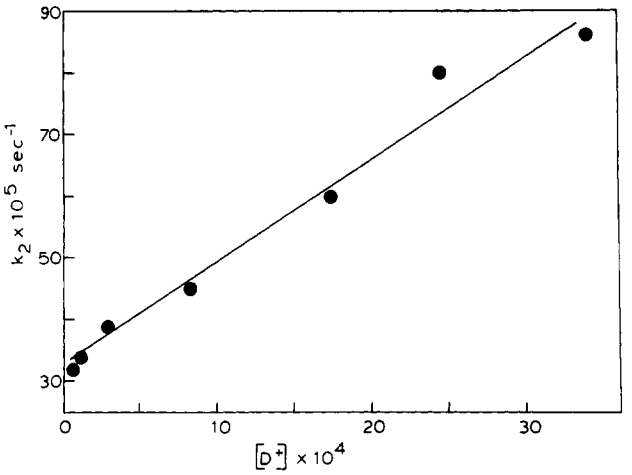

Figure 4. Graphical representation of specific acid catalysis for the ketonization of the AKBA enol intermediate in 0.100 M KCl–D_2O solutions at 31 ± 1 °C.

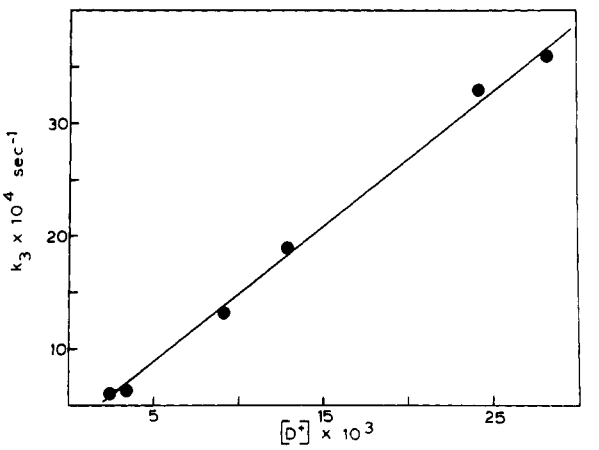

Figure 5. Graphical representation of specific acid catalysis exhibited by the rate constant, k_3, for the enolization and β-deuteration of OPA in 0.100 M KCl–D_2O solutions at 31 ± 1 °C.

is supported by the fact that the rate constant observed by Sakkab and Martell[3] of 9.10×10^{-4} s^{-1} at pD 4.60 in deuterioacetate buffer in 2.5 times larger than the rate constant, 3.33×10^{-4} s^{-1}, determined in this study in the absence of buffer at pD 4.58.

Enolization. The enolization of OPA is competitive with decarboxylation, and the disappearance of the quartet at 2.83 ppm assigned to the β proton of the keto form of OPA is the result of both these processes, as is shown in Scheme II. The NMR measures the depletion of species **2a** through decarboxylation and enolization. The fact that species **6a** is not observed by NMR, while **2a** and **2c** are, means that ketonization of **6a** is rapid and cannot be measured. The rate constant k_3 for the deuteration of the β carbon of OPA may be calculated by eq 3. It was found that the disappearance of the signal follows simple first-order behavior and may be evaluated in a manner similar to the one used in the analysis of decarboxylation. Determination of k_{obsd} for the summation of the decarboxylation and deuteration reactions makes possible the calculation of k_3, since the values of k_1 have been established. The values thus obtained for k_3 are listed in Table III.

On the basis of the behavior reported for OAA,[21,22,27] general acid, general base, specific acid, and specific base catalysis can be assumed to exist for the deuteration of the β carbon of OPA. A treatment similar to that described for the ketonization of AKBA was employed, and the behavior observed for enolization may be mathematically expressed in terms of specific acid catalysis (eq 15). Figure 5 illustrates the observed linear relationship

$$k_3 = k_3^0 + k_3^D[D^+] \quad (15)$$

between the rate constant of deuteration and deuterium ion concentration, and a linear least-squares analysis yields values of 2.70×10^{-4} s^{-1} for k_3^0 and 1.20×10^{-1} l mol^{-1} s^{-1} for k_3^D.

Summary

Research studies on the reaction kinetics of α-keto diacids in which the second carboxyl function is located in the β carbon have been advanced considerably by the application of NMR to such systems. The present findings indicate (1) the NMR method makes possible the evaluation of individual rates of simultaneous reaction involving decarboxylation, ketonization, and β-deuteration; (2) with equilibrium measurements of acid dissociation constants, the specific rate constants for decarboxylation of various protonated keto forms of OPA have been evaluated, giving the relative reactivies monoanion > bivalent anion > neutral (acid) form; (3) the ability of the neutral form to decarboxylate is further depressed by an increase in hydrogen ion concentration since greater concentrations of the diprotonated species exist in the inert hydrate form as the pH is lowered; and (4) ketonization of AKBA and β-deuteration of OPA were found to exhibit specific acid catalysis.

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Synthesis of 3,6-Disulfonated 4-Aminonaphthalimides

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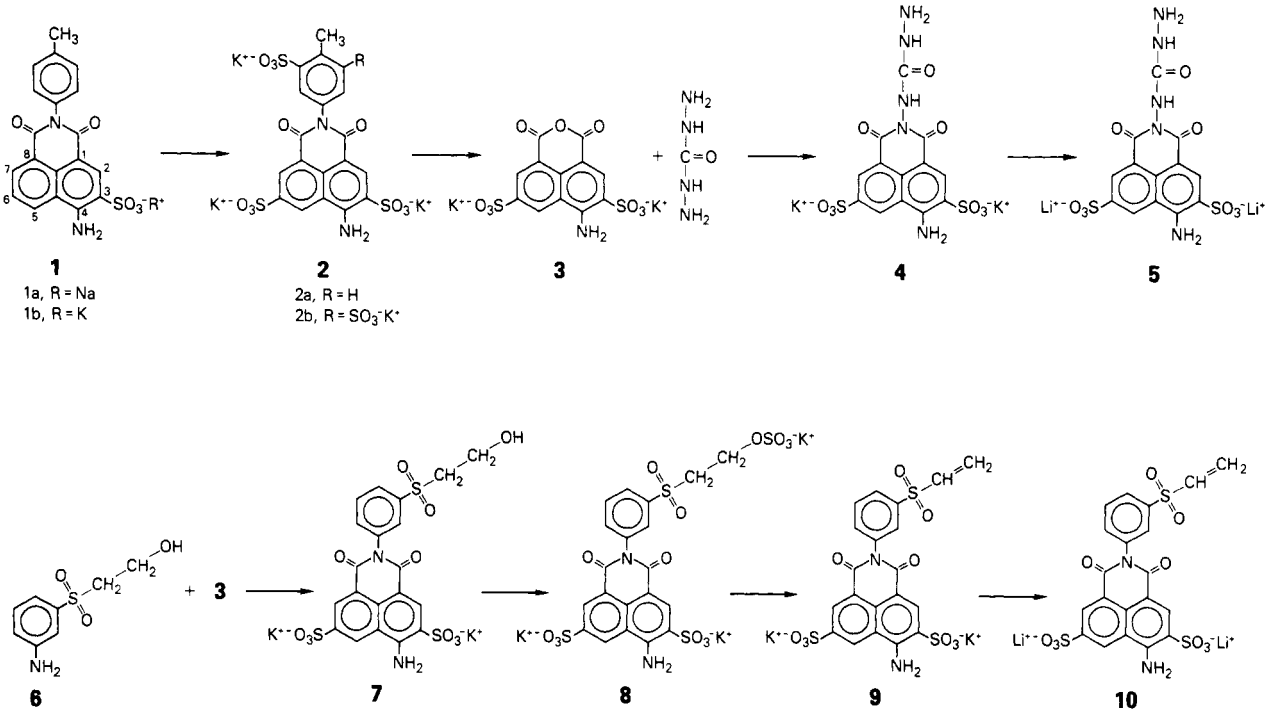
Contribution from the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20205. *Received February 2, 1981*

Abstract: 3,6-Disulfonated 4-aminonaphthalimides are stable, highly fluorescent, water-soluble compounds. A general synthesis of these compounds is presented: a primary amine is condensed in aqueous acid with 4-amino-3,6-disulfonaphthalic anhydride, and the product is isolated as its crystalline potassium, sodium, or lithium salt. The anhydride, whose preparation is described in detail, is interesting because it is stable indefinitely in boiling water and crystallizes readily when the solution is cooled. Because of their intense yellow-green fluorescence, solubility in water, and ability to be bound to cells and tissues, two of these 4-aminonaphthalimides have proved useful as biological tracers, and their synthesis is described in detail.

I report here a general route to an interesting group of compounds—3,6-disulfonated 4-aminonaphthalimides. The synthesis proceeds through amino anhydride **3**, a remarkable compound with several unusual properties. This anhydride, which is easily accessible, is stable indefinitely in boiling water. It condenses easily in aqueous solution with a wide range of primary amines, but not with its own amino group. A variety of N-substituted naphthalimides are conveniently prepared from the an-

Scheme I



hydride. The naphthalimides are fluorescent, water-soluble, and unusually stable. The compounds have high quantum yields (about 0.25) that are insensitive to pH from pH 2 to pH 10. Their excitation maxima around 430 nm (near the mercury line at 436 nm) are well separated from their emission maxima near 540 nm. These and other properties make them well suited to biological tracing.

Two compounds in this series have proved particularly useful as biological tracers.[1] Compound **5** is a highly soluble hydrazide that is nontoxic when injected into cells, that moves rapidly within cells, does not cross the cell membrane in vivo, and is bound in place by aldehyde-containing fixatives. Compound **10** is a highly soluble vinylsulfone which, although extremely stable in water (half-life measured in weeks), reacts rapidly with amines and mercaptans by Michael addition.

Results

Synthesis of 5 and 10. The compounds were synthesized as shown in Scheme I. The starting material was the wool dye brilliant sulfoflavine, C.I. No. 56205 (**1a**).[2] As obtained commercially from GAF, Inc., the dye was a yellow powder containing 56% **1a**, as judged by absorption at 420 nm. It was easily purified as the sodium salt **1a** or the potassium salt **1b** by recrystallization from water; for synthesis, however, the commercial material was satisfactory. The material was identified as **1a** on the basis of spectral and analytical data and by the transformations shown in Scheme I.

Sulfonation of **1** at 90 °C gave the highly soluble trisulfonate **2a**, which, as isolated, was contaminated by about 9% of the less soluble tetrasulfonate **2b**. Sulfonation of **1** at 130 °C gave a 90% yield of pure tetrasulfonate **2b**, which was used for the preparation of **3**. Aqueous hydrolysis of **2b** under rather unusual conditions (see Discussion) gave a 98% yield of crystalline amino anhydride **3**.

Compound **4** was prepared by condensing **3** at 60 °C with a tenfold excess of carbohydrazide in aqueous acetic acid. The hydrogen form of the carbohydrazide adduct has been given the trivial name Lucifer Yellow CH, free acid. The potassium salt of Lucifer Yellow CH, **4**, was about 1% soluble in water at room temperature. For some purposes the much more soluble lithium salt **5**, which was easily prepared by ion exchange, is preferable.[3]

The adduct **7** was prepared by reaction of **6** with **3** and was then converted to the vinylsulfone **9** by using the following sequence.[4] The alcohol disulfonate **7** was converted in good yield to the sulfate **8** by cold H_2SO_4. The sulfate ester was in turn converted smoothly to the vinylsulfone **9** by aqueous carbonate. Compound **10**, the lithium salt of Lucifer Yellow VS, is more soluble and was easily prepared by ion exchange.

4-Aminonaphthalimide-3,6-disulfonates with Substituents on the Imide N. General Procedure. Anhydride **3** (0.89 g, 2 mmol) was suspended in 20 mL of 5% acetic acid (for aromatic amines) or 20 mL of 1 M Li^+/H^+ acetate pH 5 buffer (for aliphatic amines). To the suspension 4 mmol of aromatic amine or 4 mmol of aliphatic amine hydrochloride were generally added. For three diamines (*p*-phenylenediamine, ethylenediamine, carbohydrazide), however, 40 mmol was used in order to favor formation of the monosubstituted product. The mixture was boiled until clear and then for an additional period of about the same length; reaction times ranged from 20 min to 2 days. For a few amines the mixture failed to clear because the naphthalimide was insoluble. The hot reaction mixture was treated with 0.5 g of charcoal if necessary, diluted to 125 mL with boiling H_2O, and made 1–15% in KCl (depending on the solubility of the product). The mixture was allowed to crystallize overnight at 0 °C. The product was collected and washed with 10% (w/w) KSCN and EtOH. A more soluble salt could usually be prepared by adding to a hot 1% solution of the potassium salt enough LiCl to make the solution 20% (w/w) in LiCl; sometimes more LiCl was used. For a few compounds the sodium salt was similarly prepared. Most of the compounds were characterized solely on the basis of a satisfactory NMR spectrum and not by other spectral methods or by elemental analysis. Therefore the possibility cannot be excluded that some

(1) Stewart, W. W. *Cell* **1978**, *14*, 741–759.

(2) Some commercial material sold as brilliant sulfoflavine may be a mixture of dyes, and some may not even contain compound **1a**.

(3) Chemical Abstracts currently names this compound as an isoquinoline derivative: dilithium 6-amino-2-[(hydrazinocarbonyl)amino]-2,3-dihydro-1,3-dioxo-1*H*-benz[*de*]isoquinoline-5,8-disulfonate. Whichever name is used, the counterion should be specified. The lithium salt of Lucifer Yellow CH has frequently been referred to in the biological literature simply as Lucifer Yellow CH.[1] See also: Miller, J. P.; Selvertson, A. I. *Science* (*Washington, D.C.*) **1979**, *206*, 702–704.

(4) Beech, W. F. "Fibre-Reactive Dyes", SAF International: New York, 1970.

of the derivatives may not be the expected substituted naphthalimide but a closely related compound. Crystalline derivatives of the following compounds were prepared. Except as noted, all were soluble in water and had an intense (generally yellow-green) fluorescence. **Anilines**: *p*-toluidine; *p*-anisidine; 4-chloroaniline; 4-aminophenol; 4-nitroaniline; 4-aminobenzoic acid; sulfanilic acid; 4-aminoacetophenone; 3,5-dichloroaniline; 2,4-dichloroaniline; 3,5-dinitroaniline (almost nonfluorescent); 2,3,5,6-tetrafluoroaniline; (4-aminophenyl)acetic acid; (4-aminophenyl)acetonitrile; *p*-phenylenediamine (fluorescent only in acid); *N,N*-dimethyl-*p*-phenylenediamine (fluorescent only in acid); 5-amino-2-toluenesulfonic acid; 6-amino-3-toluenesulfonic acid; potassium 4-methylaniline-3,5-disulfonate; 3-(hydroxyethylsulfonyl)aniline. **Aliphatics**: ammonia; methylamine; octadecylamine (insoluble in water; recrystallized from 80% aqueous EtOH); cyclopropylamine; allylamine; glycine; DL-alanine; aminomethanesulfonic acid; 2-aminoethanesulfonic acid; 2-aminoethanethiol; 4-methylbenzylamine; ethylenediamine; histamine (slightly soluble in water); DL-octopamine; dopamine; *l*-norepinephrine. **Hydrazines**: 4-nitrophenylhydrazine; 4-hydrazinobenzenesulfonic acid (almost nonfluorescent); 2,4-dinitrophenylhydrazine; *N*-aminomorpholine; carbohydrazide. The following compounds failed to give crystalline derivatives when treated according to the above procedure: 2,4,6-trichloroaniline; 2-aminopropane; cyclohexylamine; 2-amino-2-methylpropane; tris(hydroxymethyl)aminomethane; aminodiphenylmethane; 1-aminoadamantane.

Discussion

A striking property of **1** is its extreme resistance to hydrolysis. Prolonged reflux of **1** with aqueous NaOH or H_2SO_4 failed to give the diacid or the corresponding anhydride. Though it came as a surprise, the resistance of **1** to base hydrolysis should perhaps have been expected from reports that *N*-arylphthalimides hydrolyze easily in base to give *o*-carboxybenzamides that are resistant to further hydrolysis.[5] Sulfonation of the naphthalimide would, however, be expected to increase its hydrolytic lability by lowering both the pK_a of the toluidine moiety and the pK_a's of the naphthalic acid moiety. The sulfonates **2a** and **2b** were prepared for this reason.

The structure of the tetrasulfonate **2b** was assigned on the basis of its ^1H NMR spectrum and its hydrolysis in high yield to compound **3** and a toluidinedisulfonate. The structure of **3** was easily deduced from its elemental analysis and its NMR spectrum. Since the ^1H NMR of the isolated toluidinedisulfonate in D_2O consisted of just two singlets, it appeared to be one of the two possible symmetric toluidinedisulfonates that can be formed from *p*-toluidine. This conclusion was supported by ^{13}C NMR spectroscopy (unpublished observations), but the spectroscopic data did not indicate which of the two possible *p*-toluidinedisulfonates had been isolated. The structure was assigned by diazotization of the amino group followed by reductive deamination with H_3PO_2. The resulting highly soluble toluenedisulfonate was salted out with LiCl; ^1H NMR showed that it was a salt of toluene-2,6-disulfonic acid ($J_{3,4}$ = 8 Hz). Thus the tetrasulfonate has the structure shown in **2b**.

The structure of the trisulfonate **2a** was assigned in a similar way. In this case, however, the spectrum of the toluidinemonosulfonate, which was not isolated, could be compared directly with the spectra of the two possible *p*-toluidinemonosulfonates, since both were available commercially. The ^1H NMR of this compound in base agreed closely with that of 5-amino-2-toluenesulfonate and was quite different from that of 6-amino-3-toluenesulfonate.

The structures of **2a** and **2b** were also confirmed by synthesis from the appropriate toluidinesulfonate and anhydride **3** (see Results).

The tetrasulfonate **2b** was easily hydrolyzed in low yield to impure amino anhydride **3**, but efficient conversion proved surprisingly difficult. Basic hydrolysis of **2a** or **2b** followed by acidification at 100 °C and isolation of the product gave only a 30% yield of anhydride contaminated to varying extents by a compound with an aromatic methyl (^1H NMR); the impurity is presumably the starting material or a closely related transformation product. It was observed that simply repeating the cycle of base hydrolysis and acidification raised both the yield and the purity of the isolated product. Further repetitions of this cycle gave further improvement. Perhaps the simplest explanation is that base hydrolyzes imide **2b** to one or both of the two isomeric acid amides, which on acidification undergo ring closure to a mixture of **2b** and **3**. Formation of cyclic anhydrides from acid amides has frequently been inferred from kinetic and isotopic data,[6,7] and hydrolysis of ester amides often proceeds through the cyclic imide.[8-10]

The temperature at which the acidification was carried out proved important. Cooling the basic solution to 0 °C before acidification increased the yield of a single cycle to 90%, though the isolated product contained about 5 mol % of a contaminant having an aromatic methyl. This low temperature, however, was inconvenient, as it required strong cooling during addition of base. The conditions finally chosen involved cycling the tetrasulfonate **2b** four times from base to acid at 50 °C. These unusual conditions gave a 98% yield of pure anhydride.

Another frequent impurity in the initial preparations was the toluidinedisulfonate released by hydrolysis. At pH 2 it often crystallized from the reaction mixture as long colorless needles. Raising the pH to 4.5 before collecting the crystalline anhydride redissolved the toluidinedisulfonate without significantly affecting the solubility of the anhydride.

The anhydride **3** is an intriguing compound, not only because it provides a rather general route to substituted 3,6-disulfonated naphthalimides, but also because it is an unusual anhydride that can be recrystallized from boiling water. Its stability to hot water appeared to be due to thermodynamic rather than kinetic factors. The anhydride **3** was sparingly soluble in cold water and about 1.2% soluble in boiling water. It dissolved readily and at high concentration in cold aqueous KOH, however, presumably by formation of the dicarboxylate; when the alkaline solution was acidified, the anhydride crystallized out. Indeed this property was exploited in the preparation of **3**.

As a matter of convenience, compound **3** was prepared by hydrolysis as described above. It is also accessible, however, by reduction of 4-nitronaphthalic anhydride to 4-aminonaphthalic anhydride[11,12] and subsequent sulfonation.[13]

Another curious property of **3** is the failure of the 4-amino group to react intermolecularly with the anhydride group: compound **3** condenses readily with a wide variety of aromatic amines (see Results), but not with itself. Perhaps this convenient property is related to the exceptionally low p*K* of the 4-amino group, which was well below pH 1 as judged by absorption spectroscopy.

The stability in aqueous solution of amino anhydride **3** paralleled the unusual stability of the parent imide **1**. Unlike phthalic anhydride, which generally reacts initially with amines to give *o*-carboxybenzamides and forms phthalimides only under dehydrating conditions,[14] anhydride **3** reacted in aqueous solution with

(5) "Beilsteins Handbuch der Organischen Chemie", 4th ed.; Springer-Verlag: West Berlin, 1935; Vol. 21, pp 465–466.

(6) Bender, M. L.; Chow, Y.-L.; Chloupek, F. *J. Am. Chem. Soc.* **1958**, *80*, 5380–5384.

(7) Higuchi, T.; Miki, T.; Shah, A. C.; Herd, A. K. *J. Am. Chem. Soc.* **1963**, *85*, 3655–3660.

(8) Sondheimer, E.; Holley, R. W. *J. Am. Chem. Soc.* **1954**, *76*, 2467–2470.

(9) Sondheimer, E.; Holley, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 3767–3770.

(10) Adler, A. J.; Fasman, G. D.; Blout, E. R. *J. Am. Chem. Soc.* **1963**, *85*, 90–97.

(11) Venkataraman, K. "The Chemistry of Synthetic Dyes"; Academic Press: New York, 1952; Vol. 2.

(12) British Intelligence Objectives Sub-Committee. B.I.O.S. final report number **959**, London, H. M. Stationery Office, about 1946.

(13) Scalera, M.; Forster, W. S. U.S. Patent 2455095, 1948. See: *Chem. Abstr.* **1949**, *43*, 7710*f*.

(14) Schröder, E.; Lübke, K. "The Peptides"; Academic Press: New York, 1965; Vol. 1.

primary amines to give naphthalimides directly. Aliphatic amines, which are strong bases, were reacted in a pH 5.0 buffer, while weak bases such as aromatic amines were reacted in 5% acetic acid. A naphthalimide with a substituent on the imide N was obtained from 41 of 48 primary amines tested. These included aliphatic and aromatic amines substituted with a variety of functional groups. The failures occurred primarily with hindered aliphatic amines (see Results). The products, isolated as their crystalline potassium, sodium, or lithium salts, were yellow and were soluble in water (except for the derivative of octadecylamine), and most had an intense yellow-green fluorescence in solution.

This series of compounds was initially investigated because of the need for a highly fluorescent, water-soluble tracer that would not cross the cell membrane of live neurons. Compound **5** fills this need: when injected intracellularly into live neurons, it makes the remarkably complex branching patterns of these cells clearly apparent in the fluorescence microscope.[1] The value of the compound is greatly enhanced by its ability to be bound to tissue by conventional biological fixatives that contain aldehydes. This makes possible the detailed microscopic examination of biological specimens containing compound **5**. It is reasonable to assume that the binding of compound **5** to tissue is related to the reactivity of its free hydrazido group with aldehydes at room temperature (see Experimental Section). Compound **10** also binds to tissue, presumably by a different mechanism. It reacts rapidly with amines and sulfhydryls at room temperature. Thus it probably combines in vivo with these groups and with other tissue nucleophiles.

In conclusion, a general synthesis of 3,6-disulfonated 4-aminonaphthalimides has been presented. Most compounds in this group are water-soluble and have an intense yellow-green fluorescence. Two compounds have proved valuable as biological tracers; among the rest are doubtless others with various applications in biology.

Experimental Section

Physical Data. ^{1}H NMR spectra were usually obtained in D_2O on a Varian HR-220 220 MHz spectrometer at ambient temperature. The chemical shift in parts per million (δ) is relative to an internal standard of sodium 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$ and is followed by the integral (rounded to the nearest integer), the signal shape (s, singlet; d, doublet; t, triplet; m, multiplet), the coupling constants, when they could be determined, and, in some cases, the inferred assignment. Ultraviolet (UV) spectra were recorded on a Cary 14 spectrophotometer. The wavelength (λ) and molar extinction coefficient (ϵ) of absorption maxima are reported in the form λ (ϵ). Because many of the compounds are hygroscopic, the ϵ values are of unknown accuracy. The maximum of the corrected fluorescence emission spectrum (λ_{max}) was obtained from corrected spectra recorded on an Aminco-Bowman spectrofluorometer. Quantum yields (ϕ) were determined by integrating the corrected spectra and comparing the integrals to those for a solution of quinine in 0.1 N H_2SO_4 (assumed quantum yield: 0.51;[15] exciting wavelength 350 nm). Fluorescein in 0.1 N NaOH, included as a control, had a measured quantum yield of 1.0, in fairly good agreement with the literature value of 0.92.[16] Except where indicated, the compounds were dissolved in H_2O. Melting points were obtained in open capillary tubes using accurately calibrated thermometers. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Except as indicated, the samples were dried for analysis for 24 h at 105 °C in vacuo. Since most of the compounds are hygroscopic, the weighings were done in a drybox into an aluminum capsule, which was then sealed to prevent uptake of moisture. Analyses were generally performed in duplicate. When the expected values were not obtained, the analysis was repeated. Two values are usually reported, generally those that agree most closely with theory.

Materials. Brilliant sulfoflavine, **1a**, was obtained from GAF under the trade name Brilliant Sulpho Flavine FFA (lot number J00790).[2] 3-(Hydroxyethylsulfonyl)aniline, **6**, was obtained in crude form as a gift from American Hoechst Corp. 5-Amino-2-toluenesulfonic acid was a gift from Eastman Kodak Co.; they formerly marketed it. 6-Amino-3-toluenesulfonic acid was purchased from Aldrich Chemical Co. Charcoal was Nuchar C-N from West Virginia Pulp and Paper Co.

Brilliant Sulfoflavine. The commercial material was a yellow powder contaminated with a small amount of carbon. The absorption at 420 nm compared to that of pure **1a** indicated that the material contained no more than 56% **1a**. It lost 5.04% on drying at 105 °C in vacuo. The elemental analysis of the dried material was in approximate agreement with that expected for a mixture of: sodium salt of brilliant sulfoflavine (**1a**), 60%; Na_2SO_4, 36%; and NaCl, 4%.

Anal. Found: C, 33.53; H, 2.04; N, 4.19; Cl, 2.00; Na, 15.91; S, 12.70.

Sodium 4-Amino-*N*-(4-methylphenyl)naphthalimide-3-sulfonate (1a). One hundred grams of commercial brilliant sulfoflavine was dissolved in 2 L of hot H_2O, treated with 5 g of charcoal, filtered hot, and allowed to stand overnight at 4 °C. The product (36.2 g) was collected at room temperature. It was recrystallized from 1 L of hot H_2O, collected at 4 °C, and dried in vacuo to yield 19.8 g: UV (H_2O) 277 nm (ϵ 22 600), 420 nm (15 000); NMR δ 2.44 (3 H, s, CH_3), 7.07 (2 H, d, J = 8 Hz), 7.19 (1 H, t, J = 8 Hz, 6-H), 7.37 (2 H, d, J = 8 Hz), 7.93 (2 H, t, J = 8 Hz, 5-H and 7-H), 8.30 (1 H, s, 2-H). The triplet at δ 7.93 was apparently due to a coincidental superposition of two protons; at 100 MHz the same region showed a doublet (J = 2 Hz) and a broad singlet.

Anal. Calcd for $C_{19}H_{13}N_2NaO_5S$ (mol wt 404.37): C, 56.44; H, 3.24; N, 6.93; Na, 5.69; S, 7.93. Found: C, 56.12, 56.29; H, 3.14, 3.25; N, 6.81, 6.92; Na, 5.71, 5.80; S, 7.86, 7.90.

Potassium 4-Amino-*N*-(4-methylphenyl)naphthalimide-3-sulfonate (1b). One hundred grams of commercial brilliant sulfoflavine dissolved in 3 L of boiling 2% KCl was treated with 10 g of charcoal and filtered hot. The crystals that separated were collected and recrystallized from 1.3 L of boiling H_2O, collected and washed with EtOH, and dried at 120 °C in vacuo to give 41.6 g of minute yellow needles. This quantity represents a nominal yield of 71% based on the assumption that all the 420-nm absorption in the commercial material was due to brilliant sulfoflavine. The sample for analysis was recrystallized twice from 50 volumes of 1% KCl and once from 20 volumes of H_2O: UV (H_2O) 277 nm (ϵ 22 600), 420 nm (15 000); ϕ = 0.49, λ_{max} = 525 nm; NMR δ 2.44 (3 H, s, CH_3), 7.11 (2 H, d, J = 8 Hz), 7.38 (3 H, d, J = 8 Hz), 8.10 (2 H, t, J = 7 Hz, 5-H and 7-H), 8.39 (1 H, s, 2-H). Because compound **1b** was sparingly soluble in D_2O, the spectrum was obtained by Fourier transform spectroscopy (20 sweeps). The triplet in the spectrum of **1a** at δ 7.19, attributed to the 6-hydrogen, appeared in the spectrum of **1b** to coincide with the doublet at δ 7.38 and to be largely obscured by it.

Anal. Calcd for $C_{19}H_{13}KN_2O_5S$ (mol wt 420.48): C, 54.27; H, 3.12; K, 9.30; N, 6.66; S, 7.62. Found: C, 54.19, 54.24; H, 3.25, 3.30; K, 9.02, 9.13; N, 6.52, 6.66; S, 7.62, 7.70.

Tripotassium 4-Amino-*N*-(4-methyl-3-sulfophenyl)naphthalimide-3,6-disulfonate (2a). One hundred grams of commercial brilliant sulfoflavine was dissolved in 300 mL of fuming H_2SO_4 (30% free SO_3, w/w), and the solution was held at 90 °C for 3 h. The cooled solution was diluted to 3 L over ice, and 300 g of KCl was added. The resulting suspension was heated to give a homogeneous solution and cooled to 4 °C with stirring. The very soluble product that separated was recrystallized from 200 mL of boiling water to give, after drying in vacuo, 47.8 g of crude product, a nominal yield of 53%: NMR δ 2.76 (3 H, s, CH_3), 7.59 (1 H, d of d, J = 2 Hz, J = 8 Hz, 6′-H), 7.68 (1 H, d, J = 8 Hz, 5′-H), 7.93 (1 H, d, J = 2 Hz, 2′-H), 8.62 (1 H, s, 2-H), 8.65 (1 H, d, J = 1.5 Hz), 8.67 (1 H, d, J = 1.5 Hz). Two peaks at δ 3.05 and 8.24 suggested a 9 mol % contamination with the less soluble tetrasulfonate (**2b**).

Tetrapotassium 4-Amino-*N*-(4-methyl-3,5-disulfophenyl)-naphthalimide-3,6-disulfonate (2b). One hundred grams of commercial brilliant sulfoflavine was dissolved in 300 mL of fuming H_2SO_4 (30% free SO_3, w/w), and the solution was held at 130 °C for 24 h. The cooled solution was diluted to 3 L over ice, treated with 10 g of charcoal, and filtered. Three hundred grams of KCl was dissolved in the filtrate at 90 °C, and the resulting solution was allowed to cool to room temperature with constant stirring. Crystallization was completed by stirring for 2 days at 4 °C. The product was collected, washed with water, ethanol, and ether, and dried in vacuo to give 96.5 g, a nominal 90% yield, of a light yellow powder turning orange on hydration: UV (H_2O) 280 nm (ϵ 26 800), 428 nm (12 800); ϕ = 0.26, λ_{max} = 535 nm; NMR δ 3.03 (3 H, s, CH_3), 8.12 (2 H, s, 2′-H and 6′-H), 8.82 (1 H, s, 2-H), 8.90 (1 H, d, J = 1.5 Hz), 9.09 (1 H, d, J = 1.5 Hz).

Anal. Calcd for $C_{19}H_{10}K_4N_2O_{14}S_4$ (mol wt 774.92): C, 29.45; H, 1.30; K, 20.18; N, 3.61; S, 16.55. Found: C, 29.21, 29.33; H, 0.99, 1.07; K, 19.89, 20.05; N, 3.33, 3.45; S, 15.97, 16.15.

Dipotassium 4-Amino-3,6-disulfonaphthalic Anhydride (3). A solution of 100 g of **2b** in 2 L of 3% KOH was held for 10 min at 50 °C, then acidified with HCl to pH 2 (copious crystals) and held at 50 °C for 10 min. This cycle, between pH 12.5 and pH 2 at 50 °C, was repeated three more times. The final suspension was allowed to stir at pH 2 for 3 days at room temperature and then raised to pH 4.5 with KOH. The product was collected and washed with 5% KCl, water, ethanol, and ether. The product, dried at 80 °C in vacuo, weighed 56.6 g (98% yield) and was a stable, light yellow, nonhygroscopic powder. The material for analysis

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was recrystallized from 100 volumes of boiling H_2O: UV (0.1 M HOAc) 282 nm (ϵ 26 800), 419 nm (10 200); (0.1 M NaOH) 265 nm (ϵ 20 700), 349 nm (8850); in H_2O ϕ = 0.036, λ_{max} = 560 nm; in H_2O/OH^- ϕ = 0.037, λ_{max} = 515 nm; NMR (in D_2O/OD^-): δ 8.09 (1 H, s, 2-H), 8.09 (1 H, d, J = 2 Hz), 8.65 (1 H, d, J = 2 Hz).

Anal. Calcd for $C_{12}H_5K_2NO_9S_2$ (mol wt 449.49): C, 32.07; H, 1.12; K, 17.40; N, 3.12; S, 14.27. Found: C, 32.17, 32.23; H, 1.10, 1.16; K, 17.28, 17.38; N, 3.11, 3.18; S, 14.35, 14.50.

Dipotassium 4-Amino-*N*-[(hydrazinocarbonyl)amino]naphthalimide-3,6-disulfonate (Potassium Salt of Lucifer Yellow CH) (4). To 45 g of carbohydrazide (0.5 mol) dissolved in 1 L of 5% acetic acid was added 22.5 g of anhydride **3** (0.05 mol). (A large excess of carbohydrazide was used in order to suppress formation of the dimer.) The suspension was kept at 60 °C for 12 h with occasional stirring. To the resulting homogeneous solution was added 5 g of KCl, and the solution was stirred while it cooled to room temperature and crystallized. After 16 h of stirring at 4 °C, the product was collected, washed with 0.5% KCl, water, ethanol, and ether, and dried at 60 °C in vacuo to give 24.0 g of crystals, a yield of 92%. The sample for analysis was recrystallized (using charcoal) from 30 volumes of hot H_2O: UV (H_2O) 280 nm (ϵ 26 000), 428 nm (12 300); ϕ = 0.21, λ_{max} = 535 nm; NMR δ 8.69 (1 H, s, 2-H), 8.83 (1 H, d, J = 1.5 Hz), 8.89 (1 H, d, J = 1.5 Hz).

Anal. Calcd for $C_{13}H_9K_2N_5O_9S_2$ (mol wt 521.56): C, 29.94; H, 1.74; K, 14.99; N, 13.43; S, 12.29. Found: C, 29.85, 30.06; H, 2.14, 2.25; K, 14.69, 14.74; N, 13.35, 13.56; S, 12.24, 12.40.

Dilithium 4-Amino-*N*-[(hydrazinocarbonyl)amino]-2,3-naphthalimide-3,6-disulfonate (Lithium Salt of Lucifer Yellow CH) (5). Fifteen grams (29 mmol) of the potassium salt of the carbohydrazide adduct **4** was dissolved with heating in 375 mL of H_2O. The warm solution was passed over a 150-mequiv column of Dowex 50W-X2 that had been thoroughly washed with several cycles of acid and base according to the manufacturer's instructions and then put into the lithium form. The dye was eluted from the column with H_2O, and the dye-containing fractions were pooled, passed through a Millipore filter type GSWP 047 00 (0.22 μm), and lyophilized to give a 13.1 g (99% yield) of a fluffy orange hygroscopic powder: UV (H_2O) 280 nm (ϵ 24 200), 428 nm (11 900); ϕ = 0.21, λ_{max} = 540 nm; NMR δ 8.60 (1 H, s, 2-H), 8.75 (1 H, d, J = 1.5 Hz), 8.78 (1 H, d, J = 1.5 Hz).

Anal. Calcd for $C_{13}H_9Li_2N_5O_9S_2$ (mol wt 457.24): C, 34.15; H, 1.98; Li, 3.04; N, 15.32; S, 14.02. Found: C, 34.27, 34.29; H, 1.97, 2.01; Li, 2.86, 2.94; N, 15.20, 15.37; S, 13.79, 13.86.

3-[(Hydroxyethyl)sulfonyl]aniline (6). Seventy-five grams of commercial material and 2.5 g of charcoal were boiled briefly in 3 L of CHCl, filtered hot, cooled to room temperature, seeded heavily, and allowed to stand overnight at room temperature. The solution was held at 4 °C for another 24 h. The product, consisting of large tan crystals, weighed 55.8 g: mp 74–75 °C; NMR ($CDCl_3$, Me_4Si internal standard, 220 MHz) δ 3.33 (2 H, t, J = 5.5 Hz, CH_2), 3.98 (2 H, t, J = 5.5 Hz, CH_2), 6.87–6.96 (1 H, d of m, $J \simeq$ 9 Hz), 7.17–7.37 (3 H, m).

Anal. Calcd for $C_8H_{11}NO_3S$ (mol wt 201.24): C, 47.75; H, 5.51; N, 6.96; S, 15.93. Found: C, 47.86, 47.93; H, 5.24, 5.30; N, 6.98, 6.99; S, 15.93, 15.94.

3-[(Hydroxyethyl)sulfonyl]aniline Hydrochloride (6·HCl). Ten grams of **6** dissolved in 40 mL of 6 N HCl was crystallized by the addition of 80 mL of MeOH. The crude hydrochloride was recrystallized from 800 mL of boiling EtOH containing 1% H_2O and dried at 90 °C in vacuo to yield 7.8 g of pure hydrochloride: mp 211–214 °C dec; NMR (D_2O) δ 3.71 (2 H, t, J = 5.5 Hz, CH_2), 4.02 (2 H, t, J = 5.5 Hz, CH_2), 7.83–7.91 (2 H, m), 8.02–8.09 (2 H, m).

Anal. Calcd for $C_8H_{12}ClNO_3S$ (mol wt 237.70): C, 40.42; H, 5.09; Cl, 14.91; N, 5.89; S, 13.49. Found: C, 40.43, 40.58; H, 5.10, 5.15; ionic Cl, 14.87, 14.89; total Cl, 14.90, 14.96; N, 5.88, 5.89; S, 13.63, 13.64.

Dipotassium 4-Amino-*N*-[3-[(hydroxyethyl)sulfonyl]phenyl]-naphthalimide-3,6-disulfonate (7). Compound **7** was prepared by refluxing a suspension of 80.5 g of anhydride **3** (179 mmol) in a solution of 72 g of **6** (a twofold molar excess) in 1 L of H_2O. The reaction was followed by observing the clearing of the suspension, which occurred between 1 and 2 days. After 48 h, the homogeneous red solution was filtered hot, diluted with hot H_2O to 1.9 L, and made 2% in KCl. The solution was allowed to cool with stirring to room temperature until crystallization had occurred, then stirred overnight at 4 °C. The product, after being dried in vacuo, weighed 89.2 g, a yield of 79%: NMR δ 3.67 (2 H, t, J = 5.5 Hz, CH_2), 3.99 (2 H, t, J = 5.5 Hz, CH_2), 7.81–7.98 (2 H, m), 8.11–8.17 (2 H, m), 8.67 (1 H, s, 2-H), 8.71 (1 H, d, J = 2 Hz), 8.76 (1 H, d, J = 2 Hz).

Anal. Calcd for $C_{20}H_{14}K_2N_2O_{11}S_3$ (mol wt 632.71): C, 37.97; H, 2.23; K, 12.36; N, 4.43; S, 15.20. Found: C, 37.84; H, 2.33; K, 12.19; N, 4.39; S, 15.05.

Tripotassium 4-Amino-*N*-[3-[(sulfatoethyl)sulfonyl]phenyl]-naphthalimide-3,6-disulfonate (8). Forty grams of finely powdered **7** (63 mmol) was stirred with 120 mL of H_2SO_4 at 4 °C. Because of clumping, which was difficult to avoid, complete solution required 24 h. The reaction mixture was then diluted to 1.2 L over ice, made 5% in KCl, heated to about 50 °C to dissolve the crystals, and allowed to cool to 4 °C with stirring. The product was collected, washed with 10% and 5% KCl, suspended in 1 L of H_2O at 4 °C, and carefully neutralized with 0.1 N KOH. The neutralized suspension was heated to dissolve the crystals, filtered, made 2% in KCl, and cooled with stirring to room temperature. After crystallization had begun, the stirred mixture was set at 4 °C. The product was collected at 4 °C, washed with cold water, ethanol, and ether, and dried in vacuo to yield 42.5 g of hygroscopic crystals (90% yield): NMR δ 3.87 (2 H, t, J = 5.5 Hz, CH_2), 4.43 (2 H, t, J = 5.5 Hz, CH_2), 7.85–8.03 (2 H, m), 8.10–8.24 (2 H, m), 8.57 (1 H, s, 2-H), 8.58 (1 H, d, J = 1.5 Hz), 8.60 (1 H, d, J = 1.5 Hz).

Anal. Calcd for $C_{20}H_{13}K_3N_2O_{14}S_4$ (mol wt 750.86): C, 31.99; H, 1.75; K, 15.62; N, 3.73; S, 17.08. Found: C, 31.86; H, 1.87; N, 3.67; K, 15.57; S, 16.93.

Dipotassium 4-Amino-*N*-[3-(vinylsulfonyl)phenyl]naphthalimide-3,6-disulfonate (Potassium Salt of Lucifer Yellow VS) (9). Fifteen grams of **8** (20 mmol) was dissolved in 300 mL of H_2O. To the well-stirred solution was added 1 N NaOH at room temperature to maintain the solution at pH 10. After 15 min, 10 mL had been added; uptake stopped after 17 mL had been added, and the solution was neutralized with HCl. During the addition of base, well-formed crystals appeared. The neutralized solution was set at 4 °C overnight. The dried product, apparently pure, weighed 11.9 g, a yield of 97%. The material for analysis was recrystallized from about 30 volumes of 1% KCl: UV (H_2O) 280 nm (ϵ 26 400), 428 nm (13 300); NMR δ 6.27 (1 H, d, J = 10 Hz), 6.53 (1 H, d, J = 16 Hz), 6.98 (1 H, d of d, J = 10 Hz, J = 16 Hz), 7.78–7.96 (2 H, m), 8.05–8.14 (2 H, m), 8.66 (1 H, s, 2-H), 8.71 (1 H, d, J = 2 Hz), 8.80 (1 H, d, J = 2 Hz).

Anal. Calcd for $C_{20}H_{12}K_2N_2O_{10}S_3$ (mol wt 614.70): C, 39.08; H, 1.97; K, 12.72; N, 4.56; S, 15.65. Found: C, 38.89, 39.04; H, 2.12, 2.17; K, 12.68, 12.75; N, 4.59, 4.72; S, 15.60, 15.77.

Dilithium 4-Amino-*N*-[3-(vinylsulfonyl)phenyl]naphthalimide-3,6-disulfonate (Lithium Salt of Lucifer Yellow VS) (10). Ten grams of **9** (16.3 mmol) was dissolved with gentle heating in 300 mL of H_2O. The warm solution was run onto a 100-mequiv column of washed Dowex 50W-X2, 50–100 mesh, in the lithium form. The dye was eluted with H_2O, passed through a Millipore filter type GSWP 047 00 (0.22 μm), and lyophilized. The dried product weighed 9.39 g, more than that expected for a quantitative yield (8.95 g); the excess weight was probably due to residual water: UV (H_2O) 280 nm (ϵ 24 600), 428 nm (12 200); ϕ = 0.24, λ_{max} = 540 nm; NMR δ 6.23 (1 H, d, J = 10 Hz), 6.47 (1 H, d, J = 16 Hz), 6.93 (1 H, J = 10 Hz, J = 16 Hz), 7.77–7.93 (2 H, m), 8.02–8.11 (2 H, m), 8.64 (1 H, s, 2-H), 8.68 (1 H, d, J = 1.5 Hz), 8.73 (1 H, d, J = 1.5 Hz).

Anal. Calcd for $C_{20}H_{12}Li_2N_2O_{10}S_3$ (mol wt 550.38): C, 43.65; H, 2.20; Li, 2.52; N, 5.09; S, 17.48. Found: C, 43.61, 43.82; H, 2.03, 2.08; Li, 2.43, 2.50; N, 5.17, 5.21; S, 17.64, 17.71.

Monopotassium 4-Methylaniline-3,5-disulfonate. One hundred grams of **2b** (129 mmol) in 2 L of 3% KOH was treated exactly as above for the preparation of the anhydride **3**. After the anhydride was filtered off, acidification of the filtrate with HCl gave 11.8 g of the toluidinedisulfonate as a light tan powder. A second crop of 7.8 g was obtained by adding 50 mL of HCl and 300 g of KCl to the filtrate. The two crops were pooled and recrystallized from H_2O to yield 14.7 g (48 mmol) of pure material: NMR (60 MHz, D_2O at 90 °C) δ 2.80 (3 H, s, CH_3), 7.63 (2 H, s).

Anal. Calcd for $C_7H_8KNO_6S_2$ (mol wt 305.36): C, 27.53; H, 2.64; K, 12.80; N, 4.59; S, 21.00. Found: C, 27.38, 27.62; H, 2.63, 2.69; K, 12.61, 12.67; N, 4.48, 4.52; S, 20.69, 20.76.

Deamination of Potassium 4-Methylaniline-3,5-disulfonate. Three millimoles (0.91 g) of potassium 4-methylaniline-3,5-disulfonate was dissolved with gentle heating in 12 mL of 0.25 M KOH. The solution was cooled to 25 °C, and 0.29 g of KNO_2 was added. To this solution at 0 °C were added in turn 8 mL of 2 N HCl and 10 mL of 50% H_3PO_2, both precooled to 0 °C.

After 12 h at 0 °C and 12 h at 25 °C, 90 mL of 50% w/w LiCl (warmed sufficiently to achieve solution) was added, and the solution was kept 12 h at 4 °C. The crystals that formed were collected by centrifugation, dissolved in 30 mL of H_2O, and recrystallized by adding 90 mL of warm 50% w/w LiCl. Because of its extreme solubility, the material was not isolated in salt-free form. The NMR spectrum (60 MHz, D_2O, ambient temperature) revealed no impurities, showed that the reductive deamination was successful, and indicated the structure given above: δ 2.98 (3 H, s, CH_3), 7.50 (1 H, t, J = 8 Hz, 4-H), 8.17 (2 H, d, J = 8 Hz, 3-H and 5-H).

Hydrolysis of 2a. To 0.5 g of **2a**, suspended in 2 mL of D_2O, was added 30% NaOD dropwise until the solution remained basic. It was

then boiled briefly, cooled to room temperature, and acidified with 20% DCl. The amino anhydride **3** that crystallized was removed by centrifugation. The supernatant was again made basic with NaOD; during the addition, more anhydride crystallized and was removed by centrifugation: NMR (of supernatant) δ 2.50 (3 H, s), 6.89 (1 H, d of d, J = 2 Hz, J = 8 Hz), 7.17 (1 H, d, J = 8 Hz), 7.37 (1 H, d, J = 2 Hz). Two singlets, at δ 2.78 and 7.54, were attributed to 4-methylaniline-3,5-disulfonate (about 12 mol %). Two multiplets at δ 7.79–8.00 and 8.59–8.75, attributed to residual naphthalimide impurities, integrated to a total of 0.78 H.

5-Amino-2-toluenesulfonic Acid (Eastman): NMR (D_2O/OD^-) δ 2.49 (3 H, s, CH_3), 6.86 (1 H, d of d, J = 2.5 Hz, J = 8 Hz, 4-H), 7.14 (1 H, d, J = 8 Hz, 3-H), 7.34 (1 H, d, J = 2.5 H, 6-H).

6-Amino-3-toluenesulfonic Acid (Aldrich): NMR (D_2O/OD^-) δ 2.24 (3 H, s, CH_3), 6.84 (1 H, d, J = 8 Hz, 5-H), 7.17 (1 H, d of d, J = 2 Hz, J = 8 Hz, 4-H), 7.49 (1 H, d, J = 2 Hz, 2-H).

Reaction of 5 with Propionaldehyde and Formaldehyde. Equal volumes of 0.2 M propionaldehyde and 0.2 M **5** in D_2O were mixed at room temperature, and the NMR spectrum was recorded as soon as possible. Within 120 s the aldehydic proton ($\delta \simeq 9.67$) was greatly reduced; a new triplet (δ 7.52, J = 5 Hz) had appeared. A similar experiment with formaldehyde was complicated by the fact that the resonance from the formaldehyde protons at $\delta \simeq 4.82$ was too close to the HDO peak for adequate observation. A rapid reaction, however, seemed likely, since the first obtainable spectrum of the naphthalimide region was complex, indicating a mixture of compounds. Gradually the spectrum of this region became less complex; after 30 min most of the spectrum appeared to be due to a single compound. By then two new doublets (δ 6.68, J = 12 Hz; δ 7.12, J = 11 Hz) had appeared.

Reaction of 10 with H_2O, Ethanolamine, and Mercaptoethanol. A 60-MHz ^1H NMR spectrum of a 10% (w/w) solution of **10** in D_2O was obtained immediately after the compound was dissolved; this spectrum was the same as that subsequently obtained after the solution had stood at room temperature for 6 h, 30 h, 10 days, and 75 days. Compound **10** was distinctly less stable in weak base. The NMR spectrum of a freshly prepared 10% (w/w) solution of **10** in 0.1 M Na^+/D^+ carbonate buffer in D_2O was very similar to the spectrum of **10** in D_2O. After 1 day at room temperature, the pD 9.1 spectrum was not noticeably different, but after 9 days at room temperature the intensity of the vinyl protons was reduced, and a new peak had appeared at $\delta \simeq 3.50$. It was estimated that between 20% and 50% of the compound had been converted, presumably to the lithium salt of **7**.

The NMR spectrum of 52 mg of **10** in 0.4 mL of D_2O and 0.1 mL of 0.5 M Na^+/D^+ pD 9.1 carbonate buffer was obtained. To the sample tube was added 14 μL of ethanolamine, and within 120 s the NMR spectrum of the vinyl region was recorded. No signals were seen, indicating that at least 90% of compound **10** had reacted. The complete spectrum showed the presence of two multiplets at $\delta \simeq 3.0$ and $\delta \simeq 3.7$.

A similar experiment was performed with 2-mercaptoethanol with virtually identical results.

"Wolf and Lamb" Reactions: Equilibrium and Kinetic Effects in Multipolymer Systems

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Abstract: Two reagents reacting avidly with each other in solution are rendered mutually inactive by attaching each to a separate batch of insoluble polymer. Two-stage reactions in which a soluble reagent reacts first with one polymeric reagent and the product with the second polymeric reagent afford advantages over analogous reactions in solution. In acylation reactions of carbon acids, the simultaneous use of a polymeric strong base and a polymeric acylating reagent proved to be superior to the use of soluble reagents, both for bringing about quantitative acylations and for coping with undesirable side reactions. New polymeric strong bases were prepared: polymeric tritylllithium, para-substituted tritylllithium polymers, and polymeric lithium diisopropylamide. Active esters of polymeric *o*-nitrophenol and *N*-1-hydroxybenzotriazole were used as acylation reagents. The scope and limitation of these reactions and their application to general multiphase systems are discussed.

Polymeric reagents—reactive, low molecular weight molecules bound to a polymeric backbone—have been widely used in organic chemistry during the past two decades. The most significant advantages of these reagents over their soluble counterparts are the ease of their separation from the reaction mixture and their possible recycling. Polymeric catalysts, polymers for specific separations, carriers for sequential synthesis, polymeric blocking groups, and polymeric transfer reagents in general organic synthesis, all have utilized these advantages. Use has also been made of the fact that chain fragments within a crosslinked polymeric backbone have restricted mobility. Active species attached to the polymer can thus be effectively isolated from each other at relatively high concentrations, providing the advantages of high dilution and specificity, along with rapid kinetics. In other cases, properties of the backbone itself such as polarity, pore size, and chirality were utilized to achieve unique reactions, the polymer providing a specific microenvironment for the reaction. These aspects of polymeric reagents have been extensively reviewed.[1-14]

At present, few examples exist in which more than one polymeric reagent is used in a particular reaction. Pittman and Smith,[15] for instance, described a reaction involving the simultaneous use of two polymeric organometallic catalysts for consecutive isomerization and hydrogenation of olefins. Use of two insoluble polymers or a mixture of a soluble and an insoluble polymeric reagents for peptide synthesis has also been reported.[16,17]

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