

## Pyridinium-*N*-phenolate betaine dyes as empirical indicators of solvent polarity: Some new findings<sup>\*,‡</sup>

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**Abstract:** Solutions of the zwitterionic betaine dye 2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate (hereinafter called *standard betaine dye*) and its derivatives are solvatochromic, thermochromic, piezochromic, and halochromic. That is, the position of its longest-wavelength intramolecular charge-transfer (CT) absorption band depends on solvent polarity, solution temperature, external pressure, and the type and concentration of salts (ionophores) added to the betaine dye solution. The outstanding large negative solvatochromism of this standard betaine dye has been used to establish UV/vis spectroscopically a comprehensive set of empirical parameters of solvent polarity, called  $E_T(30)$  resp.  $E_T^N$  values, now known for many molecular and ionic solvents as well as for a great variety of solvent mixtures. This report describes relevant physicochemical properties of this standard betaine dye as well as the definition and some more recent practical applications of these solvent polarity parameters, derived from the standard betaine dye and its derivatives. In particular, the perichromism of the standard betaine dye can be used to study the polarity of microheterogeneous solutions (e.g., micelles and other organized media), surfaces (e.g., silica, alumina, cellulose), glasses (e.g., sol-gel systems), and solids (e.g., polymers), and for the construction of chemical sensors. As extension to solvatochromism, the more general term perichromism describes UV/vis band shifts of chromophore-containing solutes which are caused not only by changes in the surrounding solvent sphere, but also by their embedding in other surroundings such as micelles, vesicles, glasses, polymers, solids, interfaces, and surfaces. Some representative examples for such extended applications of the perichromic standard betaine dye are given.

**Keywords:** betaine dye; solvatochromism; solvent polarity; solvent polarity parameters; perichromism; thermochromism.

### INTRODUCTION

When UV/vis absorption spectra of suitable chromophores are measured in solvents of different polarity, the position, intensity, and shape of their absorption (and emission) bands are usually modified to a greater or lesser extent. A pronounced hypsochromic band shift with increasing solvent polarity is called *negative solvatochromism*, a corresponding bathochromic band shift is termed *positive solvatochromism* [1–3]. This solvatochromism stems from the differential solvation of the ground and first

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excited state of the solute chromophore by means of nonspecific and specific intermolecular solute/solvent interactions, which stabilize ground and excited state to a different extent: better energetic stabilization of the ground state relative to the excited state leads to negative solvatochromism, higher stabilization of the excited state relative to the ground state to positive solvatochromism. Because UV/vis spectra of dissolved chromophores are not only influenced by the surrounding solvent sphere but also by other surroundings such as micelles, vesicles, gels, polymers, glasses, solids, and surfaces, the use of the more general term *perichromism* (from Greek *peri* = around) for this phenomenon has been recommended [4].

Chemists usually attempt to understand such solvent influences in terms of the so-called *solvent polarity*, an expression that can be found nowadays in all chemistry textbooks. But what does solvent polarity really mean?

The simplicity of electrostatic models for solute/solvent interactions, considering solvents as an isotropic nonstructured dielectric continuum, has led to the use of macroscopic physical constants such as relative permittivity (“dielectric constant”), index of refraction, density, surface tension, vapor pressure, cohesive pressure, etc. (or functions thereof) as physical parameters of solvent polarity.

However, solute/solvent interactions take place on a molecular-microscopic level, with mutually interacting individual solvent molecules surrounding the ions or molecules of the solute, which is dissolved in a more or less structured noncontinuous medium. Solvent molecules are characterized by molecular properties such as dipole moment, electronic polarizability, hydrogen-bond donor (HBD) and hydrogen-bond acceptor (HBA) capability, electron-pair donor (EPD) and electron-pair acceptor (EPA) capability, etc. According to the extent of these intermolecular solvent/solvent interactions, there exist highly structured solvents (e.g., water with its strong directional hydrogen bonds, forming an intermolecular network with cavities) and less structured solvents (e.g., hydrocarbons with their weak nondirectional dispersion forces, filling the available space in a more regular manner) [5,6].

Therefore, in correlating solvent effects on chemical reactions and physical absorptions and emissions, the pure electrostatic approach often failed.

Hence, from a more pragmatic point of view, it is reasonable to define solvent polarity simply as the solvent’s overall *solvation capability* (or *solvation power*), as proposed by the author already in 1965 [7]. Accordingly, solvent polarity is simply defined as the “overall solvation capability (i) for educts and products, which determines the position of chemical equilibria; (ii) for reactants and activated complexes (“transition states”), which influences reaction rates; and (iii) for ions or molecules in their ground and first excited state, which is responsible for light absorptions and emissions in the various wavelength regimes. This overall solvation capability depends on *all*, nonspecific and specific, intermolecular solute/solvent interactions, however, excluding such interactions which lead to definite chemical alterations of the ions or molecules of the solute” [7,8].

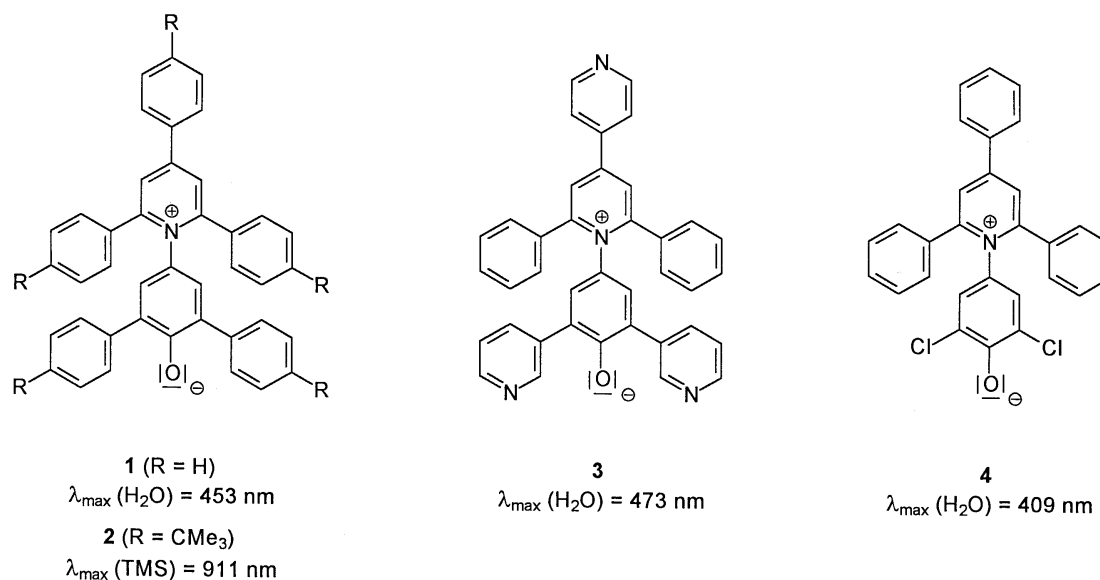
Obviously, solvent polarity such defined cannot be characterized by means of single macroscopic physical solvent parameters such as relative permittivity ( $\epsilon_r$ ), etc. Solvent polarity should be better measured empirically by means of convenient, well-understood, solvent-dependent reference processes such as, for example, the solvolysis of 2-chloro-2-methylpropane, leading to Winstein’s *Y* values [9], or the UV/vis absorption of solvatochromic 1-ethyl-4-(methoxycarbonyl)pyridinium iodide, leading to Kosower’s *Z* values [10]. A carefully selected, appropriate, sufficiently solvent-sensitive reference process, reflecting all intermolecular solute/solvent interactions as well as possible, and the empirical solvent parameters derived therefrom, can then be used to correlate other related solvent-dependent processes more effectively. This procedure is quite common in physical organic chemistry: the well-known Hammett substituent constants ( $\sigma$ ) are nothing else as empirical parameters, derived from the ionization of *meta*- and *para*-substituted benzoic acids in water at 25 °C as substituent-dependent reference process, commonly used for the correlation of substituent effects on other chemical equilibria and reaction rates [11].

Particularly useful for the empirical determination of solvent polarities are solvatochromic indicator dyes, the UV/vis absorption of which can be easily measured in a large variety of solvents, only

limited by the solubility and chemical stability of the probe dye [1,12]. By virtue of their exceptional large negative solvatochromism, *pyridinium-N-phenolate betaine dyes* are particularly suitable as UV/vis spectroscopic indicators of solvent polarity, using their long-wavelength intramolecular charge-transfer (CT) vis absorption band as easy to measure solvent-dependent reference process [12,13].

### PYRIDINIUM-*N*-PHENOLATE BETAINES AND THE $E_T(30)$ AND $E_T^N$ VALUES

The molecular structure of the pyridinium-*N*-phenolate betaine dyes **1–4**, mostly used for solvatochromic measurements, are shown in Scheme 1.



**Scheme 1** Molecular structures of some negatively solvatochromic pyridinium-*N*-phenolate betaine dyes **1–4**, commonly used as empirical solvent polarity indicators. **1**: standard dye for the determination of  $E_T(30)$  resp.  $E_T^N$  values [13]; **2**: more lipophilic penta-*t*-butyl-substituted dye for nonpolar solvents in which **1** is not soluble [13b]; **3**: more hydrophilic tripyridyl-substituted dye for aqueous solutions in which **1** is only sparingly soluble [16]; **4**: less basic dichloro-substituted dye for more acidic solutions, used for the determination of  $E_T(33)$  values [18].

The solvatochromic absorption band of standard betaine dye **1** is shifted from  $\lambda_{\max} = 810 \text{ nm}$  in diphenyl ether to  $\lambda_{\max} = 453 \text{ nm}$  in water as solvent, corresponding to a solvent-induced band shift of  $\Delta\lambda = -357 \text{ nm}$  (i.e.,  $\Delta\bar{\nu} = 9730 \text{ cm}^{-1}$  resp.  $\Delta E_T = 28 \text{ kcal/mol} = 117 \text{ kJ/mol} = 1.2 \text{ eV}$ ). This solvatochromic band shift can easily be seen with the naked eye: the solution color of **1** is red in methanol, violet in ethanol, blue in propan-2-ol, green in acetone, and yellowish-green in methoxybenzene [14]. This color change can be best demonstrated with binary mixtures of solvents with different polarity (e.g., methanol/acetone). Some simple classroom experiments to demonstrate visually the different polarity of organic solvents can be found in the *Journal of Chemical Education* [15]. For nice graphical illustrations of this solvent-dependent play of colors for solutions of **1**, see ref. [14].

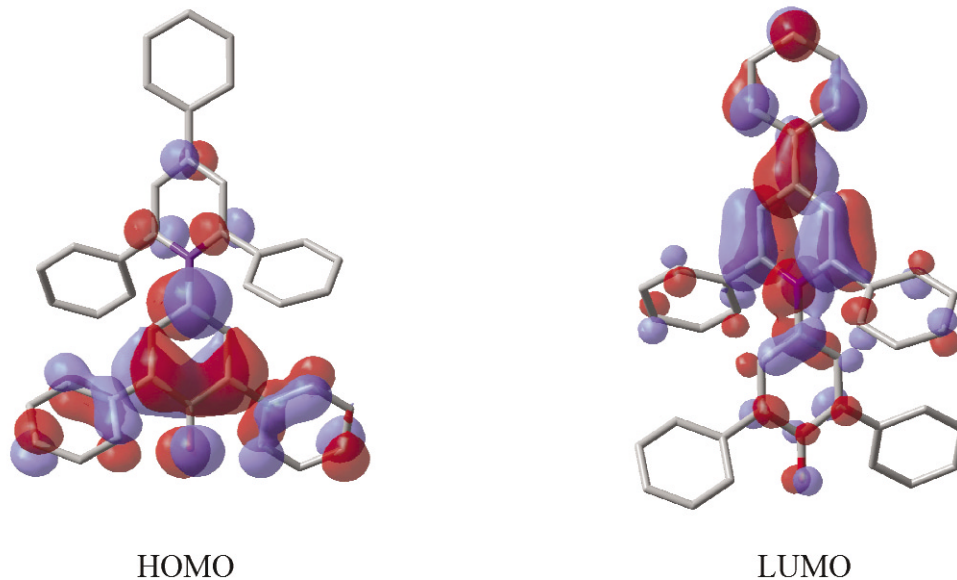
Because the standard betaine dye **1** is not soluble in nonpolar solvents such as hydrocarbons and only sparingly soluble in water, the more lipophilic penta-*t*-butyl-substituted betaine dye **2** [13b] and the better water-soluble pyridyl-substituted dye **3** [16] have been used as secondary probe dyes for the determination of solvent polarities of nonpolar and aqueous media, respectively. Pyridinium-*N*-phenolate betaine dyes cannot be used in acidic solvents because in such solvents the phenolate oxygen atom is (reversibly) protonated and the long-wavelength solvatochromic CT absorption band disappears. To

overcome this disadvantage, some less basic betaine dyes have been synthesized [17,18], amongst them the 2,6-dichlorosubstituted probe dye **4**, which is suitable for weak acidic media [18]. The  $pK_a$  value of its conjugated acid is with 4.78 nearly four orders of magnitude smaller than that of the conjugated acid of **1** (with  $pK_a = 8.65$ ).

By variation of the five peripheral phenyl groups of the basic betaine chromophore **1** by substitution or replacement, a great variety of further pyridinium-*N*-phenolate betaine dyes has been synthesized in order to adapt these indicator dyes for the intended application. Compilations of these betaine dye derivatives, together with a manifold of applications of the solvent polarity parameters derived therefrom, have already been published in earlier reports in this journal [19].

According to their inherent molecular structure (Scheme 1), (i) betaine dyes **1–4** exhibit large permanent dipole moments, suitable for the registration of dipole/dipole and dipole/induced dipole interactions; (ii) they possess large polarizable  $\pi$ -electron systems with altogether 44  $\pi$ -electrons, suitable for the registration of dispersion interactions; and (iii) the phenolate oxygen atom exhibits a highly basic EPD center, suitable for the interaction with hydrogen-bond donor solvents (HBA/HBD interactions) and with Lewis acids (EPD/EPA interactions). The positive charge of the pyridinium moiety is delocalized, therefore, interactions with EPD solvents (Lewis bases) are small and negligible.

The betaine dyes **1–4** are not planar: the X-ray structure determination of a 4-bromo-substituted derivative of **1** shows that the interplanar angle between the pyridinium and the phenolate moiety amounts to  $65^\circ$ , at least in the crystal lattice [20]. Recent AM1 and semi-empirical ZINDO-PCM calculations of the geometry and solvatochromism of betaine dye **1** have led to an interplanar angle of ca.  $49^\circ$  in the gas phase [21]. The representation of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of dye **1** in Fig. 1, calculated by the ZINDO method for the gas-phase molecule, demonstrates nicely the intramolecular CT connected with the electronic transition from the ground (HOMO) to the first excited state (LUMO) of **1**.



**Fig. 1** Representation of the HOMO and LUMO of betaine dye **1**, calculated with a semi-empirical ZINDO method by Mennucci et al. [21]:  $\lambda_{\max}$  (calculated) = 1017 nm (gas phase). Reprinted with permission of the authors and the publisher of *Molecular Physics*, Taylor & Francis Ltd. (<<http://www.informaworld.com>>).

Direct experimental evidence for the light-induced intramolecular CT within betaine dye **1** on excitation has recently been given by Schmuttenmaer et al. [22]: the electromagnetic radiation that is emitted from dissolved betaine molecules (oriented by an external electric field of ca. 10 kV/cm) on laser-induced photoexcitation has been directly measured. The light-induced CT is accompanied by movement of electronic charge from the phenolate to the pyridinium moiety and undergoes acceleration by the external electric field. This charge acceleration generates an electromagnetic transient emission which was directly measured in the terahertz ( $10^{12}$  Hz) region. The dipole moment decreases and changes its direction upon photoexcitation from ca. 15 D in the ground state to ca. -6 D in the excited state. That means, the excited-state dipole moment is antiparallel to the ground-state dipole moment and the dipole flip on photoexcitation amounts up to  $16 - (-6) = 21$  D!

The empirical parameters of solvent polarity,  $E_T(30)$ , derived from the CT vis absorption of **1**, are simply defined as molar transition energies (in kcal/mol) of the standard betaine **1** according to eq. 1,

$$E_T(30) \text{ (kcal/mol)} = h \cdot c \cdot \tilde{\nu}_{\max} \cdot N_A = 28591/\lambda_{\max} \text{ (nm)} \quad (1)$$

where  $\tilde{\nu}_{\max}$  is the wavenumber and  $\lambda_{\max}$  the wavelength of the long-wavelength CT absorption maximum of betaine dye no. **30** (= **1**), and  $h$ ,  $c$ , and  $N_A$  are Planck's constant, the speed of light, and Avogadro's constant, respectively. In the first publication [13a], the standard betaine dye **1** had by chance the formula number **30**. High  $E_T(30)$  values correspond to high solvent polarity.

The  $E_T$  values of the dichloro-substituted dye **4** have been accordingly designated as  $E_T(33)$  values by Kessler and Wolfbeis [18];  $E_T(31)$  and  $E_T(32)$  values are not known. The  $E_T$  values of dyes **1–4** are linearly correlated with each other, and the  $E_T$  values of dyes **2–4** have been used to calculate  $E_T(30)$  values for such solvents in which betaine dye **1** is not soluble enough or is protonated. For example, the  $E_T(30)$  and  $E_T(33)$  values are linearly correlated by eq. 2 [23]:

$$E_T(30) \text{ (kcal/mol)} = 0.9953 \cdot E_T(33) \text{ (kcal/mol)} - 8.1132 \quad (2)$$

$(n = 20; r = 0.9926; s = 0.8320)$

The  $E_T(30)$  solvent polarity scale ranges from 63.1 kcal/mol for water to 30.7 kcal/mol for tetramethylsilane (TMS). In order to avoid the non-SI unit "kcal/mol" and the recalculation into the SI-unit "kJ/mol", the dimensionless normalized  $E_T^N$  scale was introduced [13b], using water ( $E_T^N = 1.00$ ) and TMS ( $E_T^N = 0.00$ ) as reference solvents, according to eq. 3:

$$E_T^N = [E_T(\text{solvent}) - E_T(\text{TMS})] / [E_T(\text{water}) - E_T(\text{TMS})] = [E_T(\text{solvent}) - 30.7] / 32.4 \quad (3)$$

$E_T(30)$  and  $E_T^N$  values are known for many molecular solvents as well as binary and ternary solvent mixtures; for collections of  $E_T$  values available until 1994 see refs. [1a,12b]. More recently,  $E_T$  values have also been determined for numerous room-temperature fluid ionic liquids; for a compilation, see ref. [24]. Solvatochromic parameters for supercritical (sc) fluids have recently been reviewed by Marcus [25].

A selection of molecular and ionic solvents, the  $E_T$  values of which have been more recently determined, is given in Table 1. This collection contains  $E_T$  values for some carbonic acid esters used as nonaqueous electrolyte solvents in lithium batteries [26]; for piperylene sulfone recommended as labile ("switchable") and easily recyclable dimethyl sulfoxide (DMSO) substitute [27]; for ( $\pm$ )-tetrahydro-2-methylfuran used as frozen organic glass in matrix isolation techniques [28]; for a group of alkanolamines of industrial importance [29]; for some imidazol-based molecular [30], zwitterionic [31], and ionic solvents [30,32,33]; as well as for supercritical fluid (scf) carbon dioxide [34]. Further  $E_T$  values can be easily determined by everyone because betaine dyes **1** and **4** are commercially available [35] and **2** and **3** can be easily synthesized [13b,16].

**Table 1**  $E_T(30)$  values (in kcal/mol) and dimensionless normalized  $E_T^N$  values of some new molecular and ionic solvents, measured at 25 °C and 1 bar; for comprehensive collections, see refs. [1a,12b,24a].

Solvents	$E_T(30)$	$E_T^N$	Refs.
Water (most polar solvent)	63.1	1.000 <sup>a</sup>	[12,13]
Tetramethylsilane (least polar solvent)	30.7	0.000 <sup>a</sup>	[12,13]
.....			
1,3-Dioxolan-2-one, ethylene carbonate (40 °C)	48.6	0.552	[13b,26]
4-Methyl-1,3-dioxolan-2-one, propylene carbonate	46.0	0.472	[12b,26]
4,5-Dimethyl-1,3-dioxolan-2-one, 2,3-butylene carbonate	45.7	0.463	[26]
Ethyl methyl carbonate	37.3	0.204	[26]
.....			
2,5-Dihydro-2-methylthiophene 1,1-dioxide, piperylene sulfone (m.p. -12 °C)	45.1	0.444	[27]
(±)-Tetrahydro-2-methylfuran			
(i) at 25 °C as liquid solution	37.2	0.201	[13b,28]
(ii) at -196 °C as frozen glass	50.0	0.596	[28]
.....			
2-Aminoethanol, ethanolamine	51.8	0.651	[13b,29]
Bis(2-hydroxyethyl)amine, diethanolamine	53.1	0.691	[29]
Tris(2-hydroxyethyl)amine, triethanolamine	53.7	0.710	[29a]
2-(Methylamino)ethanol, <i>N</i> -methyl-ethanolamine	52.8	0.682	[29a]
<i>N,N</i> -Bis(2-hydroxyethyl)methylamine	51.9	0.654	[29a]
(±)-1-Amino-2-propanol, isopropanolamine	52.3	0.667	[29a]
Bis(2-hydroxy-1-propyl)amine, diisopropanolamine	50.6	0.614	[29a]
Tris(2-hydroxy-1-propyl)amine, triisopropanolamine	49.5	0.580	[29a]
.....			
1-Methylimidazol	44.6	0.429	[30]
1-(1-Butyl)imidazol	42.1	0.352	[30]
1-Ethylimidazol-3-tri(1-butyl)borane complex	43.5	0.395	[31]
1-Allylimidazol-3-tri(1-butyl)borane complex	42.9	0.377	[31]
[BMIm] <sup>+</sup> BF <sub>4</sub> <sup>-b</sup>	52.4	0.670	[32]
[BMIm] <sup>+</sup> PF <sub>6</sub> <sup>-b</sup>	52.4	0.670	[30,33]
[BMIm] <sup>+</sup> Tf <sub>2</sub> N <sup>-b</sup>	51.8	0.651	[30,33]
[BMIm] <sup>+</sup> N(CN) <sub>2</sub> <sup>-b</sup>	51.1	0.630	[33]
.....			
Supercritical fluid (scf) carbon dioxide ( $t_C = 31.0$ °C; $p_C = 7.38$ MPa)			
(i) at 35 °C and 20.68 MPa	29.0	-0.053 <sup>c</sup>	[34a]
(ii) at 40 °C and 20 MPa	29.0	-0.053 <sup>c</sup>	[34b]
(iii) at 40 °C and 50 MPa	32.4	0.053	[34b]

<sup>a</sup>By definition; see eq. 3.

<sup>b</sup>[BMIm]<sup>+</sup> is 1-methyl-3-(1-butyl)imidazolium; Tf<sub>2</sub>N<sup>-</sup> is bis(trifluoromethanesulfonyl)amide.

<sup>c</sup>The negative sign of the  $E_T^N$  values simply means that scf-CO<sub>2</sub> under these conditions is a little less polar than tetramethylsilane, the nonpolar reference compound for the  $E_T^N$  scale.

Three of the results given in Table 1 are remarkable. First, the polarity of ionic liquids such as the mentioned 1,3-dialkylimidazolium salts is with  $E_T(30) \approx 52$  kcal/mol not exceedingly high, but rather moderate within the range of the polarities of ethanol [ $E_T(30) = 51.9$  kcal/mol] and *N*-methylacetamide [ $E_T(30) = 52.0$  kcal/mol]. This corresponds to the rather low relative permittivities of  $\epsilon_r \approx 10$ –15 found for these imidazolium-based ionic liquids [36].

Second, the polarity of scf carbon dioxide is very low and in the range of saturated hydrocarbons such as cyclohexane [ $E_T(30) = 30.9$  kcal/mol]. Increasing the external pressure increases its polarity

somewhat, but its solvency remains nevertheless low [25,34]. Therefore, more polar CO<sub>2</sub>-expanded liquids such as methanol/CO<sub>2</sub> and acetone/CO<sub>2</sub> have recently gained in importance as reaction media [34a,37]. Such gas-expanded liquids (GXLs) are intermediate in their polarities between normal molecular liquids and supercritical fluids. In addition, the solvent strength of mixtures of CO<sub>2</sub> with various ionic liquids has been measured by means of solvatochromic probe dyes with the result that the strong “dipolar probe/ion” interactions are practically not influenced by the added CO<sub>2</sub> [38].

Third, the solvation capability of solvents is strongly temperature-dependent. This temperature dependence of solvent polarity can be easily studied also by pyridinium-*N*-phenolate betaine dyes such as **1** and **2**, the solutions of which are thermo-solvatochromic [12]. As shown in Table 1, the polarity of the less polar cyclic ether (±)-tetrahydro-2-methylfuran increases from  $E_T(30) = 37.2$  to 50.0 kcal/mol ( $\Delta E_T = 12.8$  kcal/mol) by decreasing the temperature from +25 to -196 °C ( $\Delta t = 221$  °C) [28]. Obviously, the effective polarity of the cybotactic region surrounding the betaine dye as frozen glass at -196 °C is much higher and reaches that of propan-1-ol [ $E_T(30) = 50.7$  kcal/mol].

Particularly useful are solvatochromic indicator dyes for the study of solvent mixtures with regard to the so-called *preferential* or *selective solvation* of dye solutes by one component of the bulk mixture [6b]. Preferential solvation means that there is an excess of the more polar solvent in the solute solvation shell as compared to the bulk composition. If the preference dominates to such an extent that one component is practically excluded from the solute solvation shell, then it is called selective solvation [6b].  $E_T(30)$  values for numerous binary mixtures of molecular and ionic solvents have been reported, demonstrating this phenomenon; see Table 3 in ref. [12b].  $E_T(30)$  values are available even for some ternary solvent mixtures [39]. Some leading recent references will guide the reader to many solvent mixtures of practical interest [14e,40–47]. Amongst them are also mixtures of molecular with ionic solvents, the solvatochromically determined solvent polarity of which is of particular importance [30,32,39c]. Mixtures of gasoline with ethanol are another topical binary solvent system and are used as automotive fuel in some countries. Betaine dye **2** can be used for the qualitative (and quantitative) analysis of such automotive fuels: solutions of **2** in pure gasoline are blue–green ( $\lambda_{\max} = 666$  nm), in pure ethanol violet ( $\lambda_{\max} = 568$  nm), and in gasoline with 25 vol % ethanol green–blue, which allows a simple naked-eye detection of ethanol in gasoline [47]. A more detailed analysis of the variation of  $\lambda_{\max}$  of **2** with the composition of the ethanol/gasoline mixture exhibits the expected preferential solvation of **2** by ethanol.

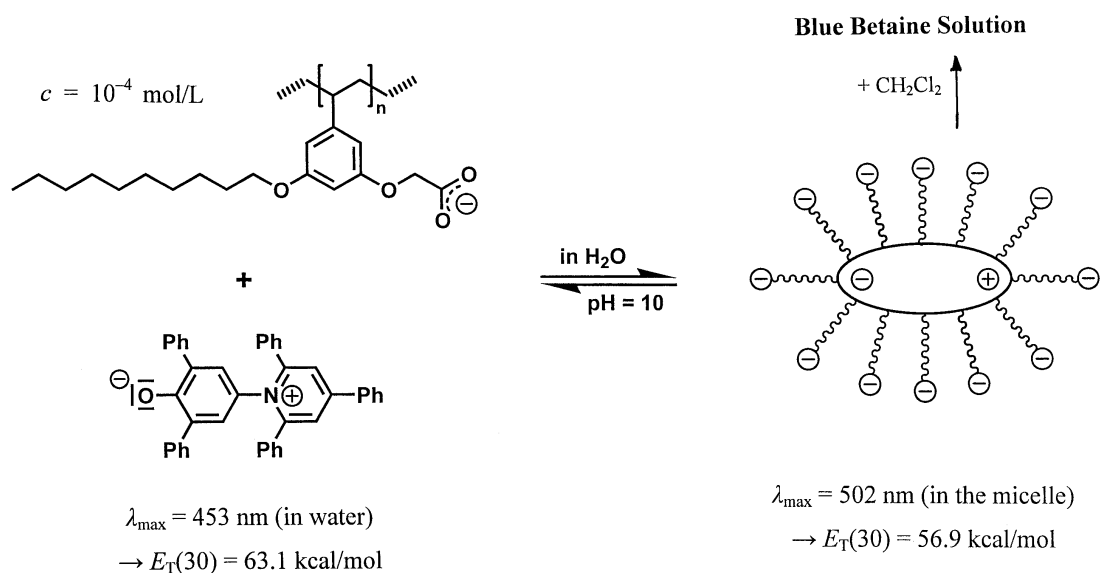
Sometimes, synergic solvent effects have been found for particular binary solvent mixtures as a result of strong intermolecular solvent/solvent interactions, mainly by means of H-bonding, which leads to an enhanced polarity of the solvent mixture, being larger as that of the two pure solvent components, which are usually a combination of HBD and HBA solvents [6b,40b,41b]. The first examples studied were mixtures of trichloromethane (HBD solvent) with acetone, DMSO, and some trialkyl phosphates (HBA solvents) [40b]. In these cases, the H-bonded species  $X=O\cdots H-CCl_3$  ( $X = C, S, P$ ) behaves as a more polar solvent than the two components alone; for further examples, see ref. [41b].

## $E_T(30)$ VALUES OF MICROHETEROGENEOUS SOLVENT SYSTEMS

Microheterogeneous or molecularly organized media comprise, among others, solutions of surfactants and dendrimers, micelles, oil-in-water and water-in-oil microemulsions, bilayer membranes, and vesicles. For example, amphiphilic molecules such as surfactants can self-associate to a variety of structured assemblies in aqueous solution above the so-called critical micelle concentration (cmc). Such a micelle consists of three different parts: the nonpolar interior, the hydrocarbon core, and the hydrophilic charged head groups located at the micelle/water surface (Stern layer). The micropolarity of these different micellar regions can be determined by means of solvatochromic dyes such as the pyridinium-*N*-phenolate betaines, which are incorporated into the micellar system under suitable conditions. First examples using betaine **1** as probe dye can be found in Table 5 of ref. [12b]; some more recent examples shall demonstrate the usefulness of this approach.

The micellization with increasing concentration of zwitterionic homologous tetraalkylammonium carboxylates,  $R-N^+Me_2-CH_2-CO_2^-$  ( $R = C_9-C_{17}$ ), in aqueous solution can be easily followed UV/vis spectroscopically after addition of betaine dye **1**, showing a strong decrease of the  $E_T(30)$  value after reaching the cmc, due to the transfer of the dye molecules from the aqueous into the less polar micellar microenvironment. In this way, the corresponding cmc values can be easily determined, which were in good agreement with cmc values derived from surface tension measurements [48a]. However, it should be mentioned that for some “ionic dye/ionic or zwitterionic surfactant” mixtures significant UV/vis band shifts have been already observed before the “true” cmc of homomicelles is reached, because of the formation of pre-micellar dye/surfactant aggregates; for recent examples, see refs. [48b–d].

The solubilization of the rather lipophilic betaine dye **1** in water has also been carried out by means of an amphiphilic polystyrene-based homopolymer, which forms polymeric micelles in aqueous solution, as shown in Scheme 2 [49].



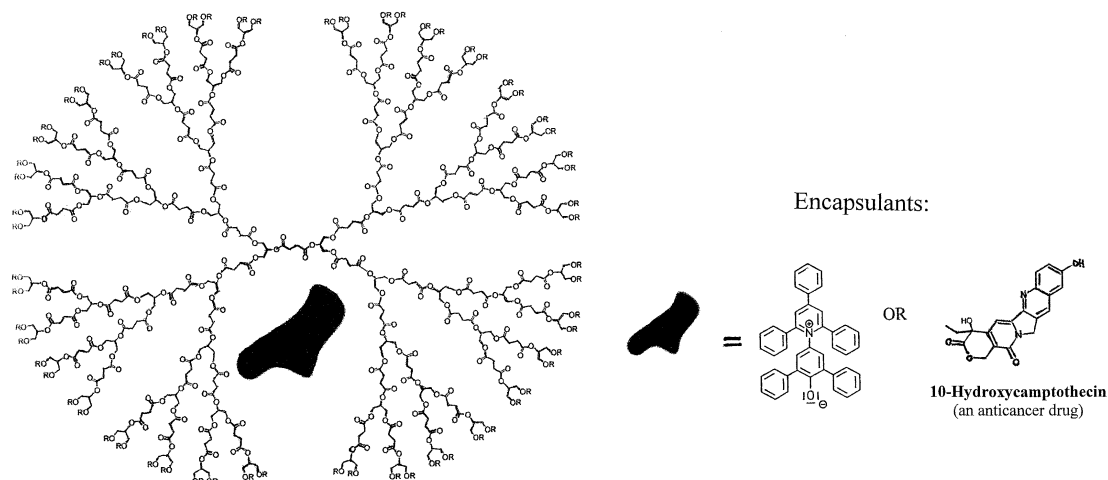
**Scheme 2** Solubilization of betaine dye **1** in water at pH = 10 by means of an amphiphilic micelle-forming polystyrene-based homopolymer [49].

Inclusion of **1** into the polymeric micelles leads to a decrease of  $E_T(30)$  from that of pure water (63.1 kcal/mol) to that of the micellar interior (56.9 kcal/mol), which corresponds to a decrease in polarity by  $\Delta E_T = 6.2$  kcal/mol, which is now in the region of glycerol (57.0 kcal/mol) [49]. By extraction of the aqueous micellar solution, containing dye **1** and the polymer, with dichloromethane, the sequestered dye is released to the organic layer to give a blue dichloromethane solution of **1**, whereas the polymer was retained in the water layer. The nanocontainer properties of this amphiphilic polymer indicate its potential as a vehicle for controlled drug delivery [49]. A major problem in pharmaceutical industry is the often poor solubility and instability of drugs in the body's aqueous environment, which reduces their therapeutic effectiveness. Therefore, polymers are sought after which can serve as supramolecular shuttles for less water-soluble and -instable drugs.

Another application of solvatochromic betaine dyes for model studies of controlled drug release is shown in Scheme 3. Betaine dye **1** can be encapsulated within a poly(glycerol/succinic acid) (PGLSA) dendrimer as a colored model substance in place of the anticancer drug 10-hydroxy-camptothecin, which is also poorly water-soluble [50].



Whereas dye **1**, dissolved in water, absorbs at  $\lambda_{\max} = 453 \text{ nm}$  ( $E_T = 63.1 \text{ kcal/mol}$ ), the encapsulated dye absorbs with  $503 \text{ nm}$  ( $E_T = 56.8 \text{ kcal/mol}$ ) at much longer wavelength ( $\Delta\lambda = 50 \text{ nm}$ ), which corresponds to the polarity of glycerol ( $E_T = 57.0 \text{ kcal/mol}$ ) or of a methanol/water (80:20 v/v) mixture ( $E_T = 56.6 \text{ kcal/mol}$ ), showing that the interior environment of the dendritic macromolecule is distinctly less polar than water [50]. The nevertheless rather high  $E_T$  value found for the dendrimer interior shows that this supramolecular assembly is additionally penetrated by water molecules. The maximum number of betaine dye molecules encapsulated within the [G4] dendrimer shown in Scheme 3 is approximately two, which corresponds to a ca. 2000-fold improvement of the dye solubility in water without dendrimer [50].

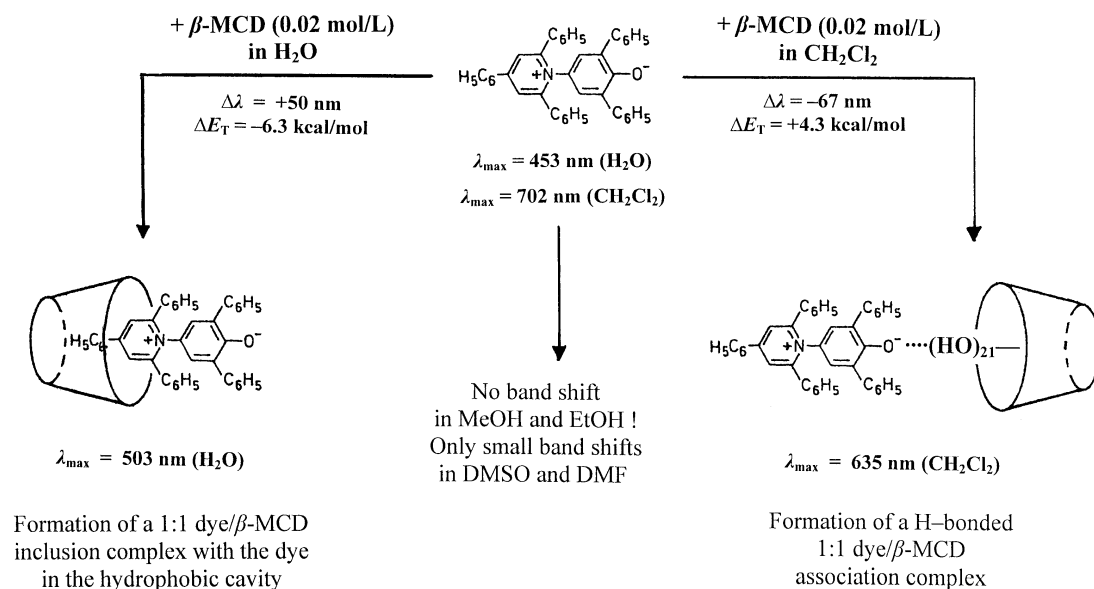


Biodendrimer with  $R = \text{H}$  or  $\text{CO-CH}_2\text{-CH}_2\text{-CO}^- \text{Na}^+$

**Scheme 3** Solubilization of betaine dye **1** (and the anticancer drug 10-hydroxy-camptothecin) in water by means of the poly(glycerol/succinic acid) biodendrimer [G4]-PGLSA-OH ( $R = \text{H}$ ). Biodendrimer = dendrimer composed of biocompatible monomers such as glycerol and succinic acid [50].

Recent attempts have been made to study the local polarity of specific cavities in biopolymers such as DNA by means of solvatochromic and fluorosolvatochromic probe dyes [51]. Solvatochromic band shifts caused by dye inclusion into protein interiors have been called *enzymichromism* [52]. The interaction of betaine dye **1** with methyl- $\beta$ -cyclodextrin ( $\beta$ -MCD) in various solvents has been studied vis-spectroscopically (Scheme 4) [53].

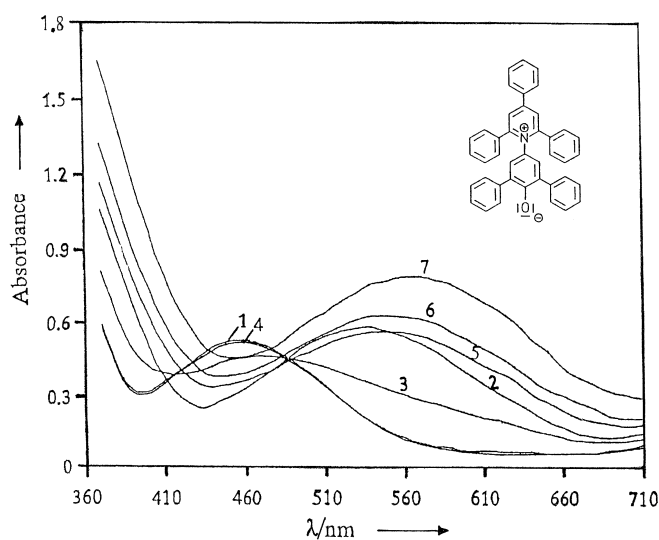
Addition of  $\beta$ -MCD to aqueous solutions of **1** leads to a distinct bathochromic band shift of  $\Delta\lambda = +50 \text{ nm}$  ( $453 \rightarrow 503 \text{ nm}$ ), suggesting the formation of a 1:1 dye **1**/ $\beta$ -MCD *inclusion* complex, with the dye located in the less polar hydrophobic cavity of cyclodextrin. Addition of  $\beta$ -MCD to dichloromethane solutions of **1** leads to a large hypsochromic band shift of  $\Delta\lambda = -67 \text{ nm}$  ( $702 \rightarrow 635 \text{ nm}$ ), which is best explained by formation of a hydrogen-bonded 1:1 dye **1**/ $\beta$ -MCD *association* complex [53]. Thus, according to its molecular structure,  $\beta$ -MCD is “amphipolar”, i.e., less polar in its lipophilic cavity and more polar at the H-bond-donating exterior.



**Scheme 4** Interaction of betaine dye **1** with methyl- $\beta$ -cyclodextrin ( $\beta$ -MCD) in water and dichloromethane as solvent [53].

Solvatochromic probe dyes such as **1** allow also the study of counterion-induced structural transformations of already formed micelles, as shown in Fig. 2 and Table 2 [54]. Aqueous micellar solutions of dye **1** with cetyl-trimethylammonium bromide (CTAB) as surfactant exhibit the expected bathochromic (red) shift of the vis absorption band of  $\Delta\lambda = +77 \text{ nm}$ , as compared to pure water; see Table 2 (solutions 1  $\rightarrow$  2: 457  $\rightarrow$  534 nm). Addition of ionophores (electrolytes) with large anions such as sodium *n*-hexanesulfonate to aqueous micellar solutions of **1** leads unexpectedly to a pronounced *hypsochromic (blue) band shift* of  $\Delta\lambda = -60 \text{ nm}$  (solutions 2  $\rightarrow$  3: 534  $\rightarrow$  474 nm). The addition of sodium *n*-hexanesulfonate alone to an aqueous solution of **1** does practically not lead to a band shift (solutions 1  $\rightarrow$  4:  $\Delta\lambda = +1 \text{ nm}$ ). The reason for this blue shift is a dislocation of the betaine dye toward more outlying, more aqueous areas of the micelles, which are now probably rod-like as a result of a counterion-induced sphere  $\rightarrow$  rod transition [54]. Addition of an excess of inorganic salts with smaller anions such as NaBr and KCl restores to a larger extent the former vis absorption found in the “pure” cationic surfactant system (red shifts for solutions 3  $\rightarrow$  5, 3  $\rightarrow$  6, and 3  $\rightarrow$  7). This spectral behavior has been found for many other micellar solutions and different betaine dyes, demonstrating that in the aqueous system (cationic surfactant + large organic anion), with  $c(\text{surfactant}) \approx 0.001 \text{ mol/L}$  and  $c(\text{anion}) \approx 0.01 \text{ mol/L}$ , the vis absorption spectra of solvatochromic betaine dyes can reflect alterations in the micellar structure [54].

Some further recent applications of betaine dyes **1**, **2**, **4**, and others for determinations of the molecular-microscopic polarity of organized media can be found (i) for various aqueous micellar systems in refs. [55–58], (ii) for some microemulsions in ref. [59], and (iii) for vesicles as spherical formations of bilayer membranes in refs. [60,61].



**Fig. 2** UV/vis absorption spectra nos. 1–7 of betaine dye **1**, measured in aqueous solution at pH = 12 (NaOH) and 25 °C, without (no. 1) and with additives (nos. 2–7); for additives, see Table 2 [54b].

**Table 2** Counterion-induced transformations of micelles formed by the cationic surfactant CTAB in aqueous solution as indicated by the band shifts of betaine dye **1**;  $c(\mathbf{1}) \approx 10^{-5}$  mol/L at 25 °C and pH = 12 [54]. The solution numbers 1–7 correspond to the UV/vis spectra in Fig. 2.

Additives	Solutions						
	1	2	3	4	5	6	7
CetMe <sub>3</sub> N <sup>+</sup> Br <sup>-</sup>	–	0.001	0.001	–	0.001	0.001	0.003
H <sub>13</sub> C <sub>6</sub> -SO <sub>3</sub> <sup>-</sup> Na <sup>+</sup>	–	–	0.01	0.01	0.01	0.01	–
Na <sup>+</sup> Br <sup>-</sup>	–	–	–	–	0.5	2	–
K <sup>+</sup> Cl <sup>-</sup>	–	–	–	–	–	–	4
$\lambda_{\max}/\text{nm}$	457	534	474	458	548	550	564

## APPLICATION OF PYRIDINIUM-N-PHENOLATES IN OPTOCHEMICAL SENSORS

The extraordinary sensitivity of the UV/vis spectra of solvatochromic betaine dyes such as **1** to small polarity changes in their molecular-microscopic surroundings (“perichromism” [4]) makes them ideal optochemical materials to monitor polar substances in nonpolar media. In general, optochemical sensors register spectral changes caused by contact of the analyte with immobilized indicator dyes, i.e., changes in the position and intensity of their absorption or fluorescence bands.

In addition, betaine dyes such as **1** are reversibly protonated at the phenolate oxygen atom in sufficiently acidic media, with disappearance of the long-wavelength solvatochromic absorption band as a consequence, making them also acid/base indicators.

These peculiar properties of the pyridinium-*N*-phenolate betaine dyes have stimulated research to include these dyes in chemical sensors, intended to interact with suitable analytes and producing a detectable change in an optochemical signal; see refs. [62] for recent reviews on chemical sensors.

Most sensors based on solvatochromic dyes as analyst include betaine dyes **1** and **2** (as well as other derivatives of **1**) [63–74], with the exception of the chemical sensor described in ref. [75], using a polymer-bound zwitterionic dye with an 1-alkyl-4-[(4-oxyphenyl)ethenyl]pyridinium chromophore (Brooker's merocyanine). The pyridinium-*N*-phenolates are either (a) dispersed in suitable polymer films or fibers, forming dye/polymer composites [63,64b,67,69,71]; (b) printed on hydrophobic porous membranes made of various polymers [73]; (c) direct covalently attached to insoluble Merrifield-type polystyrene resins [64a,65,75]; (d) entrapped and immobilized in stable organically modified silicas ("ORMOSIL"), formed by sol → gel processes to give siloxane glasses [66,68,72]; (e) impregnated in ordered mesoporous silicas (so-called SBA-15 materials) [70]; or (f) simply dissolved in suitable solvents [74].

The analytes which can be determined qualitatively or quantitatively by means of these betaine-containing optochemical devices comprise water (humidity) [63,71], alcohols [66,69], ammonia and primary amines [63a,70], volatile organic compounds (VOCs) [67,68], organics in water [73], polar solvents in hydrocarbon blends [64], host/guest interactions with  $\beta$ -cyclodextrin [75], and anions such as  $F^-$  and  $H_2PO_4^-$  [74]. The thermo-solvatochromism of dye **1** has been used to construct temperature-sensitive optochemical sensors for the detection of ambient temperatures [72] and of lower critical solution temperature (LCST) of some hydrophilic polymers in aqueous media [75].

For example, by means of an ethanol sensor based on a betaine dye-doped poly(ethylene vinylacetate) copolymer, immobilized in a flow-through cell, the ethanol content of white wine, vodka, and beer has been determined with good accuracy [69].

A new approach to sensors for VOCs (organics in water) uses a colorimetric sensor array of three cross-responsive dyes, printed on hydrophobic porous membranes of various polymers [73]. The three chemoresponsive dyes chosen were (i) metal-ion containing dyes (e.g., metalloporphyrins) that respond to Lewis basicity, (ii) pH indicators (e.g., phenyl red) that respond to Brønsted acidity/basicity, and (iii) zwitterionic solvatochromic dyes (e.g., **1**) that respond to local molecular-microscopic polarity. After exposure of the disposable planar sensor array to the analyte solution, the color changes of all dyes are readily observed and digitally imaged. The resulting color change profile obtained for the analyte solution represents a  $3N$ -dimensional vector ( $N$  = number of dyes), which can then be analyzed by standard chemometrical techniques such as Hierarchical Cluster Theory. Different organic compounds give different color change profiles, which can be used for their identification.

For example, with an acid-sensitive sensor array, different color change profiles for a series of common soft drinks (e.g., Coca-Cola<sup>®</sup>, Fanta<sup>®</sup>, Sprite<sup>®</sup>, 7-Up<sup>®</sup>, etc.) have been found [73].

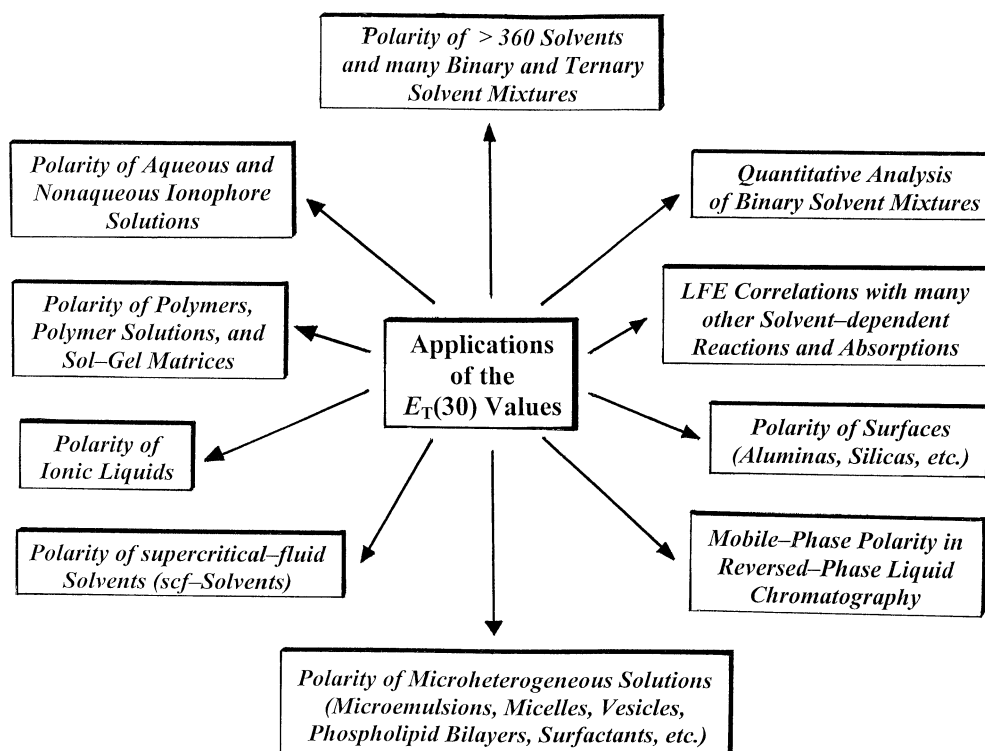
With an optochemical sensor based on betaine dye **1** covalently bound to an insoluble poly(styrene divinylbenzene) copolymer, the methanol content of hydrocarbon blend (naphtha)/methanol mixtures was easily determined [64]. The lower methanol detection limit observed was as low as 0.01 vol %! Methanol is widely used as an octane improver for gasoline.

Under the motto "teaching a new trick to an old dye", tetra-*n*-butylammonium salts with different anions were added to colorless solutions of protonated betaine dye **1** in trichloromethane: addition of  $F^-$  and  $H_2PO_4^-$  leads to a blue–green solution ( $\lambda_{\max} = 728$  nm), whereas addition of  $Cl^-$ ,  $Br^-$ ,  $HSO_4^-$ , and  $NO_3^-$  left the solution color unchanged; addition of  $I^-$  gives a yellow solution color [74]. This allows a visual discrimination of the anions studied. In contrast to the others, anions  $F^-$  and  $H_2PO_4^-$  are basic enough to accept a proton from the protonated dye **1**, which leads to reappearance of the long-wavelength solvatochromic vis absorption band of **1**. The  $I^-$  ions form an intermolecular CT complex with the pyridinium moiety of protonated **1**, which explains the yellow solution color obtained with this

anion. Obviously, according to its acid/base properties, betaine dye **1** can also act as an anionic chromogenic sensor [74].

## SUMMARY

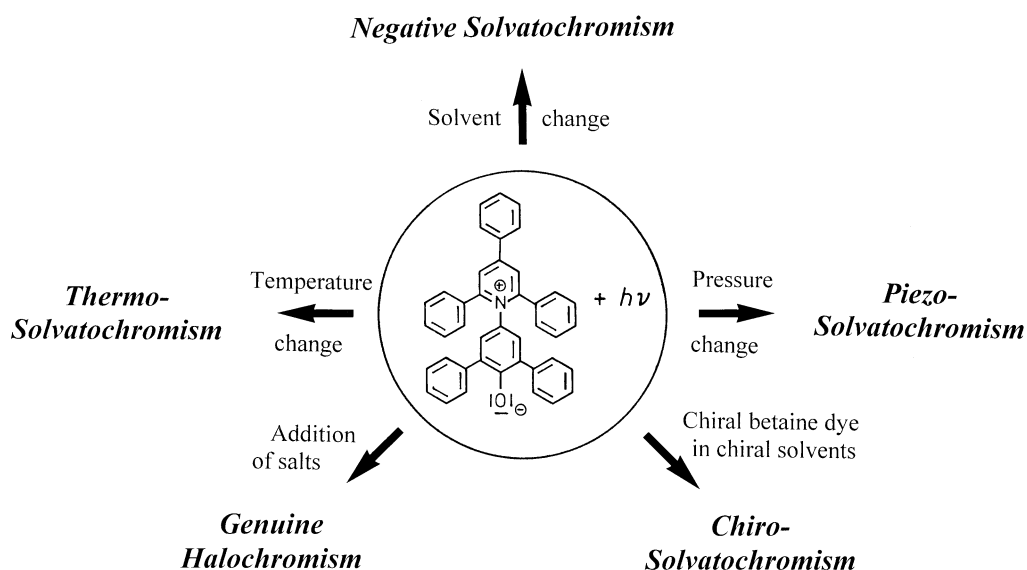
As shown in the preceding sections, negatively solvatochromic pyridinium-*N*-phenolate betaine dyes such as **1–4** have been used in a wide range of different research fields. A collection of applications of the  $E_T(30)$  values derived therefrom is given in Scheme 5. More detailed examples for applications not mentioned in this paper can be found in former reviews on this topic [12,15,19,24a,40,41].



**Scheme 5** Various applications of  $E_T(30)$  values as empirical parameters of solvent polarity.

Solutions of pyridinium-*N*-phenolates are not only solvatochromic, as demonstrated in the previous sections, they are also thermo-solvatochromic, halochromic, chiro-solvatochromic, and piezo-solvatochromic, as illustrated in Scheme 6. That means, the position of the longest-wavelength intramolecular CT absorption of betaine dye **1** (and its derivatives) depends not only on solvent polarity, but also on solution temperature, type and concentration of added salts (ionophores), type and concentration of added chiral compounds, and external pressure [12a]. Illustrative examples for the thermo-solvatochromism [28,46b,72,76,77], genuine halochromism [12b,78,79], chiro-solvatochromism [80], and piezo-solvatochromism [81,82] of betaine dye **1** and its derivatives can be found in the refs. given.

Because of the thermo-solvatochromism of solutions of dye **1**, all vis spectroscopic solvatochromic measurements with this dye [e.g., determination of  $E_T(30)$  values] have to be carried out at constant temperature with thermostatted optical cells. For example, the color of an ethanol solution of **1** is blue-violet at +78 °C ( $\lambda_{\max} = 568$  nm) and red at -78 °C ( $\lambda_{\max} = 513$ ), which corresponds to a hypsochromic band shift of  $\Delta\lambda = -55$  nm [ $\Delta E_T(30) \approx 5.5$  kcal/mol]. That is, solvent polarity is temper-



**Scheme 6** Perichromism of pyridinium-*N*-phenolate betaine dyes.

ature-dependent: a solvent has a higher solvation capability at lower temperatures than at higher ones; see Table 1 and ref. [28] for another example [( $\pm$ )-tetrahydro-2-methylfuran].

To date, betaine dye **1** still holds the world record in negative solvatochromism with a direct experimentally observed hypsochromic band shift of  $\Delta\lambda = -357$  nm for a solvent change from diphenyl ether to water. This band shift would be even larger, taking the gas-phase absorption of **1** as reference. However, because of the negligible volatility of **1**, it was not possible to measure its gas-phase absorption spectrum. Calculated or extrapolated absorption maxima of dye **1** amount to  $\lambda_{\max} = 1017$  nm [21], 1043 nm [13b], 1059 nm [83], and 1053 nm [84], leading to an  $E_T(30)$  value of ca. 27–28 kcal/mol for the gas phase as medium.

The extreme sensitivity of the vis absorption of pyridinium-*N*-phenolate betaines such as **1** to small changes in their molecular-microscopic surrounding reminds one of the behavior of the Princess in H. C. Andersen's fairy tale "The Princess and the Pea" [85]. This Princess was so sensitive to her surroundings, that she was able to feel a pea through 20 mattresses and 20 eider-down quilts on her bed.

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