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Alkylene-bridged *N*,*N*,*N'N'* – Tetrasubstituted Bis(2-amino-5-thiazolyl)methinium Salts— A New Class of Strongly Fluorescent Dyes**

Horst Hartmann* and Antje Noack

Owing to their strong fluorescence, pyronines $2a (R^1 = H)^{[1]}$ and rhodamines $2a (R^1 = Aryl)^{[2]}$ have found several practical applications, such as fluorescence and laser dyes,^[3] or, if they are specifically functionalized, for example at the amino groups, as fluorescence markers for biological substrates and polymer characterization.^[4] The fluorescence of the dyes 2a is in sharp contrast to their unbridged di- and triarylmethane



dye analogues **1** which are nonfluorescent under normal conditions.^[5] The fluorescence-enhancing effect of bridging by heteroatoms is associated, however, with a pronounced hypsochromism of the absorption of these dyes. Thus, the bridged di- and triarylmethane dyes **2a** absorb at about 550 nm. This is a nearly 50 nm shorter wavelength than the absorption wavelength of their unbridged analogous **1**.^[6]

Whereas the fluorescence-enhancement is effected by the increasing rigidity of the molecular system and originates from a restriction or diminishing of the nonradiative deactivation processes^[7] the hypsochromic effect originates from the incorporation of the lone pair of the bridging oxygen atom into the conjugation of the π system responsible for the color. This incorporation gives rise to a stabilization of the electronic ground state and, hence, to a widening of the gap between the ground and first excited state in the bridged compounds.^[6]

In agreement with this postulate no hypsochromic effect is observed in going from the unbridged compounds **1** to the alkylene-bridged di- and triarylmethane dyes **2b** in which the bridging group has no lone pair. Therefore, these compounds absorb at nearly the same wavelength as their unbridged analogues **1**, but in contrast they exhibit, analogous to the oxygen-bridged compounds **2a**, a strong fluorescence.^[8a] A practical application of the isopropylidene-bridged dyes **2b** has not been reported because the necessary educts for these compounds, the isopropylidene-substituted *N*,*N*-dialkylanilines **3b**, can only be prepared by a multistep reaction from commercially available precursors, making them far less

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accessible than the educts 3a for the oxygen-bridged compounds 2a.[8b]

Recently it was demonstrated that some heterocyclic analogues of the di- and triarylmethane dyes 1, such as the compounds 4, exhibit similar spectroscopic properties to their carbocyclic parent compounds 1.^[9] Thus, the maxima of the longest-wavelength absorptions of the bis(2-dialkylamino-5thienyl)methines **4a**^[10] and bis(2-dialkylamino-5-thiazolyl)methines $\mathbf{4b}^{[9, 11]}$ are found at nearly the same wavelength as the maxima of their nonfluorescent parent compounds 1.



This parallelism in the spectroscopic properties between the carbocyclic and heterocyclic methine dyes 1 and 4 inspired us to synthesize the alkylene-bridged analogues 5 of the bridged carbocyclic methine dyes 2 and to study their spectroscopic properties, especially their ability to fluorescence. In analogy to the synthesis of the unbridged compounds 4b from the N,N-disubstituted 2-amino-thiazoles **6b**,^[12] the first method studied for the synthesis of 5 was the reaction of N,Ndisubstituted thioureas $7^{[13]}$ with the dibromo-substituted diketone 8^[14] (Scheme 1). This method gives the expected bisthiazoles 10^[15] which were subsequently transformed, by reaction with orthoformate esters and acetic anhydride in the presence of magnesium perchlorate^[16] or, more preferably, by reaction with DMF and POCl₃ and addition of aqueous tetrafluoroboric or perchloric acid, into the bridged methine dyes 12.



Scheme 1. Synthesis of the bis(2-amino-5-thiazolyl)methinium compound.

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Although the desired products 12 could be obtained in this manner their yields were surprisingly low. The yields are reduced by the formation of by-products which probably result from an intermolecular condensation between two thiazole moieties of two educt molecules 10 which competes with the planed intramolecular condensation of the orthoformate esters with the two thiazole groups in 10. Therefore, a second route for the preparation of 12 was designed. Instead of 8 the dibromo-cyclohexanedione 9 was chosen to react with 7.^[17] The compound 9 was prepared, analogously to compound

> 8, by the bromination of its bromo-free precursor in glacial acetic acid.^[18] The reaction of 9 with the appropriate N,N-disubstituted thiourea 7 in a molar ratio of 1:2 gave the tricyclic bisthiazole derivatives 11.^[19] These products were allowed to react in acetonitrile solution with trityl tetrafluoroborate affording the desired methine tetrafluoroborates 12 in satisfactory yields.

The structures of the isopropylidene-bridged

methine dyes 12 were unambiguously confirmed by elemental analysis and NMR spectroscopy (Table 1). The dyes are deep blue and exhibit, as expected, a marked fluorescence. Figure 1 shows the absorption and emission spectrum of the morpholino-substituted compound 12a. Like most dyes of this type this compound displays a narrow intense absorption band at about 620 nm.[20] Remarkably the position of this band is shifted to longer wavelength^[21] than the longest-wavelength absorption band of the unbridged methine dye analogues 4b (552 nm).^[6] The fluorescence maxima from the isopropylidene-bridged methine dyes 12, which are dependent on the polarity of solvents, are found at about 650 nm in toluene. The small Stokes shift observed is as

Table 1. Selected data for the bridged N,N,N'N,'-tetrasubstituted bis(2amino-5-thiazolyl)methinium tetrafluoroborates 12 ($X = BF_4$).^[a,b]

12a: Yield 53% (method A)^[c] and 51% (method B); m.p. 209-211°C $(CH_3CN/diethyl ether)$; ¹H NMR ([D₆]DMSO): $\delta = 1.65$ (s, 6H, CH₃), 3.73 (t, 8H, NCH₂), 3.84 (t, 8H, OCH₂), 8.83 (s, 1H, CH); ¹³C NMR $([D_6]DMSO): \delta = 28.16, 45.74, 49.39, 65.18, 120.24, 139.89, 177.83,$ 181.36; UV/Vis absorption: $\lambda_{max} = 616 \text{ nm}$, $\log \varepsilon = 4.68$; emission: $\lambda_{max} =$ 654 nm, $\Phi = 56\%$

12b: Yield 49% (method A)^[c] and 31% (method B); m.p. 203-205°C (CH₃CN/diethyl ether); ¹H NMR ([D₆]DMSO): $\delta = 1.63$ (s, 6H, CH₃), 1.70 (m, 12H, CH₂), 3.81 (m, 8H, NCH₂), 8.73 (s, 1H, CH); ¹³C NMR $([D_6]DMSO): \delta = 22.86, 24.91, 28.23, 45.58, 50.75, 119.74, 138.72, 176.95,$ 181.37; UV/Vis absorption: $\lambda_{max} = 625 \text{ nm}$, $\log \varepsilon = 4.62$; emission: $\lambda_{max} =$ 656 nm, $\Phi = 37 \%$

12c: Yield 32% (method B); m.p. 160-162°C (CH₃CN/diethyl ether); ¹H NMR ($[D_6]DMSO$): $\delta = 1.66$ (s, 6 H, CH₃), 2.09 (m, 8 H, CH₂), 3.49 (m, 8H, NCH₂), 8.78 (s, 1H, CH); ¹³C NMR ([D₆]DMSO): $\delta = 24.72$, 28.24, 45.40, 51.07, 119.70, 139.91, 173.67, 180.89; UV/Vis absorpsion: $\lambda_{max} =$ 616 nm, log ε = 4.57; emission: λ_{max} = 649 nm, Φ = 21 %

12d: Yield 38% (method B), m.p. 150-153°C (CH₃CN/diethyl ether); ¹H NMR ([D₆]DMSO): $\delta = 1.71$ (s, 6H, CH₃), 3.76 (s, 6H, NCH₃), 7.48-7.53 (m, 6H, CH), 7.64 (m, 4H, CH), 8.68 (s, 1H, CH); 13C MMR $([D_6]DMSO): \delta = 28.37, 42.15, 46.05, 121.65, 124.55, 125.73, 130.75, 143.65,$ 145.02, 172.44, 181.88; UV/Vis absorpsion: $\lambda_{max} = 623 \text{ nm}, \log \varepsilon = 4.64;$ emission: $\lambda_{\rm max} = 669$ nm, $\Phi = 1$ %

[a] For the substitutents R2N pattern, see Scheme 1. [b] Absorption data in dichloromethane, emission data in toluene; fluorescence quantum yield relative to rhodamine B($\Phi = 86$ %). [c] Determined by ¹H NMR spectroscopy.

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Figure 1. Absorption spectrum (----) and emission spectrum (----) of 12 a.

expected, and in accordance with the rigid structure of the dyes which prevents, or at least largely suppresses, a nonradiative deactivation of the excited state.

The reported route to strongly fluorescent bis(2-amino-5-thiazolyl)methinium salts **12** also indicates a simple way for preparing specially functionalized methine dyes which can be used, analogously to specially functionalized pyronine or rhodamine dyes 2a,^[4] as fluorescence markers for biological and polymeric substrates.

Experimental Section

Preparation of the isopropylidene-bridged N,N,N',N'-tetrasubstituted bis(2-amino-5-thiazolyl)methinium salts **12**:

Method A: To a mixture of a 4-(2-(2-dialkylamino-4-thiazolyl)-2-propyl)-2dialkylamino-thiazole **10** (0.01 mol) and DMF (20 mL) POCl₃ (0.02 mol, 3.0 g) was added dropwise under stirring at RT. After stirring for 3 h the reaction mixture was added dropwise, to a cooled solution of tetrafluoroboric acid (40%, 5 mL) in methanol (20 mL). The products precipitated after addition of diethyl ether (100 mL) and were isolated by filtration. As indicated by their ¹H NMR spectra the products in each case were a mixture of the corresponding dyes **12** and their dimers, from which the desired products could not be isolated, only identified by their characteristic ¹H NMR spectra and their intense fluorescence.

Method B: A mixture of a 2,6-bis(dialkylamino)-4,4-dimethyl-4,8-dihydrothiazolo[4,5-f]benzothiazole **11** (0.01 mol) and triphenylmethyl tetrafluoroborate (3.30 g, 0.01 mol) in acetonitrile (50 mL) was heated at reflux for 24 h. After cooling and reducing the volume to 5 mL diethyl ether (20 mL) was added to the reaction mixture and the precipitated **12** was isolated by filtration.

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- [19] **11a**: Yield 76%; m.p. 220–222°C (toluene/MeOH); ¹H NMR (CDCl₃): $\delta = 1.49$ (s, 6H, CH₃), 3.41 (t, 8H, NCH₂), 3.78 (t, 8H, OCH₂), 3.82 (s, 2H, CH₂); ¹³C NMR (CDCl₃): $\delta = 23.33$, 28.16, 38.78, 48.57, 66.18, 111.60, 153.49, 169.76; **11b**: yield 66%; m.p. 275–277°C (toluene); ¹H NMR (CDCl₃): $\delta = 1.53$ (s, 6H, CH₃), 1.65 (m, 12 H, CH₂), 3.43 (m, 8H, CH₂), 3.81 (s, 2H, CH₂); ¹³C NMR (CDCl₃): $\delta = 24.06$, 25.04, 25.78, 28.89, 39.44, 50.25, 111.44, 154.25, 170.66; **11c**: yield 79%; m.p. 250–252°C (toluene); ¹H NMR (CDCl₃): $\delta = 1.59$ (s, 6H, CH₃), 2.01 (m, 8H, CH₂), 3.45 (t, 8H, CH₂), 3.83 (s, 2 H, CH₂); ¹³C NMR (CDCl₃): $\delta = 1.59$ (s, 6H, CH₃), 2.01 (m, 8H, CH₂), 3.45 (c, 6H, NCH₂), 3.83 (s, 2 H, CH₂), ¹³C NMR (CDCl₃): $\delta = 1.64$ (s, 6H, CH₃), 3.56 (s, 6H, NCH₃), 3.72 (s, 2 H, CH₂), 7.23 (m, 2H, CH), 7.42 (m, 8H, CH); ¹³C NMR (CDCl₃): $\delta = 23.81$, 28.97, 39.41, 40.53, 112.16, 124.99, 126.28, 130.13, 147.36, 153.84, 168.57.
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