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SCIENCE DIRECT

Talanta 60 (2003) 623–628

Talanta

www.elsevier.com/locate/talanta

Short communication

Prediction of the chemiluminescent behaviour of phenols and polyphenols

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Received 18 July 2002; accepted 14 October 2002

Abstract

A paper from this laboratory 'J. Anal. Chem. 73 (2001) 4301' was recently published and dealing with the first attempt to apply molecular connectivity calculations to predict a chemical property with analytical usefulness; namely, the chemiluminescent behaviour of substances when react with common strong oxidants in liquid phase. In the present work, the usefulness of molecular topology on the search for new chemiluminescent compounds is clearly demonstrated. The proposed discriminant equation, represented a success of 92.7% in the prediction. The present paper is the further step from the cited paper; it is dealing on the application of molecular connectivity calculations (former discriminant equation 'J. Anal. Chem. 73 (2001) 4301') to predict the chemiluminescent behaviour of phenols and polyphenols when they react with common oxidants in liquid phase. A number of phenols and polyphenols (close to 100) were theoretically studied by means of the discriminant equation 'J. Anal. Chem. 73 (2001) 4301', being some of them predicted as chemiluminescent with a high probability. These theoretical predictions have been empirically checked through a continuous flow manifold. A number of 33 compounds, selected between those which chemiluminescent behaviour was predicted, were assayed. A success of 100% over the theoretical predictions was obtained.

Keywords: Chemiluminescence; Phenols; Polyphenols

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1. Experimental section

1.1. Reagents

All solutions were prepared from analytical reagent grade materials by solving in reverse osmosis and deionised water.

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doi:10.1016/S0039-9140(03)00105-X

1.2. Apparatus and procedure

The continuous-flow manifold for testing the chemiluminescent substances is depicted in Fig. 1. It consisted of a peristaltic pump (Gilson-Minipuls 2, Middleton, WI) which pumped oxidant (flow—rate Q_1, 2.8 ml min^{-1}, 0.02 mol l^{-1}), medium (flow—rate Q_2 and Q_3, both 2.8 ml min^{-1}, 1 mol l^{-1}) and tested substance (flow—rate Q_4, 2.8 ml min^{-1}, 200 mg l^{-1}) solutions through PTFE tubes (0.8 mm i.d.). All solutions merged finally in a T shaped piece positioned 2 cm before entering the flow cell. The cell consists on a flat spiral-coiled quartz tube (1.0 mm i.d., 3 cm total diameter of the flow cell, without gaps between loops). The flow cell was backed by a mirror for maximum light collection and placed 2 mm from the photomultiplier tube from EMI-Thorn (end window, type 9125B16) included in the photodetector package P30CWAD5F-29 and supplied by Electron Tubes Limited (Middlesex, UK). The T-piece, flow cell and photodetector package were placed in a home-made, absolutely light-tight box. The output was fed to a computer equipped with the CT1 Counter-Timer board also supplied by Electron Tubes Limited.

2. Previous work

2.1. Introduction

Analytical interest in liquid-phase chemiluminescence (CL) has increased considerably over the last two decades and, until the present, CL has found a lot of analytical applications for the determination of both, inorganic (metal ions, inorganic anions) and organic (biomolecules, pesticides, drugs) compounds in a variety of industrial, clinical and environmental matrices.

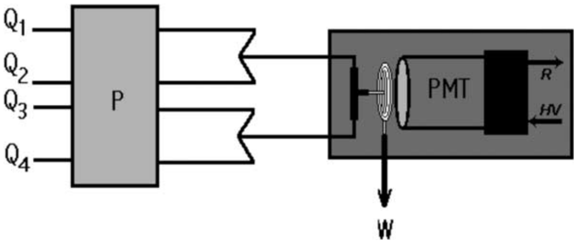

Fig. 1. Q_1: oxidant, 0.02 M; Q_2 and Q_3: medium, 1 mol^{-1}; Q_4: tested substance, 200 mg l^{-1} (or deionised water-blank). Flow rate: 2.8 ml min^{-1} each channel. HV: high voltage power supply; R: recorder; P: peristaltic pump and W: waste.

The analytical advantages of CL over common spectrophotometric procedures, include high sensitivity and a wide linear range, both of them can generally be achieved with simple and cost effective instrumentation, often home-made.

Basically, the analytical applications of liquid-phase CL can be divided into those procedures involving well known CL reactions (luminol, acridinium esters, peroxyoxalates, dioxetanes and tris(2,2′-bipyridyl)ruthenium(II)) which are responsible for the vast majority of applications; and, those procedures involving CL emission from the analyte, which is the substrate in the CL reaction and are usually identified as ‘direct CL determinations’.

In the former modality, the analyte can interact with the CL reaction, as a reagent, a catalyst, a quencher and even as a enhancer or by interaction with any of the compounds in the reaction. At present, the limited number of known systems have been broadly exploited.

The simpler approach can be the second modality, in which the previous experimental work is based on a tedious and time-consuming trial-error screening procedures between analyte and a wide range of oxidants (and sometimes reductants) in different media.

There are some empirical behaviours which can help to predict a chemiluminescent process. It is supposed when a compound or its oxidation product is fluorescent, is possible the CL emission from the oxidation of the molecule, particularly with strong oxidants plus an exothermic reaction (130–340 kJ mol^{-1}) and a simple reaction pathway. Nevertheless, there are many exceptions to this principle converting into useless the prediction on the CL emission.

The previous work [15] focussed on the application of molecular connectivity to predict the chemiluminescent behaviour of a molecule when it reacts with common oxidants in liquid phase. For this purpose, the molecular connectivity indices of 200 substances were calculated. The substances were found both as the result of the search through the analytical literature or by an empirical screening in a continuous flow assembly. Continuous-flow methods are the best way to monitor liquid-phase reactions, mainly because they provide fast and reproducible mixture of sample and reagents in a point very close to the flow cell.

2.2. Tested substances

When we faced with the problem of finding molecules which were chemiluminescent or not chemiluminescent in liquid phase as a consequence of their reaction with strong oxidants, first of all we searched in the analytical literature. It was relatively easy to find chemiluminescent (76)[1–7] molecules but it was a hard problem to find non-chemiluminescent molecules, due to most of the researchers working in the field of direct CL never reported the molecules found as non-chemiluminescent (‘negative’ results). Fortunately, we found some of them (8) in a book [1] and the main group (24) in some papers and in a personal communication [6,8].

On the other hand, with the goal to study a certain number of non-chemiluminescent substances, we carried out an experimental screening over many pharmaceuticals and some pesticides; total amount 92 compounds. We used a continuous-flow manifold like the one depicted in Fig. 1 for performing the preliminary empirical assays. The CL outputs were monitored (sample output minus blank output) with a home-made luminometer described in the experimental section. The tested oxidants were: potassium permanganate or cerium (IV), both of them merging with a sulphuric acid stream and, potassium hexacyanoferrate (III) or hydrogen peroxide, both of them merging with a sodium hydroxide solution.

A substance was considered non-chemiluminescent when the signals difference (sample minus blank) was less than twice the average background, with any tested oxidant and medium.

Last but not least, Molecular Connectivity studies with the chemiluminescent and non-chemiluminescent substances found either in the bibliography or by the reported screening, were performed.

2.3. Molecular connectivity

To design and find new compounds showing the desired chemical properties is a principal objective which focuses, nowadays, the attention of chemical laboratories.

In this way, molecular topology has demonstrated clearly its ability. Furthermore, a relatively simple formalism such as molecular connectivity is able to easily and quickly characterise molecular structures after defining the known as topological indices or topological descriptors (TDs). In this way, the molecule is assimilated to a graph, representing the atoms are by points, called vertices, and the bonds between atoms are represented by segments, called edges. Then the resulting graphs can be represented by matrices to derive one single TD or a set of them. This indices, whether well chosen, resulted in an unique characterisation of the molecular structure. Furthermore, they can be correlated with many physical, chemical or biological properties of molecules, so obtaining the QSPR or QSAR relationships and they can be used even to find new compounds with pre-determined [9] properties.

2.4. Calculation of the topological descriptors

In this work, we have used charge indices Gi [10], as well as Kier and Hall connectivity indices up forth order, ${}^{m}\chi_{t}$, [11] and topological geometric indices [12].

2.5. Linear discriminant analysis

The objective of linear discriminant analysis, LDA, which is considered as one of the ‘pattern recognition methods’, is to find a linear function able to discriminate between two different classes of objects. The analysis is carried out by using two large sets of compounds: one with proven chemiluminescent activity, and the other without chemiluminescent activity. The discriminant ability is tested by the percentage of correct classifications in each group; this is specially useful when the tested active–inactive compounds are not those used as a database. This is named a 'cross validation' test, in which connectivity indices act as independent variables discriminating activities.

Thus, a set of 200 structurally heterogeneous compounds with chemiluminescent (active group) and non-chemiluminescent (inactive group) activity has been analysed. Each group was separated in two, training and test groups. This way, it can be validated the discriminant function obtained [13]. The discriminant function (DF) chosen was:

$$DF = -87.987\,{}^{7}\chi_{\mathrm{CH}} - 276.12\,{}^{7}\chi_{\mathrm{CH}}^{\mathrm{V}} + 1.224S_{\text{–CH=}} - 35.38J_{3}^{\mathrm{v}} + 66.81J_{4}^{\mathrm{v}} - 0.20$$

$N = 96 \quad F = 19.5 \quad U$-statistics (Wilks λ) $= 0.427$

Then, the DF function was applied to structures which could be found in a personal databank with more than 50 000 heterogeneous structures. We selected as potential chemiluminescent compounds those which, tested through the discriminant function, yielded DF > 0. From all of them we selected 11 which were easily available and 30 by means of a random procedure.

The former predictions, were experimentally tested by means of the continuous-flow manifold and conditions depicted in the Fig. 1. This time, the reactions were monitored with the tested substance (Q_1), different media (Q_2 and Q_3; H_2SO_4 or NaOH, both 1 mol^{-1}) and with different oxidants (Cerium (IV), IO_4^-, $S_2O_8^{2-}$/ Ag^+, H_2O_2 and ClO_4^-, MnO_4^- and $Fe(CN)_6^{4-}$) (Q_4). Again, a substance was considered chemiluminescent when the signals difference (sample minus blank) was more than twice the average background.

From the 41 compounds whose chemiluminescent behaviour was predicted, 38 were experimentally found as chemiluminescent. It represented a success of 92.7% in the prediction. Moreover, the present results demonstrate an adequate choice of topological descriptors. Former results have been recently published [14].

3. Results and discussion

3.1. Direct—CL of phenols and polyphenols

Next, with the aim to apply the former discriminant equation to predict the chemiluminescent behaviour of phenols and polyphenols when they react with common oxidants in liquid phase, a number of phenols and polyphenols (namely 86) were theoretically assayed by means of the discriminant equation, being a lot of them (76) predicted as chemiluminescent (DF > 0).

The theoretical predictions were experimentally checked through a continuous flow manifold (Fig. 1). A number of 33 compounds, randomly selected between those who chemiluminescent behaviour was predicted, were assayed. The reactions were monitored with the tested substance (Q_1; substance solution), different media (Q_2 and Q_3; H_2SO_4 or NaOH, both 1 mol^{-1}) and with different oxidants (Cerium (IV)/H_2SO_4, MnO_4^-/H_2SO_4, N-bromosuccinimide/NaOH and $[Fe(CN)_6]^{4-}$or hydrogen peroxyde/NaOH) (Q_4).

A success of 100% over the theoretical predictions was obtained (Table 1).

A further experiment with the aim to enhance the knowledge on the chemiluminescent behaviour of the substances in front of the permanganate in acidic medium, those compounds which CL emission was higher than 100 arbitrary units, were selected. For each compound, a set of assays including different concentrations of analyte and oxidant were performed and by means of the manifold depicted in the Fig. 1. Six solutions of permanganate were prepared, ranging from 10^{-5} mol^{-1} to 5×10^{-2} M. For each permanganate solution (channel Q_4), seven different solutions of analyte, over the range 1–200 mg l^{-1} (channel Q_1), were assayed. Six different assays were obtained in different days and with freshly prepared solutions. The best sensitivity was obtained employing permanganate solutions with concentrations ranging from 10^{-2} to 10^{-3} mol l^{-1} and being in the majority of cases, 5×10^{-3} mol l^{-1} the optimum permanganate concentration.

Table 1
Theoretical classification and experimental results for tested compounds

Substance	DF	Chemiluminescence signal (arbitrary units)			
		$KMnO_4$	Ce(IV)	*N*-Bromosucinimide	$K_3Fe(CN)_6$
Sinapic acid	5.00	20.65	0.00	0.05	7.55
Ferrulic acid	4.19	59.68	0.00	0.24	64.84
p-Coumaric acid	3.94	206.61	0.00	1.44	15.34
Eugenol	3.93	740.41	0.02	0.00	11.56
Caffeic acid	3.63	230.45	0.00	3.75	27.67
Ellagic acid	3.13	14.85	0.00	113.14	198.10
Aloin	2.95	20.15	1.50	162.84	151.60
o-Coumaric acid	2.94	267.04	0	2.38	84.06
Vanillin	2.30	59.56	0.01	0.00	8.09
2,5-Dyhydroxybenzaldehyde	2.20	374.50	0.00	0.42	9.24
Quercetin	2.18	152.19	77.69	13.54	24.78
Syringic acid	2.07	67.04	0.00	0.00	0.00
4-Hydroxybenzaldehyde	2.03	225.13	0.00	0.00	2.15
β Resorcylic acid	1.93	480.15	3.93	0.00	53.70
Chlorogenic acid	1.85	61.67	0.00	1.71	33.02
Hydroquinone	1.74	487.90	0.00	0.84	3.00
Protocatechialdehyde	1.73	163.50	0.00	0.00	8.68
o-Vanillin	1.73	94.94	0.00	7.23	1.95
γ Resorcylic acid	1.67	290.42	2.39	0.00	22.79
Gentisic acid	1.60	320.23	0.00	10.55	3.13
Rutin	1.50	34.53	0.60	0.00	13.54
Isovanillin	1.45	86.62	0.00	0.00	25.94
Salicylaldehyde	1.35	234.46	0.00	0.10	0.65
Vanillic acid	1.30	84.66	0.00	1.95	5.18
4-Hydroxybenzoic acid	1.29	262.91	0.00	0.61	0.44
Naringin	1.06	42.11	0.20	0.37	3.34
Protocatechuic acid	0.89	186.02	0.00	0.15	10.35
3-Hydroxybenzaldehyde	0.54	339.37	0.00	1.19	24.32
Gallic acid	0.46	178.83	9.81	0.56	70.83
Pyrogallol	0.37	291.92	3.58	3.50	127.05
Catechol	0.34	335.99	0.00	8.80	2.66
Resorcinol	0.18	710.80	0.02	0.00	114.60
Phloruglucinol	0.09	266.75	2.75	0.11	5.10

4. Conclusions

The chemiluminescent behaviour of a set of phenols and polyphenols theoretically predicted, was empirically confirmed. However, it should be noted that there is no correlation between the DF value and the CL intensity measured.

Permanganate and ferricyanide were the oxidants in the vast majority of cases resulting in higher emission. Potassium permanganate was found as the best and the study of the influence of the concentration revealed in the majority of tests, 5×10^{-3} mol l^{-1} as the optimum permanganate concentration.

The present results demonstrate an adequate choice of topological descriptors. It is possible to discriminate the chemiluminescent activity of a compound and, therefore, to corroborate its applicability to predict chemiluminescent behaviour, and consequently, a suitable analytical procedure.

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