until the blue colour disappeared. Stirring was continued for a further 15 min and the slurry was diluted with water (150 cm^3) and extracted with ethyl acetate (3 × 150 cm^3). The extracts were washed with water (4 × 150 cm^3), brine (100 cm^3), dried (K_2CO_3) and the solvent was removed. The resulting solid was eluted from silica gel with triethylamine–ethyl acetate–hexane (10 : 25 : 65) and recrystallised from ethyl acetate and hexane to afford the methyl ether.

Yields, mps and microanalytical data for the methyl ethers prepared by this route are collated in Table 1.

(4-Ethylamino-1-naphthyl)bis(4-dimethylaminophenyl)-methyl methyl ether **3k** (31%) was obtained from commercial Victoria Blue R chloride salt.

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Paper 7/06159E
Received 22*nd August* 1997
Accepted 20*th November* 1997