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Radiochemiluminescence of carboxyquinolines

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Abstract

Carboxyquinolines, specifically 2-carboxyquinoline (quinaldic acid), 4-carboxy-2-hydroxyquinoline (kynurenic acid), 2-carboxy-4-hydroxyquinoline, 4,4′-dicarboxy-2,2′-biquinoline and 2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt in dialkylated amides are radiolyzed to novel 1,4-dihydroquinolines which emit light on addition of bases in the presence of oxygen giving rise to quinolinones. The overall quantum yields (radiolysis and chemiluminescence) are as high as 2.4×10^{-5} einstein mol^{-1}. The radiolysis and chemiluminescence mechanisms are discussed. The radiochemiluminescence reactions constitute prospective radiation dosemeters and can be used for analytical applications.

Keywords: Chemiluminescence; Radiolysis; Carboxyquinolines; Dihydroquinolines; Quinolinones; Radiochemiluminescence

1. Introduction

We have recently reported that exposure of de-aerated acridone and acridine derivatives in *N*,*N*-dialkylated amides even to the diffuse light of the laboratory or to γ-irradiation results in photolysis or γ-radiolysis, while subsequent addition of strong bases to said spent mixtures gives rise to very efficient chemiluminescence (CL) [1,2]. In the present work we wish to report the radiochemiluminescence — a term that we have coined to describe a radiolysis process leading to chemiluminescent products and subsequent CL — of carboxyquinolines such as 2-carboxyquinoline (quinaldic acid, **1a**), 2-carboxy-4-hydroxyquinoline (**1b**), 4-carboxy-2-hydroxyquinoline (kynurenic acid, **1c**), 4,4′-dicarboxy-2,2′-biquinoline (**1d**) and 2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt (**1e**) in *N*,*N*-dimethylformamide (DMF) in the presence of oxygen with bases such as sodium hydride, aqueous alkalies or tetraalkylammonium hydroxides (see Table 1). The title compounds are used in many analytical and medicinal applications. Quinaldic acid (**1a**) is used for the determination of many transition metals [3–5], while kynurenic acid (**1c**) is referred over 100 times in the last 5 years in medicinal applications. The dipotassium salt of 2,2′-biquinoline-4,4′-dicarboxylic acid (**1e**) is referred for automatic sugar chromatography and for the detection of reducing sugars in borate complex ion-exchange chromatography [6,7] as well as for protein determination [8] and for the spectrophotometric determination of copper [9,10]. Although in common with biacridinium salts and biacridylidenes the CL of bis-isoquinolinium salts with hydrogen peroxide in alkaline solutions and their reduction products with singlet oxygen has been recently reported [11,12], the radiochemiluminescence of carboxyquinolines has never been reported.

2. Experimental techniques

2.1. Reagents

2-Carboxyquinoline (quinaldic acid, **1a**), 2-carboxy-4-hydroxyquinoline (**1b**), 4-carboxy-2-hydroxyquinoline (kynurenic acid, **1c**), 4,4′-dicarboxy-2,2′-biquinoline (**1d**), 2,2′-biquinoline-4,4′-dicarboxylic acid (**1e**), 2,4-dihydroxyquinoline and 4,4′-dihydroxy-2,2′-biquinoline were purchased from Fluka and Aldrich and were used without further purification. The purity of all compounds used was checked by NMR, UV and fluorescence spectroscopy. *N*,*N*-dimethylformamide was purified and dried by the standard procedure [13]. Sodium hydride was purchased from Aldrich as powder and used without further purification. Lithium, sodium, potassium and tetramethylammonium hydroxides were used as 0.1M solutions. Working solutions were freshly made.

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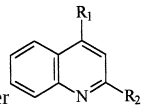
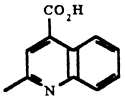
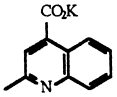
Table 1

Carboxyquinolines studied in this paper 

1	R_1	R_2
1a	H	CO_2H
1b	OH	CO_2H
1c	CO_2H	OH
1d	CO_2H	
1e	CO_2K	

2.2. Equipment

Absorption spectra were run on a JASCO V-560 spectrophotometer. Fluorescence spectra were recorded on a JASCO FP-777 Spectrofluorimeter (Scan speed 200 nm min^{-1}, emission band 3 nm). ^{1}H- and ^{13}C NMR spectra were measured on a Brucker AC 250 spectrometer. GC/MS spectra were recorded with the aid of a Hewlett–Packard Instrument. Finally, CL spectra were run on the JASCO FP-777 Spectrofluorimeter with the excitation source off, employing wide slits (20 nm) and a scanning rate of 1000 nm min^{-1}.

2.3. Chemiluminescence measurements

These were performed on a 1250 Bio-Orbit luminometer with the timer circuitry disconnected and an added slit to reduce the window area and render the instrument less sensitive. The cell's jacket was thermostatically controlled with the aid of a constant temperature bath-circulator and the temperature was maintained at 25.0±0.1°C. The light reactions were started by adding solid sodium hydride or hydroxide solutions (500 μl, 0.1M) into the solutions of the radiolyzed carboxyquinolines (500 μl, 10^{-4}M). The light intensity–time integrals thus obtained were compared with the Luminol Standard [14] which served as an absolute photon source under the same geometry. The quantum yields based on carboxyquinolines employed before radiolysis were over 10^{-5} einstein mol^{-1} for derivative **1e**. The radiochemiluminescence quantitative determination of carboxyquinolines was performed as follows: carboxyquinoline solutions of various concentrations in DMF were placed in 10 ml volumetric flasks and were radiolyzed in the ^{60}Co source for 30 min. The CL measurements were made with 250 μl samples on addition of aqueous NaOH (250 μl, 1N). The duration of light emission was not longer than 1 s.

2.4. γ-Radiolysis

γ-Radiolysis experiments were performed in a ^{60}Co, 6500 Ci, Gamma Chamber (4000 A, Isotope Group, Bhaba Atomic Research Centre, Trombay, India). The dose rate was determined with Fricke's dosemeter [15] and was found equal to 27.05 Gy min^{-1}. Doses were calculated from dose=8.39+27.05×time (min) Gy. Radiolysis was considered complete on disappearance of the characteristic absorption bands between 320 and 340 nm (radiolysis time 90–120 min, concentration of working solutions 10^{-4}M). Further radiolysis resulted in destruction of the radiochemical products and lower CL.

2.5. Product identification

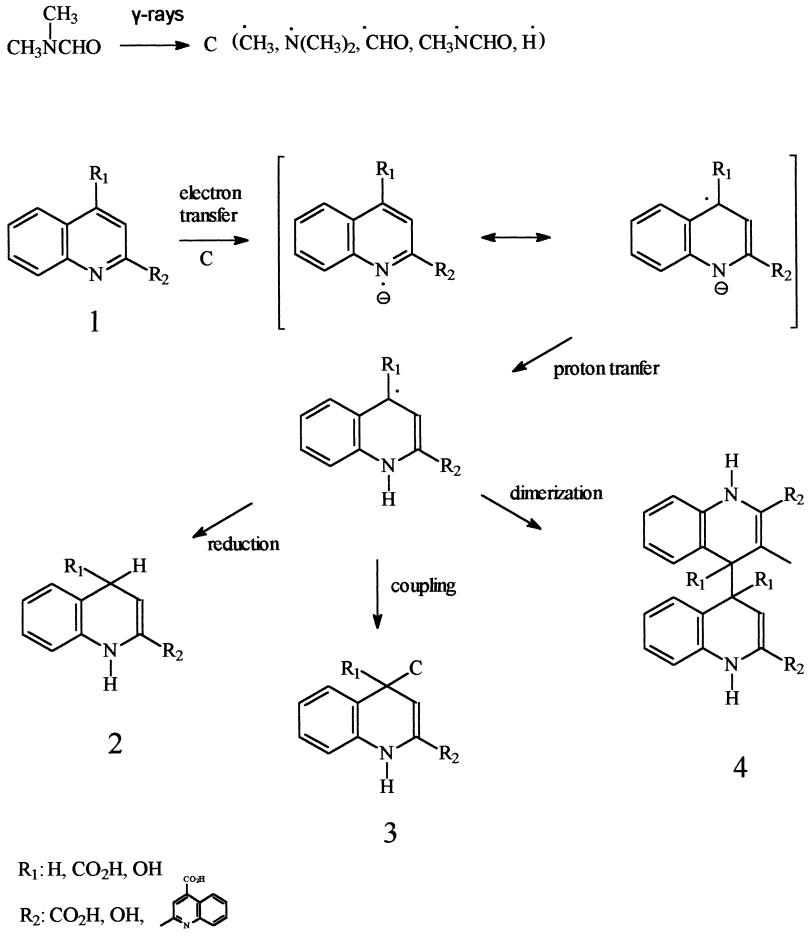
2.5.1. Radiolysis products

All efforts to isolate the radiolysis products were fruitless although the products were stable in solution at room temperature. Absorption and fluorescence spectra, however, indicated reduction of the heterocyclic ring to give 1,4-dihydroquinolines as the characteristic peak was shifted towards shorter wavelengths in common with acridine derivatives [1,2]. Furthermore, oxidation of the radiolysis mixtures with tetrachlorobenzoquinone (TCBO) [16] resulted in gradual weakening of the dihydroquinoline peak at 287 nm and concurrent increase of the quinoline peak at 343 nm. Thus the radiochemical reduction of the quinolines of the present work to dihydroquinolines was retrosynthetically verified and it should be emphasized that heating the radiolyzed solutions to over 100°C also leads back to the initial aromatic carboxyquinolines.

2.5.2. Chemiluminescence products

Product identification was performed on two carboxyquinolines, namely, **1c** and **1e** as follows. A de-aerated solution of carboxyquinoline in DMF (40 mg; 25 ml) was allowed to stand in the ^{60}Co source for 24 h. The solution was then aerated, sodium hydride (100 mg) was added, and the resulting mixture was stirred at room temperature for 1 h. The solvent was then removed and the remainder was extracted with chloroform/water and characterized by means of NMR spectrometry.

The ^{13}C spectra of the spent reaction mixtures of all the 4-quinolinones were associated with the four characteristic peaks of the aromatic ring at δ 112, 116, 129 and 133 and also the characteristic peak of the olefinic C3 at 80 ppm. In the ^{1}H (250 MHz, $CDCl_3$) spectra on the other hand, the characteristic peaks of the 4-quinolinones appeared as two doublets for protons H5 and H8 at 8.8 and 7.9 ppm, pseudotriplets for protons H6 and H7 at 7.77 and 7.55 ppm, while the olefinic proton H3, appeared as singlet at 5.8 ppm. In one case after derivatization of the 2-hydroxy-4-quinolinone with thionyl chloride to 1,4-dichloroquinoline, the MS verified our mechanism (70 eV, *m/e* 197 (M+, 100%), 162 (M+–Cl, 85%),



Scheme 1. Radiolysis products of carboxyquinolines (**1a**–**e**) in DMF.

127 (25%), 99 (6%), 81 (7%), 75 (13%), 68 (13%), and 50 (6%)).

3. Results and discussion

Within the framework of radiochemiluminescence we have earlier reported the radiolysis of azaaromatics such as acridines and acridone, reactions leading to reduction, disproportionation or coupling, with the amides playing the role of solvents-reagents [1,2]. In these reactions the coupling product was always the major product. In the course of broadening this new field we now wish to report the radiochemiluminescence of carboxyquinolines.

The radiolysis products of carboxyquinolines (**1a**–**e**) although stable in DMF solution could not be isolated by all forms of chromatography, fractional crystallization or sublimation. In any case, isolation of the radioproducts is not required in radiochemiluminescence, the radiolysis reaction mixture was employed as it was for the CL reaction and the quantum yields herein reported are those of the overall process, i.e. they are based on the carboxyquinoline employed before radiolysis. Regarding the carboxyquinoline radiolysis mechanism it is possible that the products of the DMF radiolysis (free radicals such as H, $(CH_3)_2N$, CH_3, $CH_2N(CH_3)CHO$, CHO), reduce the heterocyclic ring through electron transfer or addition to position 4; subsequent protonation of the anions thus produced leads to the 1,4-dihydroquinolines (**2**, **3** and **4**, Scheme 1). This is supported by absorption and fluorescence spectroscopy as well as some synthetic and retrosynthetic evidence presented in the previous section. Indeed, the characteristic absorption maximum of aromatic quinolines at 340 nm was shifted to 290 nm, a wavelength characteristic of 1,4-dihydroquinolines. On the other hand the fluorescence maximum at 420 nm was shifted to 380 nm a change also indicative of quinoline reduction.

Addition of base in the presence of atmospheric oxygen to the radiolysis spent reaction mixtures of the carboxyquinolines of the present work resulted in appreciable CL. The light intensities and CL efficiencies depended on the strength of the base employed and this is shown in Table 2 and Fig. 1, for carboxyquinolines (**1a**–**e**). Best results were obtained with sodium hydride and radiolyzed derivative **1e** and it should be noted here that addition of bases to carboxyquinolines without radiolysis is absolutely dark. 4-Quinolinones

Table 2
CL quantum yields and CL intensities of radiolyzed carboxyquinolines (**1a–e**) in DMF ($C=10^{-4}$M; radiolysis time 120 min)[a]

Base	$\Phi_{CL}\times10^8$ (einstein mol^{-1})					CL intensities (arbitrary units)				
	1a	**1b**	**1c**	**1d**	**1e**	**1a**	**1b**	**1c**	**1d**	**1e**
LiOH	2.5	1.0	3.2	5.1	620	3	1	4	6	530
NaOH	2.8	3.8	5.1	5.3	642	3	3	7	6	402
KOH	3.5	5.4	5.2	5.6	685	6	4	9	5	536
$(CH_3)_4NOH$	3.8	5.1	4.8	5.3	773	2	4	8	7	605
NaH	40	815	779	978	4890	10	637	702	886	3833

[a] 500 μl radiolyzed solution+500 μl alkali hydroxide, 0.1 M.

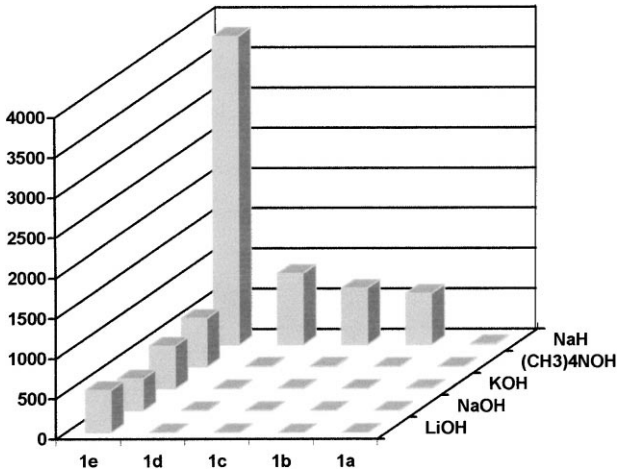
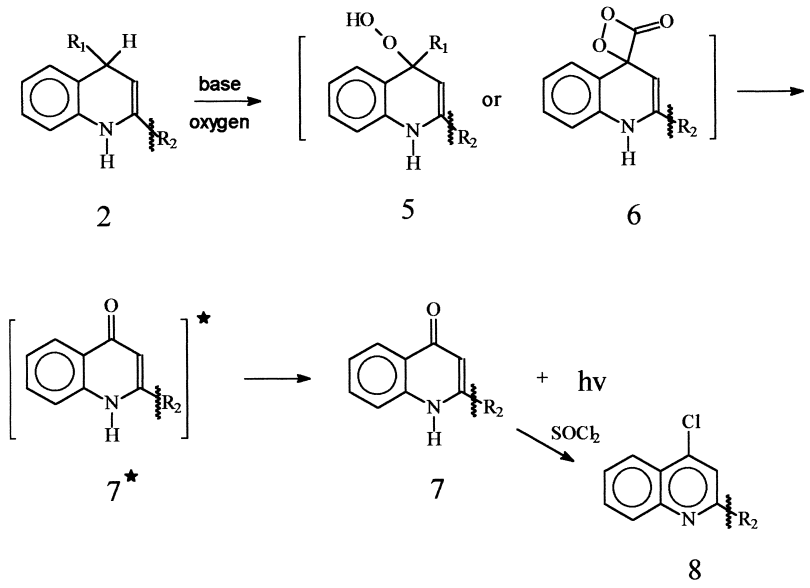


Fig. 1. CL intensities of radiolyzed carboxyquinolines (**1a–e**) in DMF on addition of bases ($C=10^{-4}$M; radiolysis time 120 min).

(**7**) are the major CL products as shown above spectrosopically and after derivatization with thionyl chloride to the respective chloroquinolines (**8**, Scheme 2).

Considerations such as (a) oxygen is required for the CL step, (b) quinolinones (**7**) are always the end products and primary emitters as indicated by the similarity of the CL spectra, the quinolinone (added in the form of 2,4-dihydroxyquinoline which in alkaline media is in equilibrium with the 2-hydroxyquinoline-4-one or added in the form of 4,4′-dihydroxy-2,2′-biquinoline which in alkaline media is in the form of 2,2′-biquinolin-4,4′-one) fluorescence spectra and the fluorescence spectra of the spent reaction mixtures (not shown), (c) linear peroxide (**5**) or dioxetanone (**6**) decomposition fulfills the energetic requirements for CL and (d) the mechanisms so far adopted for 9-substituted acridines [1,2], offer support to the mechanism of Scheme 2.

As argued above the carboxyquinolines (**1a–e**) of the present work are readily transformed to dihydroquinolines on exposure to γ-radiation and their reaction with bases is CL. It is, therefore, possible that the radiochemiluminescence reactions herein reported can be employed as radiation dosemeters. In Fig. 2, the absorbance of compound **1e**, the most efficient radiochemiluminescent derivative, is plotted versus irradiation dose. Carboxyquinoline is destroyed and as the γ-irradiation dose increases, lower absorbance values due to decreased quinoline concentration are obtained. This type of plot has the prospects of becoming a γ-radiation



Scheme 2. Proposed CL reaction mechanism of dihydroquinolines (**2a–b**) with bases in the presence of oxygen.

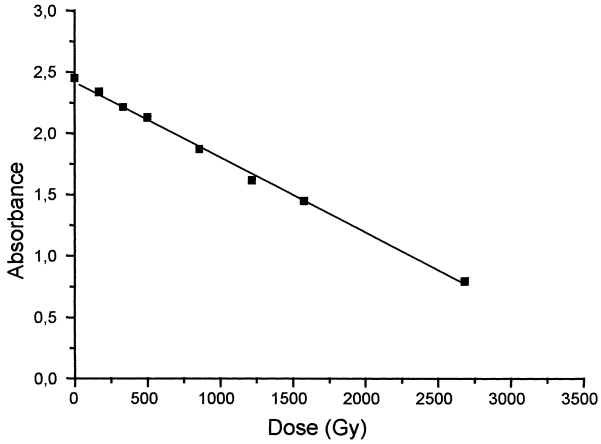


Fig. 2. Plots of absorption of 2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt (**1e**) in DMF vs. irradiation dose; $C=10^{-4}$M.

dosemeter and possibly a dosemeter for internal irradiation of solutions by radioactive isotopes in amide solvents in the region 100–2750 Gy.

Furthermore, the product in the γ-radiolysis spent mixture, on reaction with sodium hydroxide and other bases gives rise to CL whose intensities and intensity–time integrals are, as expected, also a function of radiation absorbed. The light intensities thus obtained are directly proportional to the dose absorbed and this is shown in Fig. 3, where the dose was determined with the aid of Fricke's actinometer [15].

This plot shows that this reaction can also serve as a γ-radiation dosemeter and most probably also for other ionizing radiations capable of radiolyzing the present solvents (internal dosemeters), in the region of 100–3500 Gy. It should be noted, however, that with 10^{-3}M quinolines the plot of relative CL intensity versus irradiation dose is linear between 2.0 and 14.0 kGy.

Finally, the radiochemiluminescence of the carboxyquinolines of the present work can be employed for analytical applications involving such compounds. Indeed, as it can be seen in Fig. 4, carboxyquinolines (**1c** and **1e**) can be

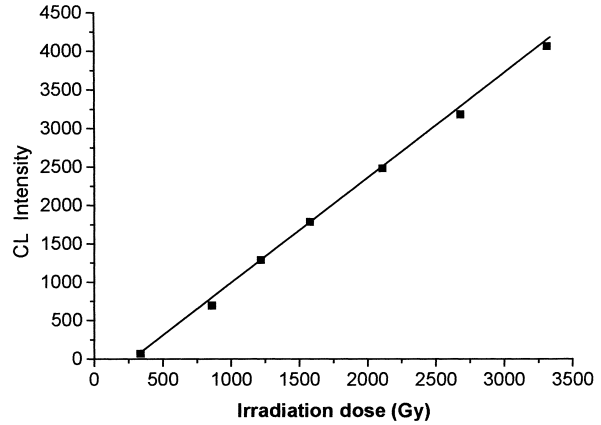


Fig. 3. CL light intensities of radiolyzed 2,2′-biquinoline-4,4′-dicarboxylic acid dipotassium salt (**1e**, $C=10^{-4}$M) in DMF on addition of NaOH, plotted vs. irradiation dose in the presence of oxygen.

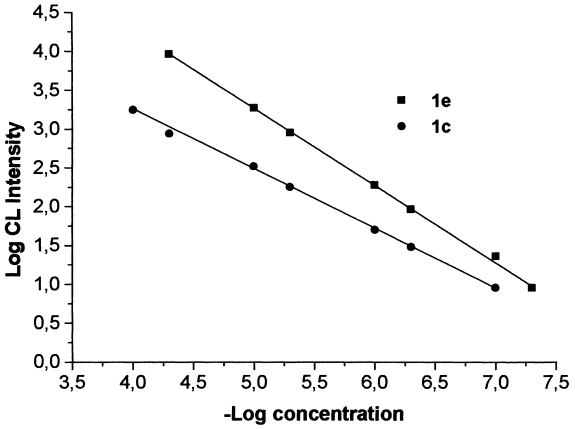


Fig. 4. Radiochemiluminescence of carboxyquinolines (**1c** and **1e**) vs. concentration (radiolysis time 30 min, 1 mm slit for **1e**, 3 mm slit for **1c**).

determined at concentrations down to 19 ppb for **1c** and 36 ppb for **1e**.

4. Conclusions

Carboxyquinolines are radiochemiluminescent. Reduction to the corresponding dihydroquinolines in the radiolysis step is followed by oxidation to the corresponding excited quinolinones in the chemiluminescence step and subsequent emission of light. Besides being an energy storage system in the sense that ionizing radiation is absorbed, stored and light is emitted at will, the radiochemiluminescence of the carboxyquinolines of the present work has the prospects of forming the basis of novel radiation dosemeters. Also, novel analytical applications for said carboxyquinolines based on the radiochemiluminescent reactions of the present work promise detection limits as low as a few ppb of sample.

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