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Reaction of Electrogenerated Cyanomethyl Anion with Cyclohexylisocyanate: Synthesis of $N$-(cyclohexylcarbamoyl)acetamide. An Unexpected Product

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Isocyanates are molecules containing the –N=C=O group (a cumulene), quite reactive (mainly under nucleophilic conditions) and particularly important in the chemical industry, as they are the precursors of polyurethanes (by copolymerization of diisocyanates with polyols), with more than 13 million metric tons of polyurethanes processed worldwide. The reactivity of isocyanates is due to the electrophilicity of the carbon atom (Scheme 1), which can be attacked by a nucleophile and, eventually, start a polymerization (aromatic isocyanates are more reactive than aliphatic ones). The catalyzed formation of oligomers is also possible, as reported in Scheme 1 starting from cyclohexylisocyanate.

Cyanoacetamides (Scheme 2) are important intermediates in organic synthesis, mainly in the synthesis of heterocycles, and compounds with possible biological activities. As an example, compounds containing a flavone and a cyanoacetamide group resulted potent inhibitors of acetylcholinesterase, with good modulation effects on self-induced Aβ aggregation and low cytotoxicity, and thus potent allies in the fight against Alzheimer’s disease. The experimental conditions for the classical chemical synthesis of acetonitriles vary depending on the desired substrates on the nitrogen atom, but usually the reaction between ethyl cyanoacetate and an amine (amine self-catalyzed or in the presence of an external base) is carried out. In order to explore isocyanates reactivity, we considered the possible cyanoacetamide synthesis starting from the corresponding isocyanate and the cyanomethyl anion (Scheme 2).

The cathodic reduction of acetoni-trile-tetraethylammonium tetrafluoroborate (ACN-TEABF4) solutions (or other tetraalkylammonium salts) leads to the formation of cyanomethyl anion, CH3CN (also acetoni-trile anion), which is a bidentate species. The mechanism of cathodic cyanomethyl anion formation is still debated and strongly depends on the experimental conditions (mainly cathode material, supporting electrolyte nature and amount of adventitious water). On a vitreous carbon cathode the proposed cathodic reduction mechanism regards the tetraalkylammonium cation, yielding a base strong enough to deprotonate the solvent acetoni-trile, while on a platinum cathode the reduction of hydrogen to hydride is possible or the intervention of the cathode itself in the electrochemical reduction is reported, yielding a ionic-metallic phase in which the platinum is negatively charged. Whatever the mechanism (and the reaction conditions), the cathodic reduction of acetoni-trile-tetraethylammonium salt solutions yields the solvent anion. It should be underlined that all authors exclude the direct cathodic reduction of acetoni-trile to the corresponding anion.

If the cathodic solution contains water, it is possible that there is a change in the electrode reaction, with the direct reduction of water and the production of molecular hydrogen and hydroxide anions, which accumulate in the diffusion layer. This reaction can lead to acetonitrile hydrolysis, with acetamide formation (Scheme 3), although the yield of such a product was not reported. It should be noted that the literature reports that the efficient hydrolysis of acetoni-trile to acetamide needs a catalyst, usually a metal ion (Cu2+, Ni2+, Zn2+, Pt+, etc.) and/or high temperature, moreover Richard and coworkers reported that “there was no detectable hydrolysis of the nitrile group of acetoni-trile... during its base-catalyzed reaction in D2O”, the base being KOH. Although the cyanomethyl anion structure can be described by two resonance forms (Scheme 4), in which the negative charge is localized alternately on the carbon atom or on the nitrogen atom, the literature reports a computational study (Hückel MO method) which stated that the maximum of electronic density is located on the carbon atom, and thus when cyanomethyl anion acts as a nucleophile, it is a carbon nucleophile. This result is confirmed by our calculations (vide infra) of the HOMO wave function where the extra electron resides (Fig. 1).

Brauman and coworkers studied the two competing pathways in gas phase reaction of the ambient nucleophile CH3CN, quantifying the two possible products in a 9:1 ratio between C and N nucleophilic addition to an acyl chloride. In addition, Wiberg and Castejon calculated the CN bond order in the gas phase reaction of the ambident nucleophile

\[ ^{14}C_{N} \equiv N^{3} \]

19 and of the corresponding deprotonation product cyanomethyl anion (2.124), evidencing a small difference, accounting for a minimal allocation of the negative charge on the CN group. Ab initio calculations showed that the higher charge density (0.6 units) is on the carbon atom of the cyanomethyl anion, and only a small amount (0.4 units) on the nitrogen atom, despite the higher electronegativity of nitrogen with respect to carbon. This is probably due to the higher stability of the C3N triple bond, with respect to the cumulene CH3=C=N double bonds. The same authors concluded that the structural and electronic reorganization needed for the internal transfer of the negative charge from nitrogen atom to carbon (or vice versa) is minimal.

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When carrying out the synthesis of cyanomethyl anion in the presence of acetonitrile, the products deriving from the reaction of these two compounds (Scheme 5) can be isolated, although usually in very low yields (1%-10%).

Starting from acetonitrile as reagent (and solvent), electrochemistry allows for acetamidation of aromatic compounds, as recently reported by Batanero and coworkers. In this case the anodic oxidation of the aromatic compound in acetonitrile allowed for the formation of the corresponding cation, which reacting with acetonitrile by Ritter reaction yielded the iminium cation and, after workup, the corresponding acetamide.

To the best of our knowledge, no acetamide derivative was ever isolated from the reaction of cyanomethyl anion and electrophiles. In continuation of our ongoing study on the reactivity of electro-generated cyanomethyl anion with organic substrates, we decided to carry out the reaction of this electrogenerated species with an aliphatic isocyanate, in order to try to understand the experimental conditions to minimize the nucleophile-catalyzed polymerization in favour of a
nucleophilic addition to the carbonyl group to yield the corresponding cyanoacetamide. We thus started using cyclohexylisocyanate as model compound (aromatic isocyanates are too prone to polymerization and were thus excluded in this study).

**Experimental**

**Materials.**—All reagents were purchased from Sigma-Aldrich and used as received. Benzaldehyde was distilled at reduced pressure (40 torr) before use. Acetonitrile (water 0.02%) was used as received. Flash column chromatography was carried out using Merck 60 kieselgel (230–400 mesh) under pressure. GC-MS measurements were carried out on a Hewlett-Packard 5890 series II gas chromatograph coupled with a Hewlett-Packard 5871 series II quadrupole mass selective detector. 1H and 13C NMR spectra were recorded at room temperature using a Bruker AC 200 spectrometer using CDCl3 as internal standard.

**N-Hexyl-2-cyanoacetamide** was synthesized as reported in the literature by reaction of n-hexylamine with ethyl cyanoacetate.

**Voltammetric measurements.**—Voltammetric measurements were performed using an Amel Model 552 potentiostat equipped with an Amel Model 731 integrator. All the experiments were carried out in a divided glass cell separated through a porous glass plug filled up with a layer of gel (i.e., methyl cellulose 0.5% vol dissolved in DMF/Et4NBF4 0.1 M); a Pt spiral (apparent area 0.8 cm2) was used as anode; an Cu spiral (apparent area 0.8 cm2), Ti, Pb, Ni, Cu or GC plates (area 0.8 cm2) were used as cathode. Anolyte: 2 ml of CH3CN-0.1 M Et4NBF4. Catholyte: 5 ml of CH3CN-0.1 M Et4NBF4. After 97 C (if not otherwise stated), corresponding to 2 F, the current flow was stopped and 0.5 mmol of cyclohexylisocyanate (or n-hexylisocyanate) or benzaldehyde were added to the catholyte. The mixture was kept under stirring at r.t. for 12 h. The solvent was removed under reduced pressure and the residue extracted with diethyl ether (3 × 20 ml). The products were isolated after usual flash column chromatography.

**Acetamide** (commercial): 1H-NMR (CDCl3), δ (ppm): 6.1 (bs, 1H, NH), 5.9 (bs, 1H, NH), 1.99 (s, 3H, CH3).

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**Electrolyses.**—Electrolyses were performed at constant current (I = 25 mA cm−2), at room temperature, under a nitrogen atmosphere, using an Amel Model 552 potentiostat equipped with an Amel Model 731 integrator. All the experiments were carried out in a divided glass cell separated through a porous glass plug filled up with a layer of gel (i.e., methyl cellulose 0.5% vol dissolved in DMF/Et4NBF4 0.1 M); a Pt spiral (apparent area 0.8 cm2) was used as anode; a Pt spiral (apparent area 0.8 cm2), Ti, Pb, Ni, Cu or GC plates (area 0.8 cm2) were used as cathode. Anolyte: 2 ml of CH3CN-0.1 M Et4NBF4. Catholyte: 5 ml of CH3CN-0.1 M Et4NBF4. After 97 C (if not otherwise stated), corresponding to 2 F, the current flow was stopped and 0.5 mmol of cyclohexylisocyanate (or n-hexylisocyanate) or benzaldehyde were added to the catholyte. The mixture was kept under stirring at r.t. for 12 h. The solvent was removed under reduced pressure and the residue extracted with diethyl ether (3 × 20 ml). The products were isolated after usual flash column chromatography.

**All products were known compounds and their NMR spectra were identical to those reported in the literature.**

**N-Acetyl-N′-cylohexylurea** was synthesized as reported in the literature by reaction of n-hexylamine with ethyl cyanoacetate.

**Figure 1.** Top (a) and side (b) views of the HOMO wave function where the extra electron resides (the majority at the C-site).

Scheme 5. Possible products from the reaction of cyanomethyl anion and acetonitrile.
Cylohexylamine (commercial): $^1$H-NMR (CDCl$_3$), δ (ppm): 2.65–2.58 (m, 1H, CH$_2$NH$_2$) 1.82–1.57 (m, 4H, cy), 1.32–1.05 (m, 6H, cy).

N,N'-dicylohexylurea (commercial): $^1$H-NMR (CDCl$_3$), δ (ppm): 4.10–4.05 (m, 2H, NH) 3.52–3.43 (m, 2H, CH$_2$NH) 1.95–1.91 (m, 4H, cy), 1.72–1.65 (m, 6H, cy), 1.37–1.08 (m, 10H, cy).

N-Acetil-N'-hexylurea$^{24}$: $^1$H-NMR (CDCl$_3$), δ (ppm): 9.94 (s, 1H, NH), 8.47 (bs, 1H, NH), 3.28 (app q, $J = 6.4$ Hz, 1H, CH$_2$NH), 2.13 (s, 3H, CH$_3$), 1.57–1.51 (m, 2H, hex), 1.30 (bs, 6H, hex), 0.92–0.86 (m, 3H, hex). $^{13}$C-NMR (CDCl$_3$), δ (ppm): 172.4, 154.7, 39.5, 31.4, 29.5, 26.5, 23.9, 22.5, 14.0.$^{26}$

3-Hydroxy-3-phenylpropionitrile (commercial): 1H-NMR (CDCl$_3$), δ (ppm): 7.40 (bs, 5H, Ar), 5.05 (t, $J = 6.2$ Hz, 1H, CHOH), 2.77 (d, $J = 6.2$ Hz, 1H, CHOH), 2.7 (bs, 1H, OH), $^{13}$C-NMR (CDCl$_3$), δ (ppm): 141.0, 128.9, 128.8, 125.5, 117.3, 70.1, 27.9.

Cinnamonic acid (commercial): 1H-NMR (CDCl$_3$), δ (ppm): 7.40 (bs, 5H, Ar), 5.05 (t, $J = 6.2$ Hz, 1H, CHOH), 2.77 (d, $J = 6.2$ Hz, 1H, CHOH), 2.7 (bs, 1H, OH), 13C-NMR (CDCl$_3$), δ (ppm): 141.0, 128.9, 128.8, 125.5, 117.3, 70.1, 27.9.

ESI-MS/MS analysis.—A Quattro Micro Tandem MS-MS detector with an electrospray ionization source (ESI) was set for acquiring full scan data in positive (pESI) mode, in the mass range 45–200 Da. ESI source parameters: capillary voltage 3000 V, desolvation temperature 350 °C, source temperature 120 °C, desolvation gas: argon. Direct infusion of samples into the source using an electrospray ionization (ESI) source Waters (commercial): ESI-MS/MS analysis.

Results and Discussion

The reaction between electrogenerated cyanomethyl anion (obtained by cathodic reduction of a solution of ACN-TEABF$_4$ in a platinum cathode, in a divided cell) and cylohexylisocyanate, directed to the synthesis of the corresponding cyanoacamide (Scheme 2), yielded an unexpected result as no traces of the expected product were present in the catholyte, while 30% of acetylated of the isocyanate was obtained (Table 1, entry 1).

This result was quite startling, as in long lasting work with electrogenerated cyanomethyl anion we never evidenced the presence of acetylated products in the reaction mixtures, whichever the reagents. Moreover, the literature reported acetylated products under electrochemical conditions using acetonitrile as solvent only under oxidative conditions$^{37}$ (see Introduction), situation very far from our (reductive conditions).

The nominal amount of water in our bottle acetonitrile was 0.02%, which accounts for about 0.05 mmol water in 5 ml solvent (more after bottle opening), while a minimal amount of water was surely present also in the supporting electrolyte. These considerations led us to think to an in situ acetonitrile hydrolysis to aceticamide, carried out by hydroxide anions derived from the cathodic reduction of water (Scheme 3). Nonetheless, some suspicions came to mind, as our experimental conditions in cyanomethyl anion generation are standardized and, as previously stated, we never obtained acetylated products in the presence of electrophiles (e.g., alkylating agents), while we obtained cyanomethylated products (whose yields depended on the reaction conditions).

In fact, as reported in the literature,$^{31}$ the cathodic limit of a solution of ACN-0.1 M Et$_4$NBF$_4$ depends on the water content. The higher the water content, the higher the cathodic limit, accounting for a change in the cathodic reaction (from the reduction of ACN-Et$_4$NBF$_4$ to the reduction of water, see Introduction), as evidenced from the voltammetric curves reported in Fig. 2. In fact, our experimental conditions are described by the blue curve, while the subsequent additions of water shifted the onset of the cathodic reduction toward more positive potentials (red and black curves).

The possibility that this strange result could be due to an occasional excess of water in our solvent-supporting electrolyte system was thus seriously taken into consideration. In fact, only a difference in water content (and thus a difference in cathodic reaction) seemed reasonable to explain the different outcome of this electrolysis with respect to all the previous ones. Moreover, it is quite improbable that electrogenerated hydroxide anion could deprotonate acetonitrile, to yield the cyanomethyl anion, as the pKas of the two reagents are highly unfavourable (pK$_a$ in ACN: water 2.5, ACN 33)$^{32}$; this explanation of our previous results was thus ruled out.

We become curious regarding this strange acetylation and for the complete absence of the cyanomethylated product, we increased the amount of charge, in order to understand if the product 2 yield

Figure 2. Cyclic voltammograms of a solution of bottle ACN-0.1 M Et$_4$NBF$_4$ (blue curve), in the presence of 0.125 M water (red curve) and 0.250 M water (black curve). GC electrode, vs mSCE, scan rate 0.200 Vs$^{-1}$. r.T. Scan: 0.0 V to $-3.0$ V to 0.0 V.
increased. The other possibility was that the acetamidated product 2 yield remained constant, all the water content being consumed. The results are reported in Table I, entries 2–4. The yield of 2 increased to 56% with a charge consumption of 2 F per mol of substrate, and decreased for a further increase of current. When the electrolysis (2 F) was carried out on a drier ACN-Et₄NBF₄ solution (Table I, entry 5, ACN kept over activated molecular sieves for 12 h), the yield of isolated 2 was 46%. Such a yield startled us, being quite sure to have diminished (but obviously not eliminated) the water content of our catholyte. Moreover, when we increased such content (Table I, entry 7) adding 1 equivalent of water to the catholyte prior to the electrolysis, the yield of 2 decreased instead of increasing. An even worse result was obtained adding water at the end of electrolysis (Table I, entry 8), quite conceivable if an anion different from OH⁻ was produced (cyanomethyl anion or acetamide anion, quenched by added water), but not if hydroxide anion was present. The presence of an anion different from OH⁻ in the catholyte at the end of electrolysis was supported by the absence or very low yield of urea or amine in the reaction mixture. It is, in fact, well known that the base-catalyzed hydrolysis of an isocyanate leads to the formation of the corresponding unstable carbammic acid, which, upon carbon dioxide loss, produces the corresponding amine. The amine can subsequently give a nucleophilic attack to the isocyanate group of a second molecule of starting material, yielding the urea.33

In order to understand a possible effect of the platinum electrode on this reaction, we carried out the same experiment as in entry 3, but removing the platinum electrode before the isocyanate addition (we usually do not remove the electrode from the catholyte before adding the reagents at the end of the electrolysis to minimize adventitious water and oxygen entering the reaction vessel). In this case the product yield lowered to 24%. Although this result could have no significance if read in an absolute way (adventitious water and/or oxygen in the electrode removal moment could lower the yield), in connection with the results described below could give indications of an electrode role.

It should be underlined that this anomalous reaction is active only under electroreductive conditions, as pointed out by the experiments reported in Table I, entries 10 and 11 (blank experiments in the absence of current).

In entries 12–16 the effect of different cathode materials on this particular reaction is reported, most probably accounting for a different activity of these materials on hydrogen evolution.34 The same result was obtained with a linear carbamate, n-hexylisocyanate 3, with 45% of acetamidation product 4 (Scheme 6).

In order to exclude that acetamidated product 2 could derive from a rearrangement of the cyanomethylated product 5 (structure in Table II), we synthesized 5 by classical means and submitted it to chemical and electrochemical reactions. To avoid any possible effect due to steric hindrance, we decided to use a linear reagent.

### Table I. Electrochemical generation of cyanomethyl anion and subsequent reaction with cyclohexylisocyanate 1

| Entry | Cathode | Charge (F) | N-(cyclohexylcarbamoyl)acetamide 2, % |
|-------|---------|------------|---------------------------------------|
| 1     | Pt      | 1.0        | 30%                                   |
| 2     | Pt      | 1.5        | 36%                                   |
| 3     | Pt      | 2.0        | 56%                                   |
| 4     | Pt      | 3.0        | 43%                                   |
| 5     | Pt      | 2.0        | 46%                                   |
| 6     | Pt      | 2.0        | 51%                                   |
| 7     | Pt      | 2.0        | 35%                                   |
| 8     | Pt      | 2.0        | 16%                                   |
| 9     | Pt      | 2.0        | 24%                                   |
| 10    | —       | —          | —                                     |
| 11    | Pt      | —          | —                                     |
| 12    | Ni      | 2.0        | 52%                                   |
| 13    | Ti      | 2.0        | 66%                                   |
| 14    | Pb      | 2.0        | 8%                                    |
| 15    | Cu      | 2.0        | 25%                                   |
| 16    | GC      | 2.0        | 16%                                   |

a) Catholyte (5 ml) and anolyte (2 ml): bottle ACN (0.02% nominal water content)–0.1 M TEABF₄ divided cell, Pt anode, rt, N₂ atmosphere, I = 25 mA cm⁻². At the end of the electrolysis, 0.5 mmol of cyclohexylisocyanate was added to the catholyte and the mixture kept under stirring at rT for 12 h. Then usual workup. b) Number of Faradays per mole of cyclohexylisocyanate. c) Isolated yields, with respect to starting cyclohexylisocyanate. d) Electrolysis conditions as in entry 3, but using ACN kept over activated molecular sieves for 12 h. e) Workup after 1.5 h from the addition of cyclohexylisocyanate to the catholyte. f) 0.5 mmol of water added to the catholyte before starting the electrolysis. g) 0.5 mmol of water added to the catholyte 5 min after the addition of cyclohexylisocyanate. h) The platinum electrode was removed from the catholyte prior to the isocyanate addition. i) 12% urea was also obtained. j) Blank test in the absence of current, but in the presence of platinum electrode. k) 27% urea was also obtained. l) 44% urea was also obtained.

Scheme 6. Acetamidation reaction of n-hexylisocyanate 3.
### Table II. Mechanistic insights.

| Entry | Reaction | Conditions | Products |
|-------|----------|------------|----------|
| 1     |          | ACN as solvent, rT, 12 h | only starting material |
| 2     |          | ACN as solvent, rT, 12 h | only starting material |
| 3     |          | ACN as solvent, rT, 12 h | only starting material |
| 4     |          | ACN as solvent, rT, 12 h | only starting material |
| 5<sup>a</sup> | electrogenerated cyanomethyl anion, ACN as solvent, rT, 12 h | only starting material |
| 6     |          | ACN as solvent, rT, 12 h | only starting material |
| 7     |          | ACN as solvent, rT, 12 h | urea/oligomers/polymers |
| 8     |          | ACN as solvent, rT, 12 h | polymers urea, acetamide, cyclohexylamine |

<sup>a</sup> Catholyte (5 ml) and anolyte (2 ml): bottle ACN-0.1 M TEABF<sub>4</sub>, divided cell, Pt anode, rT, N<sub>2</sub> atmosphere, \( I = 25 \text{ mA cm}^{-2} \). At the end of the electrolysis (2 F), 0.5 mmol of 2-cyano-N-hexylacetamide 5 was added to the catholyte and the mixture kept under stirring at rT for 12 h. Then usual workup.
corresponding to n-hexylisocyanate 3 (Table II). At first we studied the stability of this cyanoacetamide in the presence of water and acetonitrile (Table II, entry 1) and, as expected, this molecule revealed itself to be stable. Then we studied its reactivity towards isocyanate 3, in the presence or in the absence of water (Table II, entries 2 and 3), and in both cases no reaction was evidenced. Last, the reaction of cyanoacetamide with the two possible bases/nucleophiles present in our reaction vessel was carried out, i.e. with amine 6 (derived from the reaction of isocyanate with hydroxide anion and subsequent decarboxylation, Table II, entry 4) and with cyanomethyl anion (electrogenerated, Table II, entry 5). In both cases no product was obtained.

All these experiments allowed us to rule out the possibility that the acetamidated products 2 or 4 could derive from a rearrangement of the corresponding cyanoacetamide.

Last, we checked the reactivity of the isocyanate 1 towards acetamide 7, purposely added to the reaction mixture (Table II, entry 6, no reaction evidenced) or potentially present in the reaction mixture by reaction of hydroxide ion with acetonitrile (Table II, entry 7). In this last case isocyanate 1 reacted with OH\(^-\), yielding the expected products (urea and oligomers or polymers of the isocyanate). Hypothesizing the contemporary presence of hydroxide ion and acetamide in the reaction mixture at the moment of the addition of isocyanate 1, we carried out the corresponding reaction (Table I, entry 8), but only hydrolysis products were obtained. In no case acetamidated product 2 was obtained.

To confirm that we were generating the cyanomethyl anion by electrolysis, despite the water content in the solvent, we carried out the reaction with benzaldehyde yielding the corresponding \(\beta\)-hydroxynitrile 8 by cyanomethylation (previously reported by our research group\(^{35}\)). The results are reported in Scheme 7.

This reaction confirmed the effective generation of cyanomethyl anion by cathodic reduction of ACN-Et\(_4\)NB\(_4\), although the higher water content lowered the yields (overall 71% in the literature), having isolated two products deriving from the cyanomethylation of benzaldehyde (cinnamonitrile 9 is obtained from 8 by water elimination). It is to be underlined that no other product was isolated (no acetamidation product).

To ascertain the possible generation of acetamide during the electrolyses, we carried out the ESI-MS/MS analysis in infusion mode of the catholyte (no workup) after electrolysis, without the addition of the isocyanate (Fig. 3). Figure 3 shows the positive electrospray ionization (pESI) mass spectrum (in infusion mode), considering the 45–145 interval of masses (i.e., containing the masses we were interested in). Acetamide corresponds to \([M + H]^+ = 60\), DMF to 74 (DMF derives from the gel of anolyte and catholyte separator), triethylamine to 102 and tetraethylammonium to 130.

The mass spectrum points out that the amount of acetamide at the end of electrolysis does not seem to account for acetamidated product 2 when reacted with isocyanate 1 (56%). Moreover, the intensity of the Et\(_3\)N signal (although not directly comparable with the others) suggests that the main path of the electrogenerated base in this electrolysis is the Hofmann elimination from the tetraethylammonium cation. It is therefore still an open question as to whether all the acetamidated product 2 derives from acetamide anion 7 (by reaction of electrogenerated OH\(^-\) and ACN), as the amount of acetamide found at the end of the electrolysis seems not enough, or 2 is obtained in a concerted way, prior to acetamide formation. By comparison with the \(^1\)H-NMR of the ethereal extracts of the catholyte, we could evaluate the acetamide content as corresponding to about 0.05 mmol.

Considering all the results reported so far, our work can be summarized as illustrated in Scheme 8. Starting from the assumption that our solvent-supporting electrolyte contains water (we now describe it as “wet”), two possible anions can be generated from

![Scheme 7. Products obtained by reaction of cyanomethyl anion and benzaldehyde.](image-url)
the cathodic reduction (most probably at the same time, in a co-
reduction), namely cyanomethyl anion and hydroxide anion (circled
in green). These two anions follow two different routes:

• the cyanomethyl anion can act as a nucleophile toward benzalde-
hyde or cyclohexylisocyanate, yielding the corresponding hydro-
xynitrile 8 (from benzaldehyde) or cyanoacetamide 5 (from
isocyanate). Only hydroxynitrile 8 is obtained, not cyanoacet-
amide 5;

• the hydroxide anion can react with a solvent molecule, yielding the
acetamide anion 7− (circled in blue). This last anion (and not the
neutral acetamide, see Table II) can act as a nucleophile toward
benzaldehyde or cyclohexylisocyanate, yielding the corre-
sponding N-acetyl-N,O-acetal 10 (from benzaldehyde) or N-
acety lurea 2 (from isocyanate). Only N-acety lurea 2 is obtained,
not N-acetyl-N,O-acetal 10.

From these data it could be infer that, despite the co-generation of
both anions, the cyanomethyl anion reacts only with benzaldehyde,
while the acetamide anion (or hydroxide anion and acetonitrile)
reacts only with the isocyanate. This assumption could be not true,
as the N-acetyl-N,O-acetal of benzaldehyde 10 is reported to be an
unstable compound and could decompose under workup conditions,
so we cannot exclude its formation during the reaction.36

On the contrary, the cyanomethylamide 5 is a stable compound
and its absence is a real proof of the fact that it is not formed during
the reaction.

So the real question is why the cyanomethyl anion does not react
with the isocyanate.

In order to solve this problem, we have carried out a computa-
tional study on our products. In particular, we have fully relaxed
products similar to 2 and 5 (in which the alkyl substituent is a
methyl, to shorten the calculation time) according to the DFT ab-
initio scheme detailed in the Experimental section. The total energies
of the fully optimized configurations, reported in Fig. 4, have been
employed to calculate the reaction energy ER, i.e. the difference
between the total energy of the products and the ones of the starting
materials. In the case of CH3NHCONHCOCH3 (Fig. 4a) we have
obtained ER = −0.164 eV = −3.79 kcal mol−1, while in the case of
CH3NHCOCH2CN (Fig. 4b) we have calculated ER = −0.051 eV = −1.19 kcal mol−1, i.e. more than three time higher than the previous
one. This provides evidence that the reaction leading to product 2
is significantly more thermodynamically favourable than the one
leading to product 5, thus justifying the electrochemical results.

Due to the large difference between the reaction enthalpy values
calculated, the entropic term, that is typically quite small, is not
expected to play an important role so that the interpretation of the
experimental results is on enthalpy basis only.

Conclusions

With the intent to react electrogenerated cyanomethyl anion with
cyclohexylisocyanate, we carried out the galvanostatic reduction of an
ACN-Et4NBF4 solution on a platinum cathode, in a divided cell,
adding at the end of the electrolysis the isocyanate. Surprisingly, no expected product was isolated, and only the acetamidated product was obtained. This could be due to an anomalously high content of water in the catholyte, with the co-reduction of H2O and the generation of hydroxyde anion. Nonetheless, it was strange that the cyanomethylated product was not also present (even if in low yield). In fact, when reacting benzaldehyde instead of the isocyanate, the corresponding cyanomethylated product was obtained. Moreover, we checked that the cyanomethylated product of isocyanate (if present) would be a stable molecule under our experimental conditions. Intrigued by this result, we checked for acetamide in the electrolyze solution, finding it although in a lower amount than its product with cyclohexylisocyanate.

Computational analysis on the two possible products of the catholyte with the isocyanate allowed to state that the stability of two products differ, the acetamidated product being the most stable. This kind of computational analysis could open the way to the possibility to obtain predictable different products varying the experimental conditions or substrates.

The possibility of a concerted reaction, instead of acetamide anion formation prior to the reaction, is still an open question.

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References

1. C. Six and F. Richter, Ullmann’s Encyclopedia of Industrial Chemistry, 20, 63 (2012).
2. N. V. Gama, A. Ferreira, and A. Barros-Timmons, Materials, 11, 1841 (2018).
3. M. Widemann, P. J. Driest, P. Orecchia, F. Naline, F. E. Golling, A. Hecking, C. Eggert, R. Pires, K. Danielmeier, and F. U. Richter, ACS Sus. Chem. Engin., 6, 9753 (2018).
4. A. A. Fadda, S. Bondock, R. Rabie, and H. A. Etman, TÜürk. J. Chem., 32, 259 (2008).
5. S. J. Basha, P. Mohan, D. P. Yeggoni, Z. R. Babu, P. B. Kumar, A. D. Rao, R. Subramanyam, and A. G. Damu, Mol. Pharmaceuticals, 15, 2206 (2018).
6. I. Chiarotto, L. Mattiello, and M. Feroci, Acc. Chem. Res., 52, 3297 (2019).
7. C. F. Dahm and D. G. Peters, J. Electroanal. Chem., 402, 91 (1996).
8. S. Pons and S. B. Khoo, J. Am. Chem. Soc., 104, 3845 (1982).
9. J. Simonet, Y. Astier, and C. Cano, J. Electroanal. Chem., 451, 5 (1998).
10. C. Cougnon and J. Simonet, Platinum Met. Rev., 46, 94 (2002).
11. J. Simonet, Electrochem. Commun., 5, 439 (2003).
12. J. Simonet, Electrochem. Commun., 53, 15 (2015).
13. S. Pons and S. B. Khoo, Electrochim. Acta, 27, 1161 (1982).
14. J. K. Foley, C. Korzeniewski, and S. Pons, Can. J. Chem., 66, 201 (1988).
15. R.-S. Luo, X.-A. Mao, Z.-Q. Pan, and Q.-H. Luo, Spectrochim. Acta, Part A, 56, 1675 (2000).
16. E. E. Gilbert and E. J. Ramanowski, US Patent US3040095 (1962).
17. J. P. Richard, G. Williams, and J. Gao, J. Am. Chem. Soc., 121, 715 (1999).
18. R. A. Rossi, R. H. de Rossi, and A. F. López, J. Org. Chem., 41, 3367 (1976).
19. B. D. Wladkowski, J. L. Wilbur, M. Zhong, and J. I. Brauman, J. Am. Chem. Soc., 115, 8833 (1993).
20. K. B. Wiberg and H. Castejon, J. Org. Chem., 60, 6327 (1995).
21. L. Rossi, M. Feroci, and A. Inesi, Mini Rev. Org. Chem., 2, 79 (2005).
22. F. Barba, I. Barba, and B. Baranero, Electrochem. Commun., 48, 115 (2014).
23. G. C. Barrett and T. J. Grattan, Tetrahedron Lett., 43, 4237 (1979).
24. S. Siddiqui, S. I. Haider, S. S. Ahmad, and R. S. Siddiqui, Zeit. Nat. Forx., 40, 546 (1985).
25. T. M. Coady, L. V. Coffey, C. O’Reilly, and C. M. Lennon, Eur. J. Org. Chem., 5, 1108 (2015).
26. P. Giannozzi et al., J. Phys. Condens. Matter, 21, 295502 (2009).
27. G. Makov and M. C. Payne, Phys. Rev. B, 51, 4014 (1995).
28. J. P. Perdew, K. Burke, and M. Ernzerhof, Phys. Rev. Lett., 77, 3865 (1996).
29. N. Troullier and J. L. Martins, Phys. Rev. B., 43, 1993 (1991).
30. S. Grimme, S. Antony, S. Ehrlich, and H. Krieg, J. Chem. Phys., 132, 154104 (2010).
31. J. Simonet, Y. Astier, and C. Cano, Electrochim. Acta, 43, 4237 (1997).
32. F. Barba, I. Barba, and B. Baranero, Minirev. Org. Chem., 2, 79 (2005).
33. H. Ni, H. A. Nash, J. G. Worden, and M. D. Sourcek, J. Polymer Sci., Part A, Polymer Chem., 40, 1677 (2002).
34. P. Quaino, F. Juarez, E. Santos, and W. Schmickler, Beil. J. Nanotechnol., 5, 846 (2014).
35. G. Biani, M. Feroci, and L. Rossi, Eur. J. Org. Chem., 23, 3863 (2009).
36. J. Halli, K. Hofman, T. Beisel, and G. Manolikakes, Eur. J. Org. Chem., 21, 4624 (2015).