Electrochimica Acta 205 (2016) 207–214

Contents lists available at ScienceDirect

Electrochimica Acta

journal homepage: www.elsevier.com/locate/electacta

The Effect of Ring-Size on the Anodic Oxidation of 'Cyclic Amides' in Methanol

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ARTICLE INFO

Article history:
Received 10 January 2016
Received in revised form 12 April 2016
Accepted 14 April 2016
Available online 3 May 2016

Keywords:
N-acyl, α-azacycloalkenes
N-acyl, α-methoxyazacycloalkanes
N-acyl, α-methoxy, α′-azacycloalkenes
N-acyl, α,α′-dimethoxyazacycloalkanes

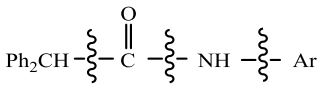
ABSTRACT

The anodic oxidation of three 'cyclic amides' of type N-acylazacycloalkanes [5- (**I**), 6- (**II**) and 7-membered (**III**) rings] has been studied in methanol under constant current electrolysis, at C anodes and in the presence of various supporting electrolytes, and different concentrations of substrates. Four major products were formed in good yields by all three substrates, namely N-acyl, α-azacycloalkenes, N-acyl, α-methoxyazacycloalkanes, N-acyl, α-methoxy, α'-azacycloalkenes and N-acyl, α,α′-dimethoxyazacycloalkanes. The relative ratios among products and selectivity were found to be highly dependent on the nature of the electrolyte used, and to a lesser extent on substrate concentration. In terms of ring-size effect it was found that the rate of oxidation and current efficiency (yield) was in the order: **I** > **II** > **III**. Also the latter two behaved similarly (but different from **I**) when various supporting electrolytes were used.

1. Introduction

It is well known [1–3] that anodic oxidation of amides involving hydrogen atom(s) at the α-position to 'N' affords the respective α-hydroxy, -alkoxy or -carboxy derivatives in the presence of nucleophiles such as water, alcohol or carboxylic acid, respectively:

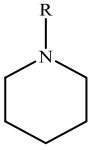
However, recently it was found [4] that when amides lack any hydrogen atom at the α-position to 'N', like in the case of $Ph_2CHCONHAr$, the anodic process leads to various types of bond cleavages (C-CO; CO-N and N-Ar), depending on the nature of the substituent attached to the aryl group:



The synthetic importance of anodic oxidation of amides has been well documented and was described in various recent publications [5–7].

Previously we studied [8] the effects of charge density, electricity consumption, and electrolytes on the anodic oxidation of N-acylazacycloalkanes (mainly, N-acylazacyclohexane) in methanol. The outcome showed a remarkable supporting electrolyte effect on both yields and selectivity, among other investigated parameters. Four major products were formed in 65-90% (combined yields): α-methoxy- and α,α'-dimethoxy cyclic amides, as well as two cyclic eneamides, a non-substituted one and α-methoxy, α'-cyclic eneamide. Their relative ratio was found to be highly dependent on the nature of the electrolyte used, electricity consumption, current density and the electrolysis technique used (CPE vs. CCE).

More recently we studied [9] the effects of anode material, supporting electrolyte and R group (involving both carbonyl and sulfone moieties) on the anodic oxidation of N-substituted piperidines, in methanol:



[R = CHO, COMe, COOMe, COPh, $COCF_3$, SO_2Me, SO_2Ph, SO_2(*p*-tolyl)]

It was found that the anodic process involves mainly mono- and dimethoxylation at the α and α'-positions to 'N', generating the corresponding mono- and dimethoxy cyclic amides. Methoxylation on graphite with Et_4NOTs favored the formation of

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http://dx.doi.org/10.1016/j.electacta.2016.04.074
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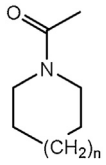
α-monomethoxy products, whereas in the presence of Et_4NBF_4, the α,α'-dimethoxy derivatives become predominant in selected cases.

The present work expands the previous one [8] by being focusing on the effect of ring-size on the outcome of constant current electrolysis (in an undivided cell) of N-acylazacycloalkanes (hereafter 'cyclic amides' involving five-, six- and seven-membered rings) (Scheme 1), upon using different but selective supporting electrolytes, and substrates' concentrations.



[**I** (n = 0); **II** (n = 1); **III** (n = 2)]

Scheme 1. N-acyl, azacycloalkanes.

2. Experimental

2.1. Materials

Reagents, electrolytes and solvents (analytical grade) were supplied by Aldrich (Bu_4NBF_4, ≥ 99%, $LiClO_4$, ≥ 99%), Fluka (Bu_4NClO_4, ≥ 99%), Acros Organics (pyrrolidine, piperidine and azepine, all ≥99%) and BioLab (methanol, AR, 99.8%, <0.05% water w/w; acetonitrile, AR, 99.8%, <0.1% water). All solvents, reagents and electrolytes were used without further purification unless otherwise indicated.

2.2. General Methods

^{1}H NMR (400 MHz, 500 MHz) and ^{13}C NMR (100 MHz, 125 MHz) spectra were recorded on Bruker DPX_{400} and DPX_{500} instruments in $CDCl_3$ or $(CD_3)_2CO$ solvents.

Mass spectral data were obtained using an Agilent 6850 GC equipped with an Agilent 5973 MSD and an Agilent HP5-MS column. A Bruker Daltonics Ion Trap MS Esquire 3000 Plus equipped with APCI (atmospheric pressure chemical ionization) analyzed by Xcalibur software (Thermo Fisher Scientific), hellium gas flow of 30 mL min^{-1}and column temperature from 160 to 280 °C were employed.

High resolution mass spectra analysis (HRMS) was obtained on LTQ XL Orbitrap ETD by direct injection electrospray ionization (ESI) sources using the time-flight mass spectrometry.

IR spectra were recorded by using FT-IR spectrometer with transparent NaCl plates.

Analytical thin layer chromatography (TLC) was performed on of aluminum sheets with aluminum oxide 60 F_{254} and silica gel 60 F_{254}. Retention time (R_f) values were determined by using a general purpose stain of cerium molybdate [containing a mixture of $Ce(NH_4)_2(NO_3)_6$ – $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$) in H_2SO_4]. Preparative TLC was carried out by using 20 × 20 cm of glass plates (or columns) coated with either silica gel 60 F_{254}. Evaporation of solvents was performed at reduced pressure using a rotary evaporator.

2.3. Cyclic voltammetry

Cyclic voltammetry measurements were performed by CHI 730C Electrochemical Workstation (CH Instruments, Inc.) in a conventional cylindrical three-electrode cell equipped with a glassy carbon disk (ϕ = 3 mm) as the working electrode; a Pt cylindrical gauze or spiral wire as the auxiliary and Ag/AgCl (NaCl, 3 M) as the reference electrode. Typically the cell contained 1 mM of substrate in 10 ml of analytical grade acetonitrile and 0.1 M electrolyte. Measurements were recorded under air at scan rates in the range of 50–300 mV s^{-1}.

2.4. Constant current electrolysis

Preparative anodic oxidation was performed at constant currents using a PAR Potentiostat/Galvanostat Model 273A, and a beaker-type undivided cell equipped with a carbon rod as anode (immersed area of ~5 cm^2) and platinum foil (~5 cm^2) as cathode. In a typical electrolysis N-azacycloalkane (1 mmol) was dissolved in methanol (25 mL) containing 0.1 M supporting electrolytes. Electrolysis took place at room temperature with current density of 20 mA cm^{-2} and was terminated after a consumption of 14F (Tables 1–4, *vide infra*). The final reaction mixture was concentrated by rotary evaporator followed by addition of a mixture of ethyl acetate and hexane for precipitating the supporting electrolyte. After filtering the liquid phase through a piece of cotton the solvents were removed in *vacuo*, and the residue was weighed and dissolved in 2 ml of $CDCl_3$. Then 0.5 ml of this solution and a weighted amount (~3–5 mg) of 1,4-dichlorobenzene (δ = 7.21) were added to the NMR tube for estimating individual yields of products on the basis of their integration relative to that of the internal standard. Since some of the products undergo facile hydrolysis/decomposition it is suggested that the analysis will be done immediately after terminating the electrolysis. Notably, this procedure of analyzing a mixture of products successfully is based on prior separation and characterization of the individual products. Their separation was carried out either by column chromatography or coated glass plates, using silica gel and different mixtures of ethyl acetate (20-50%)-hexane as eluent.

2.5. Preparation of N-acyl "cyclic amides" (*I–III*)

The N-acylazacycloalkanes were prepared according to our own procedure by reacting the corresponding cyclic amines (commercially available) with acetic anhydride. In a typical experiment, 36 mmoles of a cyclic amine (pyrrolidine, piperidine or azepine) were introduced into a 100 mL round-bottom flask. The flask (without a solvent) was cooled by ice for about 30 min. Then 40 mmoles (3.8 mL) of acetic anhydride were added dropwise by a separatory funnel to the amine while stirring by a magnetic stirrer. Then 25 mL of water were added to the mixture and the desired product was extracted into 3 × 25 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The resulting yellowish liquid was weighed and verified by GC-MS and NMR. The isolated yields of the 'cyclic amides' was around 32 mmoles (90%).

2.6. Characterization of products

^{1}H and ^{13}C NMR spectra were carried out in $CDCl_3$, and recorded at 400 MHz, δ in ppm. Most products listed below are known and some of their spectral data were published in Refs [10–12].

2.6.1. N-acetyl, 2-pyrroline (from *I*)

Fully characterized in Ref. [10].

2.6.2. N-acetyl, 2-methoxypyrrolidine [11] (from *I*)

^{1}H NMR, δ: 1.74-2.07 (m, 4H, $-CH_2CH_2$), 1.93 and 1.98 (2s, 3H, $NCOCH_3$), 3.26, 3.28 and 3.29 (3s, 3H, OCH_3), 3.1-3.5 (m, 2H, NCH_2), 4.80 and 5.30 (2m, 1H, (OCHN); ^{13}C NMR, δ: 13.58, 21.90, 22.63, 28.51, 52.32 (OCH_3), 54.40 (OCH_3), 82.23 (OCHN), 86.81 (OCHN), 173.16 (CO), 173.77 (CO); MS: m/z: 143 (M^+); 128, 113, 100, 86, 70

(100%), 58, 43; HRMS (ESI): calculated for $C_7H_{13}NO_2$ + H: 144.1019; found: 144.1015.

*2.6.3. N-acetyl, 2-methoxy, 4-pyrroline (from **I**)*

^{1}H NMR, δ: 2.15 (2s, 3H, $COCH_3$), 3.31 (s, 3H, OCH_3), 2.60 and 2.75 (2m, 2H, CH_2N), 5.60 (1m, 1H, $-CH_2-CH=$), 6.25 and 6.39 (2m, 1H, N-CH=); ^{13}C NMR, δ: 22.93 (CH_3), 39.08 (=CH-CH_2-CHN-), 56.71 (OCH_3), 84.76 (CH_2-CH-N), 112.39, 113.30 (N-CH=CH), 119.33 (=CH-CH_2), 170.91 (CO); (MS: m/z: 155 (M^+); 142, 126, 113, 100, 84 (100%), 68, 43; HRMS (ESI): calculated for $C_7H_{11}NO_2$ + H: 142.0863; found: 142.0858. Noteworthy, this product is unstable undergoes a facile decomposition (various unidentified products, including ring-opening ones) on standing or after preparative TLC (silica gel) separation (ethyl acetate (70%)-hexane (30%).

*2.6.4. N-acetyl, 2,5-dimethoxypyrrolidine (a mixture of two stereoisomers, ~1:1) [11] (from **I**)*

^{1}H NMR, δ: 1.74-2.07 (m, 4H, $-CH_2CH_2$), 2.04 and 2.07 (2s, 3H, $NCOCH_3$), 3.17, 3.19, 3.27 and 3.28 (4s, 6H, $2OCH_3$), 4.62-5.34 (6m, 2H, 2OCHN), ^{13}C NMR, δ: 14.40, 21.66, 28.05, 54.27 (OCH_3), 60.34 (OCH_3), 86.84 (OCHN), 89.73 (OCHN), 170.73, 171.99; MS: m/z: 173 (M^+); 158, 142, 126, 111, 100 (100%), 84, 68, 60, 43; HRMS (ESI): calculated for $C_8H_{15}NO_3$ + H: 174.1119; found: 174.1125. Calculated for $C_8H_{15}NO_3$ + Na: 196.0944; found: 196.1020.

*2.6.5. N-acetyl-1,2,3,4-tetrahydropyridine (a mixture of two conformers) [12] (from **II**)*

^{1}H NMR, δ: 2.07-2.20 (m, 4H, $-CH_2CH_2CH$-), 2.14 and 2.15 (2s, 3H, $NCOCH_3$), 4.95 (m, 1H, NCH_2), 3.21 and 3.23 (2s, 3H, OCH_3), 2.71, 3.51, 3.72, 4.41 and 5.33, (5m, 2H, CH_2N), 4.95 (-CH-CHN), 6.46-6.57 and 7.18 (3m, 1H, NCH-); ^{13}C NMR, δ: 20.57, 20.63, 20.91, 107.32 (CH-CHN), 125.01 (NCH); MS: m/z: 125 (M^+); 110, 96, 82 (100%), 68, 60, 54, 43; HRMS (ESI): calculated for $C_7H_{11}NO$ + H: 126.0913; found: 126.0908.

*2.6.6. N-acetyl, 2-methoxypiperidine (a mixture of two stereoisomers) [11] (from **II**)*

^{1}H NMR, δ: 1.25-2.26 (m, 6H, $-CH_2CH_2CH_2$-), 2.11 and 214 (2s, 3H, $COCH_3$), 3.21 and 3.23 (2s, 3H, OCH_3), 2.71, 3.51, 3.72, 4.41 and 5.33, (5m, 2H, CH_2N), 4.95 and 5.78 (2m, 1H, OCHN); (MS: m/z: 157 (M^+); 142, 126, 113, 100, 84 (100%), 68, 43; HRMS (ESI): calculated for $C_8H_{15}NO_2$ + H: 158.1176; found: 158.1173.

*2.6.7. N-acetyl, 6-methoxy, 1,2,3,4-tetrahydropyridine (a mixture of two stereoisomers) [11] (from **II**)*

IR (liquid): 2935, 2850, 1740 (C=C-N), 1645 (O=C-N), 1675 (O=C-N), 1415, 1390, 1320, 1100 cm^{-1}; ^{1}H NMR, δ: 1.54-2.27, (m, 4H, $-CH_2CH_2$-), 2.19 and 2.25 (2s, 3H, $NCOCH_3$), 3.36 and 3.37 (2s, 3H, OCH_3), 5.03-5.16 (2m, 1H, CH=CH-N), 5.84 (m, 1H, =CH-N), 6.45-6.48 (2m, 1H, NCH), ^{13}C NMR, δ: 16.90, 17.32, 21.43, 21.88, 25.31, 26.14, 54.51 (OCH_3), 56.14 (OCH_3), 82.70 (OCHN), 108.96 and 109.14 (CH=CHN), 121.77 and 123.40 (=CHN), 169.28 (CO); MS: m/z: 155 (M^+); 140, 123, 113, 98, 82 (100%), 68, 54, 43; HRMS (ESI): calculated for $C_8H_{13}NO_2$ + H: 156.1019; found: 156.1018; calculated for $C_8H_{13}NO_2$ + Na: 178.0838; found 178.0837.

*2.6.8. N-acetyl, 2,6-dimethoxypiperidine (a mixture of stereoisomers) [11] (from **II**)*

IR (liquid): 2965; 2850, 1640, 1420, 1200, 1100, 1050, 1000 cm^{-1}; ^{1}H NMR, δ: 1.25-2.08, (m, 6H, $-CH_2CH_2CH_2$-), 2.17, 2.18 and 2.24 (3s, 3H, $NCOCH_3$), 3.23-3.31 and 3.36 (4s, 6H, $2OCH_3$), 4.81, 4.94, 5.56 and 5.77 (4m, 2H, OCHN), ^{13}C NMR, δ: 11.11, 13.43, 18.91, 22.50, 25.25, 26.09, 29.25, 29.73, 30.22, 31.17, 36.53, 41.76, 54.42 (OCH_3), 55.17 (OCH_3), 55.59 (OCH_3), 56.73 (OCH_3), 79.20 (OCHN), 84.88 (OCHN), 172.61 (CO); MS: m/z: 185 (M^+); 172, 155, 145, 130, 114, 98, 85, 71, 58 (100%), 43.

*2.6.9. N-acetyl, 2,3,4,5-tetrahydroazepine (a mixture of two stereoisomers) [11] (from **III**)*

^{1}H NMR, δ: 1.61-2.25 (m, 6H, $CH_2CH_2CH_2$), 2.09 (1s, 3H, $COCH_3$), 3.66 and 3.73 (2m, 2H, $-N-CH_2$-), 5.22 (m, 1H, $-CH_2-CH$=), 6.38 and 6.75 (2m, 1H, −N-CH=); ^{13}C NMR, δ: 22.34 (CH_3), 26.74 (=CH-CH_2), 27.86 (CH_2-CH_2-CH_2), 31.87 (CH_2-CH-N), 45.92 (CH_2-CH-N), 119.86 (=CH-CH_2), 131.34 (N-CH=CH), 171.36 (CO); (MS: m/z: 139 (M^+); 124, 111, 97, 82 (100%), 68, 54, 43; HRMS (ESI): calculated for $C_8H_{13}NO$ + H: 140.1070; found: 140.1063.

*2.6.10. N-acetyl, 2-methoxyhexahydroazepine (a mixture of two stereoisomers) [11] (from **III**):*

IR (liquid): 2930; 2845, 1650, 1420, 1200, 1080, 930 cm^{-1}; ^{1}H NMR, δ: 1.17-2.24 (m, 8H, $-CH_2CH_2CH_2CH_2$-), 2.16 and 2.17 (2s, 3H, $NCOCH_3$), 3.20 and 3.22 (2s, 3H, OCH_3), 2.84, 3.19-3.25, 3.43 and 3.96 (4m, 2H, CH_2N), 4.88 and 5.74 (2m, 1H, OCH); ^{13}C NMR, δ: 21.53, 21.83, 21.99, 22.49, 26.69, 28.70, 29.32, 29.69, 33.95, 34.59, 39.45, 41.72, 54.10 (OCH_3), 55.26 (OCH_3), 82.35 (OCHN), 87.90 (OCHN), 172.20 (CO); MS: m/z: 171 (M^+); 156 (100%), 140, 128, 148, 114 (100%), 98, 82, 71, 43; HRMS (ESI): calculated for $C_9H_{17}NO_2$ + H: 172.1322; found: 172.1328; calculated for $C_7H_{17}NO_2$ + Na: 194.1152; found 194.1147.

Noteworthy, this product undergoes a facile hydrolysis to yield 6-acetamidohexanal [8].

*2.6.11. N-acetyl, 2-methoxy, 2,3,4,5-tetrahydroazepine (a mixture of two stereoisomers) [11] (from **III**)*

^{1}H NMR, δ: 1.61-2.25 (3m, 6H, $-CH_2CH_2CH_2$-), 2.15 (1s, 3H, $COCH_3$), 3.22 (1s, 3H, OCH_3), 5.49 (m, 1H, $-CH_2-CH=$), 5.90 (m, 1H, OCHN) and 6.05 and 6.39 (2m, 1H, N-CH=); ^{13}C NMR, δ: 18.83 (CH_2-CH_2-CH_2), 22.86 (CH_3), 27.73 (=CH-CH_2), 33.73 (CH_2-CH-N), 55.60 (OCH_3), 82.60 (CH_2-CH-N), 124.12 (=CH-CH_2), 125.44 (N-CH=CH), 171.26 (CO); MS: m/z: 169 (M^+); 154, 137, 126, 110, 98, 71, 56 (100%), 43; HRMS (ESI): calculated for $C_9H_{15}NO_2$ + H: 170.1176; found: 170.1172.

*2.6.12. N-acetyl, 2,7-dimethoxyhexahydroazepine (a mixture of two stereoisomers) [11] (from **III**)*

IR (liquid): 2940; 2850, 1650, 1420, 1370, 1200, 1140, 1100, 1070 cm^{-1}; ^{1}H NMR, δ: 1.11-2.15 (m, 8H, $-CH_2CH_2CH_2CH_2$-), 2.19, 2.25 (2s, 3H, $NCOCH_3$), 3.31, 3.32 and 3.36 (3s, 6H, $2OCH_3$), 4.55, 4.81 and 5.77 (3m, 2H, OCH), ^{13}C NMR, δ: 21.75, 22.84, 23.23, 23.37, 23.53, 26.02, 32.01, 33.12, 33.36, 33.79, 55.42 (OCH_3), 55.80 (OCH_3), 56.06 (OCH_3), 57.11 (OCH_3), 82.42 (OCHN), 85.63 (OCHN), 87.27 (OCHN), 90.12 (OCHN), 172.81 (CO), 173.35 (CO); MS: m/z: 201 (M^+); 186, 169, 144, 126, 102, 84, 71 (100%), 60, 43; HRMS (ESI): calculated for $C_{10}H_{19}NO_3$ + H: 202.1438; found: 202.1433; calculated for $C_{10}H_{19}NO_3$ + Na: 224.1257; found 224.1252.

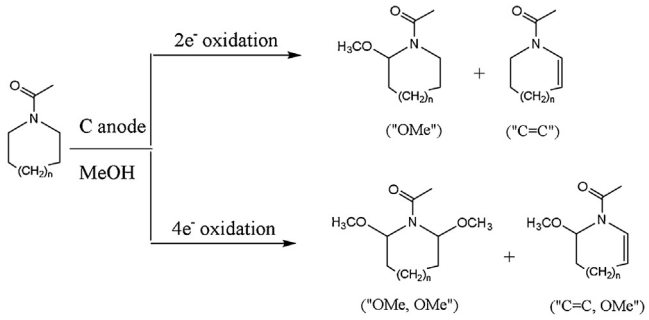
3. Results and Discussion

In this study we have adopted former experimental conditions that afforded “optimal” conditions in terms of yields of products and selectivity, as follows:

- The use of constant current technique in undivided cell (rather than CPE in a divided cell).
- Of the 5 anodes previously tested (carbon felt, graphite rod, Pt, glassy carbon and PbO_2) the C anode was chosen.
- Current density of 20 mA cm^{-2} was selected (from a studied range of 10 − 40 mA cm^{-2}).
- Electricity consumption of 14 F/mol of substrate were chosen (from a range of 5 to 14 F/mol).

The only variables in this work are the nature of selected supporting electrolytes used (n-Bu_4NClO_4, $LiClO_4$, KPF_6 and n-Bu_4NBF_4) and change in substrate concentration.

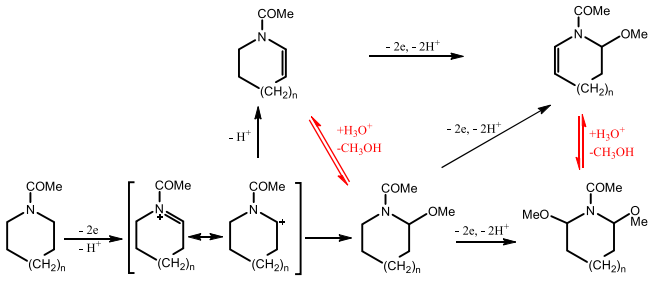
The type of products obtained are outlined in Scheme 2 and involved monomethoxylated ("OMe") and cyclic eneamides ("C=C") products due to 2e-oxidation, and dimethoxylated ("OMe, OMe") and methoxylated eneamides ("C=C, OMe") products due to 4e-oxidation.



Scheme 2. Type of products (with their designation, in parentheses).

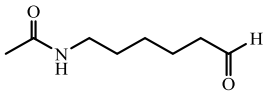
3.1. Mechanism

A plausible mechanistic scheme for the formation of 2e- and 4e-oxidation products is outlined in Scheme 3. It involves 2e-oxidation (actually stepwise) of the 'cyclic amide' and a loss of H^+ (commonly accepted for amides) to generate an iminium cation/carbocation that undergoes a nucleophilic attack by the solvent methanol to afford α-methoxylated products. The latter could undergo further 2e$^-$-oxidation to yield α,α'-dimethoxy derivatives. Scheme 3 also describes (top) the formation of two cyclic eneamides that could be generated from different precursors by various reactions. A comment added by a reviewer suggests that "formation of two or even four products in the course of electrolysis indicate presence of processes in solutions, containing different concentrations of a catalyst, probably water". Indeed, traces of water in the organic solvents, in hygroscopic supporting electrolytes and in the humid air atmosphere could play important role in determining the ratios between the two 2e-oxidation and the two 4e-oxidation products which are in equilibria (Scheme 3). Therefore, the actual ratios of these two couples should be sensitive to varying water content.



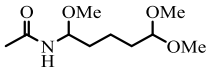
Scheme 3. A plausible mechanism for the formation of products from electrolysis of N-acylazacycloalkanes (n = 0, 1, 2) in methanol (some pathways could be reversible).

The mechanism outlined in Scheme 3 indicates that the source of H^+ stems from deprotonation following the anodic oxidation of the substrate. However it is noteworthy that this does not have to be the exclusive source of H^+ because it is well-known that certain anions, for example PF_6^- and BF_4^-, undergo solvolysis with methanol to generate HF acid (among other hydrolytic species such as, e.g., $[BF_3(OMe)]^-$ and $[BF_2(OMe)_2]^-$ [13]). Therefore, it is not surprising that under acidic conditions it is likely that both "OMe" and "OMe, OMe" products could undergo facile hydrolysis to generate the respective "C=C" and "C=C, OMe" products. Also notably that the relative instability of α-monomethoxy- and α,α'-dimethoxylated 'cyclic amides' in the presence of protons was demonstrated before in some cases by observing hydrolysis products such as, an aldehyde:



(from "OMe" of **III**, [8])

and a ketal derivative:



(from "OMe,OMe" of **II**, [9])

Finally it is noteworthy that the α-methoxy, α'-eneamide could also be formed directly from the α-methoxylated product (by further 2e-oxidation) because the E_p(ox) of the latter is *ca.* 0.6 V lower than that of the starting material. Also noteworthy is that in spite of a favorable inductive effect exerted by the monomethoxy carbocation intermediate generated from the α-methoxylated product, the α,α'-dimethoxy derivative is formed and not its isomer, the α,α-dimethoxy one, probably due to steric hindrance as well as an inductive effect exerted by the first methoxy group, causing the adjacent hydrogen to be less acidic.

3.2. Effect of supporting electrolyte

Table 1 describes product distribution resulting from anodic oxidation of substrates **I**–**III** in the presence of n-Bu_4NClO_4 as supporting electrolyte. All three substrates behave similarly,

Table 1
Product distribution (%) under 0.1 M n-Bu_4NClO_4.[a]

Ring size	Products			
	OMe	C=C	OMe, OMe	C=C, OMe
5 (**I**)	22	15	–	82
6 (**II**)	–	22	16	62
7 (**III**)	–	10	20	68

[a] [Substrate] = 1 mmol in 25 mL, in cylindrical (beaker-type) undivided cell; Constant current of 20 mA/cm^2 in MeOH; C rod anode; Yields of the only four products obtained are based on ^{1}H NMR using 1,4-dichlorobenzene as an internal standard; Electricity consumption in each case is 14F with no starting material left.

Table 2
Product distribution (%) under 0.1 M $LiClO_4$.[a]

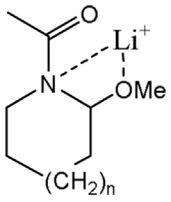
Ring size	Products			
	OMe	C=C	OMe, OMe	C=C, OMe
5 (**I**)	100	–	–	–
6 (**II**)	4	33	12	50
7 (**III**)	29	14	16	36

[a] Conditions as described in the footnote underneath Table 1.

affording the 4e-oxidation products in 78-88% yields in which the α-methoxy, α'-eneamides ("C=C, OMe") being the favorable product (62-82%) in all three cases. It is noteworthy that the fact that the "C=C, OMe" products prevail the dimethoxylated ones ("OMe, OMe") is not surprising since it is known that the latter are not very stable, especially in acidic media (see mechanistic Scheme 3).

Table 2 describes product distribution that resulted from anodic oxidation of substrates **I–III** in the presence of $LiClO_4$ as supporting electrolyte. Interestingly the results are not similar to those obtained in Table 1 although ClO_4^- anion was used in both cases. In this case the formation of 4e-oxidation products (that were the major ones previously) is inhibited or eliminated completely. For instance, substrate **I** affords the monomethoxylated product ("OMe") exclusively, and also **II** and **III** afford 2e-oxidation products in distinct amounts (37-43%). This behavior is quite surprising because one would expect that any kind of influence on products that result from *anodic* oxidation originates from changing the nature of the *anion* (not the cation!) of the electrolyte. Since a marked difference has been observed upon changing the cation from n-Bu_4N^+ (Table 1) to Li^+ (Table 2) obviously there must be a cationic (!) effect. A plausible hypothesis is demonstrated in Scheme 4 in which a 'naked' lithium cation, being less bulky than tetrabutylammonium cation, interacts with lone pairs of nitrogen and oxygen atoms in the "OMe" product, exerting a partial positive charge on them, causing further oxidation step to be more difficult. If such a phenomenon does exists then one would expect the oxidation peak potential of the monomethoxy ("OMe") product in the presence of $LiClO_4$ to be higher than that with n-Bu_4NClO_4. However, cyclic voltammetry measurements either in methanol or acetonitrile, using these two electrolytes, have not shown a distinct difference in the anodic peak potential of "OMe". Therefore, this hypothesis must be ruled out and instead, other factors (e.g., different adsorption capabilities between the supporting electrolytes and "OMe" product, different hygroscopicities between the two electrolytes, or steric effects) should be considered for affecting the outcome.

Steric effects could stem not only from product intermediates (e.g., "OMe") but also from different extent of solvation between the two cations of the electrolytes used. It is well documented that in general, for the series of alkali metal cations, the larger the cation the smaller is the hydrated radii (e.g., 3.82, 3.58 and 3.29A for Li^+, Na^+ and Cs^+, respectively) [14], or the solvated (methanol) radii (4.74, 4.16 and 3.88A for Li^+, K^+ and Cs^+, respectively [15]. Following this trend it would be reasonable to assume that the solvation of the larger n-Bu_4N^+ is less favorable than that of Li^+, causing the latter to be a bulky solvated cation. Indeed, molecular dynamics calculations [16] indicate that the first shell of Li^+ (examined for three solvents) has a well-defined order and consists of four solvent molecules ($[Li(MeOH)_4]^+$) with additional structure evident in the second solvation shell. In principle this kind of bulky solvated cation, if adsorbed at the anode surface preferentially over n-Bu_4N^+ (because it is enriched with lone-pairs and thus has greater electrostatic attraction), could certainly explain the difference between them, resulting in inhibiting the further oxidation of the "OMe" product in the presence of adsorbed $[Li(MeOH)_4]^+$ cations, generating more of the 2e-oxidation products.



Scheme 4. Plausible interactions between Li^+ and other sites of the monomethoxylated product ("OMe").

The other pronounced phenomenon observed in Table 2 is that **I** behaves quite differently from both **II** and **III**, yielding a single 2e-oxidation product exclusively. In terms of conformational differences, **I** is somewhat flatter than **II** and **III** and this could be a reason for the different outcome. This assumption is also supported by the different behavior of cyclopentanones compared to cyclohexanones which was also claimed to be of conformational origin, due to the known tendency of cyclopentanones to enolize less readily than cyclohexanones [17].

Upon replacing the perchlorate electrolytes with KPF_6 (Table 3) it appears that both types of eneamide products, namely "C=C" and "C=C, OMe", are still significant in the case of **I** and **III**, but **II** (for a puzzling reason) favors the formation of "OMe". Furthermore, when using n-Bu_4NBF_4 (Table 4), only substrate **I** continues to show a similar trend as before, whereas both substrates **II** and **III** form the respective "OMe" predominantly. It has been well-documented that the nature of the anion could dictate the type of the anodic products [18,19]. Therefore, a plausible assumption that could partially account for the different behavior is that BF_4^- anions adsorb at the anode surface more efficiently than those of PF_6^- and therefore, block more efficiently further oxidation of "OMe" to 4e-oxidation products.

Also noteworthy are some puzzling observations. For instance, with these two electrolytes only substrate **I** formed ~25% of unidentified products, a phenomenon that was not observed before with neither other electrolytes nor hardly with substrates **II** and **III**. Furthermore, **II** behaves differently from **I** and **III** (in the presence of KPF_6, Table 3) by affording the 2e-oxidation products predominantly, whereas in the presence of n-Bu_4NBF_4 (Table 4) substrate **I** becomes the exceptional while **II** and **III** behave similarly by producing "OMe" product predominantly.

Certainly the above results do not show consistency or obvious distinctive trend. One of the main reasons for this could stem from presence of different amounts of water contamination in the media that highly affect the results due to change in acidity and therefore, change in ratios between the two 2e-oxidation products and the two 4e-oxidation products which are in equilibria (see Scheme 3). Water contamination could originate from traces in the analytically grade solvents, different hygroscopicities of the supporting electrolytes, and humidity of the air atmosphere under which electrolyses were carried out. Notably, while the respective ratio between the 2e- and 4e-oxidation products are sensitive and vary upon experimental conditions (e.g., a change in humidity), the sum yields of the 2e- and 4e-oxidation products remain unaffected because each couple originates from the same intermediate.

In order to make the content of this section clearer and more focused, we have summarized it graphically and in more general terms (combined yields of 2e- *vs.* 4e-oxidation products) in an attempt to extract some useful information. It should be stated that in all figures we have focused on showing a *trend* rather than accuracy. Fig. 1 describes the dependence of formation of 4e- (A) and 2e–oxidation (B) products from **II** and **III** in the nature of the supporting electrolyte used. One can see that both 'cyclic amides' behave similarly (both afford quasi-parallel slopes) by following the *same* sequence of supporting electrolytes. In comparison, the five-membered ring (**I**) behaves somewhat differently because the trend of formation of products follows a *different* sequence of supporting electrolytes, as described in Fig. 2A (for 4e-oxidation) and 2B (for 2e-oxidation). However the common denominator is that in all cases $TBAClO_4$ promotes the formation of 4e-oxidation products whereas the 2e-oxidation products are favored by $TBABF_4$

in the case of **II** and **III**, and by $LiClO_4$ in the case of **I**, .Indeed there could be different variables that account for the different behavior between **I** and **II** and **III**, among them – e.g., conformation, steric, and ion-pairing effects.

3.3. Effect of substrate concentration

Since most of the 4e-oxidation products (80-90%) were obtained by employing n-Bu_4NClO_4 (Table 1), this electrolyte was chosen to be used for studying the effect of concentration of substrate on the outcome, after consuming fixed 5 F/mol (an arbitrary choice based on a theoretically required 4F/mol for a complete passage of 4e/molecule).

In order to facilitate the data outlined in Table 5, Figs. 3–5 have been constructed. Fig. 3 shows that most of the substrates were consumed when 1 mmol (1/25 = 0.04 M) was used, **I** being the fastest to undergo anodic oxidation. At the highest concentration studied (0.2 M), ~20% of unreacted substrate was left in each case. This means that **I** competes favorably with the oxidation of the solvent methanol, better than the other two substrates.

Fig. 4 describes the total products' yields as a function of substrate concentration. Accordingly it appears that the total percentages of products reach its maxima for substrates **I** and **II** already when 1 mmol (1/25 = 0.04 M) is used, whereas that of **III** is obtained at a higher concentration (0.2 M). Since it is likely to have a competition between the oxidation of the substrate and the solvent methanol, evidently the anodic process is most efficient with substrate **I** since no stating material is left at 0.04 M. This result also indicates that in terms of kinetics, **I** is consumed faster than **II** than **III**, in the order: **I** > **II** > **III**. For explaining this behavior, the only difference among the three substrates accounts for their ring conformations, **I** being somewhat flatter than **II** and **III**. This property could exert less steric hindrance when approaching the electrode surface.

Fig. 5 shows that for substrates **II** and **III** the formation of 2e-oxidation products is predominant (55-70%) upon employing

Table 3
Product distribution (%) under KPF_6.[a]

Ring size	Products				
	OMe	C=C	OMe, OMe	C=C, OMe	Unidentified products/Unreacted substrate
5 (**I**)	6	22	4	41	25/2
6 (**II**)	49	32	10	9	–
7 (**III**)	5	45	–	45	5/0

[a] Conditions as described in the footnote underneath Table 1.

Table 4
Product distribution (%) under n-Bu_4NBF_4.[a]

Ring size	Products				
	OMe	C=C	OMe, OMe	C=C, OMe	Unidentified products/Unreacted substrate
5 (**I**)	5	14	5	49	27/0
6 (**II**)	89	–	4	–	0/7
7 (**III**)	90	5	2	–	0/3

[a] Conditions as described in the footnote underneath Table 1.

Table 5
Results (%) of varied concentrations of substrates (at fixed 5 F/mol).

Ring size	Products											
	1 mmol (5F)[a]				3 mmol (15F)[a]				5 mmol (25F)[a]			
	s.m.[b]	2e	4e	(2e + 4e)[c]	s.m.[b]	2e	4e	(2e + 4e)[c]	s.m.[b]	2e	4e	(2e + 4e)[c]
5(**I**)	0	59	41	100	17	55	28	83	13	58	29	87
6(**II**)	15	60	25	85	24	71	5	76	16	72	12	84
7(**III**)	42	43	15	58	44	56	0	56	24	37	39	76

[a] Conditions as described in the footnote underneath Table 1 but with varied substrates' concentration and fixed electricity consumption; The numbers in parentheses indicate the passage of the total number of Faradays.
[b] Unreacted starting material (% determined by ^1H NMR using 1,4-dichlorobenzene as an internal standard).
[c] Sum of product yields (%) stemming from 2e- and 4e-oxidation (determined as in footnote 'b').

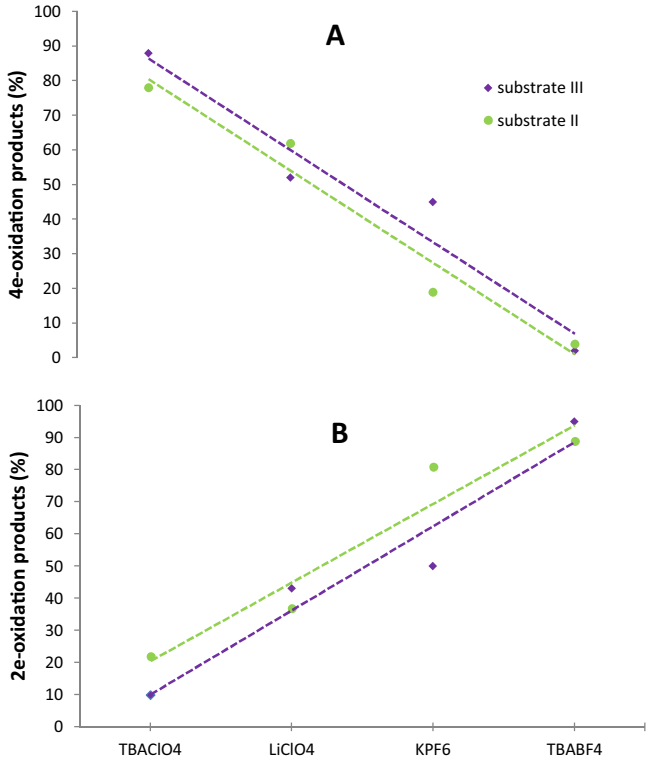


Fig. 1. Dependence of products formation (from **II** and **III**) in supporting electrolytes (conditions as described in the footnote underneath Table 1). Plots A and B refer to 4e- and 2e-oxidation products, respectively.

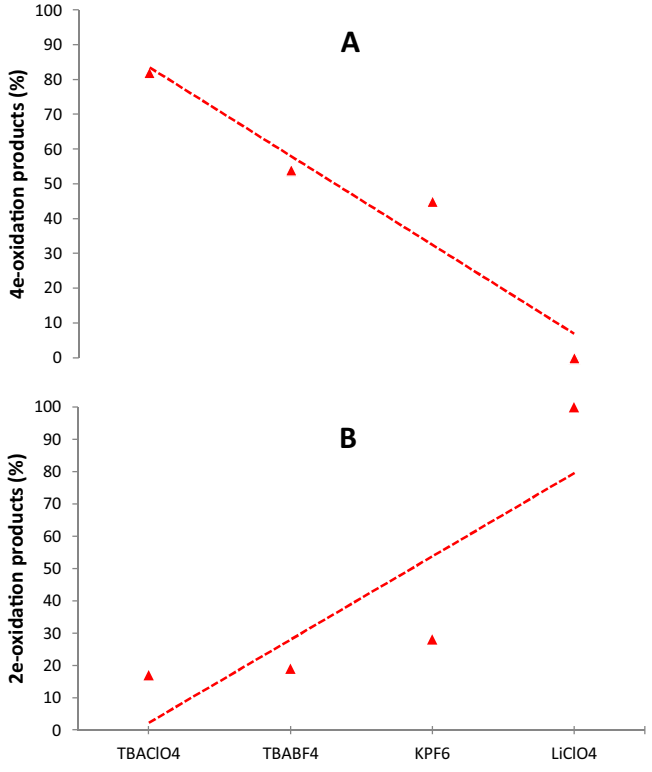


Fig. 2. Dependence of products formation (from **I**) in supporting electrolytes (conditions as described in the footnote underneath Table 1).

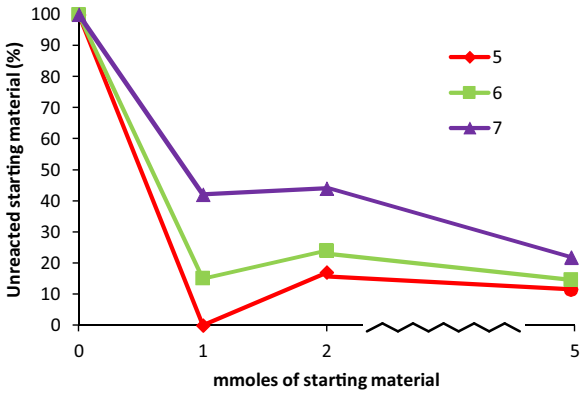


Fig. 3. Consumption of substrate with increasing its concentration (in 25 mL).

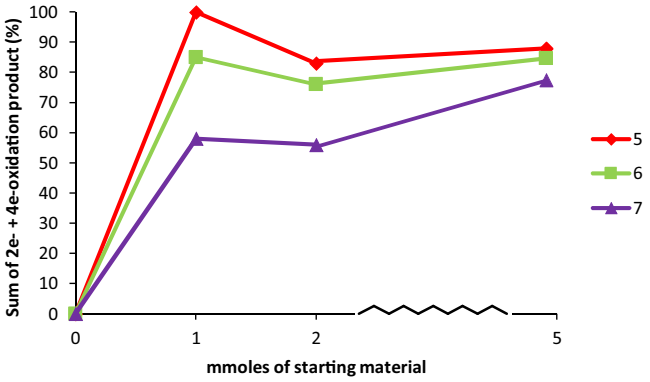


Fig. 4. Combined yields (%) of products as a function of amount of substrates (in 25 mL).

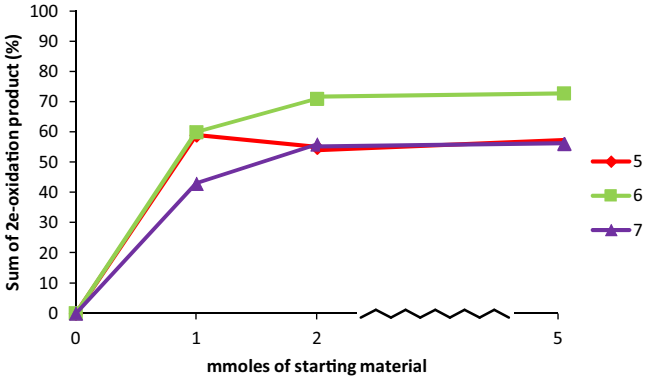


Fig. 5. Combined yields (%) of 2e-oxidation products as a function of amount of substrates (in 25 mL).

2 mmol of substrate with a little change at 5 mmols. Substrate **I** does it with 1 mmol, yielding 60% of products. Certainly considerably more electricity consumption (14F/mol) is required (at the expense of current yield) in order to change priority towards formation of 4e-oxidation products (as is demonstrated in Table 1).

4. Conclusions

The anodic oxidation of three 'cyclic amides' (**I** – **III**) have been studied by constant current electrolysis (in undivided cell) in methanol, at C anodes. Four major products were formed: two due to 2e-oxidation (α-methoxy cyclic amides ("OMe") and α-cyclic eneamides ("C=C")), and two due to 4e-oxidation products (α-methoxy, α'-cyclic eneamides ("C=C, OMe"), and α,α'-dimethoxy cyclic amides ("OMe, OMe"). The products' ratios and selectivity were found to be highly dependent on the nature of supporting electrolyte used, and to a little extent on substrate concentration. It is noteworthy that the amount of water contamination (from any source) affects the acidity and therefore, the ratio between both the 2e- and 4e-oxidation products that are in equilibrium in each case. With regard to ring-size effect it seems that **II** and **III** behaved similarly when different supporting electrolytes were used. However clearly, the oxidation of **I** is faster than the other two substrates and more efficient in terms of current yield (**I** > **II** > **III**). Finally, notably that both mono- and dimethoxy products from the anodic process are versatile synthons due to the reactivity of the methoxy group(s) adjacent to the nitrogen atom.

Acknowledgments

The authors are thankful to Dr. M. Karpasas for HRMS measurements and to Mrs E. Solomon for technical assistance.

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