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EXTRA-WEAK CHEMILUMINESCENCE OF DRUGS. II.[1] RELATIONSHIP BETWEEN THE STRUCTURE AND THE EXTRA-WEAK CHEMILUMINESCENCE OF ORGANIC COMPOUNDS

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The extra-weak chemiluminescence of one hundred and sixteen organic compounds with simple structures having various functionals were measured. It was demonstrated that alkynes, aliphatic amines, aliphatic aldehydes, epoxides and peroxides had high emission intensities.

KEYWORDS —— extra-weak chemiluminescence; structure; simple organic compound; functional group

Twenty years ago, the correlation between chemiluminescence (CL) and oxidation was described.[2] Since that report, Inaba *et al.*[3] have measured extra-weak CL and designed a novel optical electronic system, i.e. the single photoelectron counting system, which detects extra-weak CL at about 10^{-15} W or less and analyzes its emission spectrum. Usuki *et al.*[4] have also devised a new analytical method to evaluate the quality of foods by the measurement of extra-weak CL.

Contrary to expectation, the evaluation of drug stability is difficult and requires a considerable amount of time. Mizuno *et al.*[5,6] and we[1,7] have introduced an analytical method to the drug research field. With it we have detected strong emission of extra-weak light from comparatively unstable drugs but weak chemiluminescence from comparatively stable drugs in solutions, tablets, and capsules. Furthermore we[8] reported an extremely high extra-weak CL generated from the antitumor antibiotic drug, neocarzinostatin (NCS) and its chromophore (NCS-chr), and suggested that the light emission is due to a highly strained epoxide ring which is one of the functional groups of NCS-chr in its molecule.

Table I. Extra-Weak Chemiluminescence from Organic Compounds

Compounds	Emission intensity (counts/10 s) 20°C	(n)	50°C	(n)	80°C	(n)
Alkanes a)	60	(5)	67	(5)	1,067	(3)
Alkenes b)	30	(9)	79	(8)	391	(8)
Alkynes c)	40	(4)	322	(4)	4,779	(3)
Alcohols d)	16	(8)	34	(8)	300	(6)
Phenols e)	11	(3)	128	(3)	456	(3)
Ethers f)	12	(7)	122	(6)	606	(6)
Amines and its salts g,h,i)	52	(16)	92	(16)	288	(15)
Aliphatic amines g)	325	(5)	672	(5)	4,457	(4)
Other amines h)	39	(5)	74	(5)	250	(5)
Amine salts i)	15	(6)	21	(6)	52	(6)
Aldehydes j,k)	83	(11)	278	(11)	1,701	(11)
Aliphatic aldehydes j)	172	(5)	727	(5)	3,860	(5)
Aromatic aldehydes k)	45	(6)	125	(6)	860	(6)
Ketones l)	37	(7)	112	(7)	1,521	(5)
Carboxylic acids and its salts m,n)	16	(16)	34	(16)	143	(16)
Carboxylic acids m)	18	(14)	32	(14)	131	(14)
Its salts n)	7	(2)	45	(2)	266	(2)
Carboxylic esters o)	21	(4)	33	(4)	294	(2)
Carboxylic acid amides p)	20	(7)	38	(7)	300	(7)
Nitriles q)	22	(5)	141	(5)	1,027	(2)
Carbonates r)	40	(2)	193	(2)	950	(2)
Epoxides s)	89	(3)	2,236	(2)	52,000	(2)
Peroxides t)	121	(4)	310	(4)	6,610	(4)
Oxides u)	101	(3)	258	(3)	401	(3)
Micellaneous v)	21	(2)	44	(2)	-	(0)
Total means	32	(116)	93	(113)	569	(98)

Quantitative detection of the extra-weak CL arising from these organic compounds was measured by single photo counting of extra-weak sensitivity using Chemiluminescence Analyzer OX-70, Tohoku Electronic Industrial Co., Ltd., Sendai, Japan. Each sample (solid: 2 g, liquid: 3 ml) was placed in a stainless dish type cell (50x10x43 mm) and single photoelectron pulses were counted under atmospheric conditions at 20°C, 50°C and 80°C, respectively. The results were expressed by the mean value of ten 3-continuous measurements of 10 s after subtracting dark counts (about 670 counts/10 s). The mean value of each group having various functionals were calculated as follows. The CL intensity counts/10 s was converted to logarithms and the mean value of the logarithms were reconverted to the CL intensity counts.

a) *n*-hexane, *n*-dodecane, cyclohexane, diphenylmethane, *p*-cymene, b) 2-pentene, 1-dodecene, 1-tetradecene, 1-octene, 2-octene, cyclopentadiene dimer, styrene, 2-vinylnaphthalene, *trans*-stilbene, d) methanol, ethanol, isopropanol, *n*-butanol, *tert*-butanol, benzylalcohol, stearylalcohol, glycerine, e) phenol, 1-naphthol, 2-naphthol, f) diethylether, di-*n*-butylether, dioxane, tetrahydrofuran, polyethylene glycohol 20,000, anisole, diphenylether, h) aniline, diphenylamine, pyridine, quinoline, imidazole, i) methylamine·HCl, diethylamine·HCl, triethylamine·HCl, D-glucosamine·HCl, aniline·HCl, diphenylamine·H_2SO_4, k) benzaldehyde, *p*-nitrobenzaldehyde, *p*-hydroxybenzaldehyde, *p*-anisaldehyde, *p*-dimethylaminobenzaldehyde, *trans*-cinnamic aldehyde, l) acetone, ethylmethylketone, di-*n*-propylketone, cyclohexanone, acetylacetone, acetophenone, benzophenone, m) formic acid, acetic acid, *n*-heptadecanoic acid, *n*-nonadecanoic acid, benzoic acid, 1-naphthoic acid, 2-naphthoic acid, pyruvic acid, *trans*-crotonic acid, lactic acid, salicylic acid, oxalic acid, succinic acid, *trans*-cinnamic acid, n) sodium acetate, sodium benzoate, o) ethyl acetate, ethyl benzoate, phenyl benzoate, methyl acrylate, p) formamide, acetamide, dimethylformamide, dimethylacetamide, benzamide, acrylamide monomer, urea, q) acetonitrile, benzonitrile, acrylonitrile, methacrylonitrile, phenylacetonitrile, r) diethyl carbonate, propylene carbonate, u) pyridine N-oxide, quinoline N-oxide, dimethylsulfoxide, v) chloroform, benzene. c, g, j, s, and t are described in Table II.

Pyridine N-oxide and quinoline N-oxide, supplied by Prof. Yamanaka, were distilled just before the use and measured to count CL. All the other reagents, newly purchased from commercial sources, were of guaranteed grade. They were used directly or further purified if necessary.

It is now conceivable that extra-weak CL is generated from a certain functional group or groups of drugs. To clarify this assumption measurements were carried out on extra-weak CL of the organic compounds with rather simple and completely known structures.

In this communication, we describe the extra-weak CL of one hundred and sixteen organic compounds of various functional groups.

The results are shown in Table I. The extra-weak CL intensity generated from various compounds generally increases in parallel with the elevation of the temperature. The mean value of extra-weak CL counts/10 s of all the compounds are 32, 93 and 569 at 20, 50, and 80°C, respectively. Next, the mean values of emission intensity generated by various functional groups were compared. Alkynes, free aliphatic amines, aldehydes, especially aliphatic aldehydes, epoxides and peroxides have high light emission intensities of more than 3,000 counts/10 s at 80°C. On the other hand, the emission intensity of alkanes, alcohols, amine salts, and car-

Table II. Extra-Weak Chemiluminescence from Alkynes, Aliphatic Amines, Aliphatic Aldehydes, Epoxides and Peroxides

Compounds	Emission intensity (counts/10 s) 20°C	50°C	80°C
Alkynes c)			
Butylacetylene	38	28	-
Phenylacetylene	44	1,407	23,717
Propargyl alcohol	21	1,996	4,027
Diphenylacetylene	71	137	1,144
Aliphatic amines g)			
Diethylamine	209	611	-
Triethylamine	146	216	13,296
Triethylene tetramine	13,060	22,943	35,502
Tris(hydroxymethyl)aminomethane	20	16	105
Triethylene tetramine$\cdot$2HCl	458	2,818	7,963
Aliphatic aldehyde j)			
Formaldehyde (35% in water)	4	9	51
Acetaldehyde (90% in water)	626	1,668	17,531
Hexanal	59	1,144	2,463
Octanal	1,108	2,256	9,331
Dodecanal	922	5,243	41,863
Epoxides s)			
Propylene oxide	23	-	-
Epichlorohydrin	90	503	10,257
Styrene oxide	337	9,933	263,289
Peroxides t)			
tert-Butyl hydroperoxide (70% in water)	115	226	13,636
m-Chloroperbenzoic Acid	295	1,729	40,979
Di-*tert*-butyl peroxide	101	109	1,429
Dibenzoyl peroxide	56	217	2,389

boxylic acid derivatives, such as carboxylic acids themselves, carboxylic esters and carboxylic acid amides is not significant.

In Table II are listed the five groups of compounds, which have high emission intensity, needless repetition. In the alkyne group, phenylacetylene generates high emission intensity (23,717 counts/10 s) at 80°C, but diphenylacetylene, a disubstituted acetylene, is not so high (1,144 counts/10 s) even at 80°C. Aliphatic amines emit high chemiluminescent intensity at 80°C, especially triethylene tetramine which has four amino groups (35,502 counts/10 s). Epoxides, especially styrene oxide and epichlorohydrin, generate the highest emission. Finally, we may say that peroxides, especially monosubstituted peroxides such as tert-butyl hydroperoxide and m-chloroperbenzoic acid, show very high values, whereas disubstituted peroxides such as di-tert-butyl peroxide and benzoyl peroxide have lower values.

In this study, we can say that certain functional groups of organic compounds such as amine, aldehyde and its oxidation product, peracid, and peroxide groups generate strong extra-weak CL. These organic compounds with high emission intensity are easily oxidized by oxygen in air. The salts of aliphatic amines, common among the side chains of drug molecules, are employed in drug design, because amine salts are usually more stable than free amines. Drugs that generated high CL intensity are generally unstable.[1,7] The action mode of auto-oxidation of these compounds or drugs accompanied by high emission, is now under active investigation in our laboratory.

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