

Polarographic Determination of *N*-Oxides of 2-Substituted 3-Alkyl-5-chloromethyloxazolidines

J. KÖNIGSTEIN and B. STEINER

Institute of Chemistry, Slovak Academy of Sciences, CS-842 38 Bratislava

Received 11 July 1989

Accepted for publication 11 July 1991

Dedicated to Dr. Ing. Š. Bauer, DrSc., in honour of his 70th birthday

A set of selected amine oxides of 2-substituted 3-alkyl-5-chloromethyloxazolidines was studied by DC polarographic method. Cathodic waves corresponding to their two-electron polarographic reduction to the initial oxazolidines were followed. Determinations were performed in aqueous medium using Britton—Robinson buffers at pH 8 in the concentration range of 0.01—1.00 mmol dm⁻³ of amine oxides. They were controlled by acidimetric potentiometric titrations. This method is very suitable for determination of functional analytical group of amine oxides of oxazolidines with an alkyl in the position 3. It enables observation of the course of amine oxides syntheses by oxidation of oxazolidines with H₂O₂. Hydrogen peroxide and formed addition products are polarographically separated and determinable.

Analytical determination of amine oxides is the most frequently performed by oxidation-reduction titration methods where their properties to be reduced to the starting tertiary amine are utilized [1]. They are little selective and their exactness, according to the method of performance, varies from ± 0.5 to ± 3 %, expressed by the mean relative error of result. For studied *N*-oxides, potentiometric titration combined with application of iodomethane for removal of interfering tertiary amine, is very significant [2]. This method is also suitable for a longer alkyl substituent on the oxazolidine ring. From among the other methods, attention attracted chromatographic methods which are significant owing to their sensibility with typical restrictions — necessity to prepare several derivatives of compounds to be determined and longer period of determination. Methods of determination of amine oxides were reviewed by *Devínsky* [3].

Electrochemical determinations utilize capability of amine oxides to be reduced to tertiary amine. Coulometry at controlled potential has found application especially in pharmacy for the sake of high sensibility [4]. Determination of cyclic *N*-oxides by the use of classical polarography has found application as an analytical method for kinetic study of elimination reactions of cycloalkylamine oxides to olefin and hydroxylamine derivative [5]. An effort to increase sensibility led to the application of differential pulse polarography for determination especially of aliphatic amine oxides [6]. Polarography enables one to trace amine oxides of oxazolidines, hydrogen peroxide

and its adducts with tertiary amines separately and also in the mixtures [7]. Such adducts were observed and identified in the case of hexamethylenetetramine [8] and polarographically identified by us during the monitoring of syntheses of amine oxides by the oxidation of oxazolidines with hydrogen peroxide [9].

The aim of our work was to elaborate a suitable method for observation and monitoring of syntheses of oxazolidine *N*-oxides and analytical determination of purity of reaction products, respectively formation and removal of undesirable addition products with H₂O₂. Classical DC polarography has been found to be well suitable. Therefore, we have studied polarographic behaviour of selected amine oxides of oxazolidine type, the results of experimental measurements have been compared after processing by means of statistical methods suitable for smaller series of obtained data (up to 15) [10] and obtained knowledge has been utilized for ascertainment of optimal conditions of determinations.

EXPERIMENTAL

HCl solutions for potentiometric titrations and reference standards of buffer solutions were from the set Titrisol (Merck, Darmstadt). Agar, saturated with KCl was used as a material of bridges. Working solutions, in the form of aqueous Britton—Robinson buffer solutions, iodomethane, and isopropyl alcohol were of anal. grade purity,

the others were of quality pure (Lachema, Brno). Isopropyl alcohol was purified by redistillation, 2,3-dimethylquinoxaline, pure (Fluka, Buchs), was recrystallized from methanol. Synthesis, leading to the effective yields of amine oxides, was performed by oxidation of oxazolidine derivative with H_2O_2 [11]. Excessive H_2O_2 was decomposed by PtO_2 and water was removed by azeotropic distillation with butanol under diminished pressure.

Polarographic measurements were performed on a Universal Polarograph OH 105 instrument (Radelkis, Budapest) in a thermostated vessel of the shape of H with a bridge which separated reference electrode (SKE). Measurements of pH were performed on a Standard pH-meter PHM 82, in the case of potentiometric titrations in connection with Titrator TTT 80 (Radiometer, Copenhagen), in a thermostated universal vessel EA 880 using glass electrode EA 109U and calomel reference electrode EA 404 (all from Metrohm, Herisau). The temperature was maintained with accuracy ± 0.1 °C by the help of U1 thermostat (Prüfgeräte Medingen, Dresden). Calibration diagrams were evaluated on a programming calculator TI-59 in combination with a printer PC-100B (Texas Instruments, Dallas).

Polarographic measurements were performed in aqueous medium of buffer Britton—Robinson solutions under a nitrogen atmosphere. Temperature was maintained at 20 °C ± 0.1 °C and in the case of dependences of polarographic waves on temperature in the interval from 10 to 60 °C and measured gradually by 10 °C. The value of pH was 8 excepting pH dependences where pH was changed from 2 to 10 by unit of pH. Acidity of medium was adjusted to pH standards. Working solutions had a volume 10 cm³ and the average concentration of studied *N*-oxide was 0.25 mmol dm⁻³. The observation of dependences of waves size on amine oxides concentrations was

Table 1. Polarographic Data of Aqueous Solutions of Oxazolidine *N*-Oxides and Their Adducts with H_2O_2

Compound	Amine oxide		Adduct
	$E_{1/2}/V^a$	$\Delta E_{1/2}/V^b$	$E_{1/2}/V^a$
I	-1.13	0.18	-1.01
II	-1.12	0.11	-0.99
III	-1.05	0.14	-0.97
IV	-1.12	0.20	-1.02
V	-1.14	0.11	-1.01
VI	-1.19	0.13	-0.98
VII	-1.22	0.20	-1.00
VIII	-1.21	0.14	-1.02
IX	-1.15	0.26	-1.01

a) Half-wave potential against saturated calomel electrode at pH = 8, $c(N\text{-oxide}) = 0.25$ mmol dm⁻³.

b) The shift of half-wave potentials in the interval of pH = 2—10.

performed in the concentration range of 0.01 — 1.00 mmol dm⁻³. Concentrations were controlled polarographically by comparison with 2,3-dimethylquinoxaline at the same conditions.

Concentration respectively purity of measured compounds was controlled by acidimetric potentiometric titration of approximately 0.01 M isopropanolic solutions of *N*-oxides with 0.01 M- and 0.05 M-HCl. Disturbing effect of tertiary amines — oxazolidines was removed by the action of iodomethane [2] in parallelly titrated samples and the difference in consumed HCl was exploited. Weighted amounts of *N*-oxides for polarographic analyses were corrected to the results of controlling analyses.

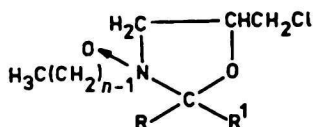
RESULTS

For polarographic study a series of amine oxides of 2-substituted 3-alkyl-5-chloromethyloxazolidines was prepared according to the procedure given in Experimental.

Table 2. Statistical Evaluation of Concentration Dependences of Oxazolidine *N*-Oxides. The Range of Concentrations 50 — 500 $\mu\text{mol dm}^{-3}$, pH 8, Temperature 20 °C

Compound	<i>a</i>	<i>b</i>	<i>r</i>	<i>s_a</i>	<i>s_b</i>	<i>s_y</i>	<i>s_r</i>
	mm	mm μmol^{-1} dm ³		mm	mm μmol^{-1} dm ³	mm	%
I	5.10	0.251	0.997338	0.0092	0.0092	2.885	2.33
II	7.52	0.292	0.99812	2.794	0.0031	2.573	2.32
III	3.76	0.242	0.99983	0.609	0.0020	1.368	1.08
IV	4.32	0.392	0.99922	2.347	0.0077	1.716	1.55
V	0.97	0.412	0.99839	1.805	0.0060	2.708	2.18
VI	2.26	0.167	0.99982	0.752	0.0016	2.241	1.90
VII	6.66	0.416	0.99880	3.155	0.0104	3.682	2.79
VIII	5.03	0.297	0.99876	6.055	0.0072	1.829	1.86
IX	4.87	0.482	0.99879	5.070	0.0260	2.348	1.84

a — intercept, *b* — slope, *r* — correlation coefficient, *s_a*, *s_b* — standard deviation of the intercept and the slope, *s_y* — standard deviation of heights of waves from ten measurements at the average $c(N\text{-oxides}) = 250$ $\mu\text{mol dm}^{-3}$, *s_r* — relative standard deviation of heights of waves.



	R	R ¹	n
I	C ₆ H ₅	H	12
II	2-HOC ₆ H ₄	H	12
III	2-furyl	H	12
IV	C ₆ H ₅	CH ₃	12
V	CH ₃	CH ₃	6
VI	CH ₃	CH ₃	12
VII	CH ₃	CH ₃	18
VIII	CH ₂ COCH ₃	CH ₃	12
IX	HC(OCH ₃) ₂	CH ₃	12

Diffuse character of polarographic currents was confirmed on the basis of their linear dependence on the root of mercury column height of indicating dropping electrode ($r \geq 0.99$) and a little change of wave height with temperature ($1-3\% \text{ } ^\circ\text{C}^{-1}$) in the temperature interval from 10 to 60 °C. The correspondence of waves magnitudes of *N*-oxides and 2,3-dimethylquinoxaline suggests a two-electron electrode process.

Polarographic data from dependences of $E_{1/2}$ on pH (2–10) in Britton–Robinson buffer solutions at 20 °C are summarized in Table 1.

The average values for studied amine oxides are as follows: $E_{1/2} = (-1.12 \text{ to } -1.22) \text{ V}$, $\Delta E_{1/2} = 0.11-0.26 \text{ V}$. In the case of addition products with H₂O₂ which are formed when excess of H₂O₂ is used for synthesis of amine oxides they are: $E_{1/2} = (-0.97 \text{ to } -1.02) \text{ V}$, $\Delta E_{1/2} = 0.05 \text{ V}$. As to H₂O₂, the polarographic wave is substantially higher and its features are well comparable with waves of adducts: $E_{1/2} = -0.99 \text{ V}$, $\Delta E_{1/2} = 0$.

Concentration dependences (wave height on concentration of amine oxide) in the concentration interval of 0.05–0.5 mmol dm⁻³ are statistically evaluated in Table 2.

By evaluating the results of the study of polarographic behaviour of *N*-oxides of 2-substituted 3-alkyl-5-chloromethyloxazolidines, hydrogen peroxide, and their addition products in common mixtures, conditions for direct DC polarographic determination were found: volume of analyzed samples 5–10 cm³, concentration 0.01–1.00 mmol dm⁻³ in aqueous Britton–Robinson buffer solutions at pH 8 and temperature 20 °C in an inert atmosphere.

DISCUSSION

Adjustment of nominal concentrations of analyzed samples of *N*-oxides was realized with regard to the results of analysis of prepared compounds by acidimetric potentiometric titrations and height of polarographic waves of standard

quinoxaline derivative [12]. It suggests that polarographic wave corresponds to a two-electron cathodic reduction of *N*-oxides to initial oxazolidines, which is in agreement with the published data [5].

The shift of $E_{1/2}$ of amine oxides waves suggests that protonation of amine oxide functional group takes place. On the contrary, invariability of $E_{1/2}$ of addition products suggests the relative stability of bonds. Small differences of $E_{1/2}$ among individual amine oxides do not allow their mutual separation. In practice, this analytical problem is rare. Sufficient difference between $E_{1/2}$ of amine oxides and addition products with H₂O₂ (respectively H₂O₂ alone) enables their determination in mutual mixtures, which is considerably significant in practice for controls of the course of syntheses, stability, and purity of amine oxides [9]. Nonzero value of a (in the case of calibrating diagrams) is probably influenced by surface phenomena.

Presented polarographic and statistical data selected so as to be suitable for rather small series of experimental measurements [10] indicate that the classical DC polarographic method of direct analytical determination of functional analytical group of 5-chloromethyloxazolidine *N*-oxides with alkyl substituent in the position 3, also in the presence of addition products with H₂O₂ respectively excessive hydrogen peroxide, corresponds to the criteria for accuracy, sensibility, reproducibility, and speed.

Acknowledgements. The authors thank A. Sedláč (Institute of Chemistry, Slovak Academy of Sciences, Bratislava) for technical assistance.

REFERENCES

- Weiss, P. T., *Determination of Organic Compounds, Methods and Procedures*, p. 247. J. Wiley, New York, 1970.
- Metcalfe, L. D., *Anal. Chem.* **34**, 1849 (1962).
- Devínsky, F., *Acta Fac. Pharm. Univ. Comenianae* **42**, 191 (1988).
- Janssen, R. W. and Discher, C. A., *J. Pharm. Sci.* **60**, 798 (1971).
- Krupička, J. and Závada, J., *Collect. Czechoslov. Chem. Commun.* **32**, 2797 (1967).
- Faith, L., Devínsky, F., and Prokopová, I., *Farm. Obzor* **52**, 111 (1983).
- Königstein, J. and Steiner, B., in *Proceedings of the 13th Conference of Organic Chemists, Smolenice, 1986*, p. 118. Faculty of Chemical Technology, Slovak Technical University, Bratislava, 1986.
- Mak, T. C. W. and Lam, Y. S., *Aust. J. Chem.* **31**, 1249 (1978).
- Steiner, B., Kočš, M., Sasinková, V., Pavliaková, D., and Königstein, J., *Chem. Papers* **44**, 281 (1990).
- Miller, J. C. and Miller, J. N., *Statistics for Analytical Chemistry*, p. 82. E. Harwood, Chichester, 1984.
- Steiner, B., Repáš, M., Sasinková, V., and Pavliaková, D., *Czechoslov. Chem. Commun.* **247581** (1988).
- Fedoroňko, M., Königstein, J., and Linek, K., *Collect. Czechoslov. Chem. Commun.* **33**, 2041 (1968).

Translated by M. Kočš