

Hot Paper

Signal Transduction Allows Temporal Control of the Potential of a Concentration Cell Driven by the Decarboxylation of an Activated Carboxylic Acid

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The use of Activated Carboxylic Acids (ACAs) allows the time-controlled operation of dissipative chemical systems based on the acid-base reaction by providing both the stimulus that temporarily drives a physicochemical change and, subsequently, the counter-stimulus with a single reagent addition. However, their application is inherently limited to acid-sensitive systems. To overcome this limitation, we herein develop a straightforward device for the transduction of the acid-base stimuli delivered by an ACA into a voltage signal that, in turn, is

used to control voltage-sensitive circuits that are not pH-responsive by themselves. The signal transducer can be easily assembled from common laboratory equipment and employs aqueous solutions of readily available chemicals. Furthermore, the operator can simply and intuitively tune the amplitude of the voltage signal, as well as its duration and offset by varying the concentration of the chemical species involved in the transduction process.

Introduction

The great and increasing interest in dissipative systems capable of being maintained in an out-of-equilibrium state^[1] by the consumption of a chemical species^[2] or absorption of radiative energy (light)^[3] is essentially motivated by the chance to achieve a temporal control of their physico-chemical properties. This is particularly true if the out-of-equilibrium state is associated with a functional and useful property. A simplified scheme for the operation of a generic dissipative system is reported in Figure 1A. The system is initially found in its resting state (A). A chemical stimulus (often referred to as “chemical fuel”)^[4,5] or a photophysical stimulus is provided and, consequently, the system passes to an out-of-equilibrium state (B), which persists as long as the stimulus is supplied. When the fuel is exhausted or the irradiation is interrupted, the system autonomously comes back to the initial resting state. For the systems driven by a chemical stimulus, the larger the amount of the added fuel, the longer the time needed for its dissipation, and the longer the time spent by the system in the out-of-

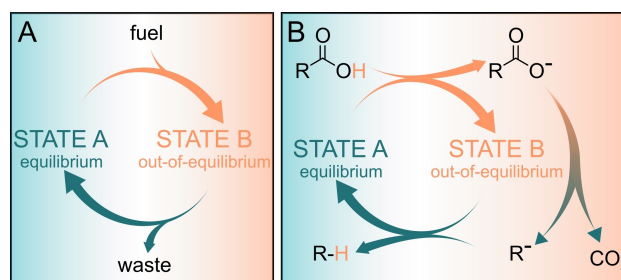


Figure 1. A) Generic switching of a dissipative system from the equilibrium state A to the out-of-equilibrium state B with the consequent conversion of a fuel to waste. B) Use of an ACA for the operation of a dissipative system. In this case, the ACA is the fuel, and the decarboxylation product represents the waste.

equilibrium state. Symmetrically, as for light-operated systems, the longer the irradiation times, the longer the duration of the out-of-equilibrium state.

As for dissipative systems driven by a chemical stimulus, we and others recently reported that activated carboxylic acids^[6] (ACAs, 2-cyano-2-phenylpropanoic acid^[7] and its derivatives,^[8] trichloroacetic acid,^[9] tribromoacetic acid,^[10] and nitroacetic acid)^[11,12] can be used as chemical fuels for the operation of systems based on the acid-base reaction. In this case, since the fuel is an acidic species, the system must possess one or more basic sites (Figure 1B). The ACA is added to the equilibrated system which, consequently, passes from state A to the protonated out-of-equilibrium state B. The latter is an out-of-equilibrium state because the conjugate base (the carboxylate anion) of the ACA is not stable and loses CO₂. The resulting carbanion is a strong base capable of taking back the proton from the protonated system, which goes back to the initial, resting state A. Changing the nature and the amount of added

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ACA one can control the time spent by the system in the out-of-equilibrium, protonated state.

Over the past few years, ACAs have been used to drive several dissipative systems including molecular switches^[7a,8,9b,12] and motors,^[9a] host-guest systems,^[11,13] translocations,^[14,15] dynamic libraries,^[16] and smart materials.^[10b,17] Although ACAs are a versatile class of reagents, their major limitation is that they can only drive the operation of dissipative systems based on the acid-base reaction. In order to overcome such limitation, we turned our efforts to develop a workaround through which the acid-base stimulus imparted by the ACA is *transduced* into an electric signal, potentially useable for other applications such as triggering external electric circuits or controlling other systems that do not respond directly to pH changes.

This chemo-electric signal transduction strategy is inspired by nature. For instance, the increase of a neurotransmitter concentration in the synaptic cleft is transduced as an action potential to the postsynaptic cell allowing signals to be transmitted and regulated.^[18]

Classic non-equilibrium systems such as those employing the Belousov–Zhabotinsky (BZ) reaction are known to be suitable for the generation of highly reproducible electric signals. These reactions have found application in the simulation of simplified models of biological systems,^[19] as well as for performing simple computations.^[20] However, their application is somewhat limited by the extreme complexity of these systems. As an example, at least 18 coupled chemical reactions are thought to simultaneously occur in a typical BZ system.^[21] As such, even qualitative predictions of the system behavior upon initial conditions change are difficult to make without the aid of complex mathematical models.^[22]

Here we report that nitroacetic acid **1**, the most reactive among the ACAs studied so far, can be used for the temporal control of the potential difference (electromotive force, emf) between the electrodes of a concentration cell, whose operation is based on the coupling of two identical pH-dependent half-cells with different and changing-over-time hydrogen ion concentration. We also show that such time-dependent voltage changes can be modulated by varying the reaction conditions, with the advantage that the system behavior is intuitive and easy to rationalize.

Results and Discussion

Approach

The well-characterized pH-dependent *p*-benzoquinone (**Q**)/hydroquinone (**QH₂**) electrochemical couple (see Figure 2, bottom, for the reduction reaction) was investigated for the operation of a concentration cell. The choice of this redox couple was dictated by its tolerance to a broad pH range as well as the wide availability, water solubility and stability of its components.

The Nernst equation for the **Q**/**QH₂** couple is reported in Eq 1, where *a* represents the activity of a given species, *F* is Faraday's constant (96485 C·mol⁻¹), *z* is the number of

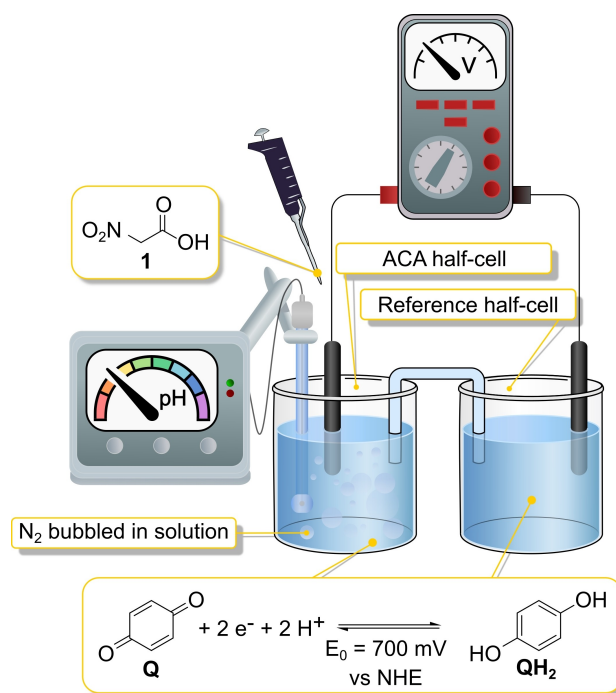


Figure 2. Top) Schematic representation of the concentration cell. Both half-cells contain **Q** and **QH₂** at the same concentration. In the half-cell to the right (“reference half-cell”, connected to the negative pole of the voltmeter) the pH is kept constant by means of a buffer while in the half-cell to the left (“ACA half-cell”, connected to the positive pole of the voltmeter), the pH is controlled over time by the addition of **1** and its subsequent and autonomous decarboxylation. Nitrogen gas is bubbled in the solution to remove the CO₂ that evolves over the course of the experiment. Bottom) Reduction half-reaction for the **Q**/**QH₂** electrochemical couple.

electrons exchanged in the half-reaction (2 electrons, for this couple), and *R* is the universal gas constant (8.314 J·K⁻¹·mol⁻¹).^[23]

$$E = E_0 + \frac{RT}{zF} \ln \frac{a_Q a_{H^+}^2}{a_{QH_2}} \quad (1)$$

A proton concentration cell is made of two half-cells with the same pH-sensitive redox couple and different proton concentrations. We designed the device using the same concentrations of **Q** and **QH₂** in both half-cells (for example 3.3 mM each). Then, in one half-cell (ACA half-cell) the pH (pH_{ACA}) is controlled by the addition of **1** and its subsequent and autonomous decarboxylation. In the other half-cell (the reference half-cell) the pH (pH_{ref}) is kept constant by means of a buffer. Nitrogen gas is slowly bubbled in the ACA half-cell to remove the CO₂ that otherwise accumulates in solution, altering the pH.^[11,12] In the ACA half-cell, the ionic force is set to μ = 0.50 M by the addition of KCl. The ion exchange between the two half-cells is ensured by means of a salt bridge (see SI, pages S2–S3 for the experimental setup).

Under these conditions, the only parameter controlling the emf of the cell is the pH difference between the two half-cells. Such emf can be calculated by applying Eq 1 to both electrodes and evaluating the difference. If one regards the reference

electrode as the negative one and incorporates all the constants, Eq 2 holds true.

$$\Delta E_{ACA-reference} \text{ (mV)} = Y(pH_{ACA} - pH_{ref}) \quad (2)$$

Where Y is a constant that, under the adopted conditions, was measured as (-55 ± 1) mV (see SI, pages S4–S5). Therefore, in the absence of side processes, at the addition of **1** to the ACA half-cell, one should expect the emf of the cell to increase to a maximum with a slope of about 55 mV/pH-unit due to the initial lowering of the pH. Then, upon decarboxylation of the nitroacetate anion and proton reuptake by the resulting nitronate, the emf should decrease again to eventually reach a value dictated by the equilibrium pH of the ACA half-cell. A schematic representation of the device is shown in Figure 2, top.

Concentration cells

In a typical experiment, the initial pH in the ACA half-cell was set to 12.00 by the addition of NaOH while in the reference half-cell a borate buffer kept the pH constant to 9.00. Then, different amounts (from 2.0 to 20 molequivalents with respect to the hydroxide ion) of **1** were added to the ACA half-cell. Both the pH and the voltage between the electrodes were measured over time before and after the addition of **1** to the ACA half-cell. The resulting curves are reported in Figure 3 (see Figures S6–S25 to better visualize the single experiment). Since the voltage was measured when essentially no current passed through the cell, the voltage read is the emf of the cell. It is apparent that in all cases a variable voltage signal was produced by the cell. Upon the addition of **1** to the ACA half-cell, the pH decreased sharply to a value dependent on the amount of **1** added to the system.^[24] Then, once the minimum was reached, except for the most diluted case (2.0 molequivalents of **1** with respect to the hydroxide ion),^[25] the pH started increasing slowly, due to the decarboxylation of the excess nitroacetic acid and the back proton transfer. Once the excess acid was fully depleted, the pH rapidly reached an inflection point, followed by a slow asymptotic rise to a maximum. Concurrently, following addition of **1**, the voltage across the cell quickly rose to a maximum. Then, excluding the run with 2.0 molequivalents of **1**, the voltage decreased to an equilibrium value passing through an inflection point.

It is worthwhile noticing that, for each run, the inflection point in the pH vs t and emf vs t curves occurs at the same time, which increases linearly with the mol equivs of **1** added to the ACA half-cell (Figure S33). In other words, the changes of pH and voltage over time are clearly coupled, with the former driving the latter.

As seen in a previous investigation, the runs can be repeated with high reproducibility, being the final, equilibrium pH in the ACA half-cell poorly dependent on the initially added amount of ACA. More precisely, such value goes from 8.7 to 8.3 on increasing initial ACA concentration.^[26] Consequently, the final, equilibrium voltage of the cell also shows little variations.

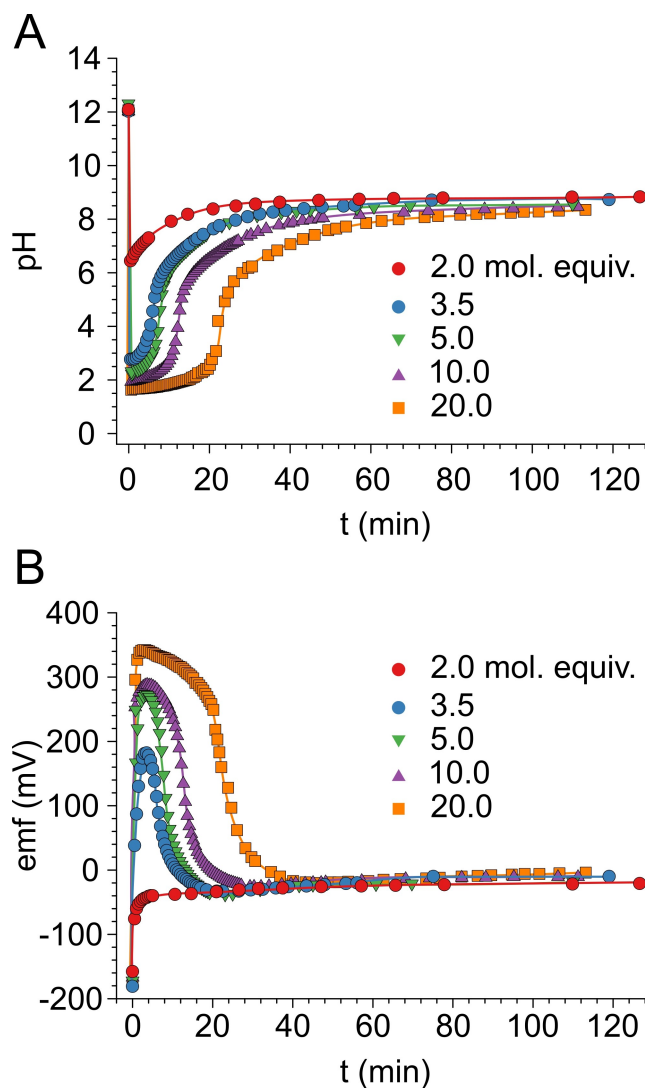


Figure 3. Effect of the different amounts of **1** added to the system. Top) Evolution of the pH of the ACA half-cell over time. Bottom) Corresponding voltage data of the galvanic cell. For all the experiments, **1** was added at time $t=0$. The data points for the experiments carried out with 2.0, 3.5, 5.0, 10, and 20 molequivalents of **1** with respect to the hydroxide ion are shown in red, cyan, green, purple, and orange, respectively. The lines between the experimental points are a guide for the eye.

Values ranging from -18 mV to -4 mV were obtained in the explored range of ACA **1** concentrations.

Time-resolved NMR spectra of the ACA half-cell solution show that the conversion of **1** to nitromethane occurs smoothly without the formation of subproducts (see Figure S34 and related caption for the spectra and details on the experiment).

The possibility of repeating the pH and voltage cycles was tested. At the end of a typical run with 5.0 molequivalents of **1** with respect to the hydroxide anion, aliquots of **1** were added to the ACA half-cell until the pH of the solution reached a value of 2. Then, the system was left to evolve, and, gratifyingly, the pH and voltage signals qualitatively reproduced those of the single-addition experiments (see Figures S35 and S36 for the pH and voltage signals respectively). In total, up to three additions

of **1** could be performed, leading to three distinct pH and voltage pulses.

In additional experiments, the pH of the reference cell was varied to reach different equilibrium voltages. Thus, phosphate buffers were used to set the pH of the reference half-cell to 7.00 and 12.00 (See Figure 4) and the ACA concentration was fixed to 10 molequivalents with respect to the hydroxide ions, which allowed to follow the reactions on a convenient timescale. As predicted by Eq 2, a higher pH of the reference half-cell led to overall higher voltages throughout the experiment as shown by a comparison of the data obtained with $\text{pH}_{\text{ref}} = 12.00$ and 9.00 (black and cyan points in Figure 4, respectively). Symmetrically, the voltages measured in the run where the reference-cell pH was set to 7.00 (red points in Figure 4) were consistently lower than those obtained when pH_{ref} was set to 9.00.

The above results are notable since they show that the emf signal of the cell can be modulated at will not only in amplitude and duration (acting on the amount of added **1** with respect to the hydroxide anion) but can also be offset to higher and lower values maintaining the general shape of the emf vs *t* curve, by regulating the pH in the reference half-cell. In particular, the operator can choose whether the cell voltage remains positive, negative, or flips throughout the experiment (runs with $\text{pH}_{\text{ref}} = 12.00$, 7.00, and 9.00, respectively). Furthermore, after the addition of **1**, the system evolves autonomously and requires no other intervention from the operator (fire-and-forget operation). Therefore, the galvanic cells here developed act as flexible, programmable signal generators.

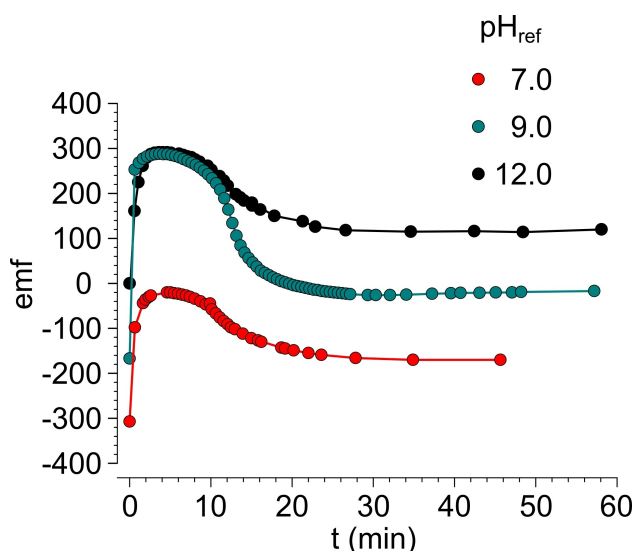


Figure 4. Effect of the pH of the reference half-cell. All the experiments were carried out with 10 molequivalents of **1** with respect to the hydroxide ion, added to the ACA half-cell at $t = 0$. For the red dataset, pH_{ref} was set to 7.00 by means of a phosphate buffer, for the cyan dataset, pH_{ref} was 9.00 (set with a borate buffer), and the black points are relative to an experiment with $\text{pH}_{\text{ref}} = 12.00$ (phosphate buffer). The lines between the experimental points are guides for the eye.

Simple Applications

Having developed a reliable, tunable device for the generation of electric signals by chemical methods, we exploited it to control systems that would not normally respond to changes in acidity. As a proof of concept, we employed our nitroacetic acid fuelled signal generator to regulate the operation of external electronic components, thus coupling a chemical phenomenon (*i.e.*, the decarboxylation of an ACA) to a purely electric event (that is the turning ON and OFF of electronic circuits) where no chemical reactions are involved.

An operational amplifier was employed to build a simple non-inverting comparator circuit which produces an output whenever the input signal is more positive than a reference voltage.^[27] The resulting comparator circuit (see Figures S37 and S38), was powered with an external battery and interfaced with the signal generator (the galvanic cell driven by **1** described in Figure 2). The comparator was fed with an external reference voltage of 100 mV with respect to the reference half-cell (the latter is from now on referred to as “ground”). When the galvanic cell voltage surpassed this value, the comparator allowed current to flow through a LED (ON state). Subsequently, as the cell voltage fell below the 100-mV threshold, the comparator output was pulled to ground, and the LED turned OFF.

The experiment is illustrated in Figure 5A where selected photos are reported. Before the addition of 5.0 molequivalents **1**, the voltage of the cell was below the activation threshold of the comparator (LED OFF, Figure 5A, left). Then after the addition, the voltage rose above 100 mV (LED ON, Figure 5A, middle), and eventually fell back below the threshold (LED OFF, Figure 5A, right). When a larger amount of **1** (10 molequivalents) was added to the system, the LED persisted in the ON state for a longer time, as expected. Figure 5B pictorially illustrates the experiment. See also Videos S1 (5.0 molequivalents **1**) and S2 (10 molequivalents **1**) for visualizing the whole experiment and pages S24 and S25 of the SI for an in-depth discussion of the circuit.

Due to the extremely high input resistance of the operational amplifier used (details on pages S24–S25), the signal generator (the galvanic cell) supplied virtually no current to the external circuit. Instead, the circuit was powered by the external battery *via* the amplifier. As such, the decrease in cell voltage over time was solely ascribable to the increase of the ACA half-cell pH, with no contribution from the consumption of **Q** and **QH₂** inside of the cell due to the flow of current. Therefore, the galvanic cell operates purely as a signal generator. As a control experiment, we loaded the ACA half-cell with trifluoroacetic acid (TFA, 5.0 molequivalents with respect to the hydroxide ion) instead of **1**. Since TFA does not undergo base-catalyzed decarboxylation under our reaction conditions, after the addition of the acid, the pH in the ACA half-cell stayed low for the whole duration of the experiment, and the voltage of the cell never fell below the 100-mV threshold (see also Video S3). Consequently, the comparator remained ON, and the LED stayed lit for 75 minutes until we disconnected it from the system.

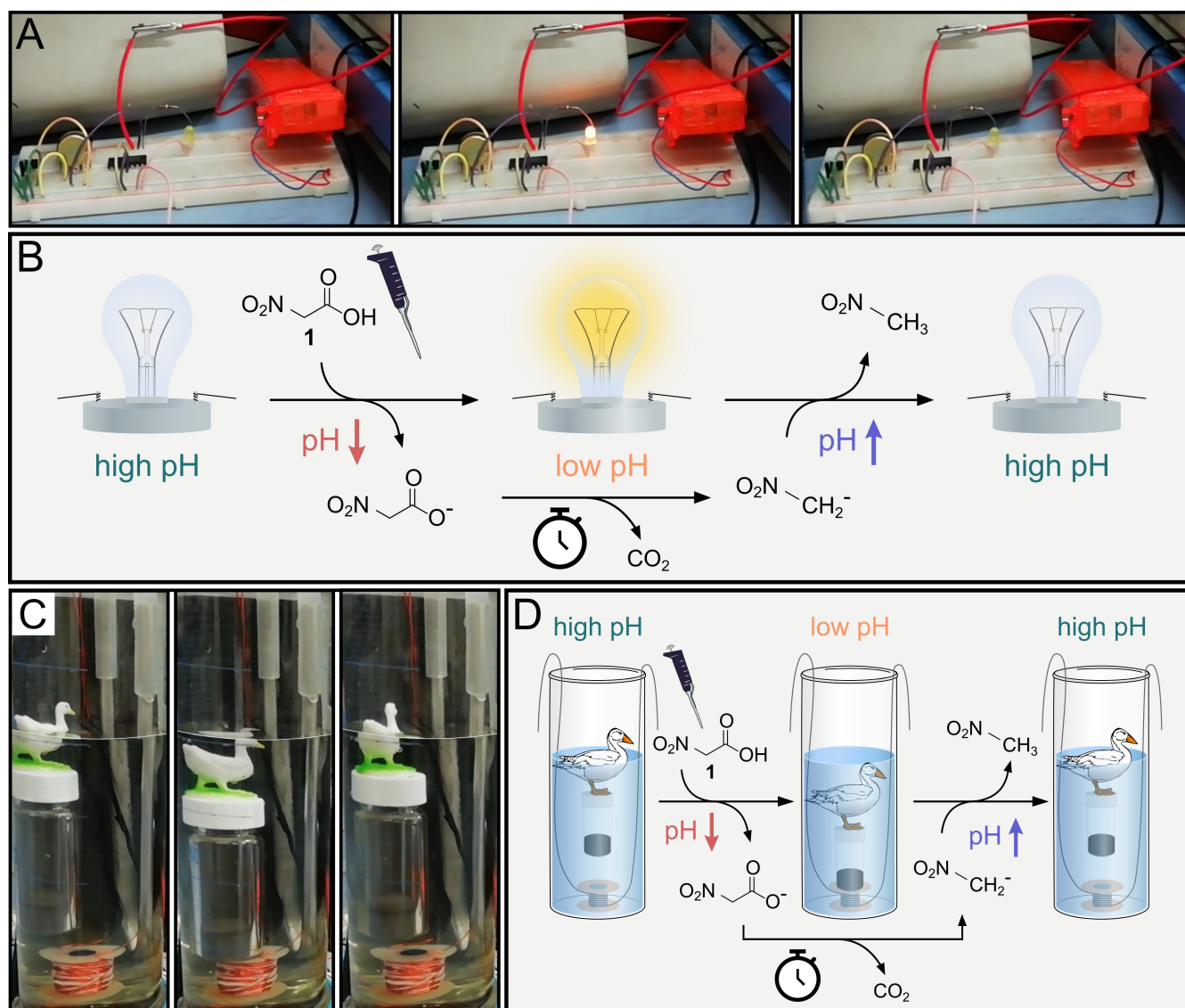


Figure 5. A) Using the galvanic cell as a signal generator to control the operation of a LED through a comparator circuit. Initially, the emf of the cell is below the comparator threshold so the LED is unlit. After the addition of 1 to the ACA half-cell, the pH drops and the emf of the cell increases until the comparator circuit is switched on, lighting the LED. As 1 decarboxylates, the pH in the ACA half-cell increases again, the emf of the cell decreases and the LED is switched off (see Video S1 and S2 in the SI). B) Schematic representation of the experiment with the LED. C) Using the galvanic cell to control the floating of a goose figurine glued onto a vial filled with iron filings. The current flowing in an electromagnet is controlled *via* the comparator circuit. Initially, the emf of the cell is below the comparator threshold so the electromagnet is OFF and the goose floats. After the addition of 1 to the ACA half-cell solution, the pH drops and the emf of the cell increases until the comparator circuit is switched on, energizing the electromagnet, and attracting the goose underwater. As 1 decarboxylates, the pH in the ACA half-cell increases again, the emf of the cell decreases and the external circuit is switched off, stopping the current flow in the electromagnet, and letting the goose re-emerge (see Video S4 in the SI). D) Schematic representation of the experiment with the electromagnet.

In a second application, we used our signal generator to control the movement of a macroscopic object, that is the immersion and emersion of a goose figurine in a water column using an electromagnet energized by an external power supply (detailed description of the circuit in Figure S39). Figure 5C and pictorially Figure 5D show one of the runs of this kind of experiments. Note that the goose figurine is attached to the cap of a vial partially filled with iron filings. At first, no current flowed in the electromagnet and the goose floated (system in OFF state, left panel). Then, after the addition of 10 molequivalents 1, current started to flow into the electromagnet attracting the goose underwater (system in the ON state, middle panel).

Finally, once the ACA fuel is exhausted, no current powered the electromagnet, and the goose re-emerged (system back in OFF state, right panel). A video of the whole experiment is available at the link reported as Video S4.

Conclusions

In this work, we showcase a new programmable system for generating transient electrical signals by chemical methods. Nitroacetic acid 1 was used to temporarily alter the pH of a solution containing a pH-sensitive redox couple, thus affecting

its electric potential, and transducing the pH change into a variation of the redox potential.

The resulting variable-potential half-cell was connected to a reference half-cell with a fixed electric potential, allowing to generate tunable voltage signals. By regulating the amount of **1** added to the system, we could change the amplitude of the signal, as well as its duration. Moreover, by tweaking the pH of the reference cell, we shifted the signal to more positive or negative voltages. Remarkably, the device we obtained could be interfaced with electric circuits, thus coupling their operation to the working cycle of an activated carboxylic acid with no intervention from the operator besides the addition of **1** in a fire-and-forget fashion. To the best of our knowledge, this work reports the first example of the transduction of a transient chemical signal due to a transient chemical stimulus^[28] into a transient voltage signal for the operation of a system that is not by itself sensitive to acids and bases. While the use of activated carboxylic acids was previously restricted solely to pH-sensitive systems, here, by transducing the pH cycle into a voltage cycle, we provided a convenient method for applying the well-known chemistry of decarboxylative fuels to systems that are otherwise unaffected by pH changes. We believe that this approach will prove useful in the switching of redox systems by means of ACAs.

Supporting Information

The authors have cited additional references within the Supporting Information.^[29,30]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Activated carboxylic acids · Dissipative systems · Device interfacing · Out-of-equilibrium · Signal transduction

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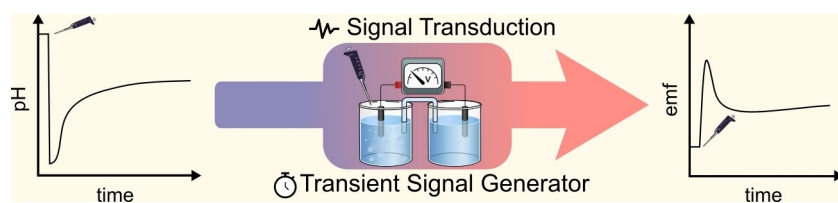
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- [23] At a given temperature, all these constants can be grouped together, to give about 30 mV at $T=298$ K. Therefore, the potential of the Q/QH_2 couple increases by about 60 mV when the pH decreases by one unit.
- [24] As the concentration of **1** increases, the reduction in pH at the ACA half-cell becomes less significant. As such, the addition of larger quantities of **1** has diminishing returns on the voltage produced by the system (Figures S30 and S31 report the effect of the concentration of **1** on the pH of the ACA half-cell and the cell voltage, respectively).
- [25] Once **1** is added to the ACA half-cell, the magnetically stirred solution needs some time to homogenize before the pH meter and the voltmeter can give reliable readings. In our reaction conditions, in the case where only 2.0 molequivalents of **1** with respect to the hydroxide ion are added, the decarboxylation of the nitroacetate anion is on the same timescale as the mixing time so no plateau in voltage nor pH is observed. When a larger excess of **1** is used (as little as 3.5 molequivalents with respect to HO^-), the time required to complete the decarboxylation is longer, thus the expected behavior is observed.
- [26] Argon (or nitrogen) bubbling is not enough to completely remove the just formed CO_2 , which, at the end of decarboxylation, remains at the constant value of its solubility in water, preventing the system to reach

- pH values higher than 9. Furthermore, the nitromethane by-product is itself an acidic species that contributes to the final pH of the system. For an extensive discussion see ref 11. The larger the amount of **1** added to the ACA half-cell, the larger the amount of nitromethane by-product at the end of the reaction, so the lower the pH of the solution.
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RESEARCH ARTICLE



Time-controlled pH variations enabled by the decarboxylation of nitroacetic acid are transduced into time-con-

trolled voltage variations. Such variations are exploited to govern the operation of simple electric devices.

Dr. G. Capocasa, Dr. F. Fratelloreto, S. Correale Cavallari, M. Valentini, Prof. Dr. O. Lanzalunga, Prof. Dr. S. Di Stefano**

1 – 8

Signal Transduction Allows Temporal Control of the Potential of a Concentration Cell Driven by the Decarboxylation of an Activated Carboxylic Acid

