DYES, CYANINE

1. Introduction

This large class of dyes with a wide variety of colors shows absorptions that cover the ultraviolet to the infrared region and, as a group, cover a wider span of the spectrum than those of any other dye class. The cyanine dyes are also among the oldest known class of synthetic dyes; the first dye was discovered in 1856 (1). The name cyanine (from the Greek *kyanos*) was attributed to its beautiful blue color; however, the dye was extremely fugitive to light and of no practical use at the time for ordinary (fabric) dyeing purposes. The great usefulness of cyanines was discovered later in photography, and they include the most powerful photographic sensitizing dyes known (2–4) (see COLOR PHOTOGRAPHY). There are several important reasons for the cyanines' prominence as sensitizers: first, they have high light absorption per molecule coupled in many cases with a single absorption band in the visible or infrared spectral region, which gives very color-selective absorption of light; second, they have a tendency to form dye aggregates that have even narrower, more color-selective absorptions than the monomeric dyes themselves; and third, they have high chemical and photochemical reactivity for dyes adsorbed to silver halides, which leads to efficient participation in photographic sensitization processes (see DYES, SENSITIZING).

The cyanine class of dyes is also useful in biological, medical, laser, and electro-optic applications. Dyes marketed as Povan [3546-41-6] (5) and Dithiazanine [7187-55-5] (6) are useful anthelmintics, and Indocyanine Green [3599-32-4] (7) is an infrared-absorbing tracer for blood-dilution medical diagnoses. "Stains-All" is a well-studied biological stain (8) and Merocyanine 540's photochemotherapeutic activity is known in some detail (9). Many commercially available red and infrared laser dyes are cyanines (10).

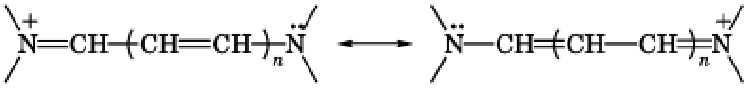
The cyanine dye literature has been reviewed (2,11–19). Ref. 12 is the best source for the heterocyclic chemistry of cyanine and related dyes. Several new syntheses and many new dye structures are discussed in later reviews (13,16) combined with compilations of physical and photophysical data (16,17).

Well-developed synthetic methods allow cost-effective manufacture of cyanines for commercial applications as well as a high degree of dye-structure design for new and innovative studies (20,21), such as solar cells, electrophotography, Langmuir-Blodgett nonlinear optical layers, and photoreceptors for processes activated by infrared solid-state lasers. Thus, tailoring the many characteristics of a dye is a well-practiced art in the cyanine class. Combinations of heterocycles, substituents, and chromophore lengths can yield a series of dye structures having parallel shifts in oxidation-reduction potentials almost independent of absorption wavelength. Steric features of substituents either enhance or decrease aggregation. Solubility in either aqueous or hydrocarbon solvents can be provided by other substituents, almost independently from those that change redox potentials or steric properties. Controlling the number of conformations of the polymethine chain, achieved by several synthetic routes, is important to enhanced infrared absorption strength.

2. Color and Constitution

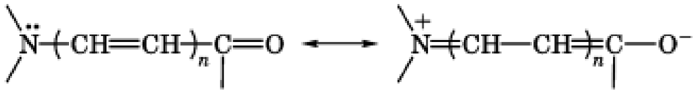
The color and constitution of cyanine dyes may be understood through detailed consideration of their component parts, ie, chromophoric systems, terminal groups, and solvent sensitivity of the dyes. Resonance theories have been developed to accommodate significant trends very successfully. For an experienced dye chemist, these are useful in the design of dyes with a specified color, band shape, or solvent sensitivity. More recently, quantitative values for reversible oxidation–reduction potentials have allowed more complete correlation of these dye properties with organic substituent constants.

2.1. Chromophoric Systems. The primary types of chromophores for cyanine dyes are the amidinium-ion system (**A**), the carboxyl-ion system (**B**), and the dipolar amidic system (**C**). For each system two extreme resonance structures are shown in (**A**), (**B**), and (**C**) where the formal charges are located at the ends of the chromophore. Intermediate resonance structures, with the charges closer to the center of the chromophore or with additional dipoles, are less important in the resonance picture of dyes. However, structural changes that favor intermediate forms have significant effects on the color of symmetrical dyes containing (**A**). For the amidic dyes (**C**), structural features stabilizing both neutral and dipolar extreme resonance forms in an equivalent manner give dyes absorbing at longer wavelengths.



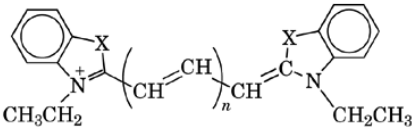
(**A**)

(**B**)



(**C**)

The important characteristics that influence the absorption wavelengths for these dyes are the length of the conjugated chain and the nature of the terminal group. Many of the early cyanine dyes comprised a chain with an odd number of methine carbon atoms (═CH—) and two heterocycles, eg, quinoline or benzothiazole. Historically, the terms simple cyanine, carbocyanine, dicarbocyanine, and such were used to designate both the specific dyes derived from quinoline as well as generic dye structures (from other heterocycles) with one, three, five, etc, methine carbon atoms (see structure (**1**)). In the dyes from quinoline, which can also be designated quinocyanines, the ring position attached to the methine chain and the *N*-substituent are usually specified. For example, 1,1′-diethyl-2,2′-cyanine (or 1,1′-diethyl-2,2′-quinocyanine) is dye (**1**), **X** = —**CH**═**CH**—, and $n = 0$. Pinacyanol is dye (**1**), $n = 1$ and can be named as 1,1′-diethyl-2,2′-carbocyanine iodide, or as 1,1′-diethyl-2,2′-quinocarbocyanine iodide. Chemical Abstracts names pinacyanol as a substituted quinolinium iodide, ie, quinolinium, 1-ethyl-2-[3-(1-ethyl-2(1H)-quinolylidene)-1-propenyl]-iodide.



(**1**)

Dyes derived from the primary chromophores (**B**) and (**C**) are designated oxonols and merocyanines, although the term neutrocyanine has also been used for (**C**). For merocyanines the simple merocyanine designation refers to a dye with zero methine carbon atoms ($n = 0$) (ie, the shortest possible linkage that retains the chromophore between the terminal groups); the term merocarbocyanine designates dyes having chromophore (**C**) with two methine carbon atoms ($n = 1$).

Several examples of the chromophoric systems (**A**), (**B**), and (**C**) are shown in Figure 1. The early dyes were single chromophore structures of the type (**A**): Williams' cyanine [862-57-7], Pinacyanol [605-91-4], and thiacarbocyanine [905-97-5]. The more complicated dye structures in Figure 1 still contain these chromophoric systems.

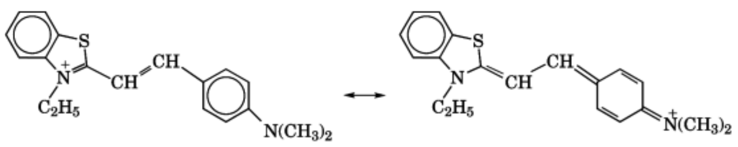
Dyes that differ only by the number of vinyl groups (—CH═CH—) in the methine chain are termed a vinylogous series. Absorption maxima for vinylogous series of dyes like (2) to (6) in Table 1 shift to longer wavelengths as the methine chain length increases. With the usual exception of the first member of each series, the shift approximates 100 nm per vinyl group in most symmetric chromophores like (**2**) (amidinium-ion system, **A**) and (**3**) (carboxyl-ion system, **B**), and these are termed nonconverging series. Less symmetric chromophores including those of the dipolar amidic systems ((**4**)–(**6**), chromophore **C**) show markedly reduced shifts as each vinyl unit is added (converging series). In the dyes the absorption shift is related to the degree of asymmetry between the structures of the heterocyclic terminal groups. Infrared absorbing dyes are primarily derived from symmetric structures; the absorption spectra for the vinylogous series of dye (**2**) (Fig. 2) are typical, with broader absorptions for the dyes with $n = 4{,}5$.

2.2. Terminal Groups.

The cyanines (**A**), oxonols (**B**), and merocyanines (**C**) were originally considered as polymethine dyes with two heterocyclic terminal groups. Hemicyanines were defined as dyes with one heterocyclic and one noncyclic terminal group. Dye bases such as (**5**), Table 1, were the nonalkylated analogues of cyanine dyes like (**2**). Currently, dyes without heterocyclic terminal groups are designated as either cyanines or polymethine dyes. In fact, almost any atom or group of atoms can function as a terminal group for dyes if the nitrogens and oxygens in the primary chromophores (**A**), (**B**), and (**C**) are replaced by electronically equivalent atoms. Dyes from novel terminal groups are quite numerous (22–24). However, the fundamental concepts and perhaps the largest class of useful cyanines are derived from dyes with heterocyclic terminal groups. The heterocycles are of two principal types: basic or electron-donating, and acidic or electron-accepting. Typical examples of terminal groups are shown in Figure 3.

Basic Heterocycles. In addition to the early benzothiazole dyes, eg, compound (**2**), other heterocyclic thiazoles as well as related oxazoles, pyrroles, and imidazoles were subsequently used for cyanines. When two different terminal groups were incorporated, certain unsymmetrical dyes absorbed at unexpectedly short wavelengths, whereas the absorption of others more closely approximated the mean wavelength for the related symmetrical dyes. These observations resulted in the concept of deviation, which related the absorption characteristics of unsymmetrical dyes to the electron-donating abilities (basicities) of the various heterocycles. It was suggested that for the weakly basic terminal *p*-dimethylaminophenyl group the importance of the two extreme amidinium resonance structures would depend on the basicity of the other terminal group (2). For the symmetrical dye (**7**), Michler's hydrol blue [14844-71-4] the two resonance structures are equivalent, but in the unsymmetrical carbocyanine "styryl" dye [41017-17-8] (**8**) the structure with the charged heterocycle is favored particularly for good electron donors (highly basic heterocycles).

(7)



(8)

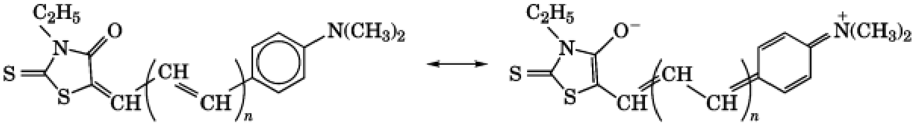
Since highly basic heterocycles accommodate the positive charge readily and maintain the aromatic nature of the dimethylamino benzene group, the resulting bond alternation induces a polyene character to the dye chromophore, and the absorption is shifted accordingly to a shorter wavelength.

A quantitative expression of these observations is shown in equation 1, where λ_{obs} is the observed absorption maximum for the unsymmetrical carbocyanine and λ_{I} is the arithmetic mean (isoenergetic wavelength) for the absorption maxima of the related symmetrical dyes.

$$\text{deviation} = \Delta\lambda = \lambda_{\mathrm{I}} - \lambda_{\mathrm{obs}} \qquad (1)$$

Many deviations are tabulated in Ref. 16 along with the structures of the basic heterocycles. The higher the deviation, the more readily the nucleus accommodates a positive charge.

Acidic Heterocycles. A similar classification is made for the acidic electron-accepting terminal groups used in dipolar (merocyanine) chromophores. The unsymmetrical dyes again incorporate the *p*-dimethylaminophenyl group, connected to the acidic group (Fig. 3) by one or three methine carbon atoms as in the merocyanine(**9**), $n = 0$ [23517-90-0]; $n = 1$ [42906-02-5]; $n = 2$ [66037-49-8]; $n = 3$ [66037-48-7].



(**9**)

For the unsymmetrical dye (a benzylidene if $n = 0$), the nonpolar resonance form was expected to be the dominant one, except when highly electron-accepting terminal groups were present. Nonpolar dyes exhibited the characteristics of polyenes, absorbing at much shorter wavelengths than expected from the arithmetic mean absorption for the two symmetrical dyes. Because of this, the least acidic (electron-accepting) groups showed the highest deviations. The least acidic heterocycles are typified by rhodanines and hydantoins (Fig. 3); the more acidic are isoxazolones and pyrazolidinediones. Acidic terminal groups with intermediate deviations include indandiones and malononitrile.

Dyes derived from these fundamental basic and acidic terminal groups are in current use today as photographic spectral sensitizers [100471-81-6] (**10**), chemotherapeutic dyes [54444-00-7] (**11**), laser dyes [53655-17-7] (**12**), and biological stains [7423-31-6] (**13**) (Fig. 4).

2.3. Solvent Sensitivity.

There is a large influence of solvents on absorption spectra for dyes, particularly for the merocyanines, (**C**). Merocyanines with widely different terminal groups illustrate the general pattern of solvent effects on the absorption maxima and peak intensities (24): Weakly polar dyes like (**4**) (Table 1) are red-shifted (longer wavelength) and show increased extinction coefficients ($\varepsilon_{\max}$) as solvent polarity increases; and highly polar dyes like (**6**) are blue-shifted and show decreased $\varepsilon_{\max}$ values for increasingly polar solvents. The large effects of the environment (solvent) around a dye on the absorption spectra led to the synthesis of hundreds of dyes to clearly document relations between structure and spectra. Early interest (25) in dye (**6**), *p*-hydroxystyryl dyes, and other dyes (24), as solvent polarity indicators, continues, and experimental attention (26,27) has led to the derivation of linear free energy relationships for strongly conjugated systems (28).

Both merocyanine and cyanine dye classes can exhibit solvent sensitivity. For dyes with long chromophoric chains of =CH− (methine) groups, the conformation and thus the absorption of charged dyes may change as a function of solvent. Dye (**6**) with $n = 3$ (Table 1), is a solvent-sensitive, infrared dye that absorbs at longer wavelength in pyridine than in pyridine-water mixtures. The all-*trans* conformations increase in pyridine where the polar terminal groups are separated by the maximum distance. The design of infrared dyes with increased absorption at long wavelengths incorporates conformation-restricting groups in the polymethine chain (see examples, Fig. 3). Additionally, the solvent sensitive "allopolar" (partly polar) cyanine dyes have been investigated extensively (11). These dyes exist in two distinct conformations: one with complete charge separation (holopolar, *H*) and the other with at least one nonionized resonance form (meropolar, *M*). The principal absorption shifts that occur between polar and nonpolar solvents are assigned to these isomers; the holopolar form predominates in polar solvents. The charge separated (holopolar) form of an allopolar infrared dye [66037-43-2] is shown as dye (**16**) in Figure 5.

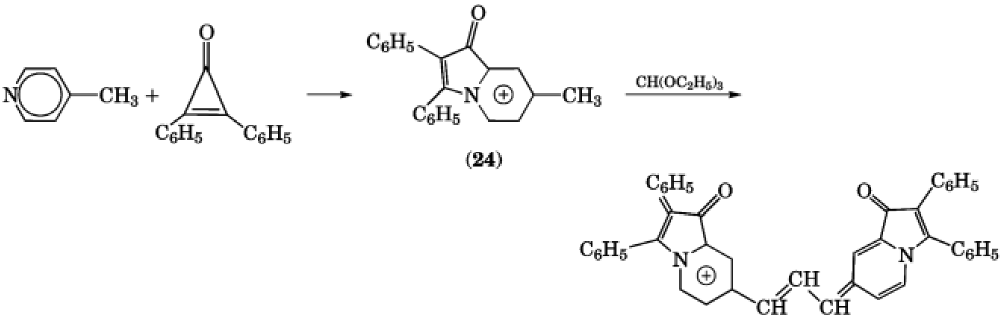
3. Synthesis of Cyanines and Related Dyes

General synthetic methods were developed after 1920 and extended to many new systems. Oxidative syntheses of dyes are primarily of historical interest (1), whereas nonoxidative syntheses are the most versatile and employ varied combinations of nucleophilic and electrophilic regents. One review lists references for the synthesis of dyes prepared before 1959 (12), and another review provides supplemental references to more recent compounds (13). Many nucleophilic and electrophilic reagents used to synthesize cyanine and related dyes are tabulated in Reference 16.

3.1. Nonoxidative Syntheses.

Dye syntheses are characterized as condensations, "two intermediates reacting under suitable conditions with elimination of some simple molecule" (11). Typical synthetic reactions, often combining reagents of quite different structure, are illustrated in Figures 5 and 6. Nucleophilic methylene bases are derived from the deprotonation of quaternary salts like 3-ethyl-2-methylbenzothiazolium iodide [3119-93-5] (Fig. 5, (**14**)]. The methylene bases react with a variety of electrophilic reagents to form dyes in which the nucleophilic reagent (**14**) is the terminal heterocyclic group for the chromophore. The quarternary salts are also converted with ortho esters or anilides to generally useful electrophilic reagents, eg, the intermediate 3-ethyl-2-[2-(acetylphenylamino)ethenyl]benzothiazolium iodide [35080-47-8] (**19**) (Fig. 6).

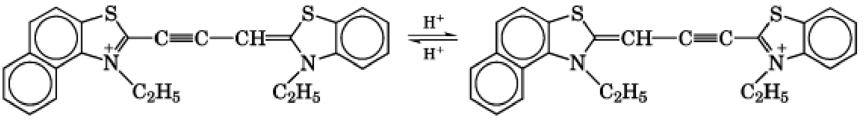
Reaction with various nucleophilic reagents provides several types of dyes. Those with simple chromophores include the hemicyanine iodide [16384-23-9] (**20**) in which one of the terminal nitrogens is nonheterocyclic; enamine tricarbocyanine iodide [16384-24-0] (**21**) useful as a laser dye; and the merocyanine [32634-47-2] (**22**). More complex polynuclear dyes from reagents with more than one reactive site include the trinuclear BAB (Basic-Acidic-Basic) dye [66037-42-1] (**23**) containing basic-acidic-basic heterocycles. Indolizinium quaternary salts (**24**), derived from reaction of diphenylcyclopropenone [886-38-4] and 4-picoline [108-89-4] provide trimethine dyes such as (**25**), which absorb near 950 nm in the infrared (23).



(24)

(25)

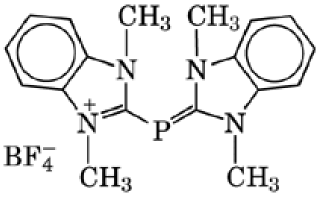
Structural variations of the reagents used in these reactions have been a primary source of progress in dye synthesis. Acetylenic reagents for cyanine dye synthesis include the well-known acetylenic quarternary salts as general electrophilic reagents for the preparation of carbocyanine dyes. A number of tautomeric pairs of acetylenic dyes have been prepared and their tautomeric equilibria determined (dyes (**26a**), (**26b**)) (29).



(26a)

(26b)

Investigations of phosphorus reagents led to simple phosphacyanines (chromophoric methine replaced by phosphorus) as in dye (**27**) [55620-79-6] and phosphacarbocyanines (30).



(27)

3.2. Ring-Closure Reactions. Some interesting dyes are prepared by ring-closure reactions at or near the dye-forming step of a synthetic sequence. The structural identity of thiacyanine was originally established by the reaction of diethyl malonate and *o*-aminothiophenol.

Highly fluorescent, rigidized dyes form readily (31). Quaternary salts such as (**28**) (with reactive *N*-alkyl groups) are formed readily from acrolein (R′ = H) and heterocyclic hydrobromide salts (Fig. 7) (31). Direct formation of dyes from the uncyclized quaternary salt (**28**) lead to the thiacarbocyanine (**29**). The reactive *N*-alkyl groups in this dye are ring-closed to give either the partly rigid thiacarbocyanine (**30**) or the completely rigid and highly fluorescent (**31**).

4. Physical Characterization of Ground-State Dyes

Crystal structure analyses of cyanine and related dyes are reviewed in Ref. 32. Most typical sensitizers are nearly planar, with angles of less than 15° between planes defined by heterocyclic rings. Distinct solvent of crystallization is present in most of the cationic dyes. X-ray crystal analyses also provide intermolecular data. Because of photographic use of cyanine and carbocyanine dyes, the cation-cation arrangements of most interest have been those for 1,1′-diethyl-2,2′-quinocyanine chloride [2402-42-8], 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolocarbocyanine iodide [3520-43-2], and 5,5′-dichloro-3,3′,9-triethylthiacarbocyanine bromide [18426-56-7] (**32**) (see Fig. 8).

4.1. Oxidation-Reduction Potentials.

With color-structure relationships extensively documented by synthetic efforts through 1960 (12), the electrochemical properties of dyes were selected for early correlation with the photographic effects of the cyanine dyes (33). However, a review of this early data suggested that completely reversible potentials were rare. Some apparent deviations are caused by specific substituents like nitro, but contributing factors like increased chain length for vinylogous series of dyes suggested that irreversible side reactions were rapid enough to affect the electrochemical measurements.

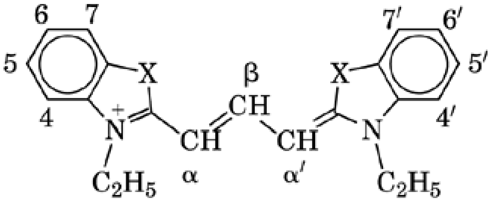
More recent research provides reversible oxidation-reduction potential data (17). These allow the derivation of better structure–activity relationships in both photographic sensitization and other systems where electron-transfer sensitizers are important (see DYES, SENSITIZING). Data for an extensive series of cyanine dyes are published, as obtained by second harmonic a-c voltammetry (17). A recent “quantitative structure–activity relationship” (QSAR) (34) shows that Brooker deviations for the heterocyclic nuclei (discussed above) can provide estimates of the oxidation potentials within 0.05 V. An oxidation potential plus a dye’s absorption energy provide reduction potential estimates. Different regression equations were used for dyes with one-, three-, five-methine carbons in the chromophore. Also noted in Ref. 34 are previous correlations relating Brooker deviations for many heterocyclic nuclei to the pK_a (for protonation/decolorization) for carbocyanine dyes; the pK_a is thus inversely related to oxidation potential values.

Dye radicals, formed during electrochemical measurements, can be very unstable and react on very short time scales (17,35). Specifically for the dicarbocyanines (36), one-electron oxidation gives a radical dication which then dimerizes by linking the (8,10′) carbons as in Figure 9 or the (10,10′) carbons in analogous chemical steps. The 8, 10, 12 positions of the methine chain have the highest electron density in the ground state dye, and in symmetric dicarbocyanines the 8 and 12 carbons are equivalent. Thus, dimerization between electron-rich methine carbons would statistically provide 8, $8' > 8$, $10' > 10$, 10′, whereas sterically the 10′ position is the least hindered. Experimentally, the following dimers were observed for the dicarbocyanine radical dication in Figure 9: $X = S$, 8, $10' > 10, 10'$; $X = C(CH_3)_2$, 10, 10′.

Substituents on the methine chain can stabilize the dye radical cation if the substituent (like methyl) is located on the high electron density carbons. However, no significant stabilization occurs when alkyl groups are on the alternate positions (like 9,11 for the dication in Fig. 9). Current results for several dyes including dicarbocyanines and carbocyanines indicate that electronic stabilization of the dication radical lengthens the radical lifetime and also enhances the reversibility of the dimerization process (37).

4.2. Dye Substituents. Cyanine dyes used as commercial imaging sensitizers or in Langmuir-Blodgett films are substituted to improve their sensitizing, chemical, and physical properties. In a structure such as (**32**) with $n = 1$, for example, the X-atom and R-substituent affect sensitization efficiency and absorption wavelength, the R′-substituent alters self-association of dye molecules, and the R″, R‴-substituents affect solubility. If R″, R‴ are octadecyl, low water solubility results even for this cationic dye and good Langmuir-Blodgett films can be prepared (38,39). If R″, R‴ are chosen from the short-chain alkyl or sulfoalkyl groups, the dyes with a net positive or negative charge are more soluble in protic solvents than the dye having counterbalancing positive and negative charges. In addition, the counterions of dyes with a net charge influence solubility; a cationic dye with chloride, bromide, iodide, or perchlorate anion, for example, will exhibit a wide range of solubility. Solubility data for a carbocyanine dye example are given in Figure 8.

Several types of nitrogen substituents occur in known dye structures. The most useful are the acid-substituted alkyl N-substituents such as sulfopropyl, which provide desirable solubility and adsorption characteristics for practical cyanine and merocyanine sensitizers. Patents in this area are numerous. Other types of substituents include: N-aryl groups, heterocyclic substituents, and complexes of dye bases with metal ions (iridium, platinum, zinc, copper, nickel). Heteroatom substituents directly bonded to nitrogen (N–O, N–NR$_2$, N–OR) provide photochemically reactive dyes.



(**33**)

Substituents on the methine chain are most important historically (8). These substituents cause two types of changes in the properties of the dyes. First, the absorption maxima shift depending on the inductive (electronic) effect of the substituent and its position in the methine chain. Azacyanines absorb at significantly shorter wavelength than the monomethine analogues, and related simple cyanines with phosphorus and arsenic atoms in the chain also absorb at shorter wavelengths. In azacarbocyanines the α-aza dyes absorb at shorter wavelength than the carbon analogues. Similar effects were found for carbocyanines with α-cyano, α-formyl, and α-nitro groups, whereas groups like α-alkyl, α-alkoxy, α-alkylthio, and α-fluoro generally shift the absorption to longer wavelengths. On the other hand, β-aza and β-cyano (nitro, C_4F_7, etc) carbocyanines absorb at longer wavelengths. Secondly, substituents that change the steric properties of the dye can affect both the color and the aggregation. Aggregation and substituent effects are described in a later section. Substituents that affect the color of dyes through steric hindrance include: small alkyl groups on the methine chain, which alter equilibria between cis and trans isomers of the chromophore; bulky alkyl groups on the methine chain or the heterocyclic nitrogen, which cause the chromophore to become non-planar; rigidizing substituents such as the six-membered carbocyclic rings in dyes (**15**) and (**16**) (Fig. 5), which decrease the number of cis isomers and enhance longer wavelength absorption by favoring the all trans isomer of infrared dyes.

Ring substituents for the carbocyanine chromophore (**33**) have been studied extensively. Up to 40 groups in the 5,5′- and 6,6′-positions are tabulated for the benzothiazole and benzimidazole dyes (13). For the thiacarbocyanines, most substituents provided absorption maxima at longer wavelengths. Halogens, alkoxy, and alkyl groups in either the 5- or 6-position provided similar shifts. Electron-withdrawing groups and conjugated substituents in the 6,6′-positions show greater bathochromic effects than in the 5,5′-positions. Certain unsaturated substituents provided polymerizable dyes. Hammett ς-ρ relations for many of these ring substituents correlate with data other than absorption maxima. Both pK_a and polarographic reduction potential correlate with ς values for several dye series, $X = N{-\!\!-}R$, O, S, and $C(CH_3)_2$ in (**33**).

Additional benzenes or heterocycles have been fused to the essential chromophores of thiazolocarbocyanine, imidazolocarbocyanine, and other dyes. These new rings are similar to substituents, since fusing benzene rings to either the 4,5- and 4′,5′-positions or the 5,6- and 5′,6′-positions in (**33**) gives a similar color change. The resulting electrochemical properties (and, therefore, chemical reactivity) depend strongly on the position of the benzene ring. Many variations in heterocyclic structure are obtained in this way, and some examples are included in Figure 3.

5. Photophysical Properties

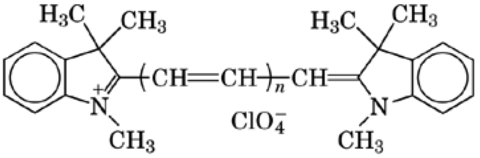
5.1. The Electronic Structure of Sensitizers.

Large conjugated molecules such as the cyanines and related dyes are well described by general quantum theories (40) as well as by resonance concepts (2,11). Both prove useful in the design and understanding of dyes. More recently, the alternating pi-electronic charge characteristic of a polymethine chain was used to define a “polymethine state”, as distinct from olefinic and aromatic conjugated systems (28). Considering the complete electronic structure of dye molecules, the filled orbitals of the ground states contain sigma (σ), pi (π), and lone-pair (n) electrons. Antibonding orbitals are typically pi* (π*) and sigma* (σ*). The long-wavelength transitions for cyanine dyes are generally high-extinction transitions involving the π-electrons and show long-axis polarizations in cyanine dyes, as determined by dichroic absorption of polarized light (stretched polymer films with dye) and by fluorescence polarization. Shorter-wavelength transitions are polarized both parallel and perpendicular to the long axis.

Most cyanines show prominent, hypsochromic vibrational shoulders at shorter wavelength associated with the long-wavelength electronic transition (Fig. 2). These vibrational shoulders include one or two vibrational quanta ($0 \longrightarrow 1$; $0 \longrightarrow 2'$), in addition to the absorption energy at λ_{max} ($0 \longrightarrow 0'$. Intensity ratios for the $0 \longrightarrow 0'/0 \longrightarrow 1'$ bands increase as the chromophoric chain is lengthened from $n = 0$ to $n = 3$ in the thiacyanine series (**2**) (Fig. 2). Distinct vibrational-frequency progressions are resolvable in the low-temperature absorption spectra of azacyanine-, cyanine- and carbocyanine-dyes. Dyes with very long methine chains show short-wavelength absorptions that are not vibrational bands (Fig. 2), but are due to nontrans isomers of the methine chain.

Excited-state properties of the cyanine and related dyes are complex. Most cyanine dyes exhibit small Stokes shifts for fluorescence maxima. Typical carbocyanines (**1**) with $n = 1$ show 14- to 16-nm shifts in methanol solution with low quantum efficiencies for fluorescence (Φ_{Fl}) of less than 0.05. The dicarbocyanine analogues also show small Stokes shifts but higher quantum yields ($\Phi_{Fl} = 0.3 - 0.5$).

Data on fluorescence, phosphorescence, excited-state lifetimes, transient absorption spectra, and dye lasers are tabulated in Ref. 16. The main nonfluorescent process in cyanine dyes is the radiationless deactivation $S_1 \longrightarrow S_0$. Maximum singlet-triplet interconversion (Φ_{ST}) in methanol for carbocyanines is about 3% (max$\Phi_{ST} > 0.03$), and the sum $[\Phi_{Fl} + \Phi_{ST}]$ is less than 0.10.

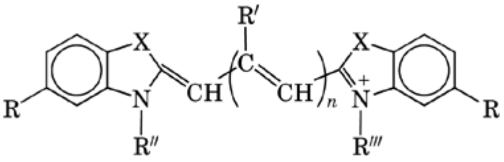


(34)

Dicarbocyanine and tricarbocyanine laser dyes such as structure (**1**) ($n = 2$ and $n = 3$, X = oxygen) and structure (**34**) ($n = 3$) are photoexcited in ethanol solution to produce relatively long-lived photoisomers ($10^{-4} - 10^{-3}$ s), and the absorption spectra are shifted to longer wavelength by several tens of nanometers (41,42). In polar media like ethanol, the excited state relaxation times for tricarbocyanine (**34**) ($n = 3$) are independent of the anion, but in less polar solvent (dichloroethane) significant dependence on the anion occurs (43). The carbocyanine from structure (**34**) ($n = 1$); exists as a tight ion pair with borate anions, represented $RB(C_6H_5)_3^-$, in benzene solution; photoexcitation of this dye–anion pair yields a new, transient species, presumably due to intra-ion pair electron transfer from the borate to yield the neutral dye radical (ie, the reduced state of the dye) (44).

5.2. Aggregation. The most notable spectral property of the cyanine dye class is the ability to self-associate or aggregate. For the more symmetrical cationic dyes, these aggregates can exhibit exceptionally narrow, high-extinction absorptions at longer wavelength than the monomeric dye absorption (Fig. 10, M = monomer). Such aggregates, termed J-aggregates for Jelley (45) who first observed them, provide exceptionally color-selective and efficient sensitization for color imaging systems. Hypsochromically shifted aggregates (dimers, trimers, H-aggregates) also occur, but their absorptions are typically as broad as the monomer (Fig. 10).

The π-systems of dyes can overlap strongly if the long dimensions of the chromophores are parallel and the methine chain/heterocycles are stacked face-to-face (as in a deck of cards) and closely spaced. Early synthetic efforts in carbocyanine dyes focused closely on substituent patterns to enhance J-aggregation and also decrease H-aggregation (11,12). Considering generalized dye structure (**37**) with $n = 1$, for example, the central methine-chain substituent R′ can be an ethyl or phenyl group to enhance J-aggregation for benzothiazole dyes (X = sulfur) such as (**35**). The R′ = methyl analogue favors dimerization and H-aggregation, as shown in Figure 10. Benzimidazole dyes [such as (**36**), (**37**), X = N − alkyl] are more crowded, so that J-aggregation is most favored for R′ = hydrogen.



(37)

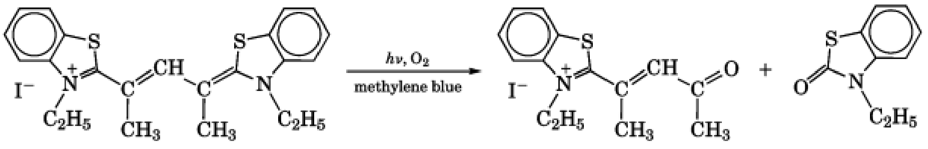
X-ray crystal structures (32,46) and molecular mechanics calculations (47,48) now provide specific data about intermolecular spacings between associated dye molecules.

In a more general description of the relation between these structures and their tendency to aggregate (11), compact dyes were defined as structures that were planar but with tightly packed substituents from a steric hindrance viewpoint; these dyes aggregated readily. Less hindered loose dyes (perhaps having several conformations) or more hindered crowded dyes (probably non-planar) do not aggregate as well. Of course, other groups such as the R-substituents also influence aggregation. For the benzoxazole dyes (**37**) (X = oxygen, $n = 1$), appropriate R-substituents (on each benzene ring) can enhance J-aggregation (producing spectral absorption near 550 nm or favor the monomeric dye (spectral absorption near 510 nm and sensitization in the short green spectral region).

Merocyanine and hemicyanine dyes are often components of thin-film multilayers such as Langmuir-Blodgett films, where tight packing of dye molecules within a layer reinforces the self-association tendencies of the dyes. Chromophores, which orient in the films due to the method of preparation, can exhibit very strong second-order nonlinear optical properties (49–51). Symmetrical cyanine dyes in polymer films show large third-order nonlinear optical properties associated with their large conjugated π-electron systems. A tricarbocyanine (heptamethine) analogue of Williams' cyanine (Fig. 1), at 10–50% weight concentrations in an ionic polymer (sodium polystyrene sulfonate), has good processability and a high third-order nonlinear optical coefficient (52). The formation, stability, and useful properties of these dyed layers shows worldwide research interest (39,52–58).

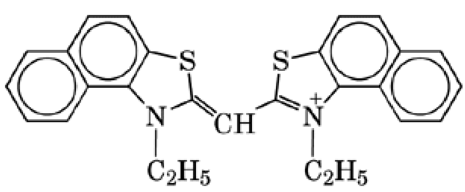
6. Reactivity of Cyanine and Merocyanine Dyes

6.1. Photoreactions. Photooxidation and photoreduction of dyes have been less studied for the cyanines and merocyanines than for noncyanine dye classes. Perhaps this is due to the low singlet-triplet intersystem crossing yields and the high propensity of cyanines to undergo rapid $S_1 \longrightarrow S_0$ radiationless deactivation (59). Low quantum yield photofading reactions in solutions of cyanine dyes are observed under both oxidative conditions (oxygen, reducible metal ions) and reductive conditions (ascorbic acid, gelatin). Direct and sensitized photooxidations of cyanine dyes have been investigated (60). Rate constants k_{pr} for sensitized dye bleaching are generally parallel to electrochemical oxidation potentials (ie, thiatricarbocyanine [3071-70-3] (**2**), $n = 3$ reacts more readily than thiacarbocyanine). The products from these reactions, including those shown in the reaction of 3,3′-diethyl-8,8′-dimethylthiacarbocyanine iodide [62222-86-0] (**38**), are consistent with 1,2-addition of singlet oxygen followed by cleavage of the ***C***—***C*** bond between the first methine carbon and the heterocyclic ring.



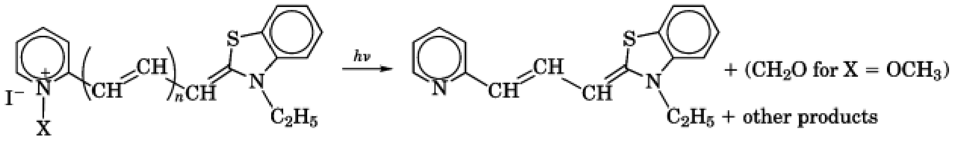
(**38**)

3,3′-Diethyl-naphthothiacyanine iodide [18474-32-3] (**39**) is photodegraded more readily as the H-aggregate, $\Phi = 10^{-2}$ as compared to 10^{-6} for the monomer. Surfactants help deaggregate dyes in solution. For a thiacarbocyanine chromophore, the deaggregation is extensive enough to produce two orders of magnitude improvement in photostability (61).



(**39**)

The tellurium analogues of cyanine dyes, tellurapyrylium trimethine dyes, are photocatalysts for the conversion of water to hydrogen peroxide (62). The tellurium (II)–tellurium (IV) cycle avoids the use of a sacrificial electron donor. Photoreactive substituents on quarternary nitrogen atoms allow typical synthetic reactions to be used while retaining the photosensitivity in the dye form (63). Both N—OR and N—NR$_2$ for the N—X part of (**40**) provide photobleachable and thermally bleachable dyes. The photolytic reaction for the *N*-methoxy dyes ($n = 1$, X = OCH$_3$ [37829-75-7]) involves initial homolytic cleavage of the N—O bond and leads primarily to dye base [61109-40-8] (**41**), chain-substituted analogues of (**41**), and other heterocyclic products.



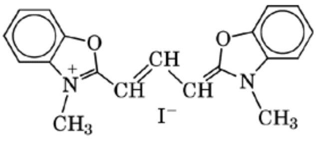
(40) **(41)**

6.2. Chemical Reactions of Dyes.

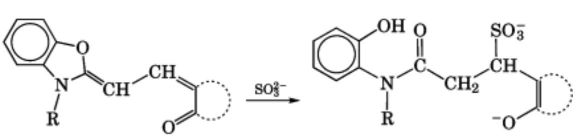
Decolorization is important for cyanines used in imaging materials. Understanding decolorization provides clues to dye reactions that may cause degradation of imaging materials during preparation and storage. For many dyes, protonation of the methine chain occurs readily and reversibly (64). Highly basic carbocyanine dyes like those from benzimidazole, eg, compound **36** protonate so readily that this provides a practical decolorization method.

The irreversible reactions of vinylogous cyanine dyes in basic media include removal of the substituent on the heterocyclic nitrogen by amines or strong base (a general preparative method for the related dye bases (65)). Substituted *N*-alkyl groups with acidic β-protons (eg, 2-carbethoxyethyl) allow dealkylation under milder conditions through reverse Michael reactions. Other carbocyanines from pyrrole or pyrrocoline are sensitive to small amounts of base at ambient temperature. This high reactivity is desirable for decolorizing sensitizers and filter dyes during photographic processing, but stable solutions of these dyes usually require dissolution of the dyes in slightly acidified solvents (see DYES, SENSITIZING).

Benzoxazole dyes exhibit irreversible degradations that involve opening of the oxazole (66). Oxacarbocyanines, eg, 3,3′-dimethyloxacarbocyanine iodide [48198-86-3] (**42**), react most readily with aqueous acid, whereas benzoxazole merocarbocyanines (**43**) react with sulfite or hydroxide ion to produce ring-opened products such as (**44**).



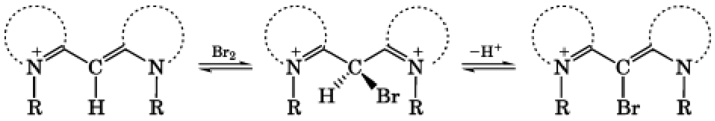
(42)



(43) **(44)**

The rate of reaction with sulfite is ca 100 times faster than the rate of reaction with hydroxide, and decreasing the Brooker basicity of the acidic nucleus in the merocarbocyanine increases the rate of reaction.

The reactions of halogens with cyanine dyes proceed readily at silver halide surfaces and in solution (67,68). The equilibria and halogenation products for simple cyanines from quinoline and benzothiazole have been reviewed (68). Initial halogenation is analogous to protonation and decolorizes the simple cyanines (**45**). Proton loss from (**46**) produces chain-halogenated dyes like (**47**) that can absorb at significantly longer wavelength than the unsubstituted cyanines. Reactions of simple cyanines, carbocyanines, and trinuclear cyanines with excess halogen have also been studied.



(**45**) (**46**) (**47**)

7. Health and Safety Factors

A wide variety of structures exist in the cyanine, merocyanine, and oxonol classes of dyes. Properties that may affect toxicity vary widely also. These include solubility, propensity to be oxidized or reduced, aggregation tendency, and diffusion through membranes. Specific acute toxicity data are listed in Table 2, and the LD_{50} data vary widely with the test used.

More general studies on toxicity were the focus of early efforts by the Ecological and Toxicological Association of the Dyestuffs and Organic Pigments Manufacturing Industry (69,70) and more recent reports (71,72). The cyanine classes of dyes did not figure prominently in these studies. Studies of cyanine dyes in biological systems have included both inhibition of cell division and growth by an oxidation–reduction series of cyanine dyes (73), and interaction of certain cationic dyes with the respiratory chain of rat liver mitochondria (74).

Powerful solvents such as dimethyl sulfoxide (common laser dye solvent) and solubilizing substituents (R'' and $R''' =$ sulfoalkyl in structure **32**) may enhance the transport of dyes in solution through skin and other membranes. Reference 75 (on laser dye solutions and toxicity) is recommended to researchers working with dye solutions. Other dyes, such as Indocyanine Green, attain useful properties (blood tracer dye) as a result of having solubilizing substituents in their structure.

8. Uses

Both patents and scientific articles have indicated a widening spectrum of uses for the cyanine dye classes (and other dyes) in innovative technological areas (8–10,19–21,52,75–85). There are certain key elements in designing cyanines and merocyanines for the following uses: (*1*) long wavelength absorption accomplished with symmetrical di- and tricarbocyanine chromophores; (*2*) solubility modification by substituent variations without significantly affecting the other properties; (*3*) well-documented ways to enhance the chromophore's response to its environment (solvent, voltage, substrate) in highly unsymmetrical dyes; and (*4*) control through dye structure over the occurrence of aggregation on many surfaces and in appropriate solution environments.

Symmetrical, long-chain cyanine dyes for laser applications provide output from 680 to 980 nm (83). Although these dyes were obtained through early screening procedures, infrared dyes for other technologies use similar structures. A long-chain indolenine-type cyanine dye, general structure as in dye (**34**), has been described as the sensitizer in optical disk memories (84).

Several hundred compounds have been applied as voltage-sensitive, optical probes of neuronal activity in the brain (81). The merocyanines and styryl dyes exhibit high voltage sensitivity, but it is now realized that optimal dye design depends on the specific experimental substrate being studied, the variability among preparations of a given substrate, and in some cases the dye sample's purity. Whereas these voltage sensitive dyes are desired to have minimal damaging effects under illumination, the goal of photodynamic therapy is a cytotoxic behavior where the dyes are present. Intense absorption in the range 600–900 nm and proper solubility/adsorption properties are required, so that dyes will accumulate in solid tumors, for example, but not be retained by normal tissue or serum. Subsequent irradiation will then be selective to the dye-containing substrate. Other dyes are designed to improve detection of ribonucleic acid (RNA) when a preparation is stained with a dye (80) and to improve bioassays by reaction of isothiocyanate-substituted, near-infrared dyes with amino moieties or proteins (84).

Cyanine dyes as labeling reagents for detection of biological and other materials by luminescence methods (86), cyanine dyes bioconjugates useful for diagnostic imaging and therapy (87), and dyes useful for labeling a variety of target molecules (88) are presented in the patent literature.

Optical properties of cyanines can be useful for both chiral substituents/environments and also third-order nonlinear optical properties in polymer films. Methine-chain substituted dicarbocyanines have been prepared from a chiral dialdehyde: (S)−(+)-2-*sec*-butylmalonaldehyde [127473-57-8] (89), where the chiral properties are introduced via the chiral *sec*-butyl group on the central methine carbon of the pentamethine (dicarbocyanine) chromophore. For a non-chiral oxadicarbocyanine, the dimeric aggregate form of the dye shows circular dichroism when trapped in γ-cyclodextrin (90). Attempts to prepare polymers with carbocyanine repeat units (linked by flexible C_5H_{10} chains) gave oligomers with only two or three repeat units (91). However, these materials did form films as well as being miscible with other film-forming polymers. Degenerate fourwave mixing measurements show high optical nonlinearity for a pure oligomer film.

Radiation sensitive mixtures comprising ir-absorbing cyanine dyes having a betaine structure or a betaine structure and containing an anion, and recording materials prepared from these compounds have been described (92). This invention also relates to a process for the production of printing plates for offset printing from recording materials.

BIBLIOGRAPHY

"Cyanine Dyes" in *ECT* 1st ed., Vol. 4, pp. 742–754, by G. H. Keyes and E. J. Van Lare, Eastman Kodak Company; in *ECT* 2nd ed., Vol. 6, pp. 605–624, by E. J. Van Lare, Eastman Kodak Company; in *ECT* 3rd ed., Vol. 7, pp. 335–356, by David M. Sturmer, Eastman Kodak Company; in *ECT* 4th ed., Vol. 7, pp. 782–809, by David M. Sturmer, Eastman Kodak Co.; "Cyanine Dyes" in *ECT* (online), posting date: December 4, 2000, by David M. Sturmer, Eastman Kodak Company.

CITED PUBLICATIONS

1. C. H. Greville Williams, *Trans. R. Soc. Edinburgh* **21**, 377 (1856).
2. L. G. S. Brooker, in C. E. K. Mees, ed., *The Theory of the Photographic Process*, 1st ed., Macmillan, New York, 1942, p. 987.
3. G. Ficken, *Chem. Ind.,* 672 (1989).
4. D. M. Sturmer and A. P. Marchetti, in J. M. Sturge, V. Walworth, and A. Shepp, eds., *Imaging Processes and Materials*, Neblette's 8th ed., Van Nostrand Reinhold, New York, 1989, p. 96.
5. U.S. Pat. 2,925,417 (Feb. 16, 1960), E. F. Elslager and D. F. Worth (to Parke-Davis and Co.); U.S. Pat. 2,515,912 (July 18, 1950), E. Van Lare and L. G. S. Brooker (to Eastman Kodak Co.).
6. U.S. Pat. 2,893,914 (July 7, 1959), M. C. McCowen and P. F. Wiley (to Eli Lilly and Co.).
7. U.S. Pat. 2,895,955 (July 21, 1959), D. W. Heseltine and L. G. S. Brooker (to Eastman Kodak Co.).
8. M. Lu, N. C. Seeman, and N. R. Kallenbach, *Biochemistry* **29**, 3407 (1990).
9. J. Davila, A. Harriman, and K. S. Gulliya, *Photochem. Photobiol.* **53**, 1 (1991).
10. F. J. Duarte and L. W. Hillman, eds., *Dye Laser Principles with Applications*, Academic Press, New York, 1990, p. 433.
11. L. G. S. Brooker, in C. E. K. Mees and T. H. James, eds., *The Theory of the Photographic Process*, 3rd ed., Macmillan, New York, 1966, p. 198.
12. F. M. Hamer, in A. Weissberger, ed., *The Chemistry of Heterocyclic Compounds*, Vol. 18, Wiley-Interscience, New York, 1964.
13. G. E. Ficken, in K. Venkataraman, ed., *The Chemistry of Synthetic Dyes*, Vol. 4, Academic Press, New York, 1971, p. 211.
14. A. I. Kiprianov, *Usp. Khim.* **29**, 1336 (1960); **35**, 361 (1966); **40**, 594 (1971).
15. D. M. Sturmer and D. W. Heseltine, in T. H. James, ed., *The Theory of the Photographic Process*, 4th ed., Macmillan, New York, 1977, p. 194.
16. D. M. Sturmer, in E. C. Taylor and A. Weissberger, eds., *The Chemistry of Heterocyclic Compounds*, Vol. 30, Wiley-Interscience, New York, 1977, p. 441.
17. J. R. Lenhard, *J. Imaging Sci* **30**, 27 (1986).
18. H. Zollinger, *Color Chemistry*, VCH, Weinheim, 1987, Chapts. 3 and 14.
19. N. Tyutyulkov, J. Fabian, A. Mehlhorn, F. Dietz, and A. Tadjer, *Polymethine Dyes: Structure and Properties*, St. Klimont Ohridski University Press, Sofia, Bulgaria, 1991.
20. M. Okawara, T. Kitao, T. Hirashima, and M. Matsuoka, *Organic Colorants; A Handbook of Selected Dyes for Electro-Optical Applications*, Elsevier, Amsterdam and New York, 1988.
21. M. Matsuoka, ed., *Infrared Absorbing Dyes*, Plenum Press, New York, 1990.
22. W. Jung, ed., *Optische Anregung Organische Systeme: Internationale Farbensymposium, Elan, 1964*, Verlag Chem., Weinheim, 1966.

23. C. H. Weidner, Eastman Kodak Co., personal communication, 1992.
24. L. G. S. Brooker and co-workers, *J. Am. Chem. Soc.* **87**, 2443 (1965); previous papers in this series.
25. L. G. S. Brooker, G. H. Keyes, and D. W. Heseltine, *J. Am. Chem. Soc.* **73**, 5350 (1951).
26. S. Arai, K. Nagakura, M. Ishikawa, and M. Hida, *J. Chem. Soc. Perkin Trans. 1,* 1915 (1990).
27. M. Niedbalska and I. Gruda, *Can. J. Chem.* **68**, 691 (1990).
28. S. Daehne and K. Hoffmann, in R. W. Taft, ed., *Progress in Physical Organic Chemistry*, Vol. 18, Wiley-Interscience, New York, 1990, p. 1.
29. J. D. Mee, *J. Am. Chem. Soc.* **96**, 4712 (1974); *J. Org. Chem.* **42**, 1035, 1041 (1977).
30. K. Dimroth, *Fortschr. Chem. Forsch.* **38**, 5 (1973); N. Gamon and C. Reichardt, *Liebigs Ann. Chem.,* 2072 (1980).
31. L. L. Lincoln and co-workers, Eastman Kodak Co., personal communication, 1974; *Chem. Commun.,* 648 (1974).
32. D. L. Smith, *Photogr. Sci. Eng.* **18**, 309 (1974).
33. S. E. Sheppard, R. H. Lambert, and R. D. Walker, *J. Phys. Chem.* **50**, 210 (1946).
34. S. G. Link, *Abstracts of the International East-West Symposium II: Factors Influencing the Efficiency of Photographic Imaging,* Oct. 30–Nov. 4, 1988, SPSE-The Society for Imaging Science and Technology, Springfield, Va., 1988, p. F-73.
35. S. Nomura and S. Okazaki, *Chem. Letters,* 2331 (1990).
36. J. R. Lenhard and R. L. Parton, *J. Am. Chem. Soc.* **109**, 5808 (1987).
37. R. L. Parton and J. R. Lenhard, *J. Org. Chem.* **55**, 49 (1990).
38. T. L. Penner, Eastman Kodak Co., personal communication, 1978.
39. P. Stroeve, D. D. Saperstein, and J. F. Rabolt, *J. Chem. Phys.* **92**, 6958 (1990).
40. S. F. Mason, in K. Venkataraman, ed., *The Chemistry of Synthetic Dyes*, Vol. 3, Academic Press, New York, 1970, p. 169.
41. C. Rulliere, *Chem. Phys. Letters* **43**, 303 (1976).
42. X. R. Zhu and J. M. Harris, *Chem. Phys.* **142**, 301 (1990).
43. M. I. Demchuk, A. A. Ischenko, Zh. A. Krasnaya, and V. P. Mikhoilov, *Chem. Phys. Lett.* **167**, 170 (1990).
44. G. B. Schuster, *Pure Appl. Chem.* **62**, 1565 (1990).
45. E. E. Jelley, *Nature* **138**, 1009 (1936).
46. K. Nakatsu, H. Yoshioka, and S. Nishigaki, *Kwansei University Annual Studies (Nishinomiga, Japan)* **29**, 213 (1980).
47. R. L. Parton, H. J. Price, and I. A. Watson, *Proceedings of the 44th Annual Conference of the Society for Imaging Science and Technology, May, 1991*, IS&T, Springfield, Va., 1991.
48. M. Ohashi, K. Kasatani, H. Shinohara, and H. Sato, *J. Am. Chem. Soc.* **112**, 5824 (1990).
49. P. N. Prasad and D. J. Williams, *Introduction to Nonlinear Optical Effects in Molecules and Polymers*, Wiley-Interscience, New York, 1991, pp. 132, 222.
50. A. Ulman, *An Introduction to Ultrathin Organic Films from Langmuir-Blodgett to Self-Assembly*, Academic Press, New York, 1991.
51. T. L. Penner, Eastman Kodak Co., personal communication, 1992.
52. S. Matsumoto, K. Kubodera, T. Kurihara, and T. Kaino, *Opt. Commun.* **76**, 147 (1990); S. R. Marder, J. E. Sohn, and G. D. Stucky, *ACS Symposium Series 455: Materials for Nonlinear Optics: Chemical Perspectives*, American Chemical Society, Washington, D.C., 1991, 712–714.
53. T. Kawaguhi and K. Iwata, *Thin Solid Films* **191**, 173 (1990).
54. S. Kuroda, K. Ikegami, and M. Sugi, *Mol. Cryst. Liq. Cryst.* **190**, 111 (1990).
55. J. Bernard and M. Orrit, *J. Luminesc.* **45**, 70 (1990).

56. H. Nakahara, H. Uchimi, K. Fukuda, N. Tamai, and I. Yamazako, *Mol. Cryst. Liq. Cryst.* **183**, 345 (1990).
57. W. Leupacher, A. Penzkofer, B. Runde, and K. H. Drexhage, *Appl. Phys. B.* **44**, 133 (1987).
58. F. J. Schmitt and W. Knoll, *Chem. Phys. Lett.* **165**, 54 (1990).
59. D. F. O'Brien, T. M. Kelly, and L. F. Costa, *Photogr. Sci. Eng.* **18**, 76 (1974).
60. G. W. Byers, S. Gross, and P. M. Henrichs, *Photochem. Photobiol.* **23**, 37 (1976).
61. E. Barni, P. Savarino, and G. Viscardi, *Acc. Chem. Res.* **24**, 98 (1991).
62. M. R. Detty and S. L. Gibson, *J. Am. Chem. Soc.* **112**, 4086 (1990).
63. J. D. Mee, D. W. Heseltine, and E. C. Taylor, *J. Am. Chem. Soc.* **92**, 5814 (1970).
64. A. H. Herz, *Photogr. Sci. Eng.* **18**, 207 (1974).
65. Ref. 12, p. 362.
66. F. J. Sauter, Eastman Kodak Co., personal communication, 1992.
67. A. van Beek and co-workers, *Rec. Trav. Chim.* **94**, 31 (1975).
68. R. Steiger, J. F. Reber, and H. Loeliger, *J. Imaging Sci.* **30**, 47 (1986).
69. R. Anliker, *J. Soc. Dyers Colour.* **95**, 317–326 (1979).
70. R. Anliker, in M. Richardson, ed., *Toxic Hazard Assessment of Chemicals*, Royal Society of Chemistry, London, 1986, 166–187.
71. K. Hunger and R. Jung, *Chimia* **45**, 297–300 (1991).
72. S. K. Khanna and M. Das, *J. Sci. Ind. Res.* **50**, 965–974 (1991).
73. S. Zigman and P. Gilman, *Science* **208**, 188–191 (1980).
74. T. E. Conover and R. F. Schneider, *J. Biol. Chem.* **256**, 402–406 (1981).
75. H. A. Kues and G. A. Lutty, *Laser Focus, Technology Update 1,* (May, 1975).
76. D. Gregory, *Chem. Ind.,* 679 (1989).
77. G. Jori, *Photochem. Photobiol.* **52**, 439 (1990).
78. M. R. Detty and co-workers, *Photochem. Photobiol.,* 1991, in press.
79. E. Buncel and S. Rajagopal, *Acc. Chem. Res.* **23**, 226 (1990).
80. U.S. Pat. 4,883,867 (Nov. 28, 1989), L. G. Lee and C-H. Chen (to Becton, Dickenson and Co.).
81. A. Grinvald, R. D. Frostig, E. Lieke, and R. Hildesheim, *Physiol. Rev.* **68**, 1285 (1988).
82. A. Grinvald, in W. M. Cowan, ed., *Ann. Rev. Neurosci.*, Vol. 8, Annual Reviews, Inc., Palo Alto, Calif., 1985, p. 263.
83. Catalog JJ-169, Kodak Optical Products, Eastman Fine Chemicals, Eastman Kodak Co., Rochester, N.Y. 14650.
84. F. Matsui in Ref. 21, p. 128.
85. M. Lipowska, G. Patonay, and L. Strekowski, *Abstracts for American Chemical Society Meeting*, Apr. 1991, Atlanta, Ga. U.S. Pat. Appl. 20020181727 (Sept. 25, 2003), C. Kawata and co-workers (to Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenky).
86. U.S. Pat. Appl. 20020146736 (Oct. 10, 2002), A. S. Waggoner (to Carnegie Mellon University).
87. U.S. Pat. Appl. 20030143159 (July 31, 2003), S. I. Achilefu and co-workers (to Mallinckrodt, Inc.).
88. U.S. Pat. Appl. 20010020098 (Sept. 6, 2001), M. H. Randall and coworkers.
89. C. Reichardt and U. Budnik, *Chem. Ber.* **123**, 2023 (1990).
90. V. Buss, *Agnew. Chem. I. E.* **30**, 869 (1991).
91. L. Yu, M. Chen, and L. R. Dalton, *Polymer* **32**, 1369 (1991).
92. U.S. Pat. Appl. 20020006575 (Jan. 17, 2002), O. Gaschler and co-workers.

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Table 1. **Absorption of Vinylogous Dyes**[a]

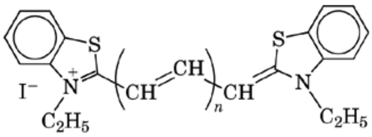
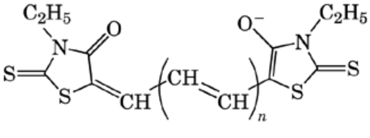
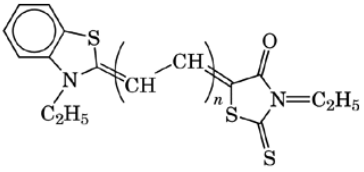
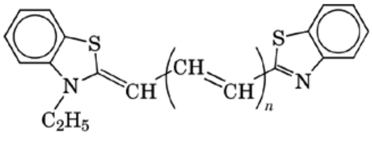
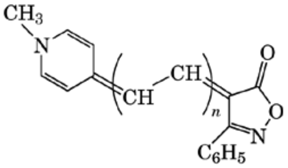
		n			
Dye	Absorption data	0	1	2	3
 (**2**)[b]					
$n = 0$ [2197-01-5]					
$n = 1$ [905-97-5]	λ_{max}, nm	423	557	650	758
$n = 2$ [514–73-8]	$\epsilon \times 10^{-4}$, L/(mol · cm)	8.5	15	23	25
$n = 3$ [3071-70-3]					
 (**3**)					
$n = 0$ [21812-35-1]					
$n = 1$ [50962-54-4]	λ_{max}, nm	542	613	714	
$n = 2$ [50962-55-5]	$\epsilon \times 10^{-4}$, L/(mol · cm)	8.2	11	14	
 (**4**)					
$n = 0$ [3377-05-7]					
$n = 1$ [3568-36-3]					
$n = 2$ [20185-07-3]	λ_{max}, nm	432	528	605	635
$n = 3$ [36652-36-5]	$\epsilon = 10^{-4}$, L/(mol · cm)	6.0	9.3	8.5	6.9
 (**5**)					
$n = 0$ [66037-47-6]					
$n = 1$ [41504-99-8]					
$n = 2$ [66037-46-5]	λ_{max}, nm	396	458	490	510
$n = 3$ [66037-54-5]	$\epsilon \times 10^{-4}$, L/(mol · cm)	5.9	5.7	6.4	

Table 1 (*Continued*)

Dye	Absorption data	n 0	1	2	3
 **(6)**					
$n = 0$ [66037-53-4] $n = 1$ [66037-52-3] $n = 2$ [66037-51-2] $n = 3$ [15736-88-6]	$\lambda_{max}{}^{c}$, nm $\lambda_{max}{}^{d}$, nm	380 400	470 515	530 610	553 710

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[a] Spectral data in methanol or ethanol for dye series **(2)**, **(3)**, **(5)**, and pyridine for **(4)** and **(6)**, a highly polar merocyanine.

[b] $n = 4$ [17094-08-5]; $n = 5$ [15979-18-7].

[c] In pyridine: water = 1 : 1.

[d] In pyridine.

Table 2. **Acute Toxicity Data for Cyanine Dyes**[a]

		Oral LD_{50}		Dermal LD_{50}		Intraperitoneal LD_{50}	
Dye name	CAS Registry number	Mouse, mg/kg	Rat, mg/kg	Mouse, mg/kg	Guinea pig, mg/kg	Mouse, mg/kg	Rat, mg/kg
indocyanine green	[3599-32-4]					60[b,c]	
cryptocyanine	[4727-50-8]	25			>50	1[b]	
DODC iodide	[14806-50-9]	25			>1000	5–10	
DTTC iodide	[3071-70-3]	400–800		>100	>1000	1	
HIDC iodide	[36536-22-8]		178(M) <100(F)		>1000		
HPTS	[6358-69-6]	2200	800–1600		1000		
IR-125	[3599-32-4]	>100					700
Q-switch 1[d]	[21016-19-3]				>1000	1600–3200	

[a] Interchemical comparisons of acute toxicity (LD_{50}) are valid only for the same species and route of administration. Except where noted in the table, all data are previously unpublished, Health and Environment Laboratories, Eastman Kodak Company, Rochester, N.Y.

[b] Material Safety Data Sheet, Sigma-Aldrich Corporation, Milwaukee, Wis.

[c] This LD_{50} was derived from an intravenous injection and not an intraperitoneal injection.

[d] For neodymium laser.