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

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The contamination with water of the cathodic ACN-Et_4NBF_4 solution gave us the opportunity to investigate alkyl isocyanate reactivity toward electrogenerated anions. The cathodic reduction of a ACN-Et_4NBF_4 solution led to the formation of both hydroxide and cyanomethyl anions. The reaction of the catholyte with cyclohexylisocyanate led to the exclusive formation of acetamidated product, with no traces of cyanomethylated one. On the contrary, when reacting with benzaldehyde only the cyanomethylated was isolated. Considering that the acetamidated product of benzaldehyde is reported to be unstable (thus its formation cannot be excluded), various experiments were carried out in order to understand the anomalous reactivity of cyclohexylisocyanate. Moreover, computational analysis allowed to state the higher stability of acetamidated product with respect to the cyanomethylated one. The possibility of a concerted reaction, instead of acetamide anion formation prior to the reaction, is still an open question.

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Isocyanates are molecules containing the –N=C=O group (a cumulene), quite reactive (mainly under nucleophilic conditions)[1] 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.[2] 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.[3]

Cyanoacetamides (Scheme 2) are important intermediates in organic synthesis,[4] 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.[5] The experimental conditions for the classical chemical synthesis of acetamides vary depending on the desired substituents 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.[4] 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 acetonitrile-tetraethylammonium tetrafluoroborate (ACN-$TEABF_4$) solutions (or other tetraalkylammonium salts) leads to the formation of cyanomethyl anion, $^{-}CH_2CN$ (also acetonitrile anion),[6] 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 acetonitrile,[7] while on a platinum cathode the reduction of hydrogen to hydride is possible[8] or the intervention of the cathode itself in the electrochemical reduction is reported, yielding a iono-metallic phase in which the platinum is negatively charged.[9–12] Whatever the mechanism (and the reaction conditions), the cathodic reduction of acetonitrile-tetraalkylammonium salt solutions yields the solvent anion. It should be underlined that all authors exclude the direct cathodic reduction of acetonitrile 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.[13,14]

It should be noted that the literature reports that the efficient hydrolysis of acetonitrile to acetamide needs a catalyst, usually a metal ion (Cu^{2+}, Ni^{2+}, Zn^{2+}, Pt^{2+}, etc.)[15] and/or high temperature,[16] moreover Richard and coworkers reported that "there was no detectable hydrolysis of the nitrile group of acetonitrile….during its base-catalyzed reaction in D_2O", the base being KOH.[17]

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.[18] 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 ambident nucleophile $^{-}CH_2CN$, quantifying the two possible products in a 9:1 ratio between C and N nucleophilic addition to an acyl chloride.[19] In addition, Wiberg and Castejon[20] calculated the CN bond order in the gas phase of acetonitrile (2.260) 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[17] 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 C≡N triple bond, with respect to the cumulene CH_2=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 viceversa) is minimal.

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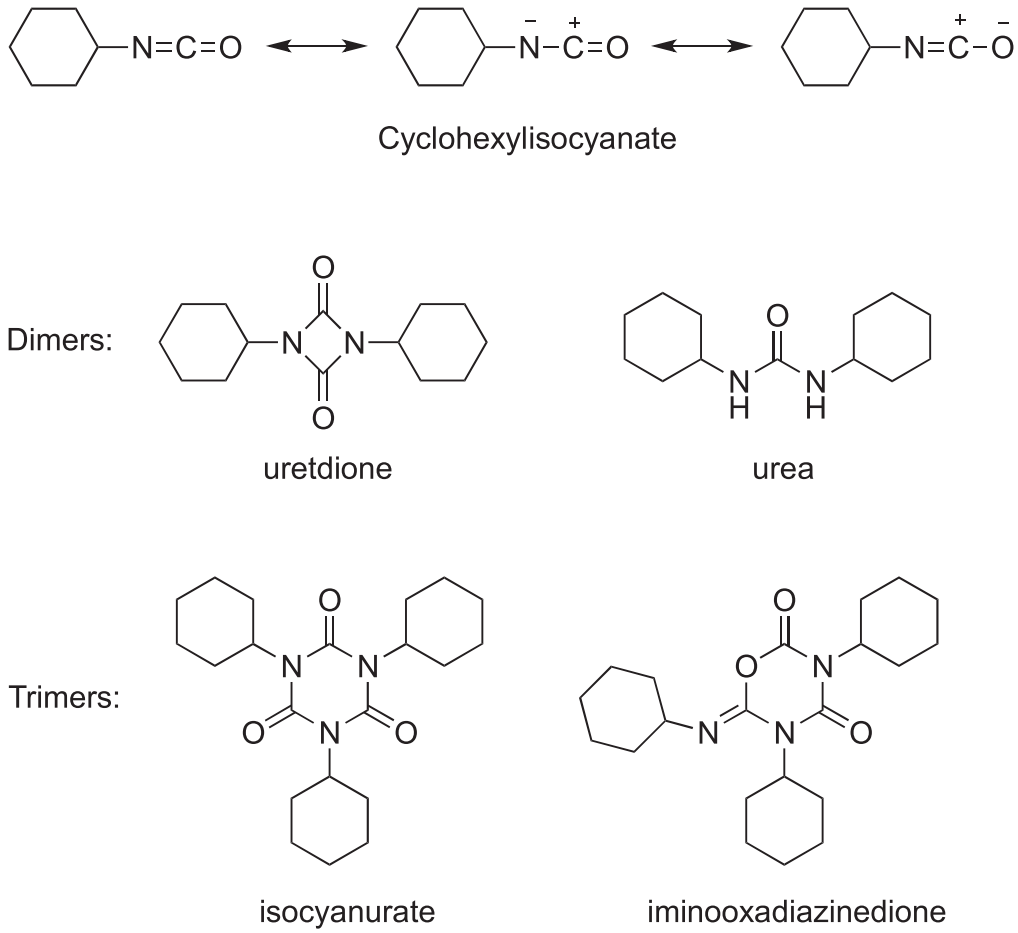
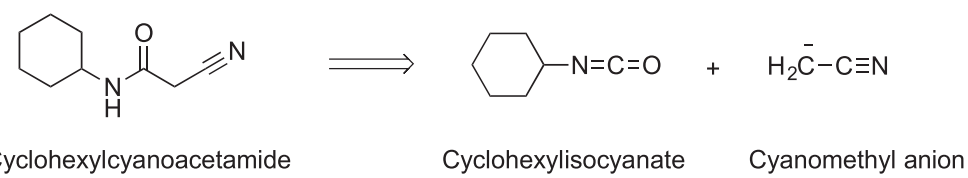
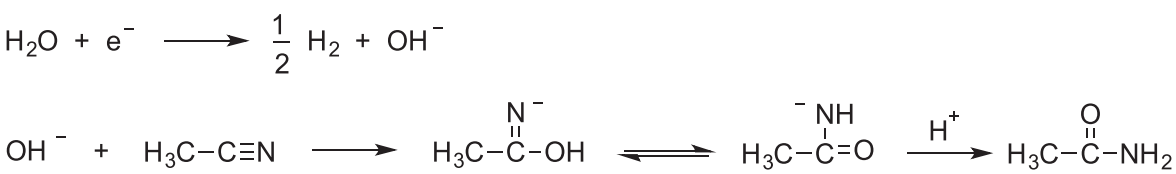


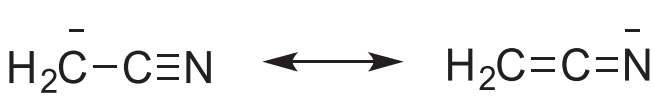
Scheme 1. Cyclohexylisocyanate structure and possible oligomers.



Scheme 2. Cyclohexylcyanoacetamide and its possible synthesis.



Scheme 3. Water reduction and acetonitrile hydrolysis.



Scheme 4. Cyanomethyl anion resonance stabilization.

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,[21] although usually in very low yields (1%–10%).[6]

Starting from acetonitrile as reagent (and solvent), electrochemistry allows for acetamidation of aromatic compounds, as recently reported by Batanero and coworkers.[22] 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.[23]

In continuation of our ongoing study on the reactivity of electrogenerated 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

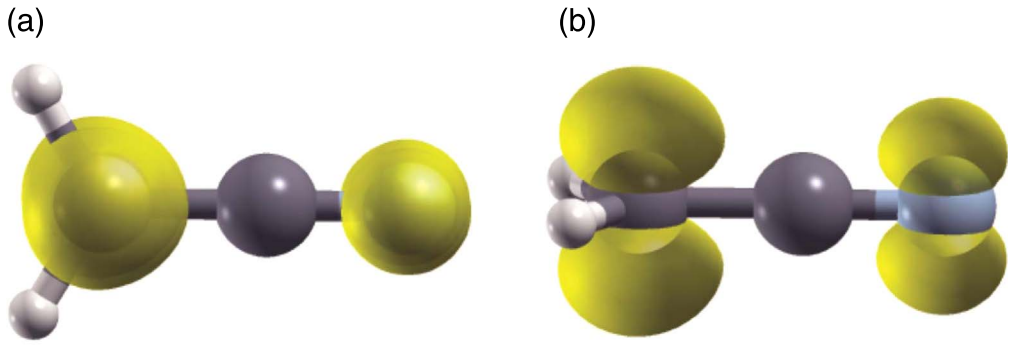
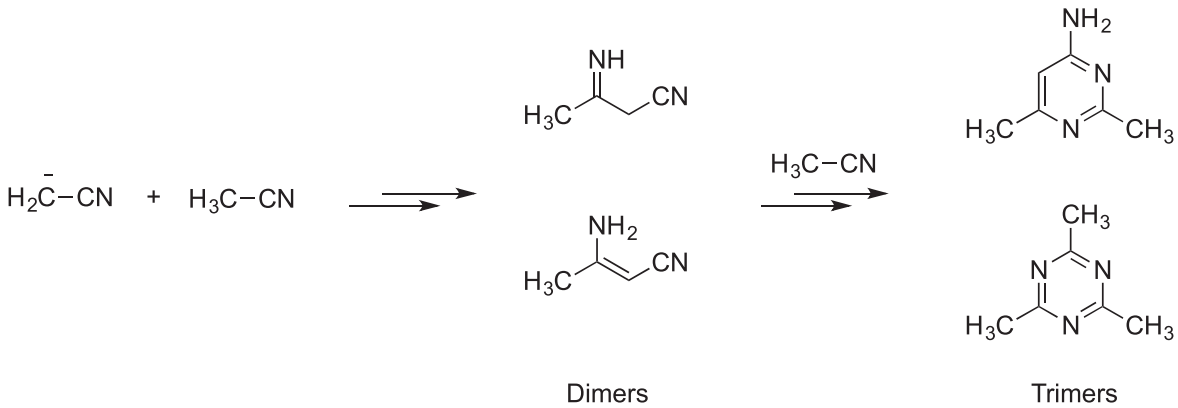


Figure 1. Top (a) and side (b) views of the HOMO wave function where the extra electron resides (the majority at the C-site).



Scheme 5. Possible products from the reaction of cyanomethyl anion and acetonitrile.

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. Et_4NBF_4 was kept at reduced pressure at 70°C for 24 h 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 SE 54 capillary column using a Hewlett-Packard 5890 series II gas chromatograph coupled with a Hewlett-Packard 5871 series II quadrupole mass selective detector. ^{1}H and ^{13}C NMR spectra were recorded at room temperature using a Bruker AC 200 spectrometer using $CDCl_3$ as internal standard.

***N*-Hexyl-2-cyanoacetylamide** was synthesized as reported in the literature[5] by reaction of *n*-hexylamine with ethyl cyanoacetate. ^{1}H-NMR ($CDCl_3$), δ (ppm): 6.32 (bs, 1H, N*H*), 3.38 (s, 2H, CH_2), 3.28 (app q, J = 6.6 Hz, 2H, CH_2NH), 1.54–1.51 (m, 2H, CH_2CH$_2$NH), 1.29 (bs, 6H, hex), 0.92–0.86 (m, 3H, hex). ^{13}C-NMR ($CDCl_3$), δ (ppm): 162.2, 115.2, 40.3, 31.3, 28.9, 26.4, 25.9, 22.4, 13.8. GC-MS, EI (m/z): 168 (M^+, 1%), 128 ($M^{+\cdot}$–CH_2CN, 100%), 97 (42%), 68 (46%).

Voltammetric measurements.—Voltammetric measurements were performed using an Amel 552 potentiostat equipped with an Amel 566 function generator and an Amel 563 multipurpose unit in a three-electrode cell; the curves were displayed on an Amel 863 recorder; acquisition software was a CorrWare for Windows version 2.8d1 Scribner, elaboration software was a CorrView for Windows version 2.8d1 Scribner. A 492/GC/3 Amel microelectrode was employed, using a Pt wire counter electrode and a modified saturated calomel electrode as reference electrode (mSCE: SCE with organic solvent junction; the oxidation peak potential of ferrocene measured on GC electrode in DMF containing 0.1 M Et_4NBF_4 as supporting electrolyte, is $E_{oxFc} = +0.512$ V vs mSCE). The scan rate was $\nu = 0.200$ Vs^{-1}. All cyclic voltammetries were recorded at room temperature on 5 ml of solvent/0.1 M Et_4NBF_4.

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/Et_4NBF_4 0.1 M); a Pt spiral (apparent area 0.8 cm^2) was used as anode; a Pt spiral (apparent area 0.8 cm^2), Ti, Pb, Ni, Cu or GC plates (area 0.8 cm^2) were used as cathode. Anolyte: 2 ml of CH_3CN-0.1 M Et_4NBF_4. Catholyte: 5 ml of CH_3CN-0.1 M Et_4NBF_4. 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*′-cyclohexylurea**[24]: ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.66 (s, 1H, N*H*), 8.46–8.43 (m, 1H, N*H*), 3.72–3.38 (m, 1H, C*H*NH), 2.12 (s, 3H, CH_3), 1.94–1.88 (m, 2H, cy), 1.73–1.55 (m, 3H, cy), 1.40–1.17 (m, 5H, cy). ^{13}C-NMR ($CDCl_3$), δ (ppm): 172.4, 153.7, 48.5, 32.8, 25.5, 24.5, 24.0. GC-MS, EI (m/z): 184 ($M^{+\cdot}$, 2%), 141 ($M^{+\cdot}$–CH_3CO, 14%), 98 ($M^{+\cdot}$–$CH_3CONHCO$, 20%), 83 (Cy, 18%), 56 (100%).

Acetamide (commercial): ^{1}H-NMR ($CDCl_3$), δ (ppm): 6.1 (bs, 1H, N*H*), 5.9 (bs, 1H, N*H*), 1.99 (s, 3H, CH_3).

Cyclohexylamine (commercial): ^{1}H-NMR ($CDCl_3$), δ (ppm): 2.65–2.58 (m, 1H, C*H*NH_2) 1.82–1.57 (m, 4H, cy), 1.32–1.05 (m, 6H, cy).

***N,N′*-dicyclohexylurea** (commercial): ^{1}H-NMR ($CDCl_3$), δ (ppm): 4.10–4.05 (m, 2H, N*H*) 3.52–3.43 (m, 2H, C*H*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, N*H*), 8.47 (bs, 1H, N*H*), 3.28 (app q, J = 6.4 Hz, 1H, CH_2NH), 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.

3-Hydroxy-3-phenylpropionitrile[25]: ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.40 (bs, 5H, Ar), 5.05 (t, J = 6.2 Hz, 1H, C*H*OH), 2.77 (d, J = 6.2 Hz, 1H, C*H*OH), 2.7 (bs, 1H, O*H*). ^{13}C-NMR ($CDCl_3$), δ (ppm): 141.0, 128.9, 128.8, 125.5, 117.3, 70.1, 27.9.

Cinnamonitrile (commercial): ^{1}H-NMR ($CDCl_3$), δ (ppm): 7.69 (d, J = 15.6 Hz, 1H, Ph-C*H*=), 7.56–7.48 (m, 2H, Ar), 7.41–7.35 (m, 3H, Ar), 6.50 (d, J = 15.6 Hz, 1H, =C*H*-CN).

ESI-MS/MS analysis.—A Quattro Micro Tandem MS-MS detector with an electrospray ionization (ESI) source Waters (Micromass) 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, cone voltage 25 V, source temperature 120 °C, desolvation temperature 350 °C, cone gas flow 40 l h^{-1}, desolvation gas flow 600 l h^{-1}. The instrument was used for infusion experiments in pESI mode, carried out in daughter mode; collision gas: argon. Direct infusion of samples into the source using an external syringe pump with a set flow rate of 5 μl min^{-1} was carried out; for each analyzed mass the parent ion and optimized collision energy (CE) value to obtain the best fragmentation pattern were selected. MassLynx Software 4.1 v (Data Handling System for Windows, Micromass) allowed data acquisition and handling and instruments control. Samples dilution of the electrolyzed solution was 1:10 with acetonitrile-water (50% v/v) and HCOOH 5 mM; 20 μl of the filtrate was injected for the analysis (Cronus Syringe Filter 0.45 μm). The samples were analyzed in triplicate.

Theoretical method.—Ab-initio calculations have been performed in the context of the Density Functional Theory (DFT) using the Quantum Espresso suite.[26] Both the electron density and the wave functions are expanded in a plane wave basis set and the Makov-Payne[27] correction has been used for the gas phase molecules considered as isolated systems in the context of periodic boundary conditions (PBC). We have employed the PBE-GGA approximation for the exchange-correlation functional[28] and Troullier Martins[29] ultra-soft pseudopotentials. The cubic supercell size was 3 nm, the energy cutoff for the wavefunctions and the electron density were respectively 90 Ry and 360 Ry, large enough to guarantee the convergence with the employed ultra-soft pseudopotentials. In particular the supercell size has been tested for the robustness of the reaction energy calculations of the isolated molecular systems in the gas phase. The energy and force thresholds were set respectively to 10^{-10} Ry and and 10^{-4} Ry/a.u. Lastly we have employed the Grimme semi-empirical correction[30] to account for the dispersion medium-long range forces.

Results and Discussion

The reaction between electrogenerated cyanomethyl anion (obtained by cathodic reduction of a solution of ACN-TEABF_4 on a platinum cathode, in a divided cell) and cyclohexylisocyanate, directed to the synthesis of the corresponding cyanoacetamide (Scheme 2), yielded an unexpected result as no traces of the expected product were present in the catholyte, while 30% of acetamidation of the isocyanate was obtained (Table I, entry 1).

This result was quite startling, as in long lasting work with electrogenerated cyanomethyl anion we never evidenced the presence of acetamidated products in the reaction mixtures, whichever the reagents. Moreover, the literature reported acetamidated products under electrochemical conditions using acetonitrile as solvent only under oxidative conditions[22] (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 acetamide, 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 acetamidated 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_4NBF_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_4NBF_4 to the reduction of water, see Introduction), as evidenced from the voltametric 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 pK_as 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 acetamidation and for the complete absence of the cyanomethylated product, we increased the amount of charge, in order to understand if the product **2** yield

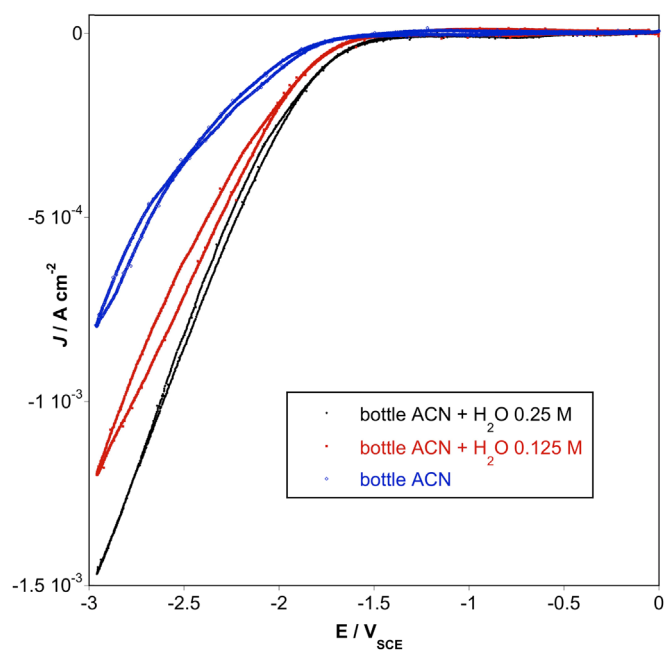
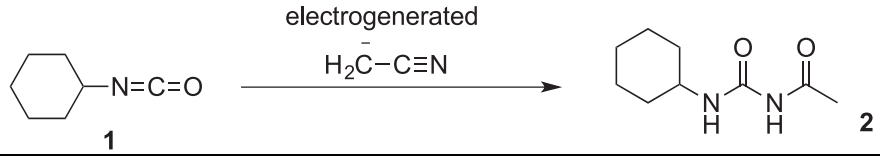


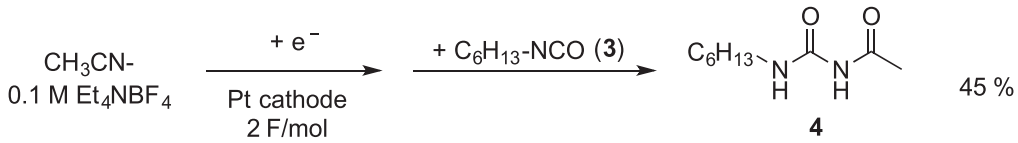
Figure 2. Cyclic voltammograms of a solution of bottle ACN-0.1 M Et_4NBF_4 (blue curve), in the presence of 0.125 M water (red curve) and 0.250 M water (black curve). GC electrode, vs mSCE, scan rate 0.200 Vs^{-1}, r.T. Scan: 0.0 V to −3.0 V to 0.0 V.

Table 1. Electrochemical generation of cyanomethyl anion and subsequent reaction with cyclohexylisocyanate 1.[a)]



Entry	Cathode	Charge (F)[b)]	*N*-(cyclohexylcarbamoyl)acetamide 2, %[c)]
1	Pt	1.0	30%
2	Pt	1.5	36%
3	Pt	2.0	56%
4	Pt	3.0	43%
5[d)]	Pt	2.0	46%
6[e)]	Pt	2.0	51%
7[f)]	Pt	2.0	35%
8[g)]	Pt	2.0	16%
9[h)]	Pt	2.0	24%[i)]
10	—	—	—
11[j)]	Pt	—	—
12	Ni	2.0	52%
13	Ti	2.0	6%[k)]
14	Pb	2.0	8%
15	Cu	2.0	25%
16	GC	2.0	16%[l)]

a) Catholyte (5 ml) and anolyte (2 ml): bottle ACN (0.02% nominal water content)−0.1 M $TEABF_4$, divided cell, Pt anode, rt, N_2 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**.

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-Et_4NBF_4 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.

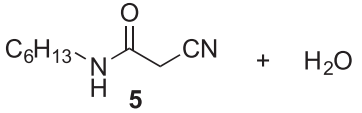
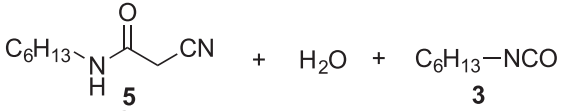
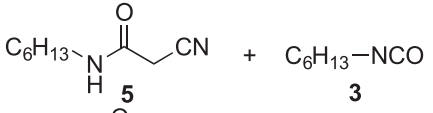
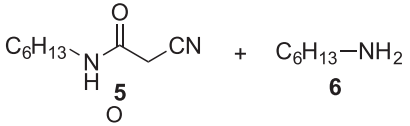
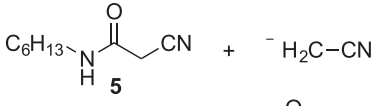
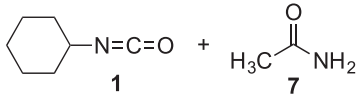
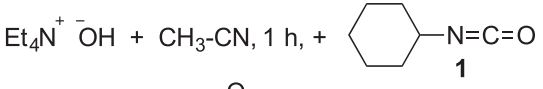
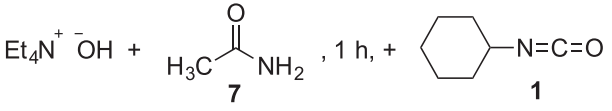
It should be underlined that this anomalous reaction is active only under electroreductive conditions, as pointed out by the experiments reported in Table I, entries 10 and 11 (blank experiments in the absence of current).

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 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[a)]		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, cyclo-hexylamine

a) Catholyte (5 ml) and anolyte (2 ml): bottle ACN-0.1 M $TEABF_4$, divided cell, Pt anode, rT, N_2 atmosphere, $I = 25$ 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.

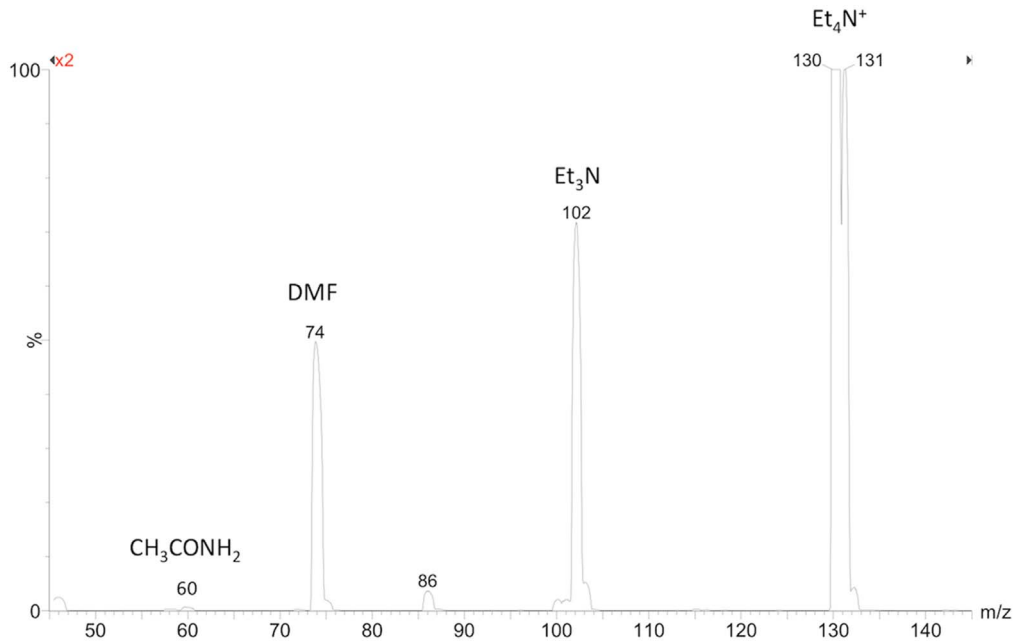


Figure 3. Positive electrospray ionization mass spectrum. Acetonitrile-0.1 M Et_4NBF_4 after electrolysis (97 C, 2 F).

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 experiment 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 β-hydroxynitrile **8** by cyanomethylation (previously reported by our research group[35]). The results are reported in Scheme 7.

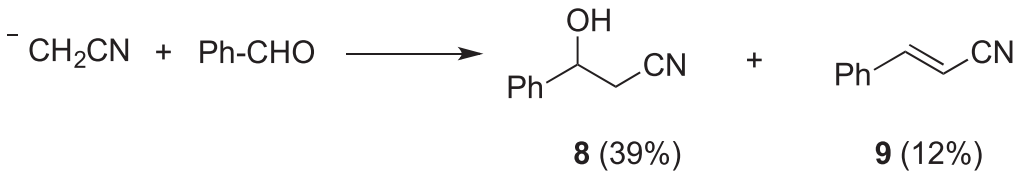
This reaction confirmed the effective generation of cyanomethyl anion by cathodic reduction of ACN-Et_4NBF_4, although the higher water content lowered the yields (overall 71% in the literature), having isolated two products deriving from the cyanomethylation of benzaldehyde (cinnamonitrile **9** is obtained from **8** by water elimination). It is to be underlined that no other product was isolated (no acetamidation product).

To acertain 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).

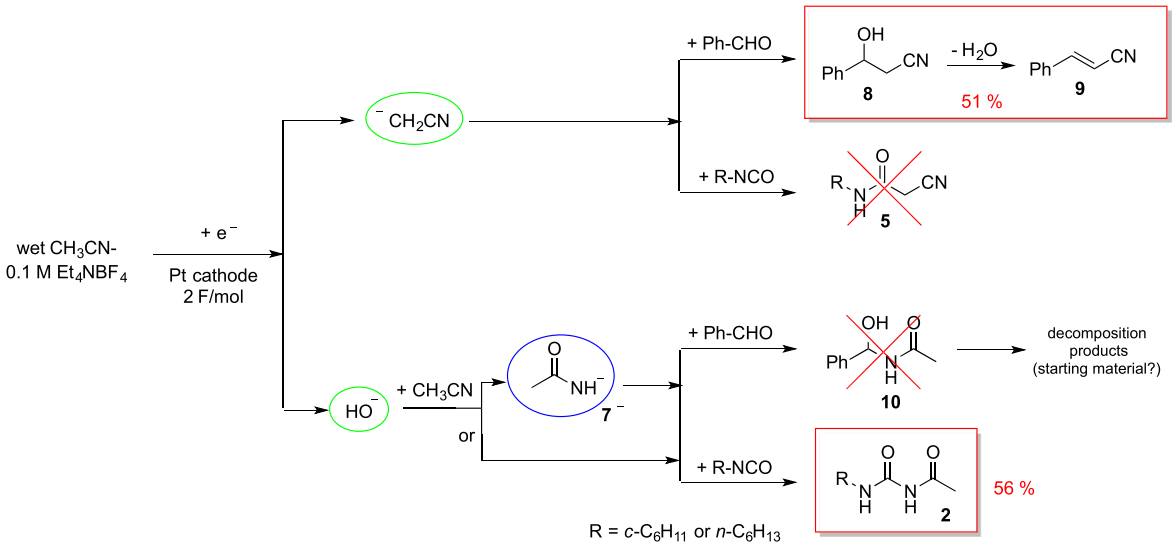
Figure 3 shows the positive electrospray ionization (pESI) mass spectrum (in infusion mode), considering the 45–145 interval of masses (i.e., containing the masses we were interested in). Acetamide corresponds to $[M + H]^+ = 60$, DMF to 74 (DMF derives from the gel of anolyte and catholyte separator), 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_3N signal (although not directely 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 wether all the acetamidated product **2** derives from acetamide anion $\mathbf{7}^-$ (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.



Scheme 8. Overview of the electrolyses described in this work.

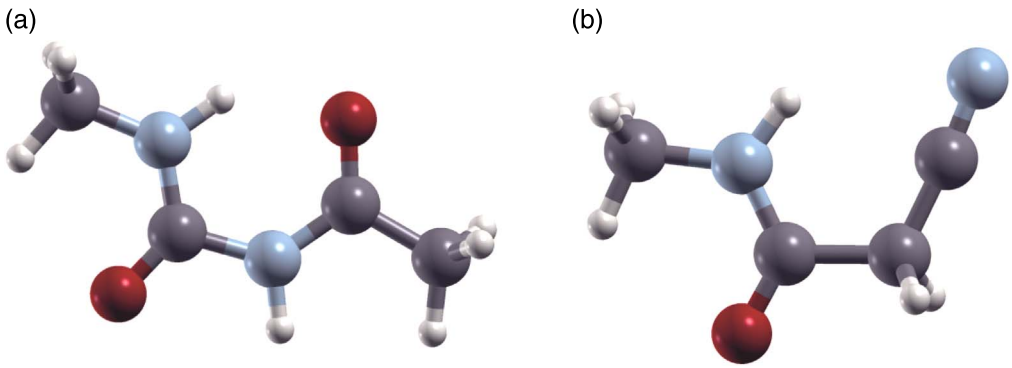


Figure 4. DFT optimized atomistic models of $CH_3NHCONHCOCH_3$ (a) and $CH_3NHCOCH_2CN$ (b).

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 benzaldehyde or cyclohexylisocyanate, yielding the corresponding hydroxynitrile **8** (from benzaldehyde) or cyanoacetamide **5** (from isocyanate). *Only hydroxynitrile **8** is obtained, not cyanoacetamide **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 corresponding *N*-acetyl-*N,O*-acetal **10** (from benzaldehyde) or *N*-acetylurea **2** (from isocyanate). *Only N-acetylurea **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 computational 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 E_R, i.e. the difference between the total energy of the products and the ones of the starting materials. In the case of $CH_3NHCONHCOCH_3$ (Fig. 4a) we have obtained $E_R = -0.164$ eV $= -3.79$ kcal mol^{-1}, while in the case of $CH_3NHCOCH_2CN$ (Fig. 4b) we have calculated $E_R = -0.051$ 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-Et_4NBF_4 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 H_2O 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.

Acknowledgments

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