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Failure analysis of clinical electrodes: degradation of the ionophore, TDDA ☆

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Abstract

To map the ischemic regions of a heart, cardiologists must ligate a blood vessel and measure changes in the various ion concentrations over time. The plunge wire electrodes that are used are subject to failure from a multitude of causes, one of which may involve the degradation of the pH-selective ionophore, tri-*n*-dodecylamine (TDDA). In this work, the stabilities of four commercial products were studied by TGA in 100% N_2, air, and 100% O_2. No significant difference in thermal stabilities or activation energies were noted. When mixtures of TDDA and four antioxidants were studied, no improvement in the rate of weight loss was noted. When accelerated aging tests were performed and these products were incorporated into membranes, the loss in pH sensitivity was apparent after only 10 min at 200°C in 100% O_2. From TGA, NMR, and IR analyses, a cleavage mechanism is suggested that involves the formation of dodecane and a secondary amide, didodecylamide.

Keywords: Atmosphere; Degradation; Electrode; Failure; Ionophore; IR; Kinetics; NMR; Plunge wire electrode; TDDA; TGA

1. Introduction

Ion-selective electrodes (ISEs) have been used extensively to measure the activities of numerous charged species in aqueous media. Representative physiological

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and electrochemical references are Hill et al. [1–3] and Ammann et al. [4,5], respectively. Both the medical and industrial communities depend upon ISEs of different designs to convey accurate quantitative information about the process under investigation, e.g. pH, blood gas, sodium, potassium, glucose, and urea concentrations. Inaccurate measurements of these parameters can have grave consequences.

The development of the ISE allowed for direct quantitative determination of electrolyte activity and spurred cardiovascular research on the effects of myocardial ischemia. Much of this early research involved examining the effects on the myocardium of coronary occlusion [1,3,6–9], drugs [8], and varying perfusate electrolyte and gas concentrations [10]. The electrodes used in these early studies were of various designs. Starting in 1976, LeBlanc et al. [11] and then Cobbe et al. [9,10,12] and Hill and Gettes [2] gradually developed the ion-selective plunge wire electrode (PWE) shown in Fig. 1 for intramyocardial pH determinations.

Prior to 1984, the membrane matrix was changed from siloxane copolymer to polyvinylchloride, and titanium dioxide was added to the cellulose acetate sponge. Noise in the pH PWEs was reduced by substituting the pH ionophore, tri-*n*-dodecylamine, for *p*-octadecyloxy-*m*-chlorophenyl-hydrazone-mesoxalanitrile. Currently the pH-selective membrane is comprised of 65.6 wt% plasticizer (dioctyl sebacate, DOS), 32.8 wt% polymer (polyvinylchloride, PVC), 1.0 wt% ionophore (tri-*n*-dodecylamine, TDDA), and 0.6 wt% anion sites (potassium tetraphenyl borate, KTPB). Electrodes that were made from this membrane have a shelf life of about six months.

In addition to this limited shelf life, Watanabe et al. [13] reported that pH electrodes used in experiments met the calibration criteria and yielded valid data

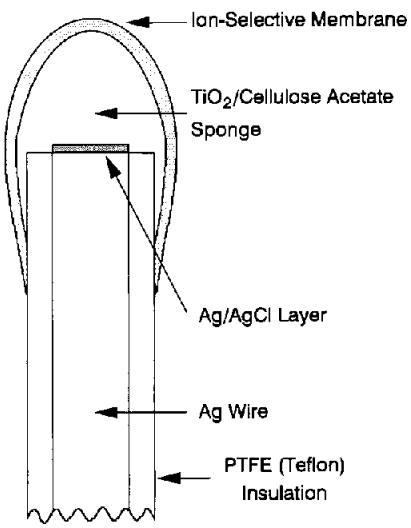

Fig. 1. Cross sectional schematic of the present plunge wire electrode (PWE).

only about 50% of the time. Failure of these electrodes to perform properly was usually attributed to a loss of integrity in the ion-selective membrane. These failures may be caused by certain mechanically, physiologically, or chemically induced phenomena. Failures caused by chemical phenomena include leaching out of membrane components; surface chemical effects induced by the environment; or, in the present work, the thermo-oxidative degradation of membrane materials.

To determine the mechanism that explains the shorter shelf life and serviceability of pH electrodes (as compared to K^+ electrodes, for example), the thermo-oxidative degradation of TDDA in the ion-selective membrane layer was studied. By understanding the membrane chemistry, future PWE performance will be improved as protocols for testing polymeric membrane electrode materials are developed.

2. Material and methods

2.1. Materials

The pH-selective ionophore consisting of three paraffinic chains ($C_{12}H_{25}$) bounded to a tertiary nitrogen as shown in Fig. 2, tri-*n*-dodecylamine (TDDA), was obtained from Aldrich, Eastman Kodak, Fluka, and Sigma.

In an attempt to retard oxidation by atmospheric oxygen at moderate temperatures (auto-oxidation), four antioxidants were purchased from Aldrich. Two were antioxidants commonly used for the stabilization of elastomers [14], diphenylamine and 1,4-phenylenediamine. These aromatic amines are chain-breaking antioxidants that decelerate the formation of oxidation products, which may include the toxic vinyl chloride monomer. Butylated hydroxytoluene (BHT) is the most widely used antioxidant in the food industry, but it is also used to stabilize polyethylene and polystyrene [15]. The fourth antioxidant, tocopherol (Vitamin E), is a dietary requirement of humans that is found in common foods.

2.2. Methods

2.2.1. Thermogravimetric analysis

Thermograms were recorded using a Dupont 950 thermogravimetric analyzer in three different specimen atmospheres, 100% N_2, air (80% N_2, 20% O_2), and 100%

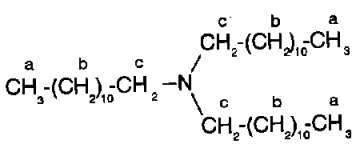

Fig. 2. Chemical formula of tri-*n*-dodecylamine (TDDA). Labels a, b, and c denote the carbon–hydrogen bond character.

O_2, at a flow rate of 250 ml min^{-1}. Specimens ($\approx$30 mg) of TDDA were heated as required up to a temperature of 470°C at a constant heating rate of 20°C min^{-1}. Data were plotted after normalization by dividing by the initial mass.

The presently used brand of TDDA (Fluka) and the four antioxidants were mixed in 10:1 ratios by weight and dissolved in HPLC-grade tetrahydrofuran, THF (Aldrich). After the THF was evaporated in the dark, thermograms were recorded in air under the same conditions as previously mentioned. Because the weight percentages of the TDDA and antioxidant are known, superposition was used, and the equivalent amounts of antioxidants were subtracted from the thermograms of the TDDA/antioxidant mixtures. The resulting thermograms were normalized and compared to the normalized thermogram of the TDDA alone to see if the antioxidants had any effect on TDDA degradation.

The TGA apparatus was also used for accelerated aging experiments. Fluka TDDA was heated isothermally at 200°C in the same atmospheres for 10, 30, and 60 min. The resulting residues were then incorporated into the present pH-selective membrane formulation: 65.6 wt% Sigma dioctyl sebacate (DOS), 32.8 wt% Aldrich VHMW PVC, 1.0 wt% (20.7 mM) Fluka TDDA, and 0.6 wt% potassium tetraphenylborate (KTPB) made from NaTPB according to the procedure of Hill and Gettes [3]. After appropriate pre-conditioning in a pH 5 citrate buffer at 25 $\pm$ 1°C, the slopes of the potentiometric responses of these membranes were determined in five standard buffers (pH 6.00, 6.86, 7.00, 7.41, and 8.00) at 25 $\pm$ 1°C. Chauvenet's criterion was used to eliminate outliers, and slopes not having correlation coefficients $r \geq 0.878$ were eliminated [16].

2.2.2. Kinetic analysis

Khanna et al. [17] conducted kinetic analysis of the thermal and thermo-oxidative degradation of aromatic polyamides. Kinetic data of 0–15% degradation were analyzed using the Freeman–Carroll method [18,19] and the equation

$$\Delta \log(dW/dt) = n\Delta \log(W_r) - (E/2.3R)\Delta(1/T),$$

in which dW/dt is the rate of mass loss at time t (mg min^{-1}), n the reaction order, W_r the sample mass remaining at time t (mg), E the activation energy (cal mol^{-1} g^{-1}), R the gas constant (cal mol^{-1} K^{-1}), and T the temperature (K). From plots of $\Delta \log(dW/dt)/\Delta \log(W_r)$ against $\Delta(T^{-1})/\Delta \log(W_r)$, the reaction order and activation energy were calculated for the TDDAs that were isothermally heated in an atmosphere of air.

3. Results

Thermograms of the four different brands of TDDA determined in atmospheres of 100% N_2, air, and 100% O_2 are shown in Fig. 3. The straight vertical lines that appear in all thermograms of the specimens which were heated in air or 100% O_2, represent the ignition points. No substantial difference in thermal stability was noted between the four different brands of TDDA. When the thermograms of the

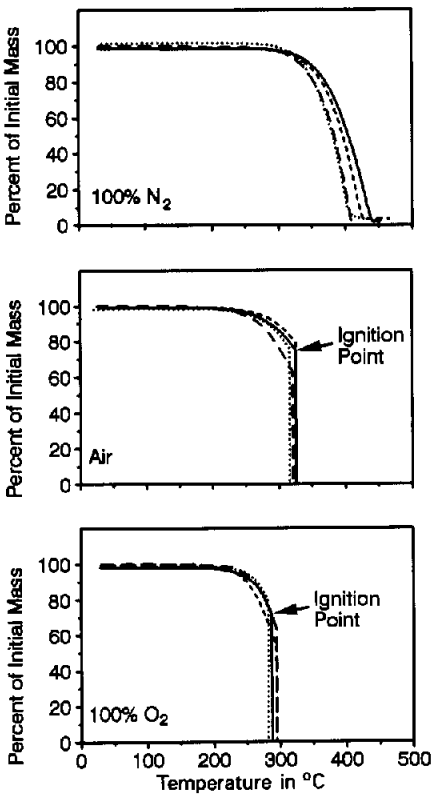

Fig. 3. Normalized thermograms of TDDAs for Aldrich (——), Eastman Kodak (— · —), Fluka (· · ·), and Sigma (– – –) products. Gas flow, 250 ml min^{-1}; heating rate, 20°C min^{-1}.

currently used Fluka brand TDDA in pH PWEs are highlighted for the three different atmospheres previously mentioned, an oxidative degradation effect is noted, as shown in Fig. 4.

Thermograms of 10:1 mixtures of TDDA with the four proposed antioxidants were compared to the TDDA alone. In air, all four of the proposed antioxidants had no effect on the rate of mass loss of TDDA. For example, Fig. 5 indicates that when a 10:1 Fluka TDDA:Vitamin E is compared to this TDDA alone, the ignition point is extended but the onset of degradation is reduced.

The outcomes of the accelerated aging experiments are shown in Fig. 6, in which the horizontal dotted lines represent the ±15% region of the ideal Nernstian slope (−59.2 mV/pH) at 25°C. PWEs having slopes in this region are generally acceptable for use in the cardiology laboratory. Table 1 shows the percentage of membranes that passed this criterion. As the air and 100% O_2 data show, oxidative degradation of TDDA has the effect of deteriorating the performance of pH-selective electrodes.

Mean activation energies for this degradation process in air of the different brands of TDDAs were calculated by the Freeman–Carroll method [18,19] and

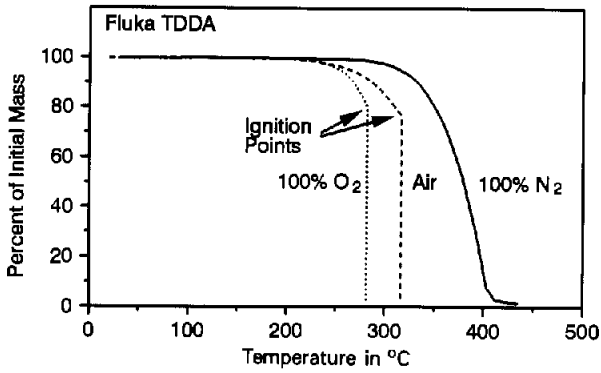

Fig. 4. Normalized thermograms of Fluka TDDA in 100% N_2 (——), air (– – –), and 100% O_2 (· · ·) atmospheres. Gas flow, 250 ml min^{-1}; heating rate, 20°C min^{-1}.

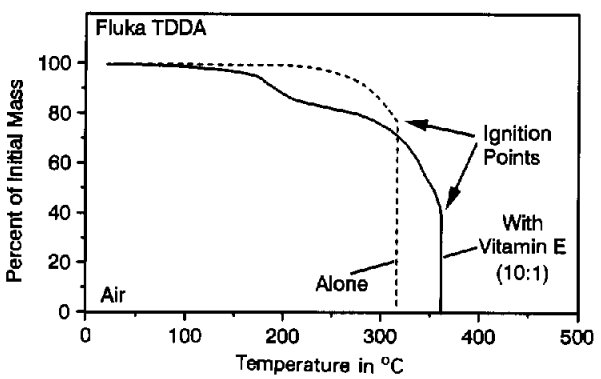

Fig. 5. Normalized thermograms of Fluka TDDA in air when tested alone (– – –) and when the ratio of TDDA: Vitamin E equals 10:1 (——). Gas flow, 250 ml min^{-1}; heating rate, 20°C min^{-1}.

ranged from 15.8 to 21.2 kcal mol^{-1} (Table 2). A one-way analysis of variance (ANOVA) of these results showed no statistical difference between the activation energies of the different brands.

4. Discussion

4.1. The effect of thermal degradation on electrode performance

The present results established that TDDA undergoes thermo-oxidative degradation in four commercial products whether or not selected antioxidants were used. Potentiometric measurements of pH membranes, which were formulated from the residues of isothermally heated TDDA, showed that the effects of aging could be accelerated. Although degradation could be identified, TGA was not independently

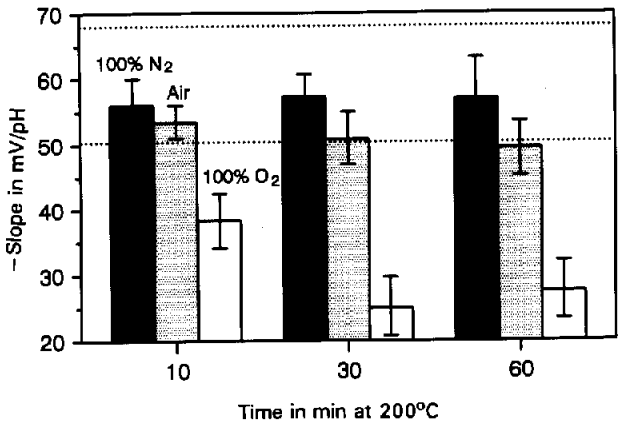

Fig. 6. Accelerated aging of Fluka TDDA. Slopes from the potentiometric responses of membranes made with TDDA isothermally heated (200°C) and maintained for various times in 100% N_2, (solid bars), air (stippled bars), and 100% O_2 (open bars).

Table 1
Slopes of pH-selective membranes made with Fluka TDDA that was isothermally heated (200°C) and maintained for various times in selected atmospheres

Atmosphere [a]	Time in min	Slope in mV/pH [b]	No. of specimens	% Passing [c]
100% N_2	10	-56.0 ± 4.2	8	87.5
	30	-57.2 ± 3.5	8	100
	60	-56.9 ± 6.3	8	87.5
Air	10	-53.4 ± 2.6	8	87.5
	30	-50.8 ± 4.1	8	75.0
	60	-49.5 ± 5.3	10	40.0
100% O_2	10	-38.4 ± 4.1	5	0
	30	-25.0 ± 3.7	4	0
	60	-27.6 ± 4.3	6	0

[a] Gas flow rate, 250 ml min^{-1}. [b] Outcomes of linear regressions of mV versus pH plots. [c] Percentage of electrodes that are $\pm 15\%$ of the ideal Nernstian slope (-59.2 mV/pH) at 25°C.

capable of discriminating a mechanism. Consequently, further data were obtained via nuclear magnetic resonance (NMR) and infrared (IR) spectroscopies.

4.2. Proton NMR spectroscopy

To elucidate further the mechanism of oxidative degradation, 0.02 ml aliquots of TDDA, whether unheated or heated to 200°C in air for 60 min, were dissolved in 1.0 ml CD_3COCD_3 (deuterated acetone) and run in a Varian XL-400 NMR spectroscopic analyzer. The proton NMR spectra were obtained for all specimens at ambient temperature under the following conditions: frequency, 400 MHz; spectral

Table 2
Activation energies (kcal mol^{-1}) for commercial TDDA products degraded in air [a]

Vendor	Aldrich	Eastman Kodak	Fluka	Sigma
Activation energy [b]	21.2 ± 3.4	20.0 ± 0.3	16.3 ± 8.8	15.8 ± 3.0

[a] Gas flow, 250 ml min^{-1}; heating rate, 20°C min^{-1}. [b] Mean $\pm$ standard deviation for three determinations.

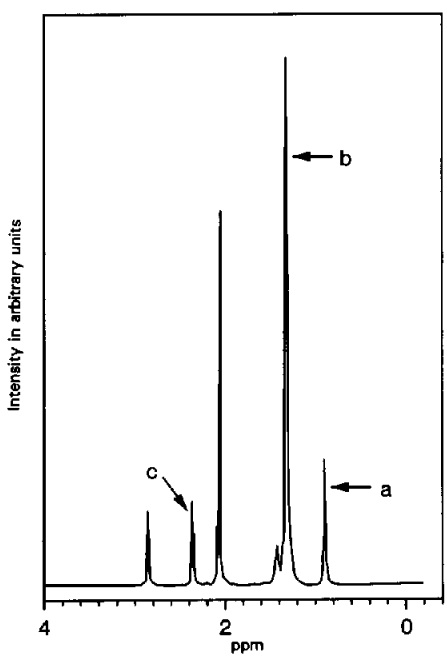

Fig. 7. Proton NMR spectrum of unheated Fluka TDDA. Labels denote the carbon–hydrogen bond character as shown in Fig. 2.

width, 5300 Hz; pulse width, 30°, spin rate, 20 Hz, and line broadening 0.2 Hz. As shown in Fig. 7, the proton NMR spectra of the unheated TDDA show five major peaks at 0.87, 1.29, 2.04, 2.34, and 2.83 ppm (where each corresponding frequency v equals 400 MHz divided by the ppm). The peak at 2.04 ppm and the smaller peak at 2.83 ppm correspond to protonated acetone and water, respectively, which comprise the 0.5% impurity in the deuterated acetone. The three major peaks of TDDA shown in Fig. 7 correspond to the three different types of hydrogen bonds seen in Fig. 2: a, 0.87 ppm; b, 1.28 ppm; and c, 2.34 ppm.

TDDA heated in air exhibits a very small peak at 2.53 ppm, and TDDA heated in 100% O_2 exhibits the same (but larger) peak, with a still larger peak at

Table 3
Hydrogen atomic percent via NMR of theoretical TDDA, unheated TDDA, and TDDA heated in air or in 100% O_2

ppm	Atom% H			
	Theoretical pure	Unheated	Heated in air [a]	Heated in O_2 [a]
0.87 ("a")	12.0	11.5	11.0	12.9
1.28 ("b")	80.0	81.8	81.9	81.7
2.34 ("c")	8.00	7.34	6.95	4.50
2.53	0	0	0.13	0.30
3.26	0	0	0	0.59

[a] Heated at 200°C for 60 min.

3.26 ppm. Integration of the area under each curve yields relative atomic percent values for hydrogen so that a comparison against theoretical values can be made. Table 3 shows hydrogen atomic percent values for theoretically pure TDDA, unheated TDDA, and heated TDDA in air and 100% O_2. No major change is evident between unheated TDDA and TDDA heated in air. A substantial reduction in hydrogen atomic percent at the 2.34 ppm peak occurs for TDDA heated in O_2, however, with a decrease from 6.95% to 4.50%. This peak corresponds to the hydrogens bound to the carbon adjacent to the nitrogen (the α-carbon). Because the peaks that occurred only in the heated TDDA were assessed from existing spectra, the extra peaks could not be positively identified.

4.3. IR spectroscopy

Using a dual-beam Perkin-Elmer 457 grating infrared spectrophotometer, the IR spectrum of Fluka TDDA was first evaluated in the unheated state, then in the heated state at 200°C in air for 60 min, and finally in the heated state at 200°C in 100% O_2 for 60 min. The IR spectra was obtained at ambient temperature by injecting each specimen into a Perkin-Elmer 186-0091 demountable cell that had KBr windows. Because TDDA first turns yellow and then darkens as oxidation proceeds, the appropriate specimen thickness was difficult to gauge. Consequently, several runs were required with spacers ranging from 0.025 to 0.175 mm between the KBr windows in the cell before satisfactory results were obtained without using a reference at medium scan times and in the normal slit program position. Fig. 8 shows a full IR spectrum of unheated Fluka TDDA (labeled as A) along with the major changes in the spectrum that can be accounted for by thermo-oxidative degradation in air (labeled as B) or 100% O_2 (labeled as C).

TDDA heated in air starts showing an extra peak in the spectrum at about 1680 cm^{-1} which increases in size for TDDA heated in O_2. This peak is probably due to the presence of a carbonyl group $>C=O$, possibly of an amide whose bands generally appear between 1690 and 1630 cm^{-1} [20,21]. Another extra peak at

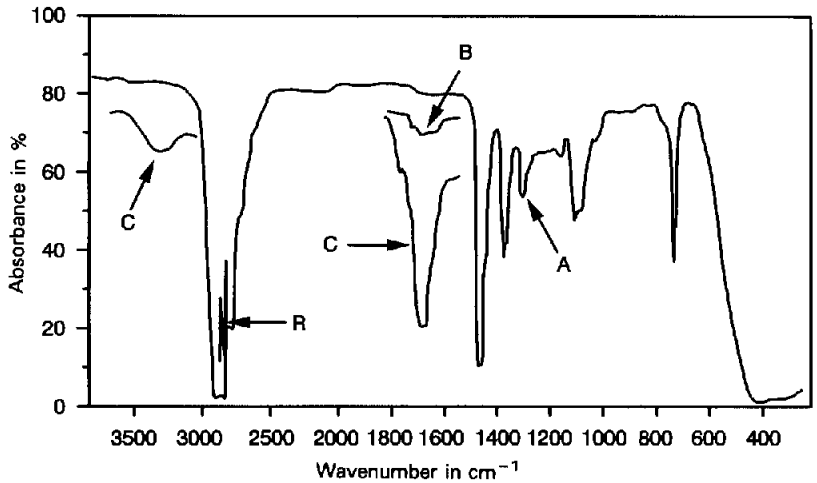

Fig. 8. Infrared spectra of Fluka TDDA: A, unheated; B, heated at 200°C for 60 min in air; C, heated at 200°C for 60 min in 100% O_2; R, reference marker of a polystyrene standard at 2851 cm^{-1} from which all peaks were adjusted accordingly.

3234 cm^{-1} is only apparent in TDDA which is heated in O_2. This peak is due to either N–H or O–H bonds [22]. The remaining peaks are due to the various stretching and bending vibrations present in all TDDA samples, unheated and heated. These other peaks are typical of tertiary amines [20] and occur at: 732 cm^{-1}, a doublet at 1084 cm^{-1} and 1109 cm^{-1}, 1309 cm^{-1}, a doublet at 1374 cm^{-1} and 1385 cm^{-1}, 1474 cm^{-1}, and a wide band at 2834 cm^{-1} to 2934 cm^{-1} with a side band of this wider band at 2793 cm^{-1}.

4.4. The proposed oxidative degradation mechanism

From the combined knowledge of the TGA, NMR, and IR experiments, the following oxidative degradation mechanism is proposed. The NMR spectra provide proof that the oxidative reaction is occurring at the α-carbon due to the decrease in the number of hydrogen atoms present at that carbon. The appearance of a wide band in the IR spectra that corresponds to carbonyl groups and the fact that the reaction is probably occurring at the α-carbon suggests that amides may be forming as a product of the oxidative degradation.

The degradation product being lost in the thermograms may be determined with some assurance, postulating the following reaction

$$2C_{36}H_{75}N + O_2 \xrightarrow{\Delta H} 2C_{24}H_{49}ON + 2C_{12}H_{26}$$

or

$$\text{TDDA} + \text{oxygen} \longrightarrow \text{didodecylamide} + \text{dodecane}$$

This reaction suggests that one of the side chains is being cleaved off becoming dodecane (see Fig. 2), and a secondary amide (didodecylamide) is being formed. Supporting evidence can be found from the thermograms shown in Figs. 3 and 4. When degradation occurs in air or 100% O_2, approximately 60–80% of the initial mass of the sample remains just prior to ignition. Because the ignition temperatures are well above the boiling point of dodecane (216.3°C at 1 atm), dodecane is probably being formed and boiled off. Although the physical properties or spectra of the proposed secondary amide, didodecylamide, could not be found in the literature, the amount of mass that remains corresponds to the weight percent of this amide, once the high-order alkane has boiled off. Consequently, the thermo-oxidative degradation of the ionophore, TDDA, leads to a failure of the electrode.

5. Conclusions

The TDDAs of four commercial producers undergo thermo-oxidative degradation with or without four different antioxidants being present. The effects of aging can be accelerated, when TDDA is conditioned in air (80% N_2, 20% O_2) or in 100% O_2 atmospheres for various times.

The activation energy for TDDA degraded in air ranges from 16 to 21 kcal mol^{-1}.

From a combination of TGA, NMR, and IR analyses, a mechanism is proposed in which one of the TDDA side chains is cleaved off and a secondary amide is formed.

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