Health Science Monitor
2023; 2(1): 39-49
Published online (http://hsm.umsu.ac.ir)

Original Article

A Sensitive Chemiluminescence Probe Based on Cerium (IV)-Sulfite Reaction for the Determination of Methamphetamine in Biological Samples and Street Drugs

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Abstract

***Background & Aims*:** Methamphetamine is one of the most widely abused drugs worldwide. Its rapid and simple detection and determination in street drugs and biological samples are of great importance for forensic science applications.

***Materials & Methods*:** In this work, a simple and sensitive chemiluminescence-based method was established for methamphetamine analysis. It is based on the enhancing effect of methamphetamine on Ce(IV)-Na_2SO_3 chemiluminescence (CL) reaction. A possible mechanism was discussed for the CL system. Optimization of chemical variables affecting the CL response of the system was performed by an experimental design approach using the central composite design.

***Results*:** Under the optimum conditions, the enhanced CL intensity was proportional to the concentration of methamphetamine in the range of 0.005-5.0 µg/mL, with a detection limit of 1.2 ng/mL.

***Conclusion*:** The developed method applied to determine methamphetamine in street drugs and human plasma samples showed satisfactory results.

***Keywords*:** Chemiluminescence, Cerium (IV), Experimental design, Methamphetamine, Sodium sulfite

Received 02 August 2022; accepted for publication 31 January 2023

Introduction

Methamphetamine (N-methyl-1-phenylpropan-2-amine; Figure 1) is a central nervous system stimulant, which is usually often synthesized from ephedrine. It is an indirect-acting sympathomimetic drug causing the release of endogenous biogenic amines, such as dopamine and noradrenaline. Within hours after oral ingestion, methamphetamine increases alertness and also causes euphoria, agitation, and confusion. Bruxism (tooth grinding) and skin flushing may also occur (1). Methamphetamine addiction is a serious global public health problem. Illicit methamphetamine is available as water soluble white crystalline powder with such street name as “speed”, “crank”, “meth”, “crystal”, or “ice”.

It is the second most widely abused drug in many areas of the world (2). Therefore, methamphetamine assay is of great importance from the point of view of toxicological, clinical, industrial and forensic science applications.

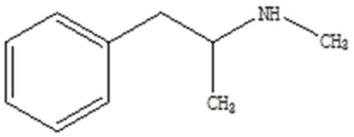


Fig. 1. Chemical structure of methamphetamine

Several analytical methods have been developed for the determination of methamphetamine in biological samples (3) and street drugs (4–7), including spectrophotometry (6,8), fluorescence (9–11), electrochemiluminescence (5,12–14), gas chromatography (GC) (15), high-performance liquid chromatography (HPLC) (16), and gas chromatographic–mass spectrometry (GC-MS) (17–19).

Chemiluminescence (CL) is the emission of light from an excited species produced by a chemical reaction. CL systems in aqueous phase usually involve a redox reaction in which an electronically-excited intermediate or product is generated and subsequently deactivate via photon emission. CL-based analytical methods show several advantages, such as high sensitivity, simplicity of instrumentation, low detection limits, large calibration ranges, and short analysis time. CL, alone or in combination with HPLC and capillary electrophoresis, has been used for the determination of various kinds of controlled drugs (20). The oxidation of sulfite by Ce(IV) is known to produce a weak CL signal (21), which can be enhanced by some fluorescent and non-fluorescent enhancers (23). On the basis of this phenomenon, analytical methods have been developed for determination of some analytes (22,24,25).

In the present study, we demonstrated that methamphetamine greatly enhances the CL signal from cerium (IV)–sulfite system. Based on this effect, a simple and sensitive CL method has been developed for the determination of low concentrations of methamphetamine. The method possesses a good accuracy, precision, and a large calibration range. It was applied for the determination of methamphetamine in street drugs and human plasma samples.

Materials & Methods

Materials:

All reagents used were of analytical reagent grade. Double distilled deionized water, obtained from Ghazi Serum Co., Tabriz, Iran, was used throughout the experiment. Pure methamphetamine was obtained from Sigma, and methamphetamine street samples were provided by the Research Center of Antinarcotics Police (Tabriz, Iran). A 100 µg/mL stock standard solution of methamphetamine was prepared by dissolving 10.0 mg of pure methamphetamine in deionized water and diluting to the mark in a 100 mL volumetric flask. Dilute standard solutions were prepared just before use. $Ce(SO_4)_2.4H_2O$, Na_2SO_3, and H_2SO_4 were purchased from Merck. Ce (IV) solution (0.01 M) was prepared in 0.1 M H_2SO_4, and Na_2SO_3 solution (0.01 M) was prepared daily.

Apparatus:

The CL signals were monitored by LUMAT LB 9507 chemiluminometer (Berthold; www.berthold.com). CL spectrum was recorded with RF-540 spectrofluorimeter (Shimadzu, Japan) using flow mode with the excitation light source being turned off. GC-FID (Shimadzu 2010; www.shimadzu.com) was used to confirm the accuracy of the developed method. Gas chromatographic separation was carried out on a CPB1-M25-025 capillary column, coated with a 0.25 µm thickness film (24.9 m×0.22 mm i.d.). Temperatures of the injector and the detector were 290 and 300ºC, respectively. Oven temperature was initially set at 80ºC (0 min) and then increased with a ramp rate of 20ºC/min to a final temperature of 270ºC (1 min).

General procedure for determination of methamphetamine:

CL analyses were carried out in a 3 mL quartz tube in the batch condition. Next, 75 µL of Na_2SO_3 (0.01 M)

was added into the cell. Then an appropriate volume of sample or standard methamphetamine solution was added, and the final volume was reached 1.0 mL with distilled water. After injection of 125 µL of Ce(IV) (0.01 M in 0.1 M H_2SO_4) by an automatic injector, monitoring CL signal versus time was started automatically. Maximum CL intensity was used as analytical signal.

Procedure for human plasma samples:

Human plasma samples were obtained from Blood Transfusion Center (Tabriz, Iran). A 0.5 mL aliquot of plasma was placed into a centrifuge tube and spiked by adding appropriate volumes of methamphetamine standard solution (10.0 µg/mL). Subsequently, 0.5 mL of 10% trichloroacetic acid was added into the tube for precipitation of proteins. Then the solution was centrifuged for 15 min. The supernatant solution was transferred into a 5.0 mL volumetric flask and diluted to the mark with water. An appropriate portion of this solution was taken for analysis. Standard addition method was used to eliminate the matrix effect. Blank correction was performed by obtaining total Youden blank and subtracting it from the responses (28, 29). For this purpose, the CL signals for four different amounts of treated samples (50, 75, 100, and 200 µL) were measured, and the regression line for plot of signal versus sample amount was determined. The y-intercept of this line is total Youden blank.

Experimental design and data analysis:

Solutions of methamphetamine (0.3 µg/mL) were prepared in the desired conditions, and their CL intensity was measured at predetermined conditions for each experiment. The data analysis was performed using the statistical package Statgraphics Centurion XVI version 16.1.11.

Results

A series of preliminary experiments with several CL systems, including Ce(IV)-Na_2SO_3, Ce(IV)-$Na_2S_2O_3$, $KMnO_4$-Na_2SO_3, and $KmnO_4$-$Na_2S_2O_3$, was performed for methamphetamine determination. The best results were obtained by Ce(IV)-Na_2SO_3 system. As shown in Figure 2a, the redox reaction of Ce(IV)-Na_2SO_3 produces a weak CL signal in the acidic medium. However, the CL intensity enhanced when sodium sulfite was reacted with Ce(IV) in the presence of methamphetamine (Figure 2, curve b). The light emission was produced immediately after injection.

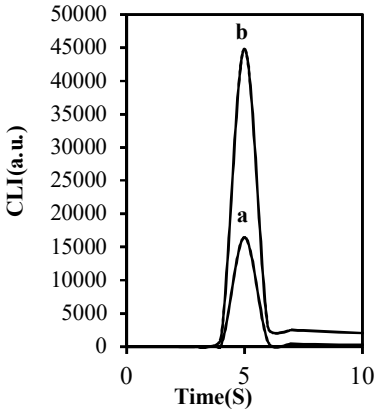


Fig. 2. Kinetic curve for Ce(IV)-Na_2SO_3 CL system, (a) alone, (b) in the presence of methamphetamine. Conditions: Ce(VI), 1.25×10^{-3} M; Na_2SO_3, 7.5×10^{-4} M; H_2SO_4, 1.25×10^{-2} M and methamphetamine, 0.3 µg/mL.

Optimization of chemical conditions:

An experimental design approach based on central composite design was implemented in order to investigate the influence of the main variables on the CL intensity of methamphetamine. The variables considered in the optimization process were Na_2SO_3, Ce(IV), and H_2SO_4 concentration. The used concentrations of variables are presented in Table 1. This model allows direct evaluation of the variables and also the first and second order interaction terms. The central composite design consists $2k+2^k+n$ runs, where k is the number of studied factors (three in this case), 2^k is the points from the factorial experiments carried out at the corners of the cube, and 2k is the points carried out on the axes at a distance of $\pm\alpha$ from the center. The distance α is selected so as to obtain rotatability (a three variable central composite design is rotatable if α=1.68) (26). The number of experiments

carried out at the center of experimental domain, n, was fixed at 3. Table 2 gives the design matrix for experiments and the relative CL signal obtained for each run. The estimated effects and interactions, as well as the evaluation of their statistical significance by ANOVA, are presented in Table 3. The corresponding Pareto chart is shown in Figure 4. As can be seen, six effects have a P-value of less than 0.05, indicating that they are significantly different from zero at 95% confidence level. Studies have indicated that Na_2SO_3 and Ce(IV) concentration, as well as their second order interactions, are significant factors affecting the response when their values change in the selected region. Also, the interactions between [Na_2SO_3] - [Ce] and [Na_2SO_3] - [H_2SO_4] are significant. In addition, H_2SO_4 concentration does not have a significant effect on the CL signal. The R-squared statistic indicates that the model as fitted explains 98.47% of variability in response. The corresponding response surfaces (Figure 5) show that the optimum values for Na_2SO_3 and Ce(IV) concentrations are 7.5×10^{-4} and 1.25×10^{-3} M, respectively. While the effect of H_2SO_4 concentration is insignificant, the CL intensity increases slightly with the elevation of this variable and reaches a maximum at the highest value.

Table 1. Variable values used in the optimization of experimental conditions

Variables (mM)	Levels				
	-1.68	**-1**	**0**	**+1**	**1.68**
Ce	0.057	0.5	1.15	1.8	2.25
Na_2SO_3	0. 079	0. 25	0.5	0. 75	0. 92
H_2SO_4	3.3	5.0	7.5	10	11.7

Table 2. Design matrix and relative chemiluminescence intensity values in central composite design for three variables: Ce(IV), Na_2SO_3, and H_2SO_4 concentration (M)

Experiment no.	Ce	Na_2SO_3	H_2SO_4	Response (a.u.)
1	0.0	0.0	0.0	43064
2	-1.0	-1.0	-1.0	37485
3	1.0	-1.0	-1.0	32675
4	-1.0	1.0	-1.0	38678
5	1.0	1.0	-1.0	39396
6	-1.0	-1.0	1.0	34236
7	1.0	-1.0	1.0	27338
8	-1.0	1.0	1.0	40619
9	0.0	0.0	0.0	42223
10	1.0	1.0	1.0	44552
11	-1.68	0.0	0.0	35920
12	1.68	0.0	0.0	31364
13	0.0	-1.68	0.0	24215
14	0.0	1.68	0.0	39045
15	0.0	0.0	-1.68	44677
16	0.0	0.0	1.68	43866
17	0.0	0.0	0.0	44425

Table 3. Estimated effects and ANOVA results for central composite design

Source	Estimate effect	Sum of squares	Df	F-Ratio	P value
A: [Ce]	43188.0	1.5864E7	1	11.90	0.0107
B: [Na_2SO_3]	-2155.56	2.3335E8	1	174.98	0.0000
C: [H_2SO_4]	8267.2	595993.	1	0.45	0.5252
AA	-417.806	1.17067E8	1	87.78	0.0000
AB	-6444.93	3.34521E7	1	25.08	0.0016
AC	4089.75	158766.	1	0.12	0.7402
BB	281.75	1.74456E8	1	130.82	0.0000
BC	-7867.66	3.07446E7	1	23.05	0.0020
CC	3920.75	3.23415E6	1	2.43	0.1634
Total error	1071.23	9.33508E6	7		

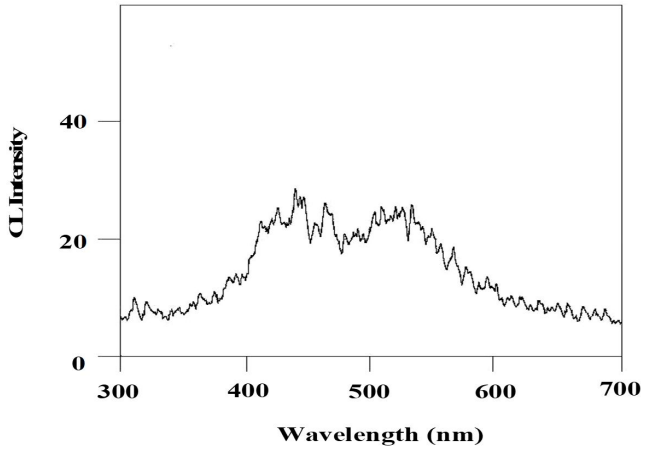


Fig. 3. CL spectrum of Ce(IV)-Na_2SO_3 system (a) in the absence and (b) presence of methamphetamine obtained with continuous flow of reagents: Ce(IV), 2.5×10^{-3} M and H_2SO_4, 2.5×10^{-2} M in one line and Na_2SO_3, 1.5×10^{-4} M with methamphetamine (20 µg/mL) in other line.

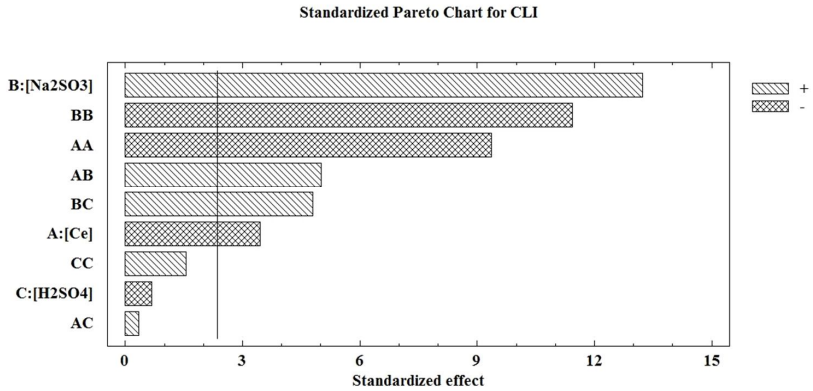
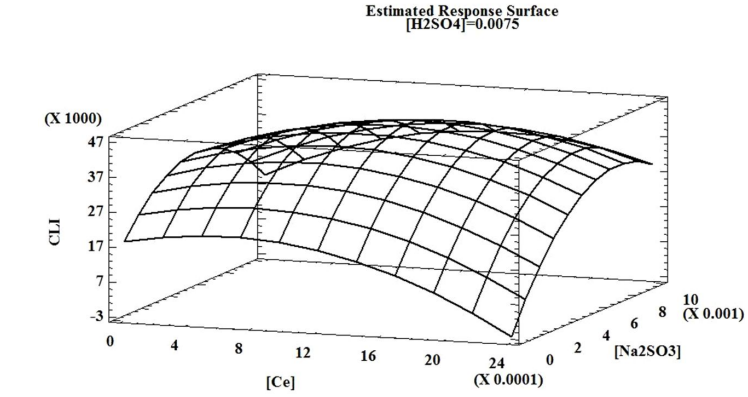
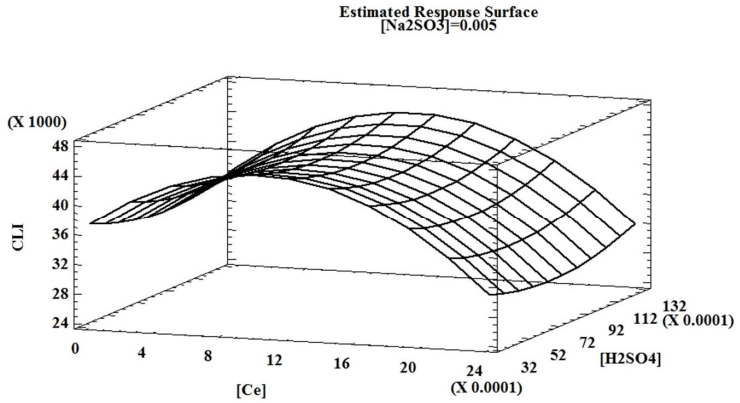


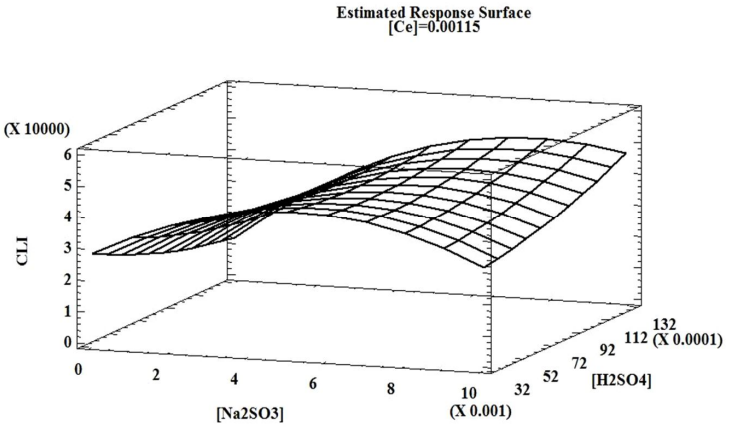
Fig. 4. Pareto chart for the standardized effects in the central composite design including two-factor interactions.



(a)



(b)



(c)

Fig. 5. Response surfaces estimated from the central composite design by plotting (a) [Ce (IV)] vs. [Na_2SO_3], (b) [Ce (IV)] vs. [H_2SO_4], (c) [Na_2SO_3] vs. [H_2SO_4].

Analytical figures of merit:

Under the optimum conditions described above, the analytical figures of merit for the determination of methamphetamine were obtained. The calibration graph was found to be linear in the concentration range of 0.005–5.0 µg/mL with a limit of detection (3 s) of 1.2 ng/mL and limit of quantification (10 s) of 4 ng/mL. The regression equation was I = (90147 ± 525) C + (17002 ± 835) with R^2 = 0.999, where I is the CL intensity in the presence of methamphetamine, and C is the concentration of methamphetamine in µg/mL. According to the calibration graph, the sensitivity of developed method is 90147. The relative standard deviations for five replicate determinations of 0.075, 0.1, and 0.8 µg/mL methamphetamine were 2.4, 1.5, and 1.8%, respectively. The results indicated that this CL system has good linearity, relatively high sensitivity, and suitable precision. Compared to some previous methods for the determination of methamphetamine in biological samples (Table 5), the developed method indicated the desirable linear rang and detection limit. Moreover, it is very simple and inexpensive.

Table 4. Results for determination of methamphetamine in street samples (n = 3).

Sample no.	Content (%) ± RSD (%)		t-statistic[a]
	CL	GC	
1	80.3 ± 1.0	78.1 ±1.0	2.4
2	87.5 ± 1.9	83.0 ±3.8	2.2
3	94.8 ± 2.3	93.6 ± 2.4	0.6

[a] t-critical = 2.73 for P = 0.05

Table 5. Comparison between the developed method for determination of methamphetamine with some published methods

Method	Detection limit (ng mL^{-1})	Linear range (ng mL^{-1})	Biological sample	Ref.
Chemiluminescence	0.086	0.25–125	urine samples	(11)
Fluorescence	1.8	6.7–400	urine samples	(11)
Fluorescence	1.7[a]	5-50 [a]	-	(32)
Fluorescence	1.6 [a]	5-250 [a]	plasma and urine samples	(33)
Electrochemiluminescence	0.1 [a]	0.5-10 [a]	plasma and urine samples	(12)
Chemiluminescence	1.2	5-5000	plasma and street samples	This work

[a] The concentration unit is µM. Ref: reference

Study of interferences:

To evaluate the selectivity of the proposed method, we investigated the effects of some common inorganic ions and organic compounds on the determination of 0.1 µg/mL methamphetamine. The tolerable concentration ratios for interferences in relative error of <5% were over 3000 for Mg^{2+}, 2000 for Zn^{2+} and NO_3^-, 1000 for Cu^{2+}, sucrose, and lactose, 500 for K^+, Cl^-, and L-cysteine, 250 for glycine, 200 for Na^+ and Ca^{2+}, 100 for glucose, and 50 for Fe^{3+} and ascorbic acid. The amounts of most of the potentially interfering species are below their tolerable levels or can decrease with diluting; therefore, there would be no direct interferences from these species in methamphetamine determination.

Analysis of real samples:

Methamphetamine was satisfactorily determined in three different methamphetamine street samples by using the developed method. As can be seen from

Table 5, the contents of methamphetamine in these samples are in the range of 80-94.0%, indicating that the purities of the samples are quite high. The accuracy of the developed method was confirmed by GC-FID method. The results are given in Table 4. Statistical analysis of these results using Student t-test showed no significant differences between the results of two methods. Moreover, these results indicate that coexisting substances, precursors, and possible by-products of synthesis do not have obvious interfering effect on the CL determination. The method was also applied to determine methamphetamine in spiked human plasma. The deproteinization procedure described in experimental section was found to be necessary. In order to eliminate the proportional and constant matrix errors, we applied the standard addition method and Youden blank correction (28, 29). The obtained results, shown in Table 6, demonstrate that the method can be applied for the determination methamphetamine in biological samples.

Table 6. Results for the determination of methamphetamine in spiked plasma samples

Plasma Sample	Add (µg mL^{-1})	Found (µg mL^{-1})[a]	Recovery (%)	t-statistic[b]
1	0.50	0.47 ± 0.02	95 ± 4.2	2.16
	0.70	0.72 ± 0.02	103 ± 2.8	2.01
2	0.50	0.49 ± 0.02	99 ± 2.1	0.50
	0.70	0.71 ± 0.12	101 ± 1.1	1.51

[a] Mean of three determinations ± standard deviation; [b] t-critical = 4.3 for n =2 and P = 0.05

Discussion

Possible mechanism for the CL enhancement by methamphetamine:

It has been proposed that the emitting species for Ce(IV)-Na_2SO_3 CL reaction is excited sulfur dioxide, which emits weaek light at wavelengths longer than 300 nm (23, 27). The CL spectrum of Ce(IV)-Na_2SO_3-methamphetamine system is shown in Figure 3. As seen, a broad emission band with peaks at around 440 and 535 nm has been obtained, which indicates that the emitting species is probably the excited SO_2*. The similar CL spectrum has been reported for the reaction between cerium(IV), sulfite, and papaverine consisting of a broad peak with maximum intensity at 535 nm and a weaker band at 440 nm (22). It should be noted that since the CL signal for Ce(IV)-Na_2SO_3 is very weak, we could not obtain CL spectrum of the system in the absence of methamphetamine. From these findings, we can conclude that more SO_2* is generated in the presence of methamphetamine. This behavior may be attributed to the possible oxidation of methamphetamine by Ce(IV) to form an intermediate radical, which reacts with sulfite to initiate a free radical reaction. The reaction between methamphetamine and Ce(IV) was proved by inspection of fluorescence spectra of methamphetamine in the absence and presence of Ce(IV). Methamphetamine exhibits a very weak fluorescence at about 290 nm (4), but after the addition of 1.25×10^{-3} M Ce(IV), the fluorescence emission completely disappears. Based on these facts, a CL mechanism can be proposed as follows (22):

$SO_3^{2-} + H^+ \rightarrow HSO_3^-$

$Ce(IV) + HSO_3^- \rightarrow Ce(III) + HSO_3^\bullet$

Ce(IV) + Methamphetamine → Ce(III) + Methamphetamine$^\bullet$

Methamphetamine$^\bullet$ + HSO_3^- → Methamphetamine + $HSO_3^\bullet$

$2HSO_3^\bullet \rightarrow S_2O_6^{2-} + 2H^+$

$S_2O_6^{2-} \rightarrow SO_4^{2-} + SO_2$*

SO_2*→ $SO_2 + h\nu$

Conclusion

A sensitive CL method was developed and validated for the determination of methamphetamine. The possible mechanism for the CL system was also discussed. The developed method showed good linearity and reproducibility and high sensitivity and

can be applied for the determination of methamphetamine in street drugs and human plasma samples. Moreover, it can be combined with HPLC or capillary electrophoresis as a sensitive detection technique. In such applications, this method offers a great simplicity since it does not need any derivatization step (as needed in peroxyoxalate CL systems (28–30) or a complicated detection cell (as needed in electrochemiluminescence methods (31).

Acknowledgments

None declared.

Conflict of interest

The authors have no conflict of interest in this study.

Funding/support

None declared.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

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