Studies on the photocyclization reaction of 8-styryl-substituted coralyne derivatives

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Abstract
The photoreactivity of four 8-styryl-substituted coralyne derivatives was examined by UV/VIS- and 1H-NMR-spectroscopy. Except for the dimethylamino-substituted derivative, these cationic azoniaheterocyclic dyes undergo photocyclization that most likely proceeds through an initial E-Z-isomerization of the double bond. Subsequent oxidation of the intermediates under aerobic conditions gave the pyrrolo-annelated quinolizinium derivatives as final products, thus providing a useful synthetic route to polycyclic azoniahetarene derivatives. The 6-(4-chlorophenyl)-substituted pyrroloquinolizinium derivative was isolated on a preparative scale, and the investigation of its photophysical properties revealed significantly red-shifted absorption ($\lambda_{\text{abs}} = 465–480$ nm) and emission bands ($\lambda_{\text{fl}} = 550–562$ nm) in comparison to the parent coralyne and the styryl-substituted derivatives.

1 | INTRODUCTION

Polycyclic cationic hetarenes have recently attracted much interest with regard to their synthesis and applications. Specifically, quinolizinium-type derivatives with a bridgehead quaternary nitrogen atom (azoniahetarenes) figure as promising lead structures for the development of DNA-binding and DNA-photodamaging agents,[1] enzyme inhibitors,[2] cystic fibrosis transmembrane conductance regulator activators,[3] fluorescent dyes and chemosensors,[4] or nonlinear optical materials.[5] As a result, several synthetic routes have been developed and explored for the synthesis of substituted or annelated quinolizinium derivatives.[6] Notably, a series of azonia aromatic natural products are known, for example, berberine, sanguinarine, sempervirine, or flavopereirine, which have favorable biological properties.[7] In this context, the synthetic berberine alkaloid coralyne (1) is of particular interest. This fully aromatic dibenzoquinolizinium derivative exhibits a very broad spectrum of biological and pharmacological activity, namely antimicrobial, antileukemic, antineoplastic and antitumor properties as well as enzyme inhibition.[8] Notably, the chemical and photophysical properties of the annelated quinolizinium are essentially maintained in coralyne, so that the synthesis of coralyne derivatives offers the opportunity to combine the desired quinolizinium properties with the latent biocompatibility and bioactivity of this alkaloid. Thus, we have demonstrated recently that the easily available 8-styryl-substituted coralyne derivatives 2a-d are duplex and quadruplex DNA-binding ligands.[9] In particular, the biocompatibility of these compounds allowed to employ the aminostyryl-substituted derivative 2d as fluorescent probe for the detection of DNA in cells.

Having the coralyne derivatives 2a-d in hands we wished to explore their potential as substrates for further functionalization. Specifically, we were interested in the photo-induced cyclization reaction to give the pyrrolo-fused products. Although pyrroloquinolizinium...
derivatives, that are members of the cyclazine family,\textsuperscript{[10]} are known already,\textsuperscript{[11]} there is, to the best of our knowledge, only one example reported for their formation through photocyclization of a styrylquinolizinium precursor.\textsuperscript{[12]} Herein, we report our studies on the photoreactivity of the styrylcorylamine derivatives 2a-d, along with some mechanistic studies, and we present the absorption and emission properties of the resulting pyrrolo-annelated product 3.

\[ \text{2a-d: } \text{Ar = C}_6\text{H}_5 \]
\[ \text{2a: } \text{Ar = C}_6\text{H}_5 \]
\[ \text{2b: } \text{Ar = 4-C}_6\text{H}_4\text{Me} \]
\[ \text{2c: } \text{Ar = 4-C}_6\text{H}_4\text{Cl} \]
\[ \text{2d: } \text{Ar = 4-C}_6\text{H}_4\text{NMe}_2 \]

2 | RESULTS AND DISCUSSION

The absorption spectra of the styryl-substituted corylamine derivatives 2a-d exhibit characteristic long-wavelength absorption bands with maxima at 436 nm (2a-c) or 469 nm (2d) in MeCN (Figure 1).\textsuperscript{[9]} The irradiation of the dyes 2a-c under aerobic conditions with 315 nm or 360 nm light did not lead to significant changes in the absorption spectra, whereas the use of 420 nm light caused a decrease of the absorption accompanied by a bathochromic shift. While the dye 2a was irradiated for more than 3 hours until no more changes in the absorption spectra were detected (Figure 1A), the complete photoreaction only took approximately 30 minutes for 2b and 2c (Figure 1B,C). Hence, the substitution with a methyl or chlorine substituent apparently enhances the photoreactivity of the substrate, since both substituents increase the electron density of the conjugated \( \pi \) system either through an inductive effect (methyl group) or, in the case of the chloro substituent, through resonance, as the latter operates as a \( \pi \) donor in conjugation with the electron withdrawing corylamine unit. The significant changes of the absorption spectra were, however, not in agreement with the expected \( E-Z \)-isomerization of the double bond. But the similar course of the spectral changes led to the conclusion that 2a-c form analogous photoproducts upon irradiation. In fact, the normalized absorption spectra after an irradiation time of 210 minutes (2a) or 60 minutes (2b and 2c), respectively, are almost superimposable and show a broad long-wavelength absorption band at 463 nm with a red-shifted

![Figure 1](https://wileyonlinelibrary.com)
shoulder between 500 and 540 nm as well as a distinct absorption band at 327 nm (Figure S1A). In contrast, the irradiation of 2d only caused minor changes in the absorption spectra providing no clear indication of a light-induced reaction (Figure 1D). Most likely, 2d forms a charge-transfer excited state that returns to the ground state by competing radiative and radiationless transitions before a photoreaction can take place.

The irradiation of 2c was followed exemplarily by 1H-NMR spectroscopy in order to obtain an insight into the underlying mechanism and a detailed analysis of the photoproduct (Figure 2, Scheme 1, conditions a). The NMR spectrum of 2c shows 13 protons in the aromatic region (>7 ppm) with characteristic signals at δ = 9.35 (s, 13-H), 8.69 (d, 6-H) and 7.31 (d, 3J = 16 Hz, CH') (Figure 2, 0 minute). After an irradiation time of 5 minutes, the signal intensities decreased, and a new signal set developed. Specifically, a newly formed doublet at δ = 7.03 with a characteristic coupling constant of 3J = 12 Hz clearly indicated an initial E-Z-isomerization of 2c. The ratio of both isomers was (E)-2c:(Z)-2c = 71:29, as calculated by integration of the signals at δ = 9.35 (13-HE) and 9.41 (13-HZ). Upon further irradiation, that is, after an induction time of about 10 minutes, the intensity of both sets of signals decreased, and a third signal set developed that consisted of 11 protons in the aromatic region (Figure 2, 10—30 minutes). The latter signals, as well as the singlets of the four methoxy groups (Figure S2), exhibited a downfield shift in comparison to the NMR signals of 2c.

The normalized absorption spectrum of the solution after an irradiation time of 30 minutes showed the same absorption bands in comparison to the one obtained upon irradiation at a concentration of cL = 20 μM (Figure S1B). This indicates that the formation of the photoproduct is essentially independent of the concentration in the range between 20 μM and 2 mM. Furthermore, the mass-spectrometric analysis (ESI) of the solution revealed the loss of two hydrogen atoms from substrate 2c (m/z = 484), and the photoproduct 3 was identified as 6-(4'-chlorophenyl)-2,3,9,10-tetramethoxydibenzo[a,g]pyrrolo[2,1,5-de]quinolizinium (3) by additional NMR-spectroscopic investigations [correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC)]. The formation of this pyrroloquinolizinium is in agreement with
the known photocyclization-oxidation reaction of a 4-styryl-substituted benzo[a]quinolizinium.\textsuperscript{[12]}

In order to synthesize the pyrroloquinolizinium 3 on a preparative scale, a 200 $\mu$M solution of 2c was irradiated with a high pressure Hg mercury lamp ($\lambda_{\text{irr}} > 390$ nm) (Scheme 1, conditions b), and the reaction was monitored by absorption spectroscopy (Figure 3). After an irradiation time of 8.5 hours, the product 3 was obtained in 26% yield, and its structure was confirmed by NMR spectroscopy ($^1$H, $^{13}$C, COSY, HSQC, HMBC), electrospray ionization mass spectrometry (ESI-MS), and elemental analysis. It should be noted that the $^1$H-NMR signals of a saturated solution of 3 in CD$_3$CN are not only much broader but also significantly shifted upfield (Figure S3) in comparison to the signals that were detected after the irradiation of a 2 mM solution of 2c (Figure 2, 30 minutes). We attribute this to the formation of dye aggregates at higher concentrations, as commonly observed for positively charged, heterocyclic systems.\textsuperscript{[13]}

As revealed by the $^1$H-NMR spectroscopic reaction monitoring, the mechanism of the formation of 3 most likely proceeds through an initial $E$-$Z$-isomerization of the double bond and a subsequent photo-induced electrocyclization to give intermediate A (Scheme 2). After the deprotonation of A, the resulting intermediate C is readily oxidized under the employed aerobic conditions to achieve aromatization and formation of product 3. In this context, it has to be noted that the intermediate C might also be formed after deprotonation of the tertiary carbenium ion B that results from a [1,2]-H shift of A.

The pyrroloquinolizinium derivative 3 is hardly soluble in various nonpolar, polar protic, and polar aprotic solvents. Nevertheless, we determined its absorption and emission properties in representative solvents (Figure 4, Table 1). Thus, the long-wavelength absorption maximum of 3 ranges from 465 nm in MeCN to 480 nm in CHCl$_3$ ($\varepsilon_{\text{max}} = 19 100$–$22 500$ M$^{-1}$ cm$^{-1}$) (Figure 4A). Thereby, the red-shift in a chlorinated solvent such as CHCl$_3$ was previously attributed to the high polarizability of these solvents.\textsuperscript{[4g]}

Furthermore, the dye 3 is fluorescent in the investigated solvents and shows broad emission bands at $\lambda_{\text{fl}} = 550$–$562$ nm with moderate emission quantum yields ($\Phi_{\text{fl}} = 0.19$–$0.27$) (Figure 4B). In comparison to the parent compound coralyne (1) and the styryl dyes 2a-c ($\lambda_{\text{abs}} = 434$–$436$ nm and $\lambda_{\text{fl}} = 473$–$484$ nm in MeCN),\textsuperscript{[9]} both the absorption and the emission bands of the pyrrolo-annelated compound 3 are significantly red-shifted due to its more extended aromatic system.

3 | CONCLUSIONS

The 8-styryl-substituted coralyne derivatives 2a-c undergo a photocyclization-oxidation reaction upon irradiation under aerobic conditions to form pyrroloquinolizininium derivatives. As revealed by $^1$H-NMR-spectroscopy, the photocyclization most likely proceeds through an initial $E$-$Z$-isomerization of the double bond. Since this reaction is straightforward and should
be applicable to similar cationic hetarenes, the irradiation of such styryl derivatives offers a useful general synthetic access to novel polycyclic azoniahetarene derivatives, specifically those containing the important coralyne lead structure. In addition, the synthesis of the respective chlorophenyl-substituted pyrrolo-annelated quinolizinium \( 3 \) by irradiation of \( 2c \) on a preparative scale enabled for the first time the analysis of the absorption and emission properties of this class of compounds. Hence, the derivative \( 3 \) exhibits significantly red-shifted absorption and emission bands in comparison to coralyne \( 1 \) and the styrylcoralyne derivatives \( 2a-c \).

### Table 1: Absorption and emission properties of pyrroloquinolizinium derivative 3

| Solvent | \( \lambda_{\text{abs}} \) (nm) | \( \lg e \) | \( \lambda_{\text{fl}} \) (nm) | \( \Phi_{\text{fl}} \times 10^{-2} \) |
|---------|-----------------|--------|-----------------|-----------------|
| MeOH    | 466             | 4.32   | 553             | 27              |
| MeCN    | 465             | 4.28   | 553             | 24              |
| DMSO    | 472             | 4.33   | 562             | 26              |
| CHCl3   | 480             | 4.35   | 550             | 19              |

Abbreviation: DMSO, dimethyl sulfoxide.

\(^a\) Solvents arranged in order of decreasing \( E_T^{30} \) values.

\(^b\) Long-wavelength absorption maximum in nm; \( c = 10 \, \mu M \).

\(^c\) Molar extinction coefficient in \( \text{cm}^{-1} \, \text{M}^{-1} \).

\(^d\) Fluorescence emission maximum in nm (Abs. = 0.10 at the excitation wavelength \( \lambda_{\text{ex}} = 450 \, \text{nm} \)).

\(^e\) Fluorescence quantum yield relative to Coumarin 153 (\( \Phi_0 = 0.38 \))\(^{[14]}\) estimated error for fluorescence quantum yields: \( \pm 10\% \).

4 | EXPERIMENTAL SECTION

4.1 | Equipment

NMR spectra were recorded with a Varian VNMR-S 600 (\( ^1\text{H}: 600 \, \text{MHz}, \, ^{13}\text{C}: 150 \, \text{MHz} \)) at 25°C. Spectra were processed with the software MestReNova (version: 12.0.1) and referenced to the respective solvent (CD\(_3\)CN: \( \delta_\text{H} = 1.94, \, \delta_\text{C} = 1.34 \)). The chemical shifts are given in ppm. Absorption spectra were recorded with a Cary 100 Bio spectrophotometer in Hellma quartz cells 110-QS (10 mm) with baseline correction at 20°C. Emission spectra were collected with a Cary Eclipse Fluorescence spectrophotometer in Hellma quartz cells 114F-QS (10 mm \( \times 4 \, \text{mm} \)) at 20°C. Elemental analyses data were determined with a HEKAtech EUROEA combustion analyzer by Mr. Rochus Breuer (Universität Siegen, Organische Chemie I). Mass spectra (ESI) were recorded on a Finnigan LCQ Deca (\( U = 6 \, \text{kV} \); working gas: Argon; auxiliary gas: Nitrogen; temperature of the capillary: 200°C). The melting points were measured with a BÜCHI 545 (BÜCHI, Flawil, CH) and are uncorrected. Solutions were irradiated with a diode-array light apparatus (Atlas Photonics LUMOS 43) or with a high-pressure Hg-lamp (Heraeus TQ 150-56001725).

4.2 | Materials

The styryl-substituted coralyne derivatives \( 2a-d \) were synthesized from coralyne \( 1 \) by a Knoevenagel type reaction as previously described\(^{[9]}\). The commercially available chemicals were reagent-grade and used without further purification. Absorption and emission spectra were recorded from solutions prepared with spectroscopic grade solvents.

4.3 | Methods

For experiments in different solvents, aliquots of the stock solution \( c = 1.0 \, \text{mM} \) in MeCN) were evaporated under a stream of nitrogen and redissolved in the respective solvent. In general, absorption spectra were

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**FIGURE 4** A, Absorption \( (c = 10 \, \mu M) \) and B, normalized emission spectra \( (\text{Abs.} = 0.10 \, \text{at} \, \lambda_{\text{ex}} = 450 \, \text{nm}) \) of derivative 3 in MeOH (red), MeCN (black), DMSO (blue), and CHCl\(_3\) (green). DMSO, dimethyl sulfoxide [Color figure can be viewed at wileyonlinelibrary.com]
determined in a range between 200 and 700 nm (260–700 nm for dimethyl sulfoxide and 240–700 nm for CHCl₃) and subsequently smoothed in the Origin software with the function “adjacent-averaging” (factor of 10).

For the photochemical studies, air-saturated solutions of 2a-d in MeCN were irradiated with a diode-array light apparatus (Atlas Photonics LUMOS 43) at λₐₐᵣ = 420 nm either in Hellma quartz cells 110-QS (10 mm) or in 3 mm NMR tubes.

For the detection of emission spectra, the excitation and emission slits were adjusted to 5 nm, the detector voltage was adjusted to 550 V. The emission spectra were smoothed with the implemented moving-average function by a factor of 5. The fluorescence quantum yields of derivative 3 were determined relative to Coumarin 153 (Φₑ = 0.38 in EtOH) according to the established procedures.[14b,14c]

4.4 Synthesis

4.4.1 6-(4’-Chlorophenyl)-2,3,9,10-tetramethoxydibenzo[a,g]pyrrolo[2,1,5-de]quinoxalinium tetrafluoroborate (3)

A solution of coralyne derivative 2c (35.6 mg, 62.0 μmol) in MeCN (310 mL, c₁ = 200 μM) was irradiated with a high-pressure Hg-lamp (150 W) at λₐₐᵣ > 390 nm under stirring for 8.5 hours (a 1% wt/vol aqueous NaNO₂ solution was used as cut-off filter). The reaction progress was monitored by absorption spectroscopy by diluting an aliquot of the reaction mixture (1:5 with MeCN). After no further changes in the absorption spectra were detected, the solvent was removed under reduced pressure. The product was crystallized from MeNO₂/MeOH at −25°C, washed with Et₂O, dried and obtained as dark, amorphous solid (9.0 mg, 16 μmol, 26%); mp > 300°C (dec.). - ¹H-NMR (600 MHz, CD₃CN): δ = 4.09 (s, 3 H, 3-OMe), 4.16 (s, 3 H, 4-OMe), 4.19 (s, 3 H, 9-OMe), 4.23 (s, 3 H, 2-OMe), 7.67 (s, 1 H, 11-H), 7.70 (d, 1J = 8 Hz, 2 H, 2’H, 6’-H), 7.77 (s, 1 H, 4-H), 7.90 (s, 1 H, 8-H), 7.90 (d, 1J = 8 Hz, 2 H, 3’H, 5’-H), 8.24 (s, 1 H, 1-H), 8.51 (s, 1 H, 7-H), 8.94 (s, 1 H, 5-H), 9.38 (s, 1 H, 12-H). - ¹³C-NMR (150 MHz, CD₃CN, signals with low signal-to-noise ratio confirmed by HMBC): δ = 57.2 (3-OMe), 57.5 (10-OMe), 57.7 (2-OMe), 57.9 (9-OMe), 103.2 (C₈), 105.0 (C₁), 106.7 (C₁₁), 110.7 (C₄), 117.5 (C₁₂), 118.9 (C₇), 121.0 (C₁₇), 123.0 (C₁₂b), 126.4 (C₆a), 126.9 (C₅), 130.0 (C₁₂a), 130.8 (C₂’, C₆’), 131.6 (C₄’, C₅’), 133.0 (C₅a), 133.4 (C₇a), 133.6 (C₁₁a), 136.9 (C₄’), 139.2 (C₆’), 139.6 (C₁’), 154.1 (C₃), 155.7 (C₂), 156.1 (C₉), 156.7 (C₁₀). – El. Anal. for C₂₉H₂₃ClBF₄NO₄ × ½ HBF₄ (615.67), calc'd (()): C 56.58, H 3.85, N 2.28, found: C 56.51, H 3.72, N 2.32. – MS (ESI⁺): m/z = 484 (100) [M – BF₄]⁺. – MS (ESI⁻): m/z = 1229 (100) [2M + BF₄]⁻.

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