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TOWARDS A HOMOLOGOUS STRUCTURAL SERIES OF SOLVATOCHROMIC π^* INDICATORS

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Two new π^* indicators of solvent dipolarity and polarizability were synthesized and characterized with respect to their solvatochromic and acid–base properties. The new dyes, *N,N*-dipropyl-*p*-nitroaniline and *N,N*-dibutyl-*p*-nitroaniline, are part of a homologous structural series of indicators with increasing lipophilic character, ranging from *N,N*-dimethyl-*p*-nitroaniline to *N,N*-dibutyl-*p*-nitroaniline. The new indicators are designed as specific polarity probes for the characterization of aqueous–organic interfacial systems. Visible absorption spectra for *N,N*-dipropyl-*p*-nitroaniline and *N,N*-dibutyl-*p*-nitroaniline show solvent-dependent bandshapes in a manner similar to that of the previously characterized diethyl species. Values of $-s$ decrease slightly from *N,N*-diethyl-*p*-nitroaniline to *N,N*-dipropyl-*p*-nitroaniline, leveling off with increasing alkyl chain length. The trend in pK_{BH^+} for the *p*-nitroanilinium ions over the range from *N,N*-dimethyl- to *N,N*-dibutyl- is consistent with known trends for the corresponding anilinium ions.

INTRODUCTION

The study of non-covalent interactions is becoming increasingly important in the investigation of interfacial systems. Of particular significance are the 'hydrophobic interactions' between high molecular weight organic assemblies and smaller aqueous phase solutes. These interactions are relevant to processes such as (1) drug delivery,[1-3] (2) pollutant transport,[4,5] (3) analytical separations[6,7] and (4) molecular recognition.[8,9] As an aid to the study of these systems, we are developing a series of indicators that respond specifically to the dipolarity and polarizability (π^*) of their environment, and which also have the added advantage of being able to bind strongly to lipophilic materials. An example of the use of these indicators would be the study of binding environments of drugs and toxins in biological systems.

π^* Indicators

The π^* indicators of solvent dipolarity and polarizability are a suite of solvent-sensitive solvatochromic dyes.[10,11] Scales of solvent dipolarity and polarizability (π^*) have been developed on the basis of several indicator solutes.[10,12] Values of π^* are calculated from the relative positions of UV–visible absorption bands of individual dyes. The π^* parameter can be related to the transition energy through a linear solvation energy relationship (LSER) of the following form;[10,11]

$$\nu_{max} = \nu_0 + s\pi^* \quad (1)$$

where ν_{max} is the frequency of maximum absorption (in cm^{-1}) for the indicator in the solvent of interest. The parameter ν_0 is the frequency of maximum absorption for the same in cyclohexane. Within the context of the π^* scale as established by Kamlet *et al.*[10] the slope s reflects the magnitude of spectral shift between two reference solvents, cyclohexane ($\pi^* = 0.00$) and dimethyl sulfoxide (DMSO) ($\pi^* = 1.00$).[10,11] Of the three solvent polarity parameters π^* (dipolarity–polarizability),[10,11] α (hydrogen bond donor acidity)[13] and β (hydrogen bond acceptor basicity),[14] the π^* parameter is of particular significance because it represents a measure of polarity without a contribution from hydrogen bonding interactions.[10,11]

Solvatochromic dyes in interfacial systems

Solvatochromic dyes are finding increasing use as probes of aqueous–organic interfaces.[15-17] Some indicators which have been used for this purpose are Reichardt's dye[18] (ET-30) and derivatives of Reichardt's dye[15] (ET-33). Reichardt's dyes have the advantage of being strongly lipophilic and have been used to probe micellization processes.[15,19] However, these dyes are non-specific, i.e. they respond to a combination of dipolarity–polarizability (π^*) and hydrogen bond

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donor acidity (α). An experimentally measured ν_{max} for ET-30 or ET-33 is linearly correlated with two parameters, π^*[10] and α.[13]

The difficulty in using ET-30 is that the individual contributions of α and π^* cannot be determined without access to a pure π^* indicator that can be solvated into the same environment as that of ET-30. Solvation of two dyes into a pure solvent is not a problem. However, for interfacial systems, the unknown location and orientation of two structurally dissimilar probes complicates the estimation of solvatochromic parameters for these systems.

There is a need for π^* indicators with stronger hydrophobic binding capability. The commonly used nitroaniline π^* indicators **1a** and **1b** (Figure 1) are too small and polar to partition effectively into a lipid-like structure from the aqueous phase. We suggest that a homologous structural series of indicators of increasing lipophilicity will supply researchers studying micelles and lipid-bilayer systems with an important tool, allowing (1) measurement of a specific parameter such as π^* for the micelle or micelle surface and (2) the use of the relationship between π^* and the systematically changing features of the dye to understand the behavior and orientation of the probe at the interface.

DNAP π^* indicators

In this work, we selected the di-*n*-alkyl-*p*-nitroanilines (DNAP) as a structural base for creating a homologous series of π^* indicators with increasing lipophilic character (Figure 1). We synthesized two new indicators, *N,N*-dipropyl-*p*-nitroaniline (**1c**) and *N,N*-dibutyl-*p*-nitroaniline (**1d**). We report for the first time some solvatochromic and chemical properties of these dyes.

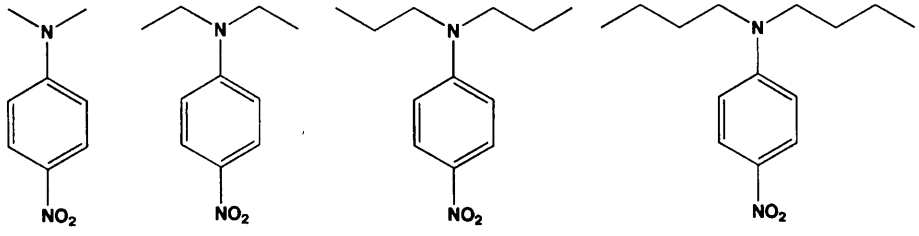
The indicators **1c** and **1d** were prepared via nitration of the corresponding aniline. The dyes were characterized with respect to their bandshape stability and their solvatochromic ($-s$) and acid–base properties (pK_{BH^+}). In this paper, we report trends in these chemical and spectroscopic properties over a range of increasing alkyl chain length (**1a–d**).

EXPERIMENTAL

Reagents. *N,N*-Dipropylaniline and *N,N*-dibutylaniline were purchased from Aldrich and TCI. Spectrophotometric-grade cyclohexane, trichloroethylene, carbon tetrachloride, anhydrous 1-methyl-2-pyrrolidinone (NMP) and deuterated chloroform were purchased from Aldrich. Sodium nitrate ($NaNO_3$), dichloromethane, spectrophotometric-grade tetrachloroethylene and pyridine were obtained from J. T. Baker. Diethyl ether and concentrated sulfuric acid were obtained from EM Science. Spectrophotometric-grade DMSO and *n*-heptane were purchased from Acros and *o*-dichlorobenzene was obtained from Kodak. Solvents used for spectroscopic measurements were further dried over 4 Å molecular sieves. Other reagents were used as received.

Synthesis of ***1c***. A 0·59 M sodium nitrate solution was prepared by mixing 2·5 g of $NaNO_3$ with 50 ml of concentrated (18 M) sulfuric acid. A 100 ml three-necked flask was fitted with an internal thermometer and a mechanical stirrer. Concentrated sulfuric acid (1·5–3·5 ml) was added to the three-necked flask and cooled in an ice-bath to approximately −4 °C. The aniline (0·0075 mol) was added slowly to the cooled sulfuric acid, maintaining the temperature between −2 and −4 °C. An equimolar amount of the $NaNO_3$ solution was added slowly over a 3–4 h period with constant stirring and cooling. After addition of the nitrating reagent, the reaction mixture was stirred for an additional 10 min and then poured over crushed ice. The yellow precipitate was vacuum filtered, washed with cold water and recrystallized from an alcohol–water mixture. ^{1}H NMR for **1c**: Varian Gemini-200 ($CDCl_3$), δ 0·93 CH_3 (t, 6H), 1·64 CH_2 (m, 4H), 3·32 CH_2 (t, 4H), 6·64 ArH (d, 2H), 8·095 ArH (d, 2H). Mass spectrum: m/z calculated 222, found 222. M.p. 52–54 °C; lit. 59 °C[20] and 62–63 °C.[21] Yield 0·99 g (60%).

Synthesis of ***1d***. Synthesis of **1d** was carried out in the same manner as for **1c**, starting with 0·0037 mol of the *N,N*-dibutylaniline. In some experiments, an excess



(1a) (1b) (1c) (1d)

Figure 1. Homologous structural series of solvatochromic π^* indicators: *N,N*-dimethyl-*p*-nitroaniline (**1a**), (b) *N,N*-diethyl-*p*-nitroaniline (**1b**), *N,N*-dipropyl-*p*-nitroaniline (**1c**) and *N,N*-dibutyl-*p*-nitroaniline (**1d**)

of the nitrating reagent was added so as to maximize reaction of the aniline. The resulting oil phase mixture of the *meta*- and *para*-substituted isomers was separated via silica gel column chromatography using methylene chloride–cyclohexane (75:25) as the mobile phase. The *para*-substituted fraction, **1d**, was collected and characterized. ^{1}H NMR for **1d**: ($CDCl_3$), δ 0·95 CH_3 (t, 6H), 1·35 CH_2 (m, 4H), 1·57 CH_2 (t, 4H), 3·33 CH_2 (t, 4H), 6·52 ArH (d, 2H), 8·07 ArH (d, 2H). Mass spectrum: m/z calculated 250, found 250. Yield 0·11 g (12%).

Spectroscopic methods. All UV–visible spectra were collected on a Cary 3 UV–visible spectrophotometer. The spectrophotometer was interfaced to an IBM-PC equipped with Cary 13E software. For each dye–solvent system, separate spectra were collected of the dye solution and of the background solvent. The spectral data were digitized and imported on to a spreadsheet. The background spectra were subtracted directly. An offset correction was applied as appropriate.

Studies of the solvent-dependent bandshapes of **1c** and **1d** were conducted by examining individual spectra of the four dyes (**1a–d**) in cyclohexane, tetrachloroethylene, *o*-dichlorobenzene and DMSO. Values of $-s$ were calculated from the ν_{max} of the individual dyes in DMSO and in cyclohexane using equation (1). In addition to the 'two-point' estimation of $-s$ (i.e. based on DMSO and cyclohexane), a seven-point correlation method was employed. In the latter estimation, UV–visible spectra were obtained for seven non-hydrogen bond donor (non-HBD) solvents, DMSO, NMP, pyridine, trichloroethylene, carbon tetrachloride, *n*-heptane and cyclohexane. The solvents represent both non-hydrogen bonding (NHB) species and hydrogen bond acceptors (HBA), taken from an original list of NHB and HBA solvents provided by Kamlet *et al.*[10] Literature values of π^* for the seven solvents were plotted against experimentally determined values of ν_{max} for each of the dyes. Values of $-s$ and ν_0 were taken as the slope and intercept, respectively. The solvent π^* values were taken from early literature, where π^* represents an average result for several indicators.[10] The experimental ν_{max} values were estimated from peak maxima (λ_{max}) using the 90% method of Kamlet *et al.*[10] In this method, λ_{max} is taken as the mid-point between two positions on the spectrum where the absorbance is 90% of the maximum absorbance.[10] Values of ν_{max} (in cm^{-1}) were calculated using the conversion 10 000/λ_{max}.

pK_{BH^+} determinations. In addition to solvatochromic characterization of the new dyes **1c** and **1d**, we estimated values of pK_{BH^+} for the *N*,*N*-dipropyl- and *N*,*N*-dibutyl-*p*-nitroanilinium ions spectrophotometrically using the H_0''' function based on tertiary aromatic amines.[22,23] The pK_{BH^+} values were estimated using the following equation:

$$pK_{BH^+} = H_0''' - \log[(\varepsilon_{mix} - \varepsilon_{BH^+})/(\varepsilon_{B:} - \varepsilon_{mix})] \quad (2)$$

where ε_{BH^+} and $\varepsilon_{B:}$ are the molar absorptivities of the protonated (BH^+) and unprotonated (B) forms of a dye, respectively. The term ε_{mix} is the molar absorptivity taken from the spectrum of a mixture of B and BH^+, where the acidity of the mixture corresponds to a known value of H_0'''.[22]

UV–visible spectra of the acid and base forms of **1a–d** were obtained using sulfuric acid–water mixtures containing 1–50% sulfuric acid. The spectral data for B and BH^+ and for a solution containing a mixture of the two species were imported on to a spreadsheet. Values of pK_{BH^+} were calculated over a range of wavelengths in a region of the spectrum where medium effects were deemed to be minimal.[23] We obtained values of pK_{BH^+} for anilinium ions of the previously characterized **1a** and **1b** so as to verify our methods.

RESULTS AND DISCUSSION

Bandshape studies

The magnitude of a π^* value is determined by the relative position of a peak maximum. These positions are clearly affected by the shape of the absorption band. The issue of the bandshape and its effect on the determination of ν_{max} has been addressed previously.[11,24] Nicolet and Laurence[24] have shown that the absorption bands of indicators used in the construction of the original π^* scale display a vibrational structure which is not constant over the entire range of solvent polarities. This phenomenon, if severe, can result in a solvent-dependent bandshape.[11,24] Of the indicators **1a–d**, it has been shown that **1a** suffers minimally from bandshape problems, whereas **1b** exhibits significant vibrational structure, leading to a solvent-dependent bandshape.[24] Based on this previous work, it is reasonable to hypothesize that the longer chain dyes, **1c** and **1d**, may be similarly affected.

Figure 2(a)–(d) show the solvatochromic bands of **1a–d** for cyclohexane, tetrachloroethylene, *o*-dichlorobenzene and DMSO. The 'hump' for bands of **1b** in cyclohexane [Figure (2b)] is consistent with previous reports, as is the 'flattened' peak for **1b** in tetrachloroethylene[24] [Figure (2b)]. As the solvent becomes more polar (i.e. *o*-dichlorobenzene and DMSO), the peak assumes a more Gaussian shape [Figure (2b)]. This progression of peak shapes is less pronounced in the spectra of **1a** [Figure (2a)], an observation also consistent with previous studies.[24] As predicted, Figure (2c) and (d) show that the spectral bands of **1c** and **1d** suffer from the same bandshape problems as **1b**.

It has been argued that bandshape variations in the visible spectra of **1b** reduce the usefulness of that

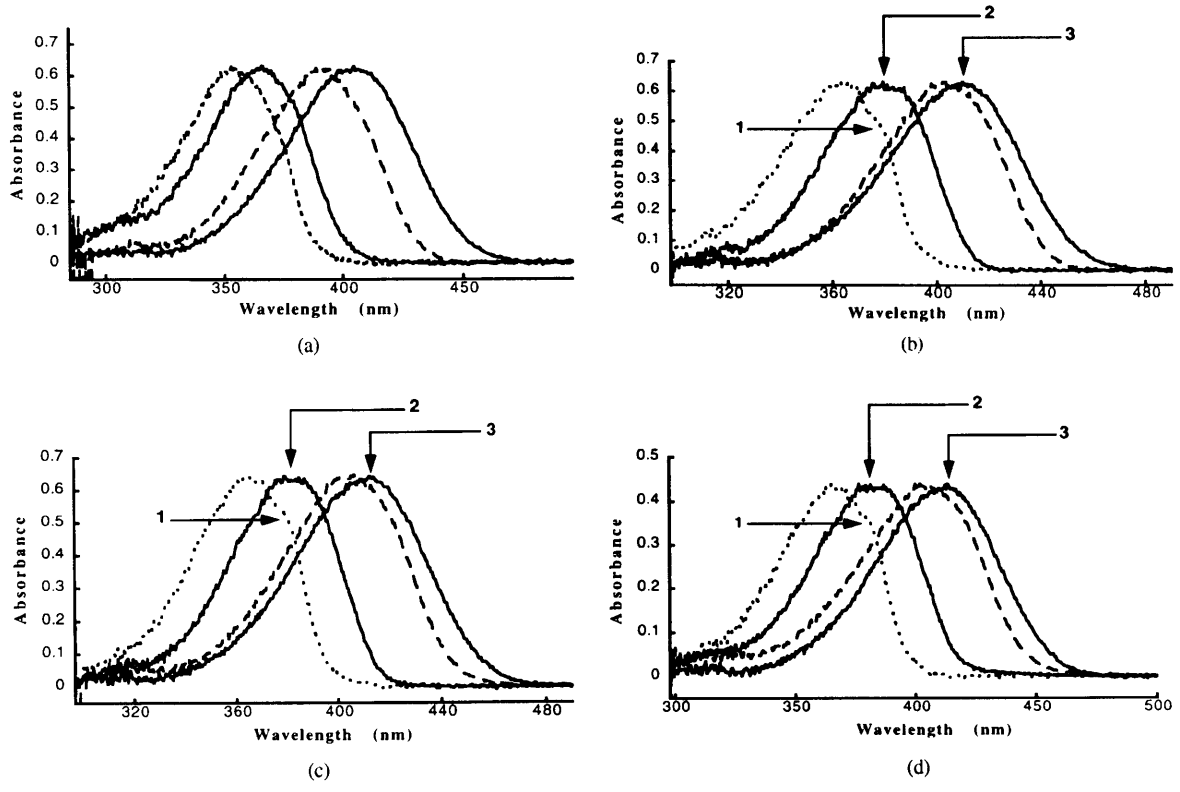


Figure 2. UV–visible spectra of (a) *N,N*-dimethyl-*p*-nitroaniline, (b) *N,N*-diethyl-*p*-nitroaniline, (c) *N,N*-dipropyl-*p*-nitroaniline and (d) *N,N*-dibutyl-*p*-nitroaniline in four solvents from left to right: cyclohexane (·····), tetrachloroethylene (———), *o*-dichlorobenzene (----) and DMSO (———). 1 = 'hump' for cyclohexane; 2 = flattened peak for tetrachloroethylene; 3 = gaussian shaped peak for DMSO

indicator.[11] This might be the case if one wished to compare π^* values obtained from **1b**, **1c** or **1d** with those obtained from **1a**. However, dyes of different structural types need to be evaluated individually. In the case of a homologous series of indicators, bandshape variations should not present a problem provided that (1) the dyes in the series behave in a similar manner and (2) the data are used comparatively.

Solvatochromic characterization

Tables 1 and 2 list values of ν_0 (in cm^{-1}) and $-s$ for **1c** and **1d**. Values for **1a** and **1b** are also listed. The $-s$ values were estimated via two- and seven-point correlation methods. We have not applied the polarizability correction factor (δ)[12,25] to these data since δ was not applied in earlier $-s$ determinations.[10] We wished to obtain our values in a similar manner, to facilitate comparison of data. Our results for **1a** and **1b** (Tables 1 and 2) are consistent in magnitude and trend with previously reported values.[10] The values of $-s$ are ≥3.00

Table 1. Value of ν_0 and $-s$ for DNAP indicators from two-point estimation; comparisons with previous literature for **1a** and **1b**

Indicator	ν_0	$-s$	Ref.
1a	28·10	3·436	10
	28·20	3·456	This work
1b	27·52	3·182	10
	27·58	3·136	This work
1c	27·39	3·007	This work
1d	27·32	3·051	This work

for both **1c** and **1d**, an indication of good spectral shifting capability, although not as good as that of **1a**. The slightly lower $-s$ values for **1c** and **1d**, compared with **1b**, suggest that the longer alkyl chains on these new dyes further increase the solvation sphere of these chromophores, thereby decreasing solvent–dye interactions. While the issue of vibrational structure and bandshape precludes the use of raw peak widths as an

Table 2. Values of ν_0 and $-s$ for DNAP indicators from seven-point estimation; comparisons with previous literature for **1a** and **1b**

Indicator	ν_0	$-s$	r	SD	Ref.
1a	28·10	3·436	0·988	0·150	10
	28·23	3·464	0·993	0·133	This work
1b	27·52	3·182	0·994	0·099	10
	27·57	3·122	0·996	0·096	This work
1c	27·41	3·021	0·994	0·112	This work
1d	27·33	3·002	0·995	0·093	This work

indication of solvent interactions, we do note a slight decrease in the width at half-maximum over the range of **1a–d** for a number of non-HBD solvents.

There is a trend in $-s$ over the range of **1a–d**, beginning with a pronounced decrease on moving from dimethyl (**1a**) to diethyl (**1b**). The values decrease slightly on moving from the diethyl (**1b**) to the dipropyl species (**1c**) and appear to level off with increasing alkyl chain length. The $-s$ values for **1c** and **1d** are reasonably close to one another and to that of **1b**. Consistency in solvatochromic behavior across a homologous series of DNAP π^* indicators will be important as it will allow the data for one probe to be compared more easily with that of another. Our results suggest that as we build longer alkyl chain indicators, we will obtain a series of dyes of increasing lipophilicity with similar solvatochromic and spectroscopic properties. Similarity of properties will be crucial in using the solvatochromic data to elucidate the behavior and orientation of the DNAP indicators in aqueous–organic interfacial environments.

It should be noted that a 45–46 nm separation of visible absorption bands for the DNAP indicators in cyclohexane vs DMSO (i.e. $-s \geq 3{\cdot}00$) is fairly good for the nitroaniline π^* dyes.[10] While solvatochromic indicators such as ET-30 and ET-33 show peak separations up to 300 nm over a range of solvents,[26] these latter shifts can be attributed to the fact that ET-30 and ET-33 respond to a combination of solvent hydrogen bond donor acidity[13] (α) and dipolarity–polarizability[10,11] (π^*).

DNAP indicators in interfacial systems: considerations

Based on the discussions of bandshape variation, one might ask why we did not select a series of dyes for which solvent-dependent bandshape is not a problem. If the sole objective of our study was to obtain indicators whose solvatochromic bands exhibit a constant Gaussian–Lorentzian shape all the way from the gas phase to very polar solvents, then we should pick a different structural form. However, probing organic surfaces from an aqueous solution is a complex task where factors *in addition* to bandshape play a role. These factors include (1) the magnitude of $-s$, (2) the position of the solvatochromic band and (3) the sorptive properties of the indicator.

Consider the following situation. The solvated surface of a micelle may have a π^* that is not too different from that of the adjacent solution. The spectrum of an indicator that is more strongly solvatochromic (i.e. larger $-s$) will display a more prominent peak shift as the dye partitions into the non-polar micellar environment. Dye spectra for micellar solutions that are shifted significantly from that of the adjacent solution are better suited to spectral deconvolution routines.[27–29] Where there is an equilibrium between dye in solution and dye in the adjacent non-polar phase, deconvolution routines are sometimes needed to obtain the spectrum of a dye as it exists on the solvated surface alone.[27–29] The DNAP indicators (**1a–d**) are more strongly solvatochromic ($-s \geq 3{\cdot}00$) than many of the previously reported π^* indicators, the values of $-s$ of which lie between 2·00 and 3·00.[10] Good spectral shifting capability is especially important where bands are broadened owing to multiple interactions of the indicator in the complex interfacial environment.

In using a chemical probe to characterize a solvated surface, it desirable to have a dye whose spectrum is not severely overlapped with that of the sorption medium. The positions of the solvatochromic bands for DNAP indicators lie well within the visible region of the spectrum, a clear advantage with respect to spectral background subtraction. This is not true for all π^* indicators. For example, the solvatochromic band of 4-nitroanisole lies largely within the UV region, where it may overlap with absorption bands due to UV-absorbing substrates. Materials such as hydrocarbon-bonded silicas or micelles of surfactants with an aromatic component show strong UV absorption. Where the spectrum of an indicator is merged with that of a complex substrate, resolving the two contributions can be difficult.

The third consideration is that of sorptive properties. With two hydrocarbon chains, the DNAP indicators have the potential to be fairly hydrophobic. Previous studies of solvated surfaces have shown that **1a** and **1b** are more lipophilic than other small π^* indicators.[16,17] Our preliminary studies on **1c** and **1d** indicate that these longer chain probes bind more strongly to micelles of sodium dodecyl sulfate than **1a** or **1b**.

It is desirable to create a species that is strongly bound and which has good partitioning capability. The solvation sphere of the indicator should be as uniform as possible. Lack of uniformity in the dielectric properties of a dye's solvation environment may present interpretational problems for solvatochromic data obtained in interfacial systems.[30,31]

Trends in pK_{BH^+}

In aqueous systems, compounds **1a–d** possess a solvatochromic band only when the aniline nitrogen is in its unprotonated form. The acid–base and solvatochromic properties of the DNAP indicators are closely tied. A preliminary analysis of the basicity of **1c** and **1d** is therefore warranted. As with the $-s$ values, there are trends in values of pK_{BH^+} for **1a–d** which reflect the effect of increasing alkyl chain length. In this part of our work, we focus on (1) the determination of pK_{BH^+} for **1c** and **1d** and (2) how those values fit in with known trends in the basicity of di-*n*-alkyl-substituted anilines and nitroanilines.[32–37] At this point, we emphasize that values of pK_{BH^+} reveal a small part of the protonation behavior of a weak base.[38;39] Additional thermodynamic measurements[39–42] and solvation parameters which can be obtained from use of alternative acidity functions are ultimately needed in order to create a complete picture.[38,39,43–46]

Values of pK_{BH^+} for **1c** and **1d** are given in Table 3. Previously reported values for *N,N*-dimethyl-*p*-nitroanilinium and *N,N*-diethyl-*p*-nitroanilinium and also values for the homologous series of anilinium ions are listed for comparison. It is known that the trend in the basicity of anilines on moving from the dimethyl to the dibutyl species cannot be explained solely in terms of an inductive effect. If this were the case, then one would expect the basicity to increase linearly with increasing alkyl chain length, as would be predicted from calculated gas-phase acidities.[47] The trend in pK_{BH^+} on moving from *N,N*-dimethyl-*p*-nitroanilinium to *N,N*-dibutyl-*p*-nitroanilinium can be explained in terms of a combination of inductive effects and differential solvation of the nitroaniline vs that of the nitroanilinium ion.

We interpret the relatively large increase in basicity of **1b** over **1a** as being due primarily to inductive effects. However, solvation of B and BH^+ plays a role and may be explained as follows. There is a decrease in solvation of the aniline nitrogen on the diethyl species over that of dimethyl. However, because the alkyl chains are not too long at this point, the corresponding nitroanilinium ions are solvated to the same extents. Hence **1a** is the weaker base of the two.

As the alkyl chains become longer, as in the case of *N,N*-dipropyl- and *N,N*-dibutyl-*p*-nitroanilinium, inductive effects play a smaller role. In addition, there may be a steric hindrance to solvation of the protonated species.[36] Hence the acidity of BH^+ increases as we move from diethyl to dipropyl. An increase in chain length from dipropyl to dibutyl would appear to make little difference in solvation of the protonated form.

We note that the interplay between the electron donor ability of *n*-substituted alkyl groups vs their steric effects has been invoked in the context of $-s$ values for nitroaniline π^* indicators.[10] There may be important links between trends in $-s$ and pK_{BH^+} across a wider range of DNAP indicators, which will be further explored.

Table 3. Estimated values of pk_{BH^+} for di-*n*-alkylanilinium and -*p*-nitroanilinium ions in water at 25 °C

Species	1a	1b	1c	1d
Anilinium	5·98[a] 5·07[b]	6·56[a] 6·52[b]	5·59[a]	5·7[a]
p-nitroanilinium	0·65[c] 0·56	1·75[c] 1·70	1·06	1·08

[a]Ref. 34.
[b]Ref. 35.
[c]Ref. 37.

CONCLUSIONS

New, more hydrophobic, forms of the DNAP π^* indicators, **1c** and **1d**, have a UV–visible spectroscopic behavior that is similar to that of **1b** but not **1a**. Solvent-dependent bandshape occurs in the spectral bands of **1c** and **1d**, and must be accounted for when applying these solvatochromic probes to the characterization of solvents and materials. Values of $-s$ and pK_{BH^+} exhibit variation over the range from dimethyl to dipropyl, **1a–c**. Further increases in alkyl chain length (**1d**) exert a minimal effect on these parameters. We are currently building dipentyl and dihexyl DNAP indicators so that we can further observe and confirm these trends.

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REFERENCES

1. A. Leo, C. Hansch and D. Elkins, *Chem. Rev.* **71**, 525–554 (1971).
2. D. W. Yesair, F. J. Bullock and J. J. Coffey, in *Drug Metabolism Reviews 1*, edited by F. J. Di-Carlo, pp. 37–46. Marcel Dekker, New York (1973).
3. U. F. Westphal and P. K. Knoefel, in *Absorption, Distribution, Transformation and Excretion of Drugs*, edited by P. K. Knoefel, pp. 56–76. Charles C. Thomas, Springfield, IL (1972).
4. D. E. Kile and C. T. Chiou, *Environ. Sci. Technol.* **23**, 832–838 (1989).
5. C. T. Chiou, *Environ. Sci. Technol.* **19**, 57–62 (1985).
6. J. G. Dorsey and K. A. Dill, *Chem. Rev.* **89**, 331–346 (1989).

7. J. G. Dorsey, *Chromatography Mag.* **5**, 13–20 (1987).
8. I. A. Vakser and C. Aflalo, *Proteins* **20**, 320–329 (1994).
9. K. Kobayashi, Y. Asakawa, Y. Kato and Y. Aoyama, *J. Am. Chem. Soc.* **114**, 10307–10313 (1992).
10. M. J. Kamlet, J. L. M. Abboud and R. W. Taft, *J. Am. Chem. Soc.* **99**, 6027–6038 (1977).
11. C. Laurence, P. Nicolet, M. Tawfik Dalati, J. L. M. Abboud and R. Notario, *J. Phys. Chem.* **98**, 5807–5816 (1994).
12. M. J. Kamlet, J. L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.* **48**, 2877–2887 (1983).
13. R. W. Taft and M. J. Kamlet, *J. Am. Chem. Soc.* **98**, 2886–2894 (1976).
14. M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.* **98**, 377–383 (1976).
15. M. A. Kessler and O. S. Wolfbeis, *Chem. Phys. Lipids.* **50**, 51–56 (1989).
16. J. L. Jones and S. C. Rutan, *Anal. Chem.* **63**, 1318–1322 (1991).
17. R. S. Helburn, S. C. Rutan, J. Pompano, D. Mitchem and W. T. Patterson, *Anal. Chem.* **66**, 610–618 (1994).
18. K. Dimroth and C. Reichardt, *Fresenius' Z. Anal. Chem.* **215**, 344–350 (1966).
19. K. A. Zachariasse, N. Van Phuc and B. J. Kozankiewicz, *J. Phys. Chem.* **85**, 2676–2683 (1981).
20. N. Nagornow, *J. Russ. Phys–Chem. Soc.* **29**, 699 (1897).
21. T. Ibata, Y. Isogami and J. Toyoda, *Bull. Chem. Soc. Jpn.* **64**, 42–49 (1991).
22. E. M. Arnett and G. W. Mach, *J. Am. Chem. Soc.* **86**, 2671–2677 (1964).
23. L. P. Hammett, *Physical Organic Chemistry: Reaction Rates, Equilibria and Mechanisms*, 2nd ed., Chapt. 9. McGraw-Hill, New York (1970).
24. P. Nicolet and C. Laurence, *J. Chem. Soc., Perkin Trans 2* 1071–1079 (1986).
25. M. J. Kamlet, T. N. Hall, J. Boykin and R. W. Taft *J. Org. Chem.* **44**, 2599–2604 (1979).
26. C. Reichardt, *Chem. Rev.* **94**, 2319–2358 (1994).
27. S. C. Rutan, *Anal. Chem.* **63**, 1103A–1109A (1991).
28. Y. Hayashi, S. C. Rutan, R. S. Helburn and J. M. Pompano, *Chemom. Intell. Lab. Syst.* **20**, 163–167 (1993).
29. S. C. Rutan, personal communication.
30. C. Lerf and P. Suppan, *J. Chem. Soc., Faraday Trans.* **88**, 963–969 (1992).
31. L. Onsager, *J. Am. Chem. Soc.* **58**, 1486–1493 (1936).
32. N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.* **54**, 3469–3485 (1932).
33. H. C. Brown and A. Cahn, *J. Am. Chem. Soc.* **72**, 2939–2943 (1950).
34. H. T. Taylor, *Nature (London)* **181**, 265 (1958).
35. E. Folkers and O. Runquist, *J. Org. Chem.* **29**, 830–832 (1964).
36. C. P. Nash and G. E. Maciel, *J. Phys. Chem.* **68**, 832–836 (1964).
37. J. W. Eastes, M. H. Aldridge and M. J. Kamlet, *J. Chem. Soc. B* 922–928 (1969).
38. V. Lucchini, G. Modena, G. Scorrano, R. A. Cox and K. Yates, *J. Am. Chem. Soc.* **104**, 1958–1959 (1982).
39. A. Bagno, R. L. Boso, N. Ferrari and G. Scorrano. *J. Chem. Soc., Chem. Commun.* 2053–2054 (1995).
40. S. Bohm, M. Decouzon, O. Exner, J. F. Gal and P. C. Maria, *J. Org. Chem.* **59**, 8127–8131 (1994).
41. M. Meot-Ner and L. W. Sieck, *J. Am. Chem. Soc.* **105**, 2956–2961 (1983).
42. B. Wilson, R. Georgiadis and J. E. Bartmess, *J. Am. Chem. Soc.* **113**, 1762–1766 (1991).
43. R. A. Cox and K. Yates, *J. Am. Chem. Soc.* **100**, 3861–3867 (1978).
44. J. F. Bunnett and F. P. Olsen, *Can J. Chem.* **44**, 1899–1916 (1966).
45. A. Bagno, V. Lucchini and G. Scorrano, *Can. J. Chem.* **68**, 1746–1749 (1990).
46. A. Bagno, G. Scorrano and R. A. More O'Ferrall, *Rev. Chem. Intermed.* **7**, 313–352 (1987).
47. J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th ed., Chapt. 8. Wiley, New York (1992).