JOC Article

Paired Electrosynthesis of Cyanoacetic Acid

Belen Batanero and Fructuoso Barba*

Department of Organic Chemistry, University of Alcalá, 28871 Alcalá de Henares, Madrid, Spain

Carlos M. Sánchez-Sánchez and Antonio Aldaz

Department of Physical Chemistry, University of Alicante, 03080 Alicante, Spain

fructuoso.barba@uah.es

Received December 19, 2003

Cyanoacetic acid is formed by cathodic reduction of CO_2 and anodic oxidation of the tetraalkylammonium salt anion; the process is conduced in acetonitrile using a divided cell with a medium porosity glass-frit diaphragm. A mechanism for this paired electrochemical reaction is proposed.

Introduction

The synthesis of cyanoacetic acid (CA) and its derivatives is of much interest due to their industrial importance as starting materials.[1] CA is mainly used for the production of the fungicide Cymoxanil,[2] the cough remedy Dextromethorphan,[3] and antivirals such as Acyclovir,[4] Ganciclovir,[5] or Famciclovir.[6] Cyanoacetates have important applications in the field of adhesives and are also used for the synthesis of pharmaceuticals (such as the antiepileptic valproic acid[7]), agrochemicals (preparation of the rice herbicide Pyrazosulfuron-ethyl[8]), dyes (C.I. Disperse Yellow 31 (Celliton Fast Yellow 7G[9])), and UV absorbers (Etocrylene[10]).

The conventional synthesis of CA is carried out by the reaction of chloroacetic acid and alkaline cyanides. It is a dangerous and environmentally unfriendly process that should be replaced by a "green process". For these reasons, a large number of patents have described its preparation using less dangerous reactants.[11−14] One of the more interesting pathways involves the generation of $^{-}CH_2CN$, which is added to carbon dioxide. This anion can be obtained by either chemical or electrochemical methods. Kawamata et al.[13] describe its formation by reaction between acetonitrile and alkaline phenoxides using DMF as solvent. More recently, Gennaro et al.[15] have prepared it by cathodic reduction of chloroacetonitrile in an undivided cell with a sacrificed aluminum anode. Several syntheses of CA have already been performed by different electrochemically (e.g., the anodic oxidation of cyanoethanol[16] or β-cyanoethyl ethers).[17] In these instances, large amounts of HCN were obtained, thereby rending these syntheses inconvenient and dangerous.

Tyssee published a patent[14] in 1976 describing a method to introduce a carboxylate group onto electrogenerated $^{-}CH_2CN$ by cathodic reduction of acetonitrile. The current yield was only 5.8 g of CA/faraday. In the patent, the nature of the electrodes is described: mercury, cadmium, carbon, and lead were used as cathodes, while the nature of the anode was irrelevant to the electrochemical process. The electrolyses were performed in a two-compartment cell with a medium-porosity glass-frit diaphragm and tetraalkylammonium salts as supporting electrolyte. However, as we demonstrate in the present work, the electrosynthesis of CA does not take place in the cathodic compartment, but takes place in the anodic compartment through a paired reaction that is described here for the first time. We show that the presence of CA in the catholyte is due to its diffusion from the anolyte.

General Electrochemical Procedure

Voltammetric Experiments. Voltammetric curves with IR drop compensation were obtained with an Amel 2053 potentiostat, an EGC 175 Universal Programmer, and a Kipp-Zonen XY recorder. A three-electrode cell was employed with a Pt bead (12.9 mm^2) as working electrode and a coiled wire Pt as counter electrode. As reference, a

---

* To whom correspondence should be addressed. Tel: 34 91 8854617. Fax: 34 91 8854686.

[1] Hildbrand, S.; Pollak, P. Malonic acid and derivatives. In *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed. [Online] Wiley-VCH: New York, 2002.

[2] Davidson, S. H. E.I. du Pont de Nemours and Co. US Pat. 3,954,992, 1973.

[3] Schnider, O.; Gruessner, A. *Helv. Chim. Acta* **1951**, *34*, 2211.

[4] Schaefer, H. J. Wellcome Foundation Ltd. DE 2539963, 1976. Matsumoto et al. *Chem. Pharm. Bull.* **1988**, *36*, 1153.

[5] Verheyden, J. P.; Martin, J. C. Syntex, Inc. US Pat. 4,355,032, 1982; US Pat. 4,423,050, 1983.

[6] Kincey, P. M. EP 355986, 1990.

[7] Chignac, M. et al. Labaz US Pat. 4,155,929, 1979.

[8] Yamamoto, S. et al. *Nipon Noyakv Gakkaishi.* **1996**, *21*, 259.

[9] Hafenrichter, S. *Textil-Praxis.* **1961**, *16*, 273.

[10] Holderbaum et al. BASF AG. DE 19519894, 1996.

[11] Bulls, A. R.; Fellmann, J. D.; Periana, R. A. PCT Pat WO 9212962, 1992.

[12] Kaneko, H.; Masuda, T. Jpn Pat. 07233135, 1995.

[13] Kawamata, M.; Takahashi, T.; Fujikake, S. Jpn Pat. 7571627, 1975.

[14] Tyssee, D. A. US Pat. 3,945,896, **1976**.

[15] Isse, A. A.; Gennaro, A. *J. Electrochem. Soc.* **2002**, *149*, D113−117.

[16] Wermeckes, B.; Beck, F. *Chem. Ber.* **1985**, *118*, 3771.

[17] Wermeckes, B.; Beck, F. *Electrochim. Acta* **1985**, *30*, 1491.

10.1021/jo0358473 CCC: $27.50

Ag/AgCl electrode connected to the cell solution through a Luggin capillary was employed. No correction for the junction potential was made. The solution was deaerated by N_2 bubbling for 20 min. To avoid any concentration change in the cell solution, the gas was previously saturated by bubbling it through a similar solution. The sweep rate was 50mV/s.

Electrochemical Synthesis. The electrolyses were carried out using both potentiostatic and constant current conditions in a concentric cell with two compartments separated by a porous (D3) glass-frit diaphragm and equipped with a magnetic stirrer. As cathode, platinum or lead plates were used, and as anode, a platinum net or carbon plates were employed. As reference, a Ag/AgCl-(satd) electrode was used. The solvent-supporting electrolyte system (SSE) was a nominally anhydrous 0.05 M solution of the different electrolytes: tetraalkylammonium tetrafluorborate, perchlorate, bisulfate, chloride, or bromide and lithium perchlorate in anhydrous acetonitrile. The volumes of catholyte and anolyte were 15 and 45 mL, respectively.

For controlled potential electrolyses the catholyte was an SSE solution saturated with CO_2 by continuous bubbling of this gas, and the anolyte was a CO_2-free SSE solution. The applied potential depended on the nature of the employed SSE. The initial current was 200 mA and remained almost constant during the electrolysis. The reaction was finished after a given charge was circulated through the cell. After that, the solvent in the anolyte chamber was removed under reduced pressure. The residue was extracted with ether/water (when water-soluble electrolytes were used), and the organic phase was dried over Na_2SO_4 and concentrated by evaporation. When tetrabutylammonium tetrafluorborate was used as electrolyte the residue was extracted with $CHCl_3$/NaOH (5%), and the aqueous phase was neutralized, further concentrated, and extracted with ether. Finally, the ether solution was dried over Na_2SO_4 and then removed by evaporation. A portion of this residue was treated with methanol and some drops of sulfuric acid in order to identify by gas chromatography (GC) the acid formed, as the corresponding methyl ester.

For electrolyses carried out under constant current, the same experimental conditions were employed; a divided cell with platinum net as anode was used but a constant current of 200 mA (current density of 15 mA/cm^2) was applied.

Results

Voltammetric Experiments. Figure 1 shows the voltammetric curves obtained for the different SSE systems employed: Bu_4NBr, Et_4NCl, Bu_4NHSO_4, $LiClO_4$, Et_4NClO_4, and Bu_4NBF_4.

The increase of the current corresponds to the oxidation of the anion of the supporting electrolyte. Figure 2 shows the voltammetric curves, corresponding to a negative potential direction scan, in the presence or absence of CO_2. Notice that the foot potential for reduction of CO_2 occurs before reduction of acetonitrile starts.

Electrolysis Experiments. For electrolyses carried out at a controlled anodic potential of +3.22 V with a platinum net anode and using Bu_4NBF_4 as electrolyte, 435 mg of CA, which corresponds to 21 g of CA/faraday (current efficiency 24.7%) was isolated from the anodic compartment after 0.021 F was circulated through the cell. An increase of the circulated charge to 0.07 F did not change the current efficiency of the process (see Table 1).

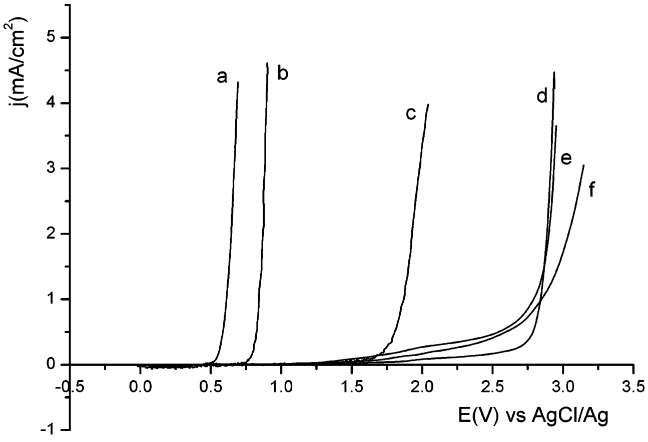


FIGURE 1. Voltammetric curves of the different SSE solutions. Only the positive potential going scan is shown. Solvent: acetonitrile. Supporting electrolyte concentration: 0.15 M. Key: (a) Bu_4NBr, (b) Et_4NCl, (c) Bu_4NHSO_4, (d) $LiClO_4$, (e) Et_4NClO_4, (f) Bu_4NBF_4. Scan rate: 50 mV/s. Working electrode: Pt.

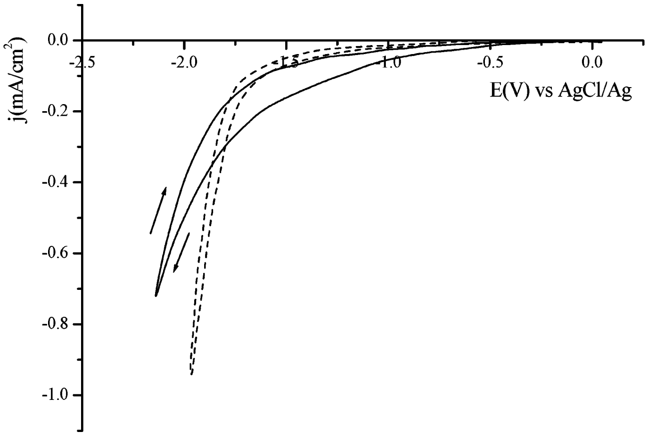


FIGURE 2. Voltammetric curves of SSE: acetonitrile/Bu_4NBF_4 (0.15 M). Solid trace: CO_2-saturated SSE solution, dash trace: CO_2-free SSE solution. Scan rate: 50 mV/s. Working electrode: Pt.

TABLE 1. Yields (g/F of CA) and Current Efficiencies Obtained under Different Experimental Conditions

electrolyte	anodic potential (V, vs Ag/Ag$^+$)	no. of Faradays passed through the cell	yield (g/F)	current efficiency (%)
Bu_4NBF_4	+3.22	0.021	21	24.7
Bu_4NBF_4	+3.2	0.07	20.7	24.3
Et_4NClO_4	+2.92	0.021	19.6	22.7
Bu_4NHSO_4	*a*	0.021	20.7	24.1
Et_4NCl	+1.67	0.021	4	4.6
Bu_4NBr	+0.82	0.021	traces	

[a] Electrolysis under constant current conditions, $I = 200$ mA.

When Et_4NClO_4 was used as the electrolyte (a controlled potential of +2.92 V was applied to get 200 mA of current), similar results to those with Bu_4NBF_4 were obtained. Using Et_4NCl as the supporting electrolyte and carrying out the electrolysis at +1.67 V led to a significant decrease of the current efficiency and only 4 g of CA/faraday was obtained. If the electrolysis was carried out at +0.82 V using Bu_4NBr as the supporting electrolyte, only traces of CA were found. In this case, dibromoacetonitrile was obtained as the major product (MS *m*/*e* (relative intensity) EI: 201 ($M^+ + 4$, 24), 199 ($M^+ + 2$, 48), 197 (M^+, 26), 120 (100), 118 (94), 93 (33), 91 (31), 81 (69), 79 (69)); a small amount of bromoacetonitrile was also found.

Due to the possible industrial interest in this paired reaction, the electrolysis was also carried out using one of the cheapest tetraalkylammonium salts, Bu_4NHSO_4, as the electrolyte. The results were similar to those obtained with Bu_4NBF_4 (see Table 1).

The type of separator employed in the divided cell has a strong influence upon the CA yield. Thus, when a cation-exchange membrane (Nafion) was used in place of a glass-frit diaphragm, CA was not formed.

If the electrolysis is carried out by bubbling CO_2 into the anolyte, not the catholyte chamber, then CA is not obtained.

The electrolysis has also been performed in an undivided cell. Thus, using Bu_4NBF_4 as electrolyte under the same experimental conditions as described above, the yield on CA decreased to 2.4 g/faraday.

Results similar to those obtained at constant potential were obtained for electrolysis carried out at constant current, even if the nature of the cathode was changed. For example, a constant current electrolysis (current density: 15 mA/cm^2) using Bu_4NBF_4 as supporting electrolyte in a divided cell and with Pb as cathode afforded similar results than those obtained at controlled potential. It was also demonstrated that when the concentration of the supporting electrolyte drops near during the electrolysis, the current also drops to zero.

Discussion

Before suggesting a mechanism it is necessary to clarify the following questions:

(1) In which compartment does the formation of CA take place?

The fact that CA was not obtained in a CO_2-saturated catholyte when a cation exchange membrane was used clearly points out that CA is not generated by cathodic reduction of acetonitrile and further attack of the anion $^-CH_2CN$ upon CO_2. Moreover, under our experimental conditions acetonitrile is not reduced at the cathode, because 3-aminocrotonitrile tetraalkylammonium salts were not detected in the catholyte. The literature[18,19] indicates that these compounds should be formed if reduction of acetonitrile occurred. Thus, it is highlighted that CA is formed only in the anolyte and that the CA detected in the catholyte is only the result of its diffusion from the anolyte.

(2) What is the nature of this migrating "CO_2-compound"? It is obvious that the formation of 1 equiv of CA in the anolyte requires the transport of 1 equiv of CO_2-reduction product from the catholyte to the anolyte. It is known that in the first electron transfer for the reduction of CO_2 a radical anion is obtained.[20−22] However, it has also been published that the CO_2-radical anion, formed in the CO_2 cathodic reduction in acetonitrile/tetraalkylammonium salts, evolves to formate.[23] For this reason an electrolysis was carried out in absence of CO_2, but in the presence of tetraethylammonium formate dropped into the anodic compartment. In this case, no CA was detected.

Another possibility described in the literature[24] involves the formation of oxalate in the catholyte through dimerization of the electrogenerated CO_2-radical anion. In our case, small amounts of oxalic acid were found in the catholyte. To eliminate the oxalate anion as the species that migrates to the anolyte, electrolysis in absence of CO_2, but in the presence of added tetraethylammonium oxalate, dropped into the anodic compartment, was carried out. However, no traces of CA were detected.

It has been postulated[24,25] that the CO_2-radical anion reacts with a CO_2 molecule to afford the $^-OCOOCO^\bullet$ radical anion dimer. Recently, it has also been postulated[26] that two CO_2-radical anions can react by a head-to-tail reaction affording the dianion $^-OCOOCO^-$. However, the existence of a negative charge on a carbonyl carbon seems highly unlikely, and this species should immediately evolve to CO and CO_3^{2-}, as described.[24]

In conclusion, the nature of the migrating molecule to the anodic compartment should be either a CO_2-radical anion or the higher stabilized dimer $^-OCOOCO^\bullet$ radical anion.

(3) What is the nature of the anodically generated species that reacts with the migrating "CO_2-compound"?

It is well-known that acetonitrile is a very stable molecule with a wide potential window, in both the positive and the negative potential regions, and it is also very well-known that the positive potential limit for the SSE is fixed by the anodic oxidation of the anion of the supporting electrolyte.[27]

As we have noted, the applied potential for the synthesis of CA depends on the supporting electrolyte employed and it corresponds to the oxidation potential of the anion of each electrolyte.

Cauquis et al. had demonstrated[28] that the anodic oxidation of supporting electrolyte anions leads to radical intermediates. For instance, oxidation of tetrafluorborates at a platinum anode in acetonitrile yield the adduct[29] $CH_3CN.BF_3$. Its formation can be explained by

---

[18] Foley, J. K.; Korzeniewski, C.; Pons, S. *Can J. Chem.* **1988**, *66*, 201.

[19] Batanero, B.; Barba, F.; Martín, A. *J. Org. Chem.* **2002**, *67*, 2369.

[20] Desilvestro, J.; Pons, S. *J. Electroanal. Chem.* **1989**, *267*, 207.

[21] Amatore, C.; Saveant, J.-M. *J. Am. Chem. Soc.* **1981**, *103*, 5021.

[22] Gressin, J.-C.; Michelet, D.; Nadjo, L.; Saveant, J.-M. *Nouv. J. Chim.* **1979**, *3*, 545.

[23] Kushi, Y.; Nagao, H.; Nishioka, T.; Isobe, K.; Tanaka, K. *Chem. Lett.* **1994**, 2175.

[24] Keene, R. R. In *Electrochemical and Electrocatalytic Reactions of Carbon Dioxide*; Sullivan, R. B. P., Krist, K., Guard, H. E., Eds.; Elsevier: New York, 1993; Chapter 1, p 9.

[25] Nielsen, M. F.; Utley, J. H. P. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; Marcel Dekker, Inc.: New York, 2001; Chapter 21, p 831.

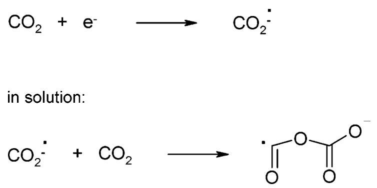
[26] Flyunt, R.; Schuchmann, M. N.; von Sonntag, C. *Chem. Eur. J.* **2001**, *7*, 796.

[27] Lund, H. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; Marcel Dekker, Inc.: New York, 2001; Chapter 5, p 263.

[28] Cauquis, G.; Serve, D. *J. Electroanal. Chem.* **1970**, *27*, 3−6.

[29] Lund, H. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; Marcel Dekker, Inc.: New York, 2001; Chapter 5, p 264.

SCHEME 1



SCHEME 2

At the anode:

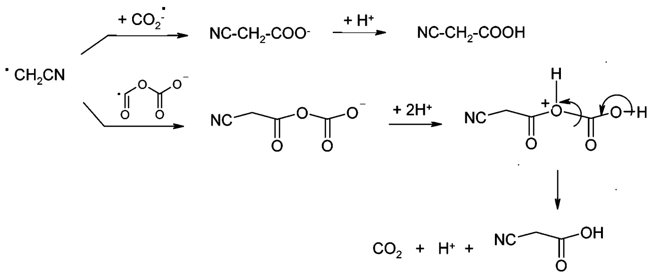
$R_4N^+X^-$ $-e^-$ $\longrightarrow$ R_4N^+ + $X^\cdot$

$X = F_4B^-, ClO_4^-, HSO_4^-, Cl^-, Br^-$

in solution:

$X^\cdot$ + CH_3CN $\longrightarrow$ HX + $^\cdot CH_2CN$

SCHEME 3



decomposition of $BF_4^\bullet$ into BF_3 and the radical $F^\bullet$. When tetraalkylammonium chloride, bromide, or hydrogen sulfate are used, obviously $Cl^\bullet$, $Br^\bullet$, or $^\bullet HSO_4$ are respectively generated.

(4) What is the final reaction between these electrogenerated species?

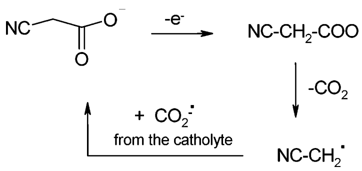
The anodically electrogenerated radical from the electrolyte anion abstracts a hydrogen atom of the solvent, acetonitrile, in an homogeneous reaction yielding $^\bullet CH_2CN$ radicals.[30] It should be noticed that the C−H bond energy of $H-CH_2CN$ is 360 kJ mol^{-1}.[31] Reaction of the later radical with a CO_2-radical anion, or with the corresponding dimer $^-OCOOCO^\bullet$, and further protonation (see proposed mechanism) affords CA. The radical $^\bullet CH_2CN$ is formed through an homogeneous reaction in the bulk of the solution.

Taking into account each of these points, we propose the mechanism shown in Schemes 1−3.

To account far the relatively moderate yield of CA obtained in our paired reaction, a preparative-scale anodic oxidation of CA was performed at constant potential (+3.22 vs Ag/AgCl), Pt anode, and CH_3CN/Bu_4NBF_4 as SSE. Oxidation of CA took place together with the oxidation of the anion of the supporting electrolyte.

However, the regeneration of CA in the paired reaction (under cathodically bubbled CO_2) is plausible by reaction between the decarboxylated product and the reduced-CO_2 molecule (see Scheme 4).

SCHEME 4



The reason CA is obtained, although in a small amount, using Et_4NCl, but only traces of this acid are obtained when Bu_4NBr is used can be explained considering that the abstraction of $H^\bullet$ by $Cl^\bullet$ radical is more exothermic than that of $Br^\bullet$,[32] affording in this way larger amount of $^\bullet CH_2CN$. These $^\bullet CH_2CN$ radicals can react either with the "reduced" form of CO_2 to give $HOOCCH_2CN$ or with electrogenerated $Cl^\bullet$ to form $ClCH_2CN$. It is also known that the polyhalogen substitution almost invariably occurs, as side process, even if there is a large molar ratio of substrate to halogen.[33] However, when R_4NBr is used the formation of dibromoacetonitrile is the main process. A plausible explanation is that the $Br^\bullet$ radical reacts with acetonitrile, as we have previously pointed out, to give $BrCH_2CN$. This fact causes a decrease on the concentration of $^\bullet CH_2CN$, to the level of traces, decreasing the rate of the reaction between this radical and the migrating "reduced CO_2". Then, the "reduced CO_2" acts as an electrogenerated base[23] versus the acidic protons of $BrCH_2CN$, affording a very stabilized anion $(BrCHCN)^-$ that reacts with Br_2 (formed by coupling of two $Br^\bullet$) or with Br^+ (formed in the anodic oxidation of $Br^\bullet$) leading to Br_2CHCN.

Concluding Remarks

Herein we describe an interesting alternative to the synthesis of cyanoacetic acid through the generation of $^\bullet CH_2CN$ radical, obtained by anodic oxidation of electrolyte anions and subsequent reaction with solvent molecules (acetonitrile). These radicals $^\bullet CH_2CN$ are coupled with cathodic CO_2-reduced species, coming through the medium-porosity glass-fritt diaphragm, to afford the desired product.

We also show that the process could be of high industrial interest and for this reason the reaction has been carried out with the cheapest tetraalkylammonium salt Bu_4NHSO_4 as the electrolyte system and under constant current conditions, obtaining similar results than those under controlled potential or employing expensive electrolytes.

Acknowledgment. This work was supported by the Spanish Ministry of Science and Technology through projects BQU2001-1083 and BQU2000-0460. B.B. thanks this Ministry for the "Ramón y Cajal" contract, and C.S. also thanks the University of Alicante for his FPU scholarship.

JO0358473

---

[30] Ohmori, H.; Ueda, C.; Yamagata, K.; Masui, M.; Sayo, H. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1065.

[31] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, 2001; p 1041.

[32] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: New York, 2001; p 1038.

[33] *Advanced Organic Chemistry*, 5th ed.; Smith, M. B., March, J., Eds.; John Wiley and Sons, Inc.: New York, 2001; p 907.