One-Pot Anodic Conversion of Symmetrical Bisamides of Ethylene Diamine to Unsymmetrical *gem*-Bisamides of Methylene Diamine
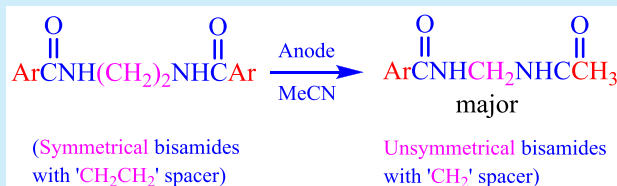
Tatiana Golub,[†] Gui-yuan Dou,[‡] Cheng-chu Zeng,[‡] and James Y. Becker[*,†]

[†]Department of Chemistry, Ben-Gurion University of the Negev, Beer Sheva 84105, Israel

[‡]Beijing Key Laboratory of Environmental and Viral Oncology, College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, China

S Supporting Information

ABSTRACT: Symmetrical bisamides of ethylene diamine of type $ArCONHCH_2CH_2NHCOAr$ undergo anodic C−C bond cleavage in acetonitrile−$LiClO_4$ under controlled-potential electrolysis. The electrogenerated carbocation intermediates react with the solvent acetonitrile to afford unsymmetrical *gem*-bisamides of type $ArCONHCH_2NHCOMe$ in a one-pot reaction. The yields of the latter products are moderate (up to 60%). Other minor products involve two symmetrical *gem*-bisamides of type $ArCONHCH_2NHCOAr$ and $MeCONHCH_2NHCOMe$ and fragmentation products (e.g., $ArCONHCHO$, $ArCONH_2$, and $ArCN$).

$$ArCNH(CH_2)_2NHCAr \xrightarrow[MeCN]{Anode} ArCNHCH_2NHCCH_3 \text{ (major)}$$

(Symmetrical bisamides with 'CH₂CH₂' spacer)

Unsymmetrical bisamides with 'CH₂' spacer)

The importance of amides and polyamides (from both carboxylic acid and amine derivatives) is well documented. They have been involved in many biologically active and pharmaceutical compounds.[1] For example, they have been used as antimicrobial and anti-inflammatory agents with antioxidant activities.[2] They were applied as ligands in the Ullmann coupling reactions[3] in synthetic chemistry. In addition, bisamides derived from various diamines and fatty acids have been widely used as lubricants.[4]

Preparation of *symmetrical* bisamides is widely known and most common via condensation reactions between aldehydes and primary amides, utilizing different homogeneous and heterogeneous catalysts,[5] from diamines, utilizing the corresponding carboxylic acids (or their chlorides),[6] and from nitriles.[7] Recently, it was shown that *symmetrical* methylene-bisamides could be prepared quite efficiently from aromatic nitriles (or amides) by use of DMSO both as methylene source and as oxidant in the presence of $NiCl_2$ as the catalyst:[7b]

$$ArCN + DMSO \xrightarrow[AcOH, 130\,°C]{NiCl_2} (ArCONH)_2CH_2$$
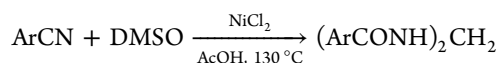
However, in contrast, preparation of *unsymmetrical* bisamides is rare, and only limited examples are available: for instance, in a complicated stepwise manner, first by preparing benzamide derivatives (e.g., by reacting 2-phenyloxazoles precursors with Br_2) followed by generating diacylimines in the presence of Lewis acid, and final addition of nitriles,[8] or by reacting monophenylamide of malonic acid with various aromatic amines (to yield products of potential HIV-1 integrase inhibitors).[9]

The present work describes a unique one-pot anodic transformation of *symmetrical* bisamides of type Ar-$CONHCH_2CH_2NHCOAr$ (derived from ethylenediamine)

Scheme 1. Type of Symmetrical Bisamides Studied

$$ArCNH(CH_2)_2NHCAr$$
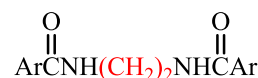
Ar = Ph (**1**), p-MeC_6H_4 (**2**), p-$MeOC_6H_4$ (**3**), p-ClC_6H_4 (**4**), p-BrC_6H_4 (**5**), p-$NO_2C_6H_4$ (**6**), p-CNC_6H_4 (**7**), m-CNC_6H_4 (**8**), m-FC_6H_4 (**9**), $PhCH_2$ (**10**), Cyclobutyl (**11**)

(Scheme 1) to *unsymmetrical gem*-bisamides of type $ArCONHCH_2NHCOCH_3$ (derived from methylene diamine) by controlled-potential electrolysis in acetonitrile.

Cyclic voltammetry data for the *symmetrical* bisamides described in Scheme 1 are shown in Table 1. Most of them show one irreversible anodic peak in the range of 2.13−2.33 V (vs Ag/AgCl) indicating a minor effect of the substituent attached to the aromatic ring. Some substrates (**2**, **4**, and **5**) show an additional irreversible oxidation wave around 2.50 V that could be attributed to the oxidation of ClO_4^-.

To the best of our knowledge, until our recent publication on anodic oxidation of α,ω-bisamides (derived from α,ω-diaminoalkanes)[10] under constant-current electrolysis in methanol, nothing has been known about their electrochemical properties. In that work, we investigated *symmetrical* bisamides involving two to four methylene groups as spacers (between the two amide functionalities). It was found that bisamides involving three and four methylene groups as spacers afforded mono- and dimethoxylation products at the α-position to the N atom. For example:
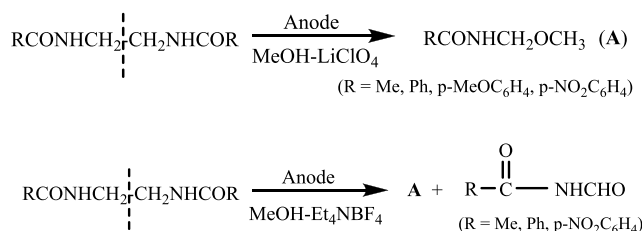
Table 1. Oxidation Potentials of Bisamides of Type ArCONHCH$_2$CH$_2$NHCOAr and RCONHCH$_2$CH$_2$NHCOR[a]

substrate	Ar (or R)	E_p (V)
1	Ph	2.13
2	p-Me	2.16
3	p-CH$_3$O	2.17
4	p-Cl	2.17
5	p-Br	2.12
6	p-NO$_2$	2.26
7	p-CN	2.32
8	m-CN	2.33
9	m-F	2.23
10	PhCH$_2$	2.33
11	cyclobutyl	2.10

[a]By cyclic voltammetry, in CH$_3$CN−0.1 M LiClO$_4$. Working electrode: glassy carbon (1.5 mm diameter disk). Auxiliary electrode: a Pt wire. Scan rate (V/s) = 0.05. Potentials are quoted versus Ag/AgCl reference electrode.

Scheme 2. Products Emerged from Bisamides Containing a CH$_2$CH$_2$ Group as a Spacer under Constant-Current Electrolysis in Methanol
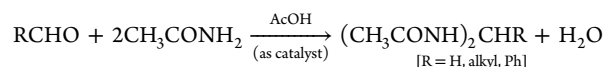
$$\text{RCONHCH}_2 | \text{CH}_2\text{NHCOR} \xrightarrow[\text{MeOH-LiClO}_4]{\text{Anode}} \text{RCONHCH}_2\text{OCH}_3 \quad (\textbf{A})$$
(R = Me, Ph, p-MeOC$_6$H$_4$, p-NO$_2$C$_6$H$_4$)

$$\text{RCONHCH}_2 | \text{CH}_2\text{NHCOR} \xrightarrow[\text{MeOH-Et}_4\text{NBF}_4]{\text{Anode}} \textbf{A} + \underset{\text{(R = Me, Ph, p-NO}_2\text{C}_6\text{H}_4)}{R-\overset{\overset{\displaystyle O}{\|}}{C}-\text{NHCHO}}$$

Scheme 3. Products Obtained from Anodic Oxidation of 1 under CPE

PhCONHCH$_2$NHCOMe (**1A**) – (major)
PhCONHCH$_2$NHCOPh (**1B**);
MeCONHCH$_2$NHCOMe (**1C**);
PhCONHCHO (**1D**).

$$\underset{\substack{(n = 3, 4)}}{\underset{\text{PhCNH(CH}_2)_n\text{NHCPh}}{\overset{\overset{\displaystyle O}{\|}\qquad\overset{\displaystyle O}{\|}}{}}} \xrightarrow[\text{MeOH}]{\text{Anode}} \begin{array}{c} \overset{\displaystyle OCH_3}{|} \\ \text{PhCONHCHCH}_2\text{CH}_2\text{NHCOPh} \\ + \\ \overset{\displaystyle OCH_3}{|} \\ \text{PhCONHCHCH}_2\text{CHNHCOPh} \\ \underset{\displaystyle OCH_3}{|} \end{array}$$
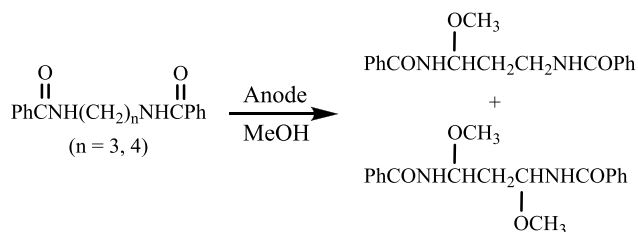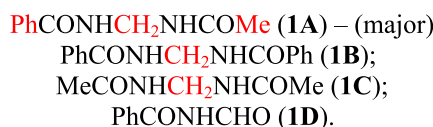
However, when the spacer contained only two methylenes, the anodic process led mostly to CH$_2$−CH$_2$ bond cleavage to afford fragmentation products of type RCONHCH$_2$OCH$_3$ and RCONHCHO (Scheme 2), depending on the nature of the supporting electrolyte used, as demonstrated in Scheme 2.

The present work describes the initial outcome from anodic oxidation of PhCONH(CH$_2$)$_2$NHCOPh (**1**) as a model of *symmetrical* bisamide under controlled-potential electrolysis (CPE) in acetonitrile. This unique anodic process was investigated at different anodes and in the presence of various electrolytes (Table 2). The types of products obtained are listed in Scheme 3:

It appears that under all experimental conditions studied the major product (**1A**) stems from a C−C bond cleavage at the spacer, yielding a carbocation (PhCONHCH$_2^+$) that undergoes a Ritter-type reaction with acetonitrile, in addition to formation of other products (vide infra, Scheme 4). Eventually, the major products obtained are *unsymmetrical* bisamides. Their best yields (~50%, without any further optimization attempts) were achieved at a C (rod or felt) anode and in the presence of LiClO$_4$. In addition, *symmetrical gem*-bisamides of type RCONHCH$_2$NHCOR (R = Ph, CH$_3$) were generated as minor products, among other types of minor products stemming from C−N bond splitting (in PhCONHCHO and PhCONH$_2$) and C−C (in PhCOOH). It is noteworthy that the first synthesis of *symmetrical gem*-bisamides was achieved via a condensation reaction between aldehydes and acetamide in 1933 by Noyes:[11]

$$\text{RCHO} + 2\text{CH}_3\text{CONH}_2 \xrightarrow[\text{(as catalyst)}]{\text{AcOH}} (\text{CH}_3\text{CONH})_2\text{CHR} + \text{H}_2\text{O}$$
$$[\text{R = H, alkyl, Ph}]$$

Following the results obtained for the model bisamide **1**, all other bisamides were oxidized in acetonitrile−0.1 M LiClO$_4$ at a C rod anode in a divided cell by CPE. The outcome is described in Table 3 (no attempt has been made to optimize yields). Again, in most cases the corresponding *unsymmetrical*

Table 2. Effect of Anode Material and Other Parameters on the Anodic Oxidation of PhCONH(CH$_2$)$_2$NHCOPh (1) as a Model Substrate by CPE in Acetonitrile[a]

1 (mmol)	Q (F/mol)	electrolyte/anode	1A	1B	1C	1D	PhCONH$_2$ + PhCN	PhCOOH	unreacted substrate
							products[b]		
1	2.7	Et$_4$NBF$_4$/C felt	41	16	2	11	5	7	8
1	4	Et$_4$NBF$_4$/C felt	16	3	2	19	8	30	22
1	1.8	LiClO$_4$/C rod	48	13	2	8	5	2	22
1[c]	2.5	LiClO$_4$/Pt plate	30	5	2	15	5	20	11
1	3	LiClO$_4$/C felt	50	9	19	2	7	5	8
1	2	LiClO$_4$/C felt	40	7	5	10	7	16	15
2	3	LiClO$_4$/C felt	39	5	7	9	14	15	11
2	4	LiClO$_4$/C rod	50	1	13	5	8	2	21

[a]CPE was carried out at rt in a divided cell at a C (rod or felt) anode; stainless steel as the cathode; and Ag wire as reference electrode. The anolyte contained 1−2 mmol of substrate in 35 mL of acetonitrile−0.1 M electrolyte. [b]Products: PhCONHCH$_2$NHCOMe (**1A**); PhCONHCH$_2$NHCOPh (**1B**); MeCONHCH$_2$NHCOMe (**1C**); and PhCONHCHO (**1D**). Yields are based on integration of signals in the ^{1}H NMR spectra and compared with benzoquinone as a standard internal standard in the tube. [c]In this experiment, the aldehyde PhCONHCH$_2$CHO was obtained in 12% yield.
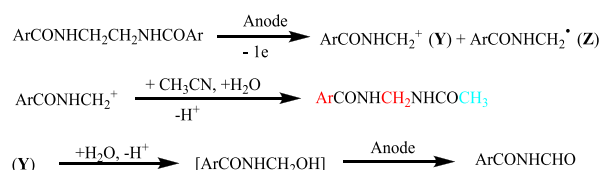
Table 3. Results of Anodic Oxidation of *Symmetrical* Bisamides (1−11) in Acetonitrile by CPE[a]

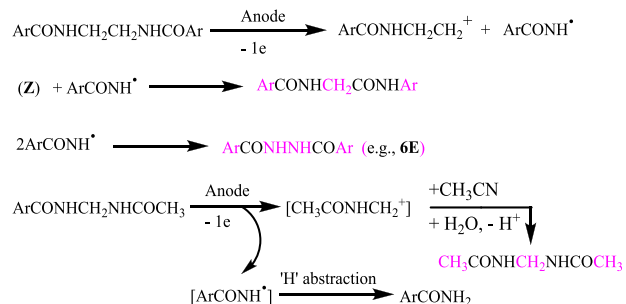| substrate	applied potential[c] (V)	F/mol	products[b]					
			A	B	1C	ArCONH$_2$	ArCN	unreacted substrate
1	1.95	2	46	12	4	8	9	21
2	2.0	3.5	60	3		17	15	5
3	2.0	5			24	4	17	55
4	2.0	3	51	10		19	17	3
5	2.1	4	46			16	32	6
6[d]	2.1	4	40	20	5	10	15	5
7	2.1	4	31	5	18	3	40	3
8	2.05	4	30	8	4	17	25	16
9	2.15	4	37	6		8	44	2
10 (Ar = PhCH$_2$)	2.25	4				16	27	57
11 (Ar = cyclobutyl)	2.0	4			45	15	13	27

[a]In a divided cell containing 1 mmol of substrate in 35 mL of anolyte 0.1 M LiClO$_4$. Cell temperature was maintained at 40 °C by water bath to allow solubility of all substrates. Oxidation at the peak potential on a C rod anode; SS cathode and Ag wire as reference electrode. [b]Yields are based on ^{1}H NMR integration compared with benzoquinone as internal standard. [c]Slightly more positive than the peak potential (vs Ag wire quasi-reference electrode). [d]An additional known[12] product, a hydrazine derivative, (p-NO$_2$C$_6$H$_4$CONH)$_2$ (**6E**), was isolated in 5% yield. Trace amounts of the corresponding hydrazines were also detected from electrolysis of substrates **4**, **8**, and **9**.

Scheme 4. Plausible Mechanisms for the Formation of *Symmetrical* and *Unsymmetrical gem*-Bisamides (and Other Products As Outlined in Tables 2 and 3)

Plausible formation of *unsymmetrical gem*-bisamides:

$$ArCONHCH_2CH_2NHCOAr \xrightarrow[-1e]{Anode} ArCONHCH_2^+ (Y) + ArCONHCH_2^\bullet (Z)$$

$$ArCONHCH_2^+ \xrightarrow[-H^+]{+ CH_3CN, +H_2O} ArCONHCH_2NHCOCH_3$$

$$(Y) \xrightarrow{+H_2O, -H^+} [ArCONHCH_2OH] \xrightarrow{Anode} ArCONHCHO$$

Plausible formation of *symmetrical gem*-bisamides:

$$ArCONHCH_2CH_2NHCOAr \xrightarrow[-1e]{Anode} ArCONHCH_2CH_2^+ + ArCONH^\bullet$$

$$(Z) + ArCONH^\bullet \longrightarrow ArCONHCH_2CONHAr$$

$$2ArCONH^\bullet \longrightarrow ArCONHNHCOAr \ (e.g., \textbf{6E})$$

$$ArCONHCH_2NHCOCH_3 \xrightarrow[-1e]{Anode} [CH_3CONHCH_2^+] \xrightarrow[+ H_2O, -H^+]{+CH_3CN} CH_3CONHCH_2NHCOCH_3$$

$$[ArCONH^\bullet] \xrightarrow{'H' \ abstraction} ArCONH_2$$

Scheme 5. Electrochemical Formation of Aromatic Nitriles at the Cathode

$$ArCONH_2 \longrightarrow ArCONHLi \longrightarrow ArC(OLi)=NH \longrightarrow ArCN + LiOH$$
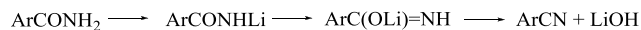
gem-bisamides were formed in moderate yields (up to 60%, for **2**). With electron-withdrawing substituents (NO$_2$, CN, and F) the yields were slightly lower (30−40%). However, when the amides involved an alkyl group (such as benzyl or cyclobutyl) instead of an aromatic one, no unsymmetrical bisamides were generated. Instead, the major products obtained were RCONH$_2$, RCN, and the symmetrical *gem*-bisacetamide **1C**, MeCONHCH$_2$NHCOMe, leaving a considerable amount of unreacted starting material.

Scheme 4 describes suggested mechanisms for the formation of *unsymmetrical* and *symmetrical gem*-bisamides (and other byproducts) obtained by CPE of symmetrical aromatic bisamides **1−9**. It seems that the bond cleavage at the CH$_2$−CH$_2$ bond is preferred by aromatic bisamides, resulting in generation of a stable aroyliminium ion intermediate. The latter leads to *unsymmetrical gem*-bisamides primarily. However, the reason that aliphatic bisamides (**10** and **11**) do not afford the corresponding *unsymmetrical gem*-bisamides is still unclear, and certainly more work has to be done to clarify this point. Noticeably, whereas bisamide **10** undergoes NH−CH$_2$ bond cleavage preferentially, substrate **11** undergoes CH$_2$−CH$_2$ bond cleavage but affords *symmetrical gem*-bisacetamide **1C** as the major product. However, in this case, one cannot rule out the possibility that the latter *symmetrical* bisamide is generated from initial formation of the *unsymmetrical* bisamide RCONHCH$_2$NHCOCH$_3$ that undergoes further fast anodic cleavage at the RCONH−CH$_2$ bond to yield **1C**. It is also noteworthy that the formation of a symmetrical hydrazine derivative **6E** supports our hypothesis of the formation of an amidyl radical of type ArCONH($^\bullet$) as the intermediate (line 8 in Scheme 4).

As to the formation of nitriles (ArCN), this type of product was found previously in the case of electro-generation of diphenyl acetonitrile.[13] It is likely that they could be formed by dehydration of the corresponding amides. Such a process could take place at the cathode where Li metal is generated (by reduction[14] of the electrolyte LiClO$_4$), according to Scheme 5:

In conclusion, the present work describes a practical and simple one-pot transformation of *symmetrical* aromatic bisamides of type ArCONHCH$_2$CH$_2$NHCOAr to *unsymmetrical gem*-bisamides of type ArCONHCH$_2$NHCOCH$_3$ in moderate yields by employing controlled-potential oxidation in acetonitrile.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02917.

Full experimental procedures, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: becker@bgu.ac.il.

ORCID ●

Cheng-chu Zeng: 0000-0002-5659-291X

James Y. Becker: 0000-0002-2618-769X

Notes

The authors declare no competing financial interest.

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(14) When the solvent acetonitrile is very dry and the electrolyte is $LiClO_4$, the stainless steel cathode gets coated with a brown color (Li metal) during electrolysis. Taking it out of the cell and adding drops of water slowly to the surface of the coated cathode results in a vigorous reaction accompanied by a white smoke and complete disappearance of the brown coating.