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Synthesis of Novel Quinaldine-Based Squaraine Dyes: Effect of Substituents and Role of Electronic Factors

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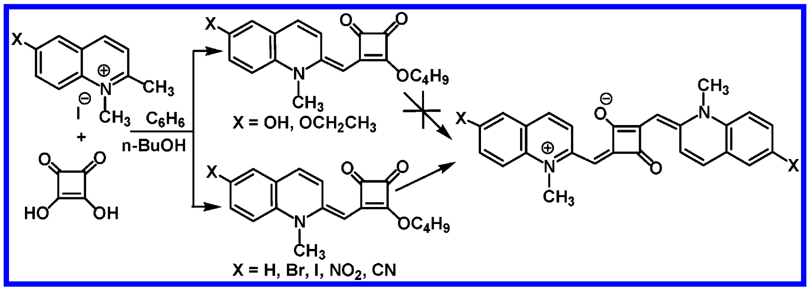
ABSTRACT



Condensation of squaric acid with quinaldinium salts containing electron-donating substituents gave only the semisquaraines. However, with salts possessing electronegative and electron-withdrawing groups, the squaraine dyes were isolated in quantitative yields. The semisquaraines formed undergo condensation with highly nucleophilic salts yielding the unsymmetrical squaraine dyes. These results demonstrate the role of electronic factors and provide valuable information for the design of efficient squaraine-based sensitizers that can have potential applications in photodynamic therapy.

Squaraines form a class of dyes possessing sharp and intense absorption bands in the red to near-infrared region.[1] The photophysical and photochemical properties of these have been studied extensively,[1,2] because their absorption and photochemical characteristics make them highly suitable for a number of industrial applications. These include, photoreceptors in copiers,[3] photoconductors in organic solar cells,[4] and IR absorbers in organic optical disks.[5] The semisquaraine derivatives and the squaraine dyes also find application as sensors for metal ions and biologically important molecules.[6] Due to the very low intersystem crossing efficiency of these dyes,[1,2] their potential as sensitizers in photodynamic therapy (PDT)[7] has not yet been explored.

Our objective has been to explore the use of suitable squaraine dyes as sensitizers for PDT. In this context, we

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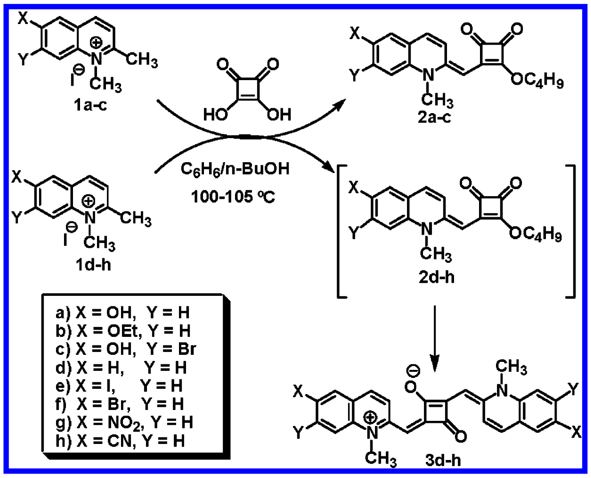
Scheme 1



have recently synthesized a few halogen-substituted squaraine dyes and investigated their photophysical[8] and in vitro photobiological[9] properties. The encouraging results obtained from these studies prompted us to design new sensitizers with improved photophysical and photobiological properties. We felt that quinaldine-based squaraine dyes could be potential sensitizers because these dyes are expected to have improved photophysical properties such as long-wavelength absorption (>700 nm) in the near-infrared region and high extinction coefficients ($>10^5$ M^{-1} cm^{-1}).[10] Moreover, the benzene ring of the quinaldine moiety can be suitably substituted so as to enhance their triplet quantum yields as well as their cellular pharmacokinetics.

Herein we report the synthesis of a few quinaldine-based squaraine dyes and the interesting effects of various substituents on the dye-forming reaction. It has been observed that semisquaraines are formed as the sole product in the reaction of quinaldinium salts containing electron-donating substituents with squaric acid. Interestingly, they could be converted into the squaraine dyes by reacting with the quinaldinium salts having electronegative and/or electron-withdrawing groups. These results demonstrate the role of electronic factors and the usefulness of this strategy for the synthesis of unsymmetrical squaraine dyes with improved photophysical and photobiological properties.

With a view to synthesizing 6-hydroxyl-substituted quinaldine-based squaraine dye, we have carried out the reaction between the quinaldinium salt **1a** and squaric acid with 2:1 equivalents, respectively, in a mixture (1:1) of benzene and *n*-butanol (Scheme 1). Since the expected squaraine dye (squaraine dyes in general are highly colored) is a brightly colored compound with absorption in the near-infrared region, we monitored the progress of the reaction by absorption spectroscopy (Figure 1). As is evident from Figure 1, no absorption band in the near infrared region was observed during the initial stages of the reaction. However, an absorption band around 485 nm was observed within 4 h of the reaction and this band increased in intensity with reaction time. After prolonged heating, a faint absorption around 715 nm was observed, which showed negligible enhancement in intensity with increasing reaction time, indicating thereby that the dye is formed in insignificant amounts. Similar observations were made when the condensation reactions were carried out with the quinaldinium salts **1b** and **1c** and squaric acid (Scheme 1) (Figures S1 and S2, Supporting Information).

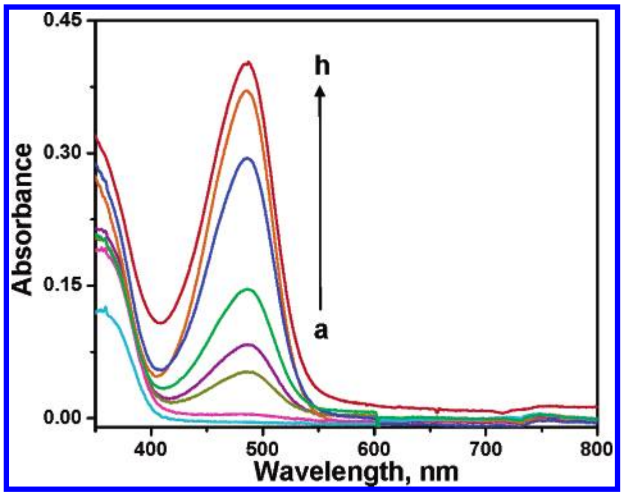


Figure 1. Change in absorption spectra obtained for the reaction between the quinaldinium salt **1a** and squaric acid in a mixture (1:1) of benzene and *n*-butanol at various time intervals. Time: (a) 0, (b) 1, (c) 2, (d) 4, (e) 6, (f) 9, (g) 12, and (h) 15.5 h.

For a better understanding of the dye-forming reaction, we have monitored the progress of the reaction between squaric acid and the unsubstituted quinaldinium salt **1d**, reported earlier (Figure 2).[10] As can be seen from Figure 2, after about an hour, the absorption spectrum showed two absorption bands at 485 nm as well as at 714 nm. The intensity of both these bands increased with an increase in reaction time. After about 7 h, the absorption at 485 nm decreased with time, while the absorption band at 714 nm intensified and reached a plateau by about 19 h (inset of Figure 2). The initial formation of the absorption band at 485 nm, followed by its decrease in intensity with concomitant increase in absorption around 714 nm (isosbestic point around 540 nm), indicates that the species having absorption at 485 nm is an intermediate in the dye-forming reaction.

On the basis of spectral and analytical evidence and literature information, we assign the species formed with absorption at 485 nm to the semisquaraine intermediate **2d**, in the reaction between squaric acid and the corresponding quinaldinium salt. The species with absorption at 714 nm is assigned to the squaraine dye **3d** (experimental details, Sup-

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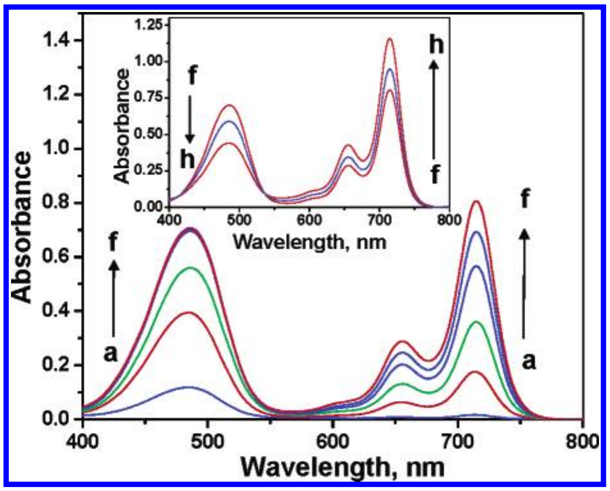


Figure 2. Change in absorption spectra obtained for the reaction between the quinaldinium salt **1d** and squaric acid in a mixture (1:1) of benzene and *n*-butanol at various time intervals. Time: (a) 1, (b) 2, (c) 3, (d) 5, (e) 7, and (f) 9 h. Inset shows the change in absorption spectra obtained for the same reaction after long reaction time intervals. Time: (f) 9, (g) 11, and (h) 16 h.

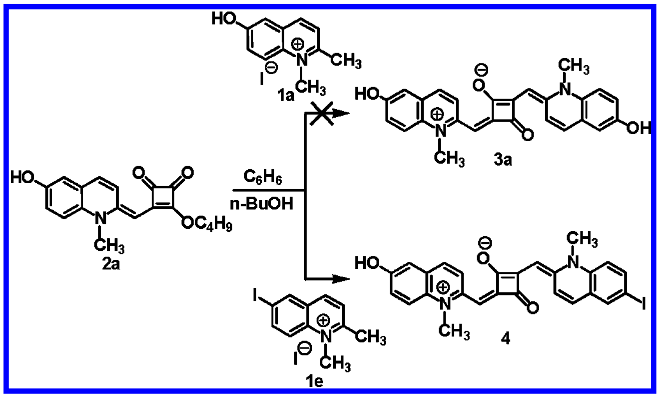
porting Information).[10] The reaction between the quinaldinium salts with electron-donating groups (**1a**–**c**) and squaric acid did not result in the formation of the corresponding squaraine dyes (Scheme 1). Instead, only butyl adducts of the semisquaraines **2a**–**c** were isolated in 90–95% yields.

To investigate the effect of substituents on the formation of the semisquaraine intermediates and subsequently the squaraine dyes, we have synthesized the substituted quinaldinium salts **1e**,**f**, which can induce electron-withdrawing and inductive effects on the quinaldine moiety. The quinaldine derivatives and their corresponding quaternary salts **1e**,**f** were prepared by reported procedures with modifications wherever necessary (experimental details, Supporting Information).

The reaction of the quinaldinium salt **1e** with squaric acid under analogous conditions gave the corresponding squaraine dye **3e** in 85% yield through the intermediacy of the semisquaraine **2e**. The absorption spectra recorded at various reaction time intervals, showed the formation of the semisquaraine intermediate **2e** (λ_{max} 492 nm) and the squaraine dye **3e** (λ_{max} 725 nm) with an isosbestic point at 545 nm (Figure S3, Supporting Information). Similar observations were made with the quinaldinium salts substituted with bromine (**1f**) and electron-withdrawing nitro (**1g**) and cyano (**1h**) groups. These salts on reaction with squaric acid gave their corresponding squaraine dyes **3f**–**h** in 84–96% yields (Scheme 1), which were characterized on the basis of spectral data and analytical results (experimental details, Supporting Information).

The variation in the reactivity of the substituted quinaldinium salts **1a**–**h** with squaric acid can be explained on the basis of the electronic effects of the various substituents. Squaraine dye-forming reaction involves the reaction between an electron-rich aromatic derivative and squaric acid.[11] The success of the reaction depends mainly on the nucleophilicity of the aryl species.[12] In the present study, the nucleophile is an enamine[13] formed from the quinaldinium salt, which reacts with the squaric acid resulting in the formation of the semisquaraine. Subsequently, the semisquaraine undergoes further reaction with another moiety of the enamine to give the squaraine dye (Scheme 1).

Scheme 2



The presence of electron-donating groups on the benzene ring of the quinaldinium salts **1a**–**c** reduces the acidity of the hydrogen atoms of the 2-methyl group and thereby decreases the formation of the enamine nucleophile. Nevertheless, the enamine formed reacts with squaric acid, resulting in the corresponding semisquaraines **2a**–**c**. Further, the electrophilic terminus of these semisquaraines is rendered less reactive by the electron-donating substituents, and hence further reaction with the less acidic salts becomes extremely difficult. As a result, the reaction stops with the formation of the semisquaraine only in the case of the salts **1a**–**c**. However, in the presence of electronegative (**1e**,**f**) and electron-withdrawing substituents (**1g**,**h**), the hydrogen atoms of the 2-methyl group are relatively more acidic and thereby favor the formation of the enamine nucleophile very efficiently. These salts yield higher concentrations of the nucleophile and hence results in the corresponding semisquaraine intermediates **2e**–**h** followed by formation of the corresponding squaraine dyes **3e**–**h** in quantitative yields.

To confirm the above suggestion, we have examined the reaction of the semisquaraine **2a**, which possesses a weak electrophilic terminus with quinaldinium salts of varying acidity (**1a** and **1e**). Interestingly, we observed the formation of the unsymmetrical dye **4** only with the highly reactive salt **1e**, which can generate the enamine nucleophile efficiently. As expected, negligible reaction was observed with the less acidic salt **1a** as indicated in Scheme 2. The progress of the reaction between **2a** and the salts **1e** and **1a** was followed spectroscopically (Figure 3).

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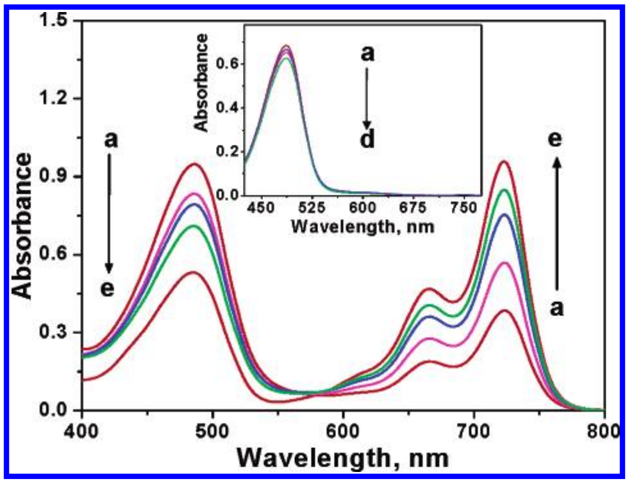

Figure 3. Change in absorption spectra obtained for the reaction between the semisquaraine **2a** and the quinaldinium salt **1e** at various time intervals. Time: (a) 1, (b) 2, (c) 4, (d) 6, and (e) 8 h. Inset shows the change in absorption spectra obtained for the reaction between **2a** and the salt **1a** at various time intervals. Time: (a) 0, (b) 1, (c) 4, and (d) 6 h.

As the reaction progressed, in the case of **1e**, a new band at 723 nm appeared, which increased in intensity with time and with a concomitant decrease in intensity of the band at 485 nm, indicating the formation of the squaraine dye **4** (Figure 3). However, when the reaction of the semisquaraine **2a** with the less reactive quinaldinium salt **1a** was attempted under similar conditions, none of the squaraine dye **3a** was formed (inset of Figure 3). In this case, we observed a nonnegligible decrease in absorbance at 485 nm; however, this was found to be <7% even after 6 h of refluxing (100−105 °C) under the reaction conditions.

In conclusion, we have demonstrated that substitution on the benzene ring of the quinaldine moiety can affect the reaction between the quinaldinium salts and squaric acid, resulting in the formation of the corresponding squaraine dyes. The quinaldinium salts with electron-donating substituents hinder the formation of the dye and result only in the formation of the semisquaraine, while electronegative and electron-withdrawing substituents facilitate the formation of the corresponding squaraine dyes with the intermediacy of the corresponding semisquaraines. These electronic effects, observed during the course of our studies, could provide valuable information on the choice of substituents for the design of novel and efficient sensitizers based on squaraine dyes. Efforts are underway in our laboratory to evaluate the potential applications of these dyes as sensitizers in photodynamic therapy.

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Supporting Information Available: Synthetic details along with spectroscopic data of the quinaldine derivatives, the quinaldinium salts, the semisquaraines, and the squaraine dyes, ^{1}H and ^{13}C NMR spectra of the representative semisquaraines and squaraine dyes, and the absorption spectra showing the progress of the condensation reaction between squaric acid and the quinaldinium salts **1b**, **1c**, and **1e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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