



# A redox-flow battery with an alloxazine-based organic electrolyte

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1           **A redox flow battery with an alloxazine-based organic electrolyte**

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10

11           **Redox flow batteries (RFBs) can store large amounts of electrical energy**  
12 **from variable sources, such as solar and wind. Recently, redox-active organic**  
13 **molecules in aqueous RFBs have drawn substantial attention due to their rapid**  
14 **kinetics and low membrane crossover rates. Drawing inspiration from nature, here**  
15 **we report a high-performance aqueous RFB utilizing an organic redox compound,**  
16 **alloxazine, which is a tautomer of vitamin B<sub>2</sub>'s isoalloxazine backbone. It can be**  
17 **synthesized in high yield at room temperature by single-step coupling of inexpensive**  
18 ***o*-phenylenediamine derivatives and alloxan. The highly alkaline-soluble alloxazine**  
19 **7/8-carboxylic acid (ACA) produces a RFB exhibiting open-circuit voltage**  
20 **approaching 1.2 volts and current efficiency and capacity retention exceeding 99.7%**  
21 **and 99.98% per cycle, respectively. Theoretical studies indicate that structural**  
22 **modification of alloxazine with electron donating groups should allow further**

23 **increases in battery voltage. As an aza-aromatic molecule that undergoes reversible**  
24 **redox cycling in aqueous electrolyte, alloxazine represents a class of radical-free**  
25 **redox-active organics for use in large-scale energy storage.**

26 Improved methods for storing electrical energy from intermittent renewable  
27 sources are needed to support the rapid deployment of photovoltaic (PV) and wind  
28 power.<sup>1-3</sup> A promising approach for safe and cost-effective stationary energy storage uses  
29 redox flow batteries (RFBs), in which the energy is stored in fluids held outside the  
30 power conversion electrochemical cell.<sup>4,5</sup> This permits the independent engineering of  
31 energy (electrolyte volume and/or concentration) and power (cell area) capacities and  
32 enables the attainment of the high energy-to-power ratios (i.e. long discharge durations at  
33 rated power) necessary to deliver energy from PV and wind when it is needed. Since the  
34 invention of RFBs in the 1970s, the development efforts for its electrolyte materials – the  
35 core component of RFBs – have concentrated on single metal ions such as vanadium,  
36 iron and chromium, where the battery voltages are fixed by the reduction potentials of  
37 these ions, and their solubilities and stabilities are governed by the pH and composition  
38 of the supporting electrolyte.<sup>6,7</sup> However, their development has been impeded by one or  
39 more shortcomings such as high electrolyte corrosivity, toxicity, cost, membrane cross-  
40 over rate, or sluggish reaction kinetics.

41 Contrary to the limited numbers of metal ions suitable for RFBs, organic  
42 molecules display high chemical diversity, allowing optimization of electrolyte properties  
43 such as higher solubility (by adding solubilizing groups), higher voltage (by varying the  
44 electron donating properties of functional groups), and lower membrane cross-over rate  
45 (by tuning the molecular size or net charge on the molecules). Recently, researchers have

46 demonstrated RFBs of much improved performance by rational design of organic-based  
47 electrolyte materials (summarized in Table 1).<sup>8-13</sup> For instance, Huskinson *et al.* utilized a  
48 sulfonic-acid functionalized 9,10-anthraquinone, which showed fast kinetics and high  
49 solubility in a supporting electrolyte of sulfuric acid; by pairing it up with cheap  
50 bromine/hydrobromic acid, the team showed approximately a three-fold reduction of the  
51 potential cost of electrolyte materials, compared with state-of-art all-vanadium RFBs.<sup>8,9</sup>  
52 The toxicity and corrosivity of bromine, however, limit its use to industrial and utility  
53 settings. By switching from acidic to alkaline supporting electrolyte, Lin *et al.*  
54 demonstrated a less corrosive and non-toxic RFB using hydroxylated 9,10-anthraquinone  
55 and a food additive, ferrocyanide, targeted for residential and commercial usage.<sup>10</sup> To  
56 reduce membrane cost while maintaining a low membrane crossover rate, Janoschka *et*  
57 *al.* prepared polymeric methyl viologen and (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl  
58 (TEMPO) which showed almost no sign of membrane crossover when cheap dialysis  
59 membranes were used in place of expensive cation-exchange membranes.<sup>11</sup> Despite these  
60 great advances, each system still has potential for further improvement, such as replacing  
61 toxic halogen species with high-performance organic molecules, increasing the ion  
62 conductivity and energy density of alkaline systems, and reducing the high electrolyte  
63 viscosity associated with the dissolution of polymers at practical concentrations. To  
64 accelerate the development of organic-based RFBs, more compounds with useful redox  
65 potential, high solubility, and ease of synthesis are highly desired. Previous aqueous  
66 organic-based RFBs have utilized only three types of stable redox-active species: **1)**  
67 quinones, **2)** TEMPO and **3)** methyl viologen, as shown in Table 1. To date, tailored  
68 improvements have been proven possible only in quinone systems.

69           Gaining inspiration from naturally occurring flavin cofactors, here we report a  
70 novel alloxazine-based aqueous organic RFB. Alloxazines can be synthesized via a  
71 simple and high-yielding coupling reaction between *o*-phenylenediamine derivatives and  
72 alloxan in acetic acid and boric acid at room temperature and atmospheric pressure  
73 (Table 2).<sup>14–16</sup> Functionalization of alloxazine with a carboxylic acid group renders the  
74 alloxazine molecule highly soluble in alkaline solution – up to 2 M in pH 14 KOH, which  
75 corresponds to a charge density of 108 Ah/L. By pairing it up with ferri/ferrocyanide as  
76 the positive electrolyte, we built a high-performance RFB characterized by an open-  
77 circuit voltage approaching 1.2 V and current efficiency and capacity retention exceeding  
78 99.7% and 99.98% per cycle, respectively. Enabled by a high-throughput computational  
79 study, a relationship between different alloxazine functional groups and their effects on  
80 reduction potential was established and exploited to guide the design of future alloxazine-  
81 based electrolyte materials. For instance, by replacing the carboxylic acid group with  
82 another alkaline-soluble hydroxyl group, the battery voltage can be further raised by  
83 almost 10%.

#### 84 **Rational Design of Electrolyte Material**

85           Designing an appropriate organic molecule as electrolyte material starts from  
86 identifying redox-active cores followed by functionalization of the core structure to  
87 achieve a practical reduction potential and solubility. We observed that riboflavin 5'  
88 phosphate (FMN), a highly water-soluble compound derived from vitamin B<sub>2</sub>, undergoes  
89 two-electron reduction *via* a flavin semiquinone radical intermediate on its isoalloxazine  
90 backbone (Supplementary Fig. 1).<sup>17,18</sup> In alkaline solution, it exhibited high reversibility  
91 and a low reduction potential of –0.53 V vs. SHE (Fig. 1a). Further exploration of its

92 isoalloxazine motif led to the discovery that lumichrome, an alloxazine derivative that  
93 differs from isoalloxazine by its diazabutadiene double bond configuration, exhibited a  
94 much lower reduction potential of  $-0.70$  V vs. SHE (Fig. 1b). Alloxazine had previously  
95 been studied in the solid state as an anode material for non-aqueous lithium and sodium  
96 ion batteries.<sup>19</sup> However, the low solubility of alloxazine in a wide range of solvents  
97 presents a challenge for solution-phase applications. To increase its solubility in aqueous  
98 solution, we functionalized the alloxazine core with an alkali-soluble carboxylic acid  
99 group by coupling *o*-phenylenediamine-4-carboxylic acid (a.k.a. 3,4-diaminobenzoic acid)  
100 with alloxan to afford an isomeric mixture of alloxazine 7/8-carboxylic acid (ACA) in  
101 almost 100% yield (Supplementary Fig. 2). The reduction potential of ACA from CV  
102 measurement is  $-0.62$  V vs. SHE (Fig. 1c). The larger separation between its oxidation  
103 and reduction peaks than those of FMN and lumichrome is likely due to slower kinetics.  
104 From our rotating disk electrode (RDE) measurement, the reduction rate constant was  
105 measured to be  $1.2 \pm 0.2 \times 10^{-5}$  cm s<sup>-1</sup> (Supplementary Fig. 3). Nevertheless, this value is  
106 still an order of magnitude higher than that of the slower side of all-vanadium RFBs.<sup>6</sup>

107 Besides the large shift in reduction potential moving from isoalloxazine to  
108 alloxazine, we also observed a significant increase in chemical stability in alkaline  
109 conditions. Whereas cyclic voltammetry (CV) measurement of 0.5 M FMN in an alkaline  
110 solution revealed an almost 70% decrease in reduction signal within 2 weeks, an ACA  
111 solution at the same concentration showed almost no sign of degradation (Supplementary  
112 Fig. 4). Quantification of ACA stability was achieved by proton nuclear magnetic  
113 resonance (<sup>1</sup>H NMR) analysis of a 0.5 M solution of ACA maintained at pH 14 over the  
114 course of six weeks. The decomposition of ACA, assuming first-order kinetics ( $R^2 =$

115 0.991), had a rate constant of  $1.39 \times 10^{-3} \text{ day}^{-1}$ , equivalent to a solution half-life of 500  
116 days (Supplementary Fig. 5). This combination of lower reduction potential ( $-0.62 \text{ V vs.}$   
117  $-0.53 \text{ V}$ ) and higher chemical stability (500 days vs. 10 days half-life of FMN at pH 14),  
118 made ACA a much better candidate for an electrolyte material.

### 119 **Electrochemical Full-cell Study**

120 To demonstrate ACA in a full cell, we paired ACA with ferri/ferrocyanide (Fig.  
121 1c and d). The battery was assembled using 0.5 M ACA (1.5 mmol) as the negative  
122 electrolyte and 0.4 M ferrocyanide (4.5 mmol) + 40 mM ferricyanide (0.46 mmol) as the  
123 positive electrolyte. Both solutions were adjusted to pH 14 by KOH. Excess quantities of  
124 ferrocyanide and ferricyanide were used to ensure the negative terminal remained the  
125 capacity-limiting side for the purpose of evaluating its electrochemical stability during  
126 cycling. The resulting alkaline aqueous RFB showed an open-circuit voltage (OCV)  
127 approaching 1.2 V. The OCV versus state-of-charge (SOC) monotonically increased from  
128 10% to 90% SOC (Fig 2a). Polarization studies conducted at room temperature showed a  
129 peak power density of  $0.35 \text{ W cm}^{-2}$  at a current density of  $0.58 \text{ A cm}^{-2}$ . The linearity of  
130 the polarization curves allows us to derive a polarization area-specific resistance (ASR),  
131 which is  $1.03 \Omega \text{ cm}^2$  at 50% SOC. About 70% of this cell ASR is contributed by the  
132 membrane (Supplementary Fig. 6), similar to our previous observation.<sup>10</sup> Note that ACA  
133 redox kinetics does not show up as a significant kinetic overvoltage loss (i.e. a non-  
134 linearity at the low overvoltage region) in the polarization curve, likely owing to the large  
135 surface area provided by the porous carbon electrodes. The electrochemical stability of  
136 ACA was evaluated based on an extended charge-discharge study over 400 cycles (Fig.  
137 2c). The current efficiency exceeded 99.7% at  $0.1 \text{ A cm}^{-2}$ , which is indicative of

138 negligible side reactions during cell cycling and a low crossover rate through the  
139 membrane. The round-trip energy efficiency in this cycling experiment averaged around  
140 63%. The battery exhibited a remarkably high capacity retention rate of more than 91%  
141 over 400 cycles, or a capacity loss rate of 0.023% per cycle. To further analyze capacity  
142 retention, we compared the total charge from the cell before and after cycling using  
143 chronoamperometry to charge and discharge the cell at constant voltage (Supplementary  
144 Fig. 7). From this result, the measured capacity retention from 400 cycles was 95%, i.e.  
145 the loss rate was 0.013% per cycle. We believe the discrepancy between this  
146 measurement and the capacity retention observed during constant-current cycling was  
147 due to an increase of system resistance (which we infer from decreasing energy  
148 efficiency with cycle number); this effect moved the charging and discharging curves  
149 closer to the cutoff voltages, resulting in less complete charging and discharging with  
150 increasing cycle count (Supplementary Fig. 8). We expect further cell development,  
151 including variations in pH, membrane and sealing method, to lead to further improvement  
152 of capacity retention. By increasing the concentration of ACA to 1 M, we increased the  
153 electrolyte charge density by almost two-fold (Supplementary Fig. 9a). Together with  
154 adjusted cell compression and higher ACA concentration, we were able to improve  
155 round-trip energy efficiency to 74%, while retaining the same level of current efficiency  
156 (99.7%) and capacity retention per cycle (99.95%) (Supplementary Fig. 9b).

### 157 **Theoretical Modeling and Screening**

158 One useful feature of organic electrolyte materials is the ability to optimize their  
159 properties through chemical modification, a process that can be accelerated by virtual  
160 testing with computational methods.<sup>8,20</sup> We assayed the chemical landscape around the



161 alloxazine backbone by computing the properties of derivatives bearing one to four  
162 copies of each of seven functional groups. Selected examples of alloxazine derivatives  
163 subjected to the theoretical modeling are shown in Table 3 (a complete table of the rest of  
164 the studied alloxazine derivatives can be found in supplementary table 1).

165 Figure 3 shows the variation in predicted standard reduction potential ( $E^0$ ) within  
166 the alloxazine class. The additive effect of electron donating and electron withdrawing  
167 groups is observed as they lower and raise the reduction potential, respectively, across a  
168 range of 400 mV. Hydroxyl, methyl and methoxy substituents afford the largest increases  
169 in cell potential. We prepared 7/8-hydroxyalloxazine and 7,8-dimethylalloxazine via the  
170 aforementioned *o*-phenylenediamine-alloxan coupling chemistry (Table 2,  
171 Supplementary Fig. 10 and 11). CV of these two compounds showed values below  
172  $-0.73$  V ( $\sim 110$  mV lower than ACA), potentially raising the battery voltage by another  
173 10% (Fig 3c and d).

174 In addition to tuning its reduction potential, modification of alloxazine with  
175 appropriate functional groups could also improve its chemical stability. Alloxazines  
176 undergo ring-opening reaction in aqueous solvent via addition of water to the amidic  
177 carbonyls followed by continuing hydrolysis to redox-inactive species (Supplementary  
178 Fig. 12).<sup>21</sup> Increases in pH catalyze the hydrolysis process, as observed in the FMN  
179 stability study and informed by literature.<sup>22,23</sup> Nevertheless, the low  $pK_a$  values at the  
180 amide nitrogen (8.4 and 11.4 for lumichrome<sup>24</sup>) result in the accumulation of two  
181 negative charges in the imidic conjugate system at high pH values; this process ultimately  
182 hinders the hydrolysis reaction by lowering the electrophilicity of the carbonyl groups.<sup>25</sup>  
183 Since the redox center and the center of electrophilic reactivity are separate in alloxazines,

184 design strategies are available to decrease chemical reactivity, such as tuning the  
185 electrophilicity of alloxazines via different functional groups. We evaluated all the  
186 screened alloxazines based on their predicted equilibrium constant,  $K_{\text{hyd}}$ , for the  
187 reversible hydration of the carbonyl groups (Fig. 3b), with lower value of  $K_{\text{hyd}}$   
188 corresponding to less electrophilic carbonyls. We found that the same electron-donating  
189 groups that contribute toward the desired reduction potential values also have a protecting  
190 effect against hydrolysis, as is the case with amides in general (i.e. hydrolysis rate of  
191 amides in basic medium has a linear dependence in  $K_{\text{hyd}}$ ).<sup>26</sup> For instance, hydroxyl  
192 derivatives lower  $K_{\text{hyd}}$  by as much as two orders of magnitude, thereby shifting the  
193 equilibrium toward the redox-active “de-hydrated” form.

## 194 **Conclusions**

195 By drawing inspiration from vitamin B<sub>2</sub>, we introduced a novel family of organic  
196 molecules for RFB applications. The alloxazine redox-center exhibits sufficiently high  
197 electrochemical and chemical stability, and sufficiently low reduction potential, to be  
198 exploited as a negative electrolyte material in an alkaline RFB. Synthesis of a  
199 functionalized alloxazine redox-active center was carried out via a very simple coupling  
200 chemistry utilizing only *o*-phenylenediamine derivatives, alloxan, acetic acid and boric  
201 acid, without employing high temperature or pressure. We paired alloxazine 7/8-  
202 carboxylic acid with ferri/ferrocyanide to demonstrate a high-performance alloxazine-  
203 powered RFB. The current efficiency exceeded 99.7% while its capacity retention over  
204 400 charge-discharge cycles was shown to be ~95% cumulatively, or 99.98% per cycle.  
205 With a better understanding of the alloxazine system enabled by theoretical modeling, we  
206 have designed and characterized another two alloxazine-derived molecules promising

207 almost 10% further increase in battery voltage. The introduction of aza-aromatic redox-  
208 active species opens up a new direction in designing organic electrolyte and delivers a  
209 promising pathway to accelerate development of aqueous organic RFBs.

210 **Methods**

211 **Chemical synthesis and characterization** 3,4-diaminophenol was purchased from Aurum Pharmatech and  
212 used as received. All other chemicals were purchased from Sigma Aldrich and used as received.

213 Alloxazines were prepared following previously reported methods.<sup>14-16</sup> In general, *o*-phenylenediamine (5  
214 mmol) was added to 45 mL acetic acid followed by alloxan (5.5 mmol) and boric acid (5.5 mmol). The  
215 reaction mixture was stirred at room temperature and atmospheric pressure under nitrogen. The reaction  
216 times for various alloxazine derivatives are summarized in Table 2. After reaction, the product was  
217 collected by vacuum filtration, washed with acetic acid, water, and diethyl ether, and air dried overnight.  
218 The products were analyzed by <sup>1</sup>H NMR and used for chemical and electrochemical measurement without  
219 further purification. <sup>1</sup>H NMR spectra were recorded using Varian INOVA 500 (500 MHz) NMR  
220 spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are  
221 referenced to residual protium in the NMR solvent (D<sub>2</sub>O, δ 4.80 ppm and (CD<sub>3</sub>)<sub>2</sub>SO, δ 2.50 ppm). The  
222 isomeric ratio between major and minor product during the preparation of ACA and 7/8-hydroxyalloxazine  
223 was estimated based on their peak integration ratio (highlighted in Supplementary Fig. 2 and 10).

224 **Stability test by <sup>1</sup>H NMR** In a nitrogen-filled glove bag, a sample of ACA (0.5 M) was dissolved in a  
225 solution of 40% wt. KOD in D<sub>2</sub>O (used as received from Sigma-Aldrich) which was then adjusted to pH 14  
226 with the appropriate amount of D<sub>2</sub>O. The sample was sealed inside a J. Young tube and analyzed by <sup>1</sup>H  
227 NMR. Analyses of the same sample were performed after 14, 21, 28, and 42 days. Between analyses, the J.  
228 Young tube was returned to the glove bag where it was kept in the dark. The proportion of ACA that had  
229 decomposed was determined by integrating the peaks at 6.48 ppm and comparing it to the peaks at 6.60  
230 ppm and 6.86 ppm, which come from the starting material. From this data, the rate constant of ACA  
231 decomposition was calculated assuming first-order kinetics (Supplementary Fig. 4).

232 **Solubility measurement by UV-Vis spectroscopy** Saturated solution of ACA was prepared by addition of  
233 ACA to a pH 14 solution until precipitate formed. KOH was added if necessary to maintain the solution pH.  
234 Aliquots of the supernatant were diluted with a pH 14 KOH solution and its absorbance measured using  
235 UV-Vis spectrophotometry (Ocean Optics FLAME-S-UV-VIS; cuvettes are made out of polystyrene with a

236 path length of 1 cm). Readings were interpolated based on a standard calibration curve prepared by  
237 measuring the absorbance of known concentrations of ACA (Supplementary Fig. 13).

238 **Electrochemical analysis** Three-electrode cyclic voltammetry tests (CV) were performed using a glassy  
239 carbon working electrode, a Ag/AgCl reference electrode (pre-soaked in 3 M NaCl solution) and a  
240 platinum counter electrode. For the full cell measurements, cell hardware from Fuel Cell Tech.  
241 (Albuquerque, NM) was used to assemble a zero-gap flow cell configuration, similar to previous reports.<sup>27</sup>  
242 POCO graphite flow plates with serpentine flow fields were used for both sides. A 5 cm<sup>2</sup> geometric surface  
243 area electrode comprised a stack of two or three sheets of Sigracet SGL 10AA porous carbon paper,  
244 pretreated by baking in air at 400 °C for 24 h. A sheet of Nafion 212 membrane, pretreated in DI water  
245 overnight, served as the ion-selective membrane. The rest of the space between the plates was gasketed by  
246 either Kalrez or Teflon sheets. The electrolytes were fed into the cell through PFA tubing, at a rate of 60  
247 mL/min controlled by Cole-Parmer Masterflex L/S peristaltic pumps. All electrochemical tests were  
248 performed using a Gamry Reference 3000 potentiostat.

249 **Rotating disk electrode (RDE) measurement** RDE experiments were conducted using a BASi RDE  
250 (RDE-2) instrument equipped with a glassy carbon working electrode, a Ag/AgCl reference electrode (pre-  
251 soaked in 3 M NaCl solution) and a platinum counter electrode. The electrode was rotated at a specific  
252 speed while the voltage was linearly swept from -0.70 V to -1.20 V versus Ag/AgCl. The reduction rate  
253 constant of ACA was calculated from the Tafel equation using the following parameters:  $n = 2$ ; Faraday's  
254 constant  $F = 96,485 \text{ C mol}^{-1}$ ; electrode area  $A = 0.0707 \text{ cm}^2$ , ACA concentration  $C = 2 \times 10^{-6} \text{ mol cm}^{-3}$ ;  
255 kinematic viscosity  $\nu = 0.01 \text{ cm}^2 \text{ s}^{-1}$  (Supplementary Fig. 3). The experiment was performed three times.

256 **Electrolyte preparation** For SOC, polarization and 400-cycle charge-discharge studies, the positive  
257 electrolyte was prepared by dissolving ferrocyanide (1.9 g, 4.5 mmol) and ferricyanide (0.15 g, 0.46 mmol)  
258 in 1 M KOH solution (11.25 mL) to afford 0.4 molar electron concentration and 2.7 molar K<sup>+</sup> ion solution  
259 (11 Ah/L charge density). The negative electrolyte was prepared by dissolving ACA (0.39 g, 1.5 mmol) in  
260 2.5 M KOH solution (adjusted to final volume of 3 mL) to afford 1 molar electron concentration and 2  
261 molar K<sup>+</sup> ion solution (27 Ah/L charge density). For high concentration ACA cycling experiment, the  
262 positive electrolyte was prepared by dissolving ferrocyanide (3.8 g, 9 mmol) and ferricyanide (0.3 g, 0.91

263 mmol) in 1 M KOH solution (22.5 mL) to afford 0.4 molar electron concentration and 2.7 molar  $K^+$  ion  
264 solution (11 Ah/L charge density). The negative electrolyte was prepared by dissolving ACA (0.78 g, 3  
265 mmol) in 4 M KOH solution (adjusted to final volume of 3 mL) to afford 2 molar electron concentration  
266 and 4 molar  $K^+$  ion solution (54 Ah/L charge density).

## 267 **Computational studies**

268 *Libraries considered.* We have analyzed all the possible substitutions for each functional group on all the  
269 possible sites of the alloxazine core. The functional groups assessed are carboxylic acid, fluoro, hydroxyl,  
270 methoxy, methyl, phosphonic acid and sulfonic acid. Substitution on the alloxazine amide nitrogens were  
271 not considered as they destabilize alloxazines under alkaline condition. A total of 105 backbones were  
272 analyzed. Initial conformations were generated that used a random-distance matrix approach at the mmff94  
273 level of theory. Geometries were further refined using DFT and single-point calculations were performed  
274 using larger basis sets and solvent corrections. The following methods were tested for obtaining  
275 equilibrium geometries and total energies: PM7, PM7 + implicit COSMO solvation, PBE/6-31G\*,  
276 B3LYP/6-31G\*. In addition, single point calculations were performed at both B3LYP/6-311+G(d,p) and  
277 B3LYP/6-311+G(d,p) combined with CPCM implicit solvation. Their relative performance is compared in  
278 the supplementary information file. For both target properties we obtained the smallest error using  
279 B3LYP/6-311+G(d,p) CPCM. Reduction potentials were predicted from the energy difference between the  
280 reduced and oxidized forms of alloxazines, assuming a two-electron two-proton process. Prior to  
281 conducting predictions, we assessed the performance of various quantum chemical methods to calculate the  
282 two-proton two-electron redox potential of alloxazine and isalloxazine rings at  $pH = 7.4$  using a  
283 calibration scheme analogous to the one reported for quinones. The calibration dataset was composed of 23  
284 experimentally-reported molecules, with  $E^0_{pH=7}$  ranging between  $-380$  meV and  $-80$  meV versus RHE.<sup>28</sup>  
285 Our results suggest that quick semiempirical methods and gas-phase DFT calculations afford results with  
286 mean errors around 20 meV. DFT calculations in implicit solvent with a larger basis set reduce the average  
287 error to under 10 meV. The performance of various methods is reported in Supplementary Table 2. We then  
288 corrected  $E^0$  values to  $pH = 14.0$ . Pourbaix diagrams were estimated combining experimental and predicted  
289  $pK_a$  values ( $pK_a^{ox} = 8.3, 11.4$ ;  $pK_a^{red} = 6.7, 10.0$ ). The shift from  $pH = 7.4$  to  $pH = 14.0$  for alloxazines is

290 thus estimated at  $-320$  meV. To calculate hydration equilibrium, we used an experimental dataset from the  
291 literature including aldehydes, ketones, esters and amides and mapped theoretical reaction energies at 0 K  
292 to experimentally-determined hydration equilibrium constants in water.<sup>29</sup> The calibration dataset was  
293 composed of 41 experimentally-reported molecules, with  $\log K_{\text{hyd}}$  ranging between  $-15$  and 5. DFT  
294 calculations in implicit solvent result in mean errors close to 1 log unit. The performance of various  
295 methods is reported in Supplementary Table 2.

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368 **Author Contributions**

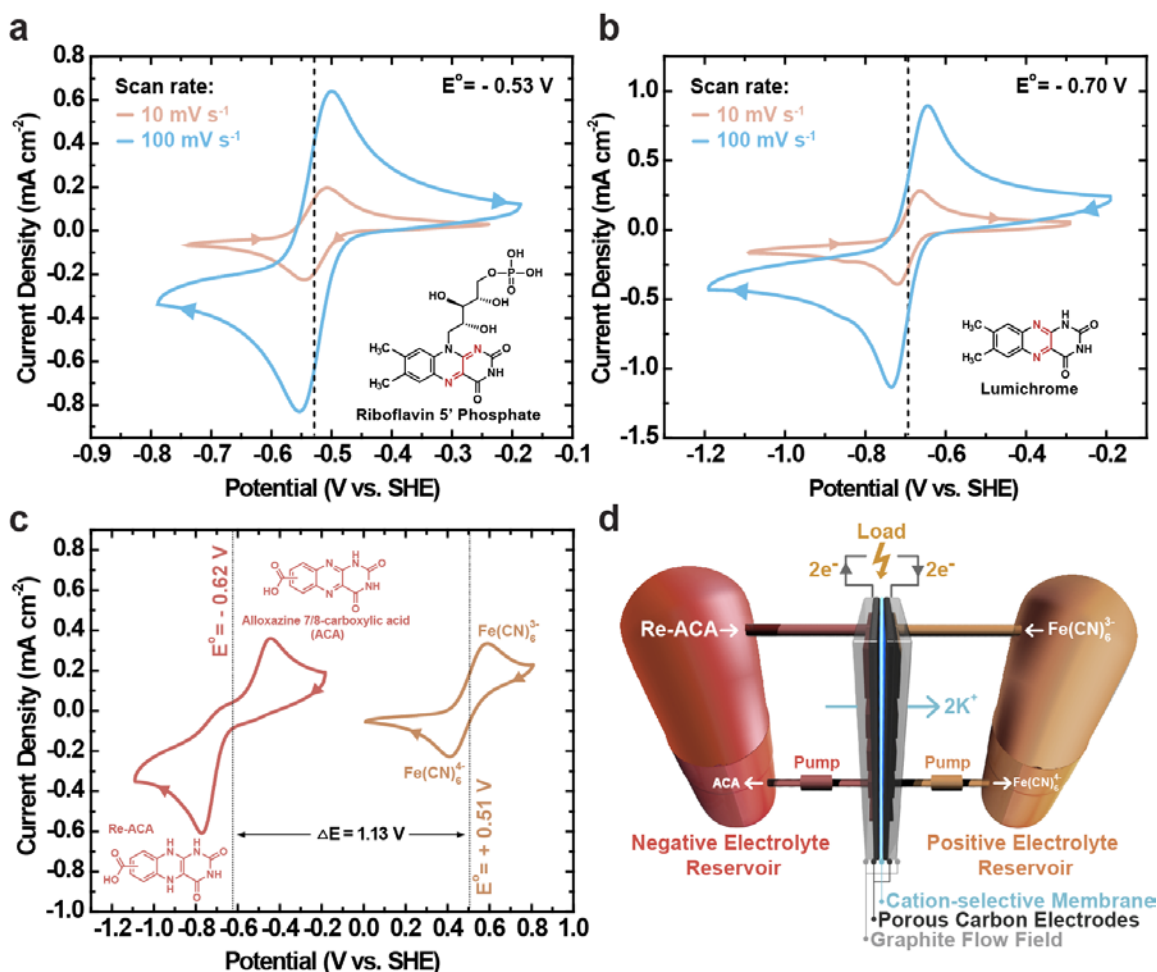
369 K.L., R.G.G. and M.J.A. formulated the project. K.L., and L.T. synthesized the  
370 compounds. K.L., E.S.B. and L.T. collected and analyzed the NMR data. K.L., Q.C.,  
371 E.S.B. and A.V. collected and analyzed the electrochemical data. K.L. and A.V.  
372 measured solubility. R.G.B. and A.A.-G. performed theoretical analysis. K.L., R.G.G.  
373 and M.J.A. wrote the paper, and all authors contributed to revising the paper.

374 **Additional Information**

375 Supplementary information is available online. Reprints and permissions information is  
376 available online at [www.nature.com/reprints](http://www.nature.com/reprints). Correspondence and requests for materials  
377 should be addressed to R.G.G and M.J.A.

378 **Competing interests**

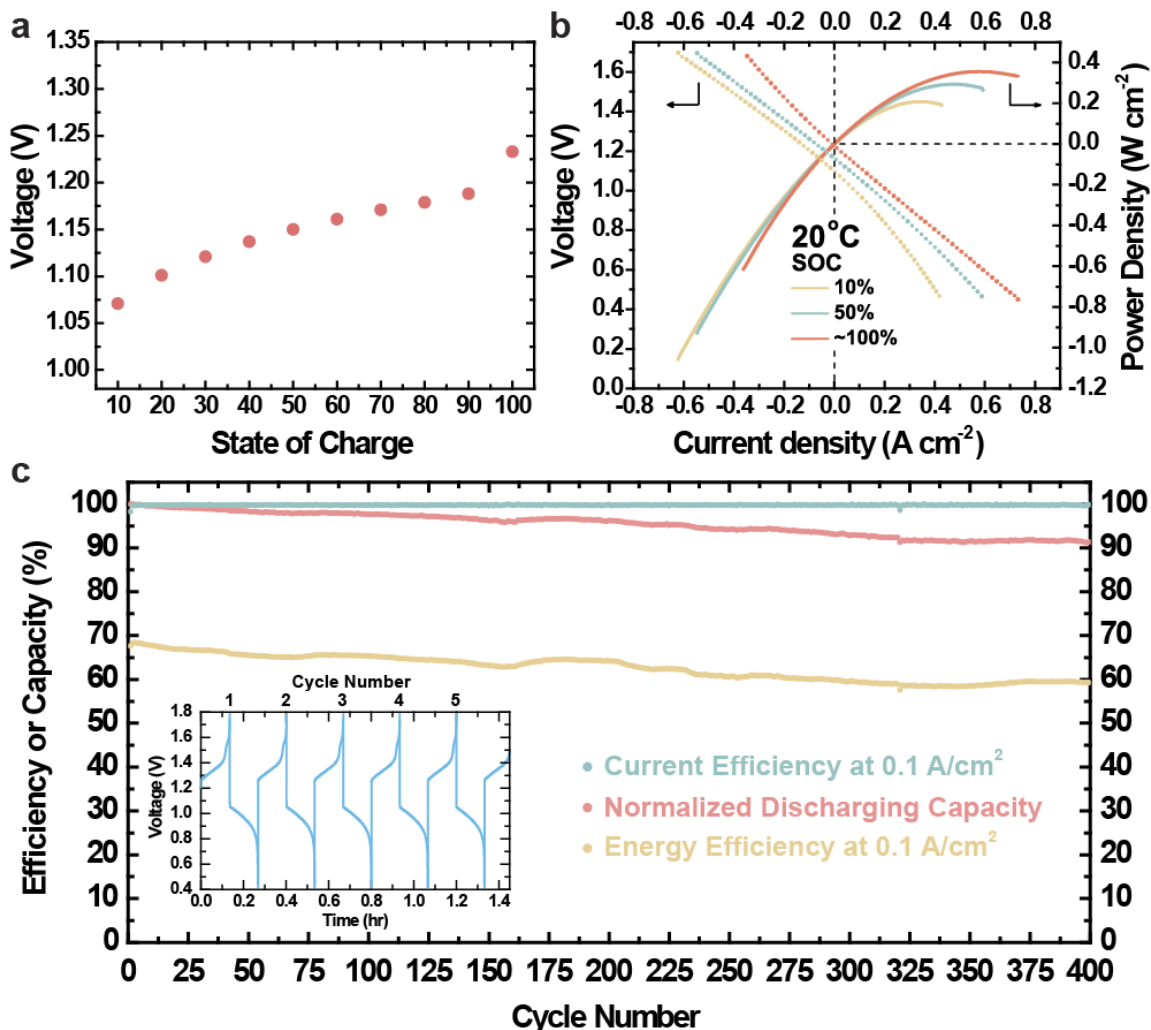
379 The authors declare no competing financial interests.



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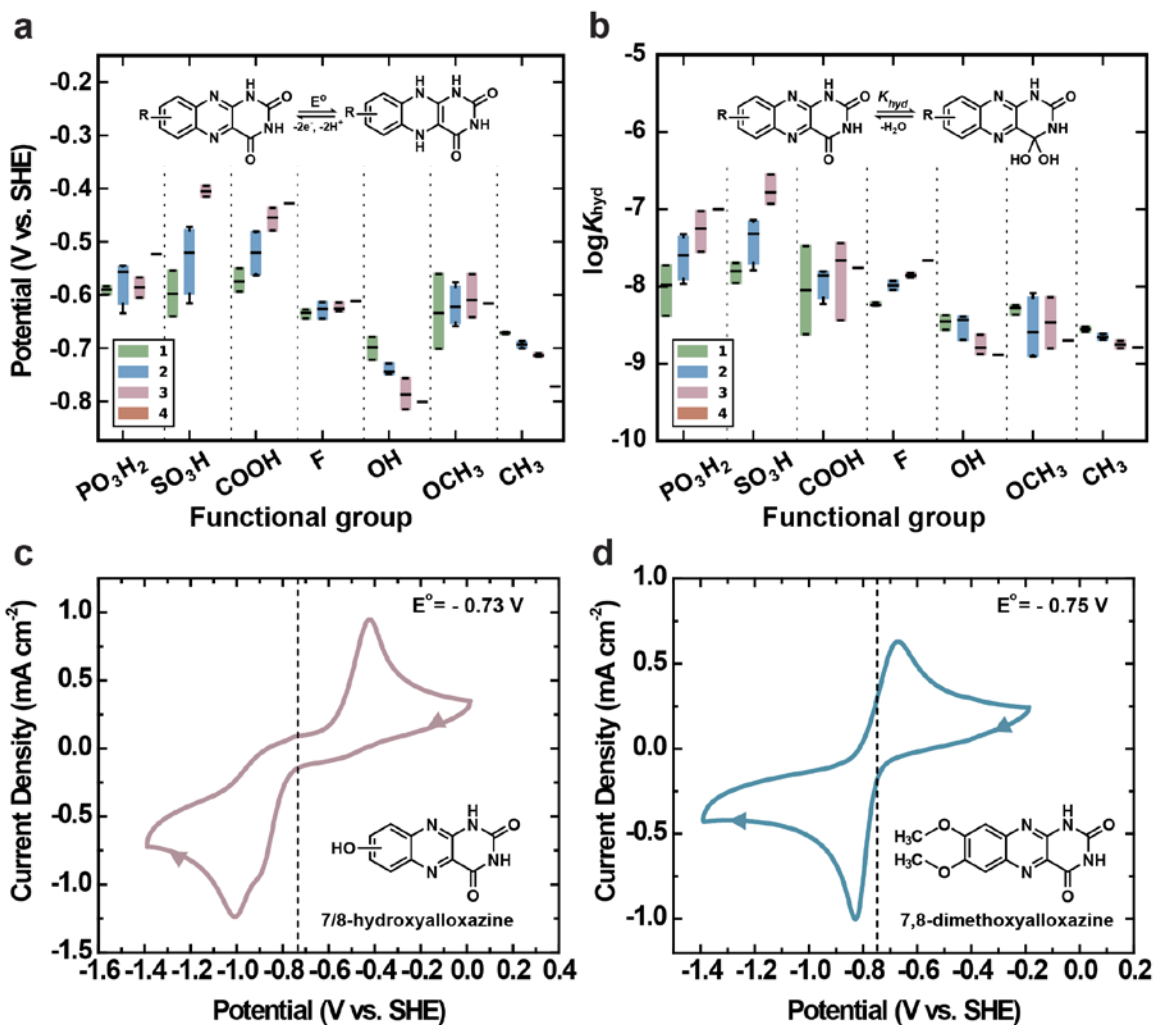
381 **Figure 1 | Cyclic Voltammogram and Cell Schematic.** **a** and **b**, Molecular structures  
 382 and cyclic voltammogram of 2 mM riboflavin 5' phosphate (FMN) and lumichrome,  
 383 respectively, scanned at 10 mV/s and 100 mV/s on glassy carbon electrode. **c**, Cyclic  
 384 voltammogram of 2 mM alloxazine 7/8-carboxylic acid (ACA) (red curve) and  
 385 ferrocyanide (gold curve) scanned at 100 mV/s on glassy carbon electrode; arrows  
 386 indicate scan direction. **d**, Schematic of cell in discharge mode. Grey arrow indicate flow  
 387 direction of electrons and white arrows indicate electrolyte solution flow. Blue arrow  
 388 indicates migration of cations across the membrane. Essential components of  
 389 electrochemical cells are labeled with color-coded lines and text.

390



391  
 392 **Figure 2 | Cell Performance** (a) Cell open-circuit voltage (OCV) vs. state-of-charge  
 393 (SOC). All potentials were taken when the cell voltage stabilized to within  $\pm 1 \text{ mV}$ . 100%  
 394 SOC was reached by a potentiostatic hold at  $1.5 \text{ V}$  until the current decreased to below  
 395  $5 \text{ mA/cm}^2$ . (b) Cell voltage & power density vs. current density at  $20 \text{ }^\circ\text{C}$ , at 10%, 50%,  
 396 and  $\sim 100\%$  SOC. Electrolyte composition:  $0.5 \text{ M ACA}$  and  $0.4 \text{ M ferrocyanide} + 40 \text{ mM}$   
 397  $\text{ferricyanide}$  were used in negative electrolyte and positive electrolyte, respectively. (c)  
 398 Capacity retention, current efficiency and energy efficiency values over 400 cycles at  $0.1$   
 399  $\text{A/cm}^2$ . The normalized discharging capacity is evaluated based on the capacity of the  
 400 first discharge cycle. (Inset: Representative voltage vs. time curves during 400 charge-  
 401 discharge cycles at  $0.1 \text{ A/cm}^2$ , recorded between the 1<sup>st</sup> and 5<sup>th</sup> cycles.)

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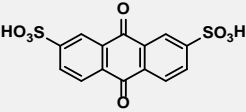
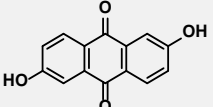
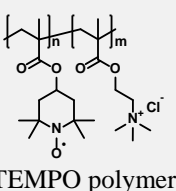
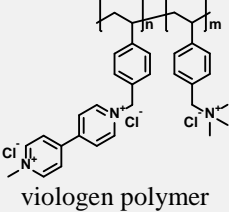
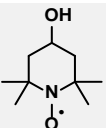
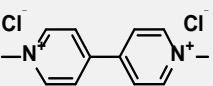


403

404 **Figure 3 | Theoretical Calculation and Cyclic Voltammetry of alloxazines.** (a)  
 405 Predicted reduction potential at the B3LYP 6-311+G\*\* CPCM level of theory for  
 406 substituted alloxazines at pH=14.0 vs. RHE as a function of number and type of  
 407 substituent. (b) Predicted  $\log K_{\text{hyd}}$  at the B3LYP 6-311+G\*\* CPCM level of theory for  
 408 substituted alloxazines as a function of number and type of substituent. The bars  
 409 represent the statistical distribution of predictions of all the possible substituted  
 410 molecules with the given number of substituted sites. The bottom and top of the bar are  
 411 the first and third quartiles, and the band inside the box is the median. The lines  
 412 extending vertically from the boxes indicate the maximum and minimum of the range. (c)  
 413 and (d) Molecular structures and cyclic voltammogram of 1 mM 7/8-hydroxyalloxazine  
 414 and 7,8-dimethoxyalloxazine, respectively, scanned at 100 mV/s on glassy carbon  
 415 electrode.

416

417 **Table 1 | High Performance Organic-based Aqueous Redox Flow Batteries.** This  
 418 table focuses primarily on comparing molecular structures of redox-active organic  
 419 molecules and evaluating their electrochemical stability based on capacity retention.

Positive Electrolyte	Negative Electrolyte	No. of Cycles (Condition)	Capacity Retention per Cycle (%) <sup>a</sup>	Energy Density (Wh/L)	Voltage (V)	Year of Publication	Merit (limitation)
bromine/ hydrobromic acid	 anthraquinone-2,7-disulfonic acid	10	99	16	0.86	2014 <sup>8</sup>	Low cost and high performance (toxic bromine)
	750	99.84	16	2014 <sup>9</sup>			
ferrocyanide	 2,6-dihydroxy-anthraquinone	100	99.1	6.8	1.2	2015 <sup>10</sup>	Non-toxic and less corrosive electrolyte (reduced ion conductivity w.r.t. proton)
 TEMPO polymer	 viologen polymer	100	~ 99.75 <sup>b</sup>	10	1.15	2015 <sup>11</sup>	Cheap dialysis membrane (high electrolyte viscosity)
		10,000 (non-flow cell)	> 99.99				
 4-hydroxy-TEMPO	 methyl viologen	100 (low conc.)	> 99.99	8.4	1.25	2015 <sup>13</sup>	Low cost all-organic electrolyte (low current density)
		100 (high conc.)	99.89				

420 <sup>a</sup> Capacity retention per cycle was derived from total capacity retention divided by total number of charge-  
 421 discharge cycles.

422 <sup>b</sup> The capacity retention value was estimated based on the capacity retention vs. cycle number graph in  
 423 figure 4 from reference 11.

424 **Table 2 | Reaction Scheme and Summary of Alloxazine Synthesis from Literature.**  
 425 Alloxazines with different functional groups (-R) can be prepared by coupling *o*-  
 426 phenylenediamine derivatives with alloxane in the presence of acetic acid and boric acid.

Rc1ccc(N)cc1N + O=C1NC(=O)C(=O)N1  $\xrightarrow[\text{boric acid}]{\text{acetic acid}}$  Rc1ccc2nc3c(nc2=O)nc(=O)[nH]3

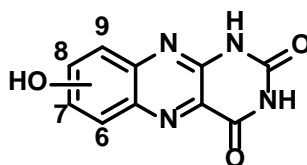
**o-phenylenediamine**      **alloxane**      **alloxazines**

o-phenylenediamine	alloxazines	Reaction Time (h)	Yield (%)	Reference
	 alloxazine	2	87	Chen <i>et al.</i> <sup>14</sup>
			95	Gonzalo <i>et al.</i> <sup>15</sup>
	 lumichrome	2	95	Chen <i>et al.</i> <sup>14</sup>
	 alloxazine 7/8-carboxylic acid (ACA)	3	100	Linden <i>et al.</i> <sup>16</sup>
			95	<i>This work</i>
	 7/8-hydroxyalloxazine	3	86	<i>This work</i>
	 7,8-dimethoxyalloxazine	2	89	Chen <i>et al.</i> <sup>14</sup>
			94	<i>This work</i>

427



428 **Table 3 | Theoretical Calculation and Substitution Patterns of Alloxazines.** Predicted  
 429 standard reduction potential ( $E^{\circ}$ ) and logarithmic hydration equilibrium constant ( $\log K_{\text{hyd}}$ )  
 430 for alloxazines with hydroxyl functional group(s).



hydroxylated alloxazines

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No.	Position (-OH)				B3LYP 6-311+G** CPCM	
	6	7	8	9	$E^{\circ}$ (V)	$\log K_{\text{hyd}}$
<b>1 Substituent</b>						
<b>1</b>	H	H	H	-OH	-0.69	-8.4
<b>2</b>	H	H	-OH	H	-0.72	-8.7
<b>3</b>	H	-OH	H	H	-0.68	-8.5
<b>4</b>	-OH	H	H	H	-0.77	-8.3
<b>2 Substituents</b>						
<b>5</b>	-OH	-OH	H	H	-0.75	-8.4
<b>6</b>	-OH	H	-OH	H	-0.71	-8.6
<b>7</b>	-OH	H	H	-OH	-0.77	-8.2
<b>8</b>	H	-OH	-OH	H	-0.76	-9.3
<b>9</b>	H	-OH	H	-OH	-0.68	-8.4
<b>10</b>	H	H	-OH	-OH	-0.73	-8.7
<b>3 Substituents</b>						
<b>11</b>	-OH	-OH	-OH	H	-0.81	-8.9
<b>12</b>	-OH	-OH	H	-OH	-0.74	-8.3
<b>13</b>	-OH	H	-OH	-OH	-0.82	-8.7
<b>14</b>	H	-OH	-OH	-OH	-0.74	-8.9
<b>4 Substituents</b>						
<b>15</b>	-OH	-OH	-OH	-OH	-0.80	-8.9

## A redox flow battery with an alloxazine-based organic electrolyte

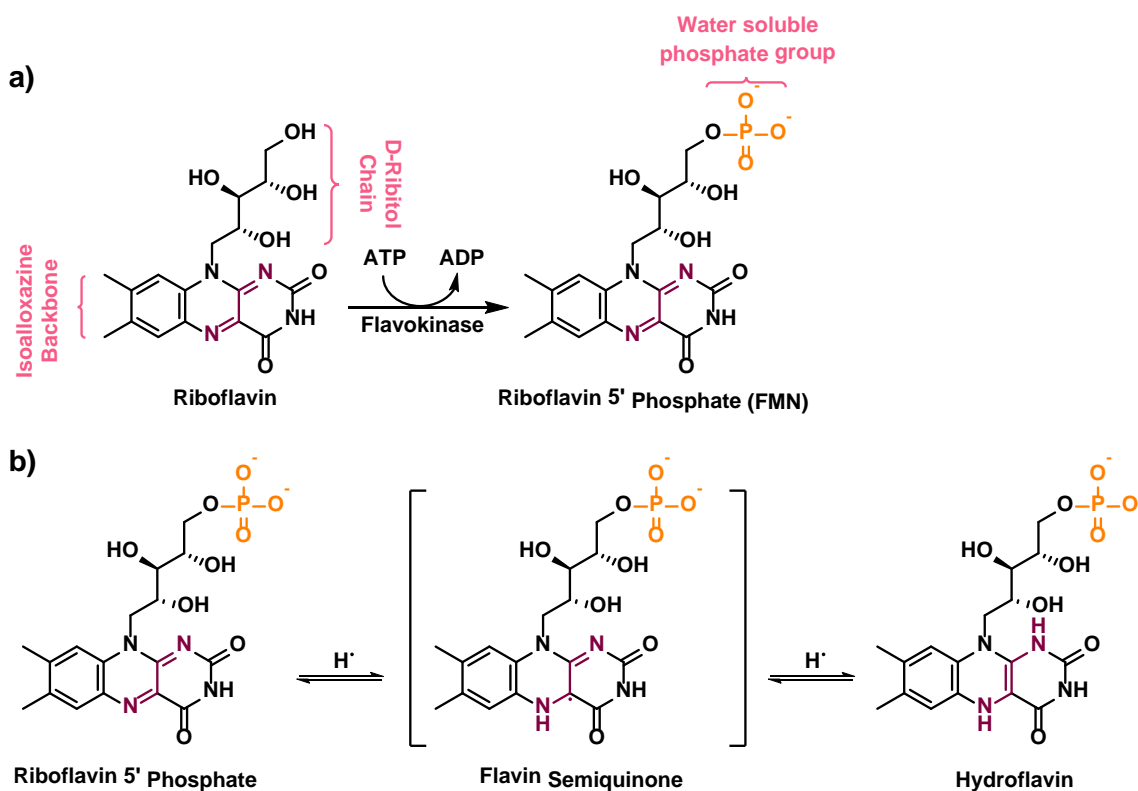
Kaixiang Lin<sup>1</sup>, Rafael Gómez-Bombarelli<sup>1</sup>, Eugene S. Beh<sup>1,2</sup>, Liuchuan Tong<sup>1</sup>, Qing Chen<sup>2</sup>, Alvaro Valle<sup>3</sup>, Alán Aspuru-Guzik<sup>1</sup>, Roy G. Gordon<sup>1,2\*</sup>, Michael J. Aziz<sup>2\*</sup>

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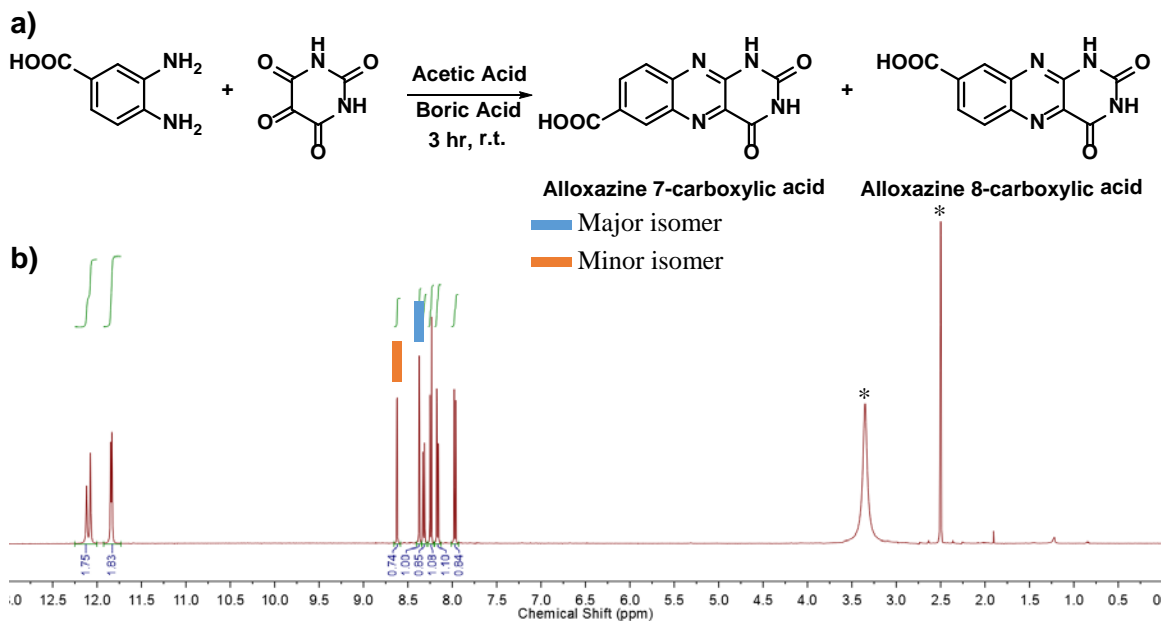
<sup>2</sup>Harvard John A. Paulson School of Engineering and Applied Sciences, 29 Oxford Street, Cambridge, Massachusetts 02138, USA.

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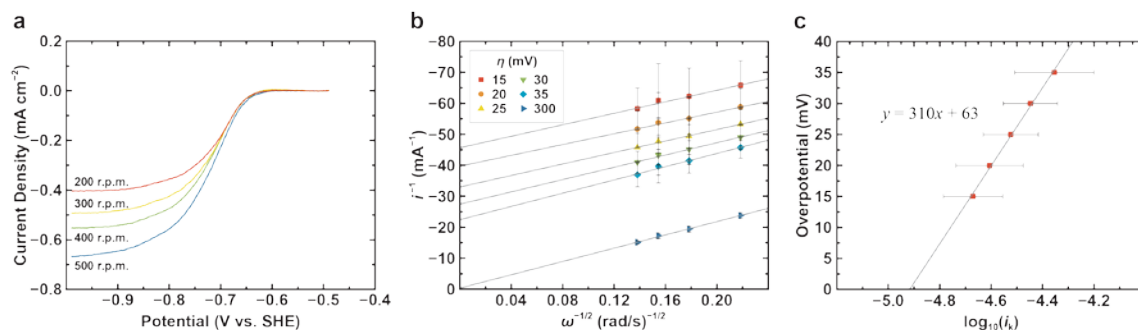
\*Correspondence to: RGG (gordon@chemistry.harvard.edu) and MJA (aziz@seas.harvard.edu)



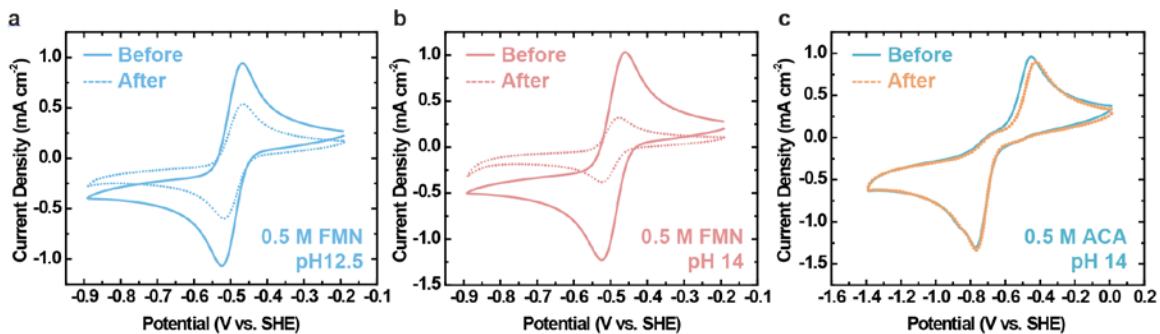
**Supplementary Figure 1.** (a) Biosynthesis of riboflavin 5' phosphate (FMN) from riboflavin (vitamin B<sub>2</sub>). (b) Stepwise reduction of FMN into hydroflavin.<sup>18</sup>



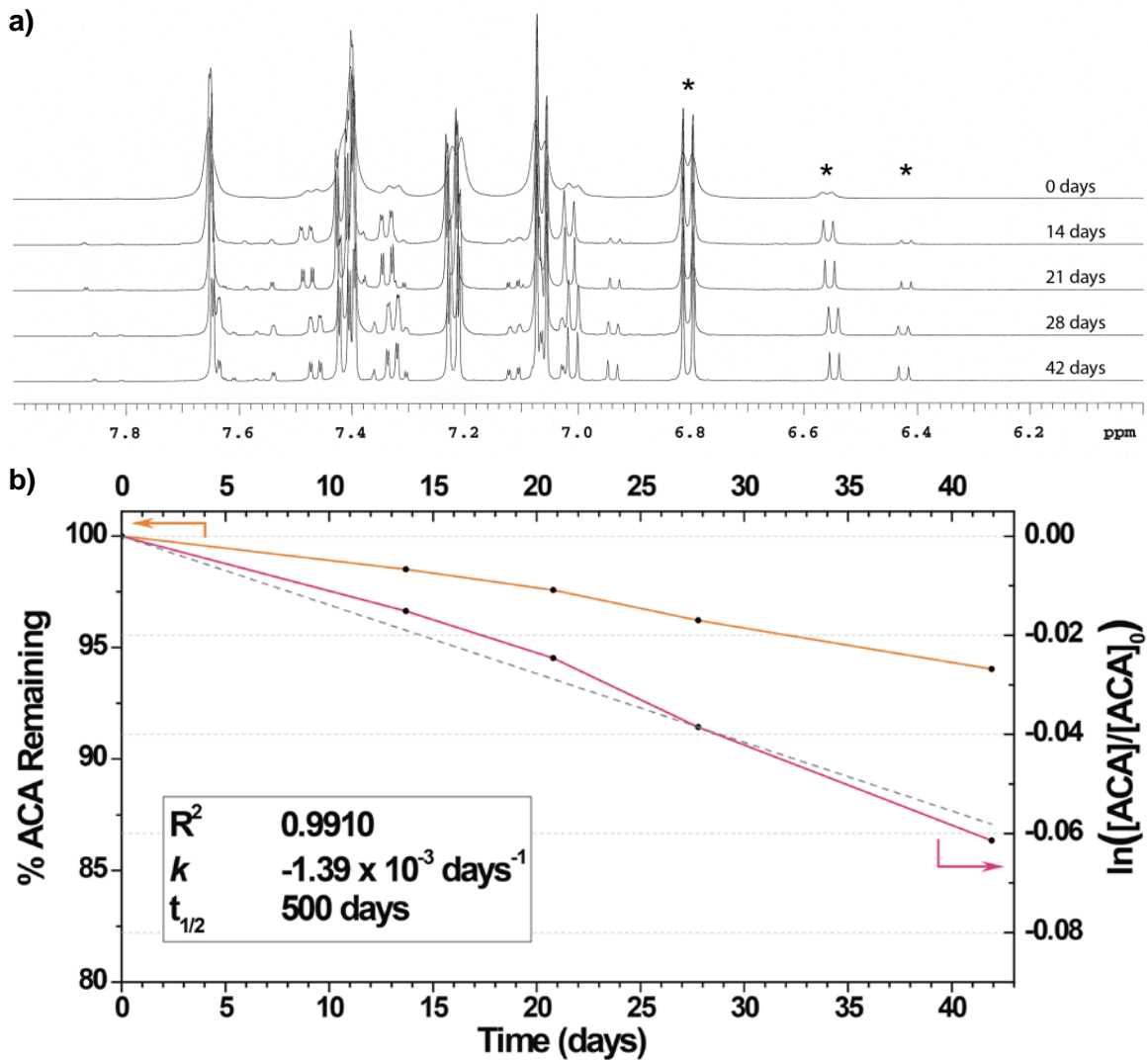
**Supplementary Figure 2.** (a) Synthetic scheme of alloxazine 7/8-carboxylic acid. (b)  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ) spectrum of alloxazine 7/8-carboxylic acid. Major isomer:  $\delta$  12.02 (s, 1H), 11.79 (s, 1H), 8.29 (d,  $J = 1.9$  Hz, 1H), 8.18 (d,  $J = 8.8$  Hz, 1H), 8.09 (dd,  $J = 1.9, 8.8$  Hz, 1H). Minor isomer:  $\delta$  12.06 (s, 1H), 11.80 (s, 1H), 8.55 (d,  $J = 2.0$  Hz, 1H), 8.25 (dd,  $J = 2.0, 8.8$  Hz, 1H), 7.90 (d,  $J = 8.8$  Hz, 1H). Solvent peaks are labeled with asterisks. Final yield: 95%.



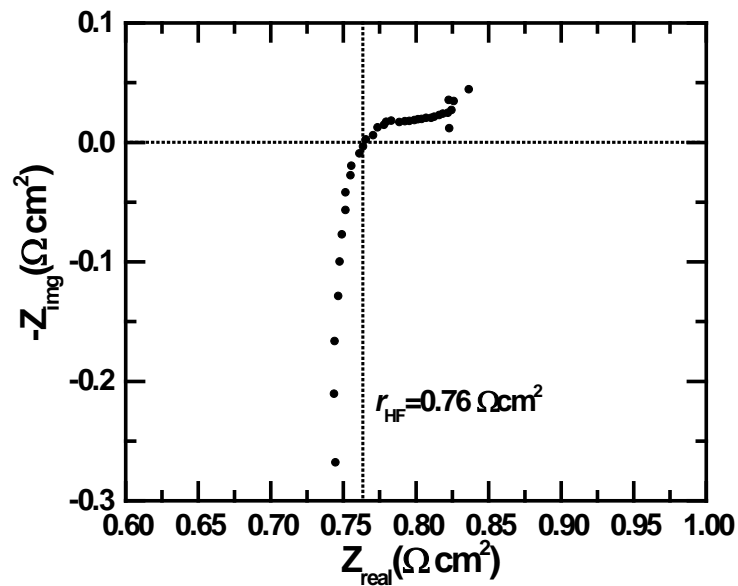
**Supplementary Figure 3.** (a) Plot of potential versus current density at different rotation rates of the RDE. The solution is 2 mM ACA in 1 M aqueous KOH, using a rotating disk electrode (RDE) of glassy carbon. Rotation rates are indicated. (b) Koutecký-Levich plot ( $i^{-1}$  versus  $\omega^{-1/2}$ ) of 2 mM ACA in 1 M aqueous KOH. The current response,  $i^{-1}$ , is shown for six different ACA reduction overpotentials  $\eta$ . (c) Fit of RDE experimental data to the Tafel equation constructed using the current response in the absence of mass transport limitations at low ACA reduction potentials;  $i_k$  is the current extrapolated from the zero-intercept of the fitted lines in (b) (i.e. at infinite rotation rate). The line of best fit has the equation  $y = 310x + 63$ , from which  $\alpha = 0.47(4)$  and  $k_0 = 1.2(2) \times 10^{-5} \text{ cm s}^{-1}$  were calculated. Data are averaged over three runs; the numbers reported in parentheses indicate the standard deviation in the last reported digit.



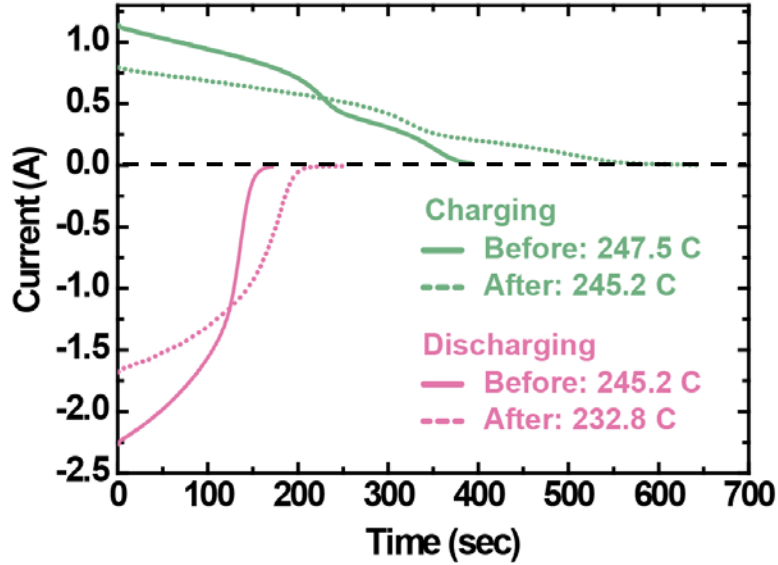
**Supplementary Figure 4.** (a) Cyclic voltammogram of  $1/1000^{\text{th}}$  dilution of riboflavin 5' phosphate (FMN) at pH 12.5 before (solid line) and after (dotted line) 14 days, scanned at 100 mV/s on a glassy carbon electrode. (b) and (c) Cyclic voltammogram of  $1/1000^{\text{th}}$  dilution of riboflavin 5' phosphate (FMN) and alloxazine 7/8-carboxylic acid (ACA), respectively, at pH 14 before (solid line) and after (dotted line) 14 days, scanned at 100 mV/s on a glassy carbon electrode.



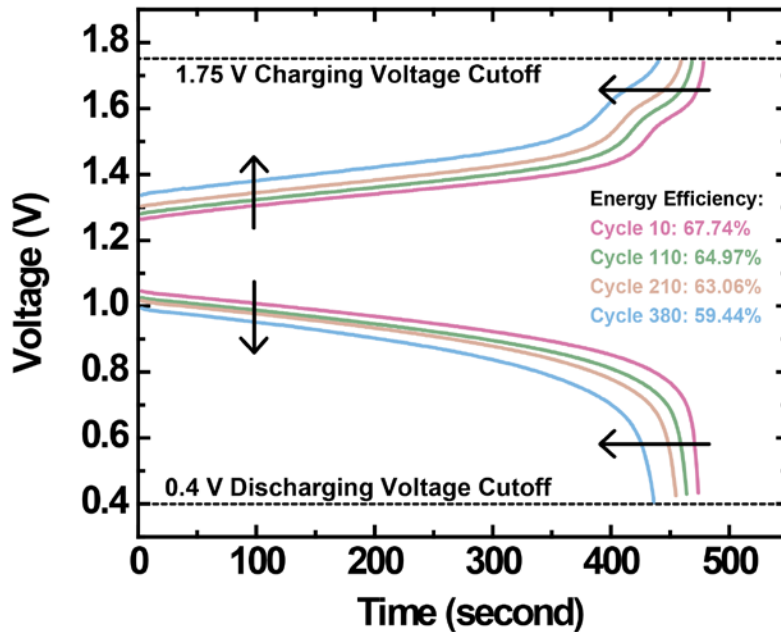
**Supplementary Figure 5.**  $^1\text{H}$  NMR study of ACA stability in solution. (a)  $^1\text{H}$  NMR spectra of a sample of 0.5 M ACA at pH 14 after various time points. The proportion of ACA that had decomposed was determined by comparing the area of the doublet that emerges at 6.43 ppm to the sum of the areas of the doublets at 6.55 ppm and 6.81 ppm, which come from the starting material. The peaks of interest are marked with a star. (b) Graphical depiction of the percentage of ACA remaining in the sample as a function of time (orange trace, left axis), as well as the same data replotted assuming first-order kinetics (pink trace, right axis). The gray dashed line represents the least-squares linear fit to the data in the pink trace.



**Supplementary Figure 6.** Electrochemical impedance spectroscopy (EIS) of the ACA-ferrocyanide cell discussed in **Fig. 3a and 3b**. The EIS data were captured at 50% SOC. A high-frequency ASR ( $r_{\text{HF}}$ ) was taken at  $\sim 80$  kHz to be  $0.76 \Omega \text{ cm}^2$ . This comprises the membrane ionic resistance, the electrode electronic resistances, and the contact resistances, but not the electrolyte resistances. As the sum of the cell contact resistance and the electrode electronic resistance was previously measured in a dry-cell (a setup identical to the flow cell, but without the membrane and the flowing electrolyte) to be  $\sim 0.02 \Omega \text{ cm}^2$ , the membrane resistance, by subtraction, is thus  $\sim 0.74 \Omega \text{ cm}^2$ .

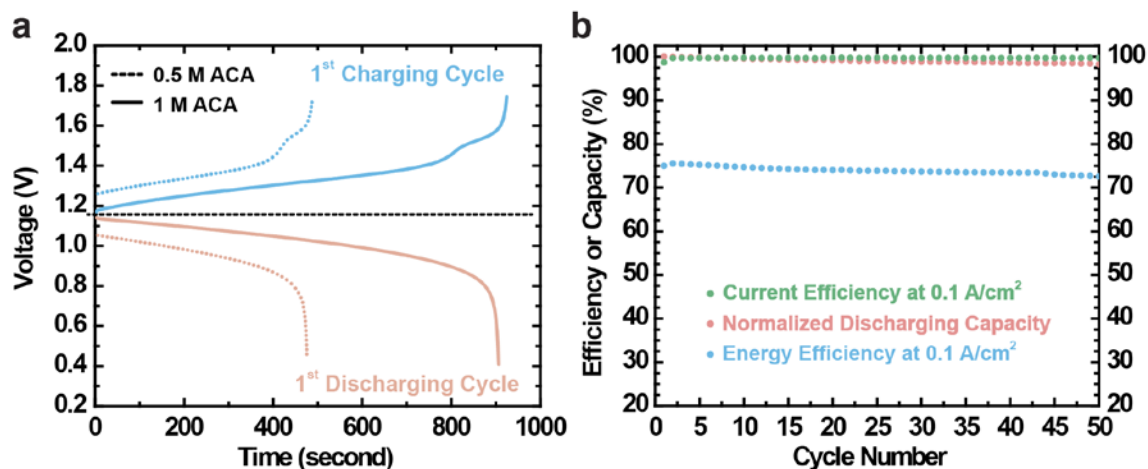


**Supplementary Figure 7.** Chronoamperometric (constant voltage) charging and discharging of ACA before (solid line) and after (dotted line) the 400 cyclic charge-discharge study. Black dashed line indicates zero current. Integration of the curves gives a 95% discharge capacity retention after 400 cycles.

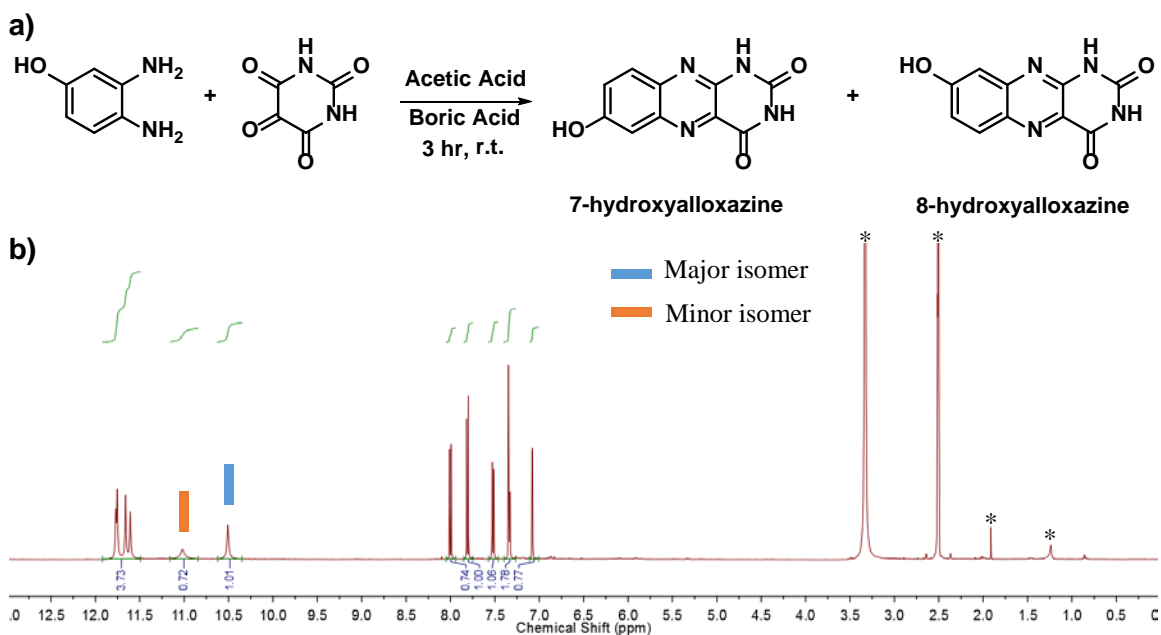


**Supplementary Figure 8.** Charging and discharge profiles of ACA at cycle no. 10, 110, 210 and 380 in the 400-cycle charge-discharge study. Black dashed lines indicate the voltage cutoffs. Black arrows represent the shifting directions of the curves during the course of the cycling study.

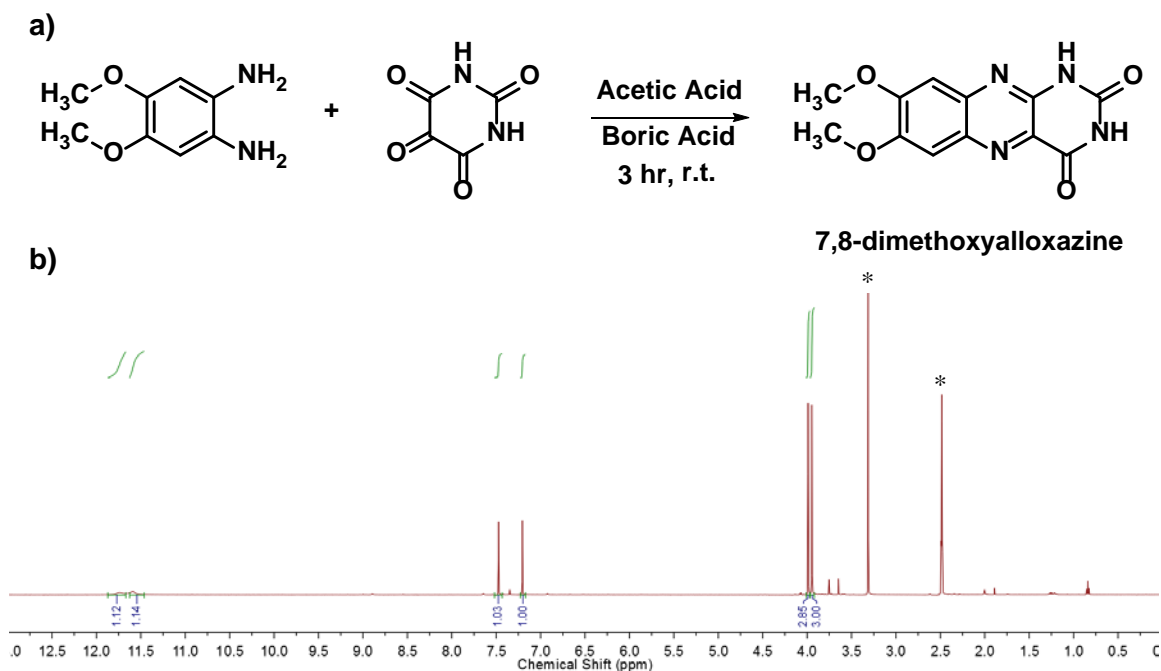




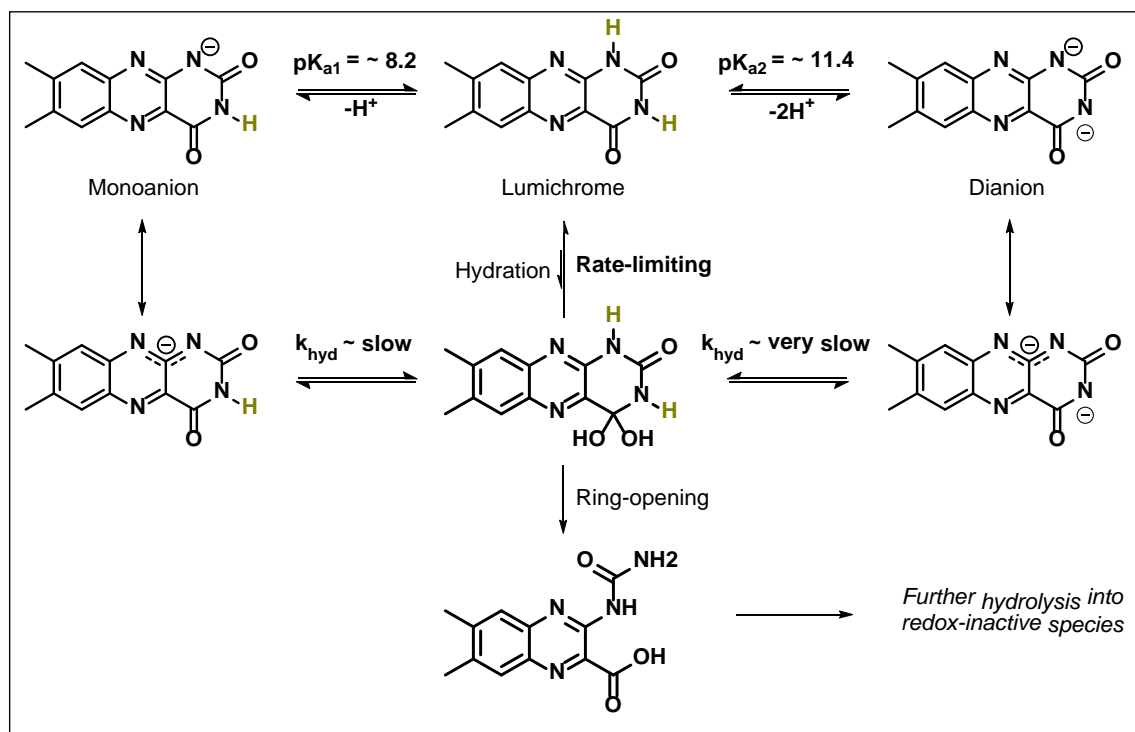
**Supplementary Figure 9.** (a) Representative voltage vs. time curves of the 1<sup>st</sup> charge-discharge cycle at 0.1 A/cm<sup>2</sup> for 0.5 M ACA (dotted line) and 1 M ACA (solid line) vs. 0.4 M ferrocyanide + 40 mM ferricyanide. (b) Capacity retention (97.5%), current efficiency (99.7%) and energy efficiency (74%) values measured over 50 charge-discharge cycles of the 1 M ACA negative electrolyte at 0.1 A/cm<sup>2</sup>. Normalized discharging capacity is evaluated based on the capacity of the first discharge cycle.



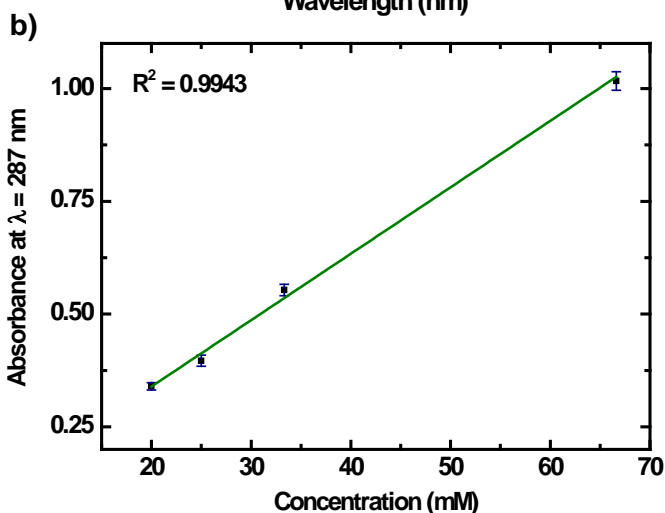
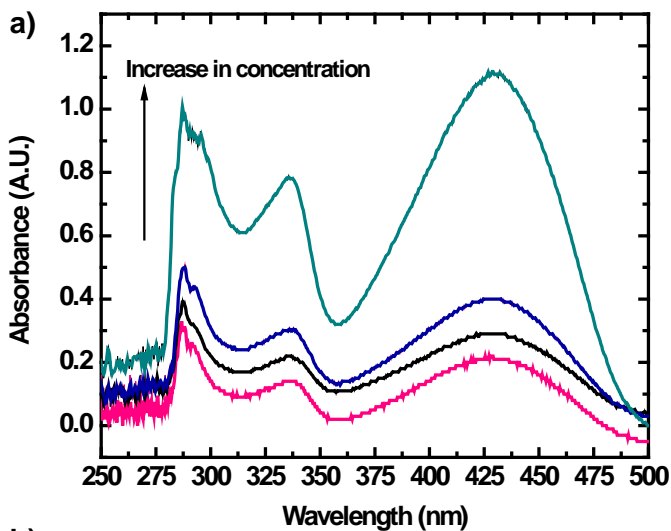
**Supplementary Figure 10.** (a) Synthetic scheme for 7/8-hydroxyalloxazine. (b)  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ) spectrum of 7/8-hydroxyalloxazine. Major isomer:  $\delta$  12.02 (s, 1H), 11.79 (s, 1H), 8.29 (d,  $J = 1.9$  Hz, 1H), 8.18 (d,  $J = 8.8$  Hz, 1H), 8.09 (dd,  $J = 1.9, 8.8$  Hz, 1H). Minor isomer:  $\delta$  12.06 (s, 1H), 11.80 (s, 1H), 8.55 (d,  $J = 2.0$  Hz, 1H), 8.25 (dd,  $J = 2.0, 8.8$  Hz, 1H), 7.90 (d,  $J = 8.8$  Hz, 1H). Solvent peaks are labeled with asterisks. Final yield: 86%.



**Supplementary Figure 11.** (a) Synthetic scheme of 7,8-dimethoxyalloxazine. (b)  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ) spectrum of 7,8-dimethoxyalloxazine  $\delta$  12.02 (s, 1H), 11.79 (s, 1H), 8.29 (d,  $J = 1.9$  Hz, 1H), 8.18 (d,  $J = 8.8$  Hz, 1H), 8.09 (dd,  $J = 1.9, 8.8$  Hz, 1H). Solvent peaks are labeled with asterisks. Final yield: 94%.

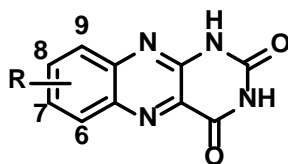


**Supplementary Figure 12.** Deprotonation, hydration and ring-opening reactions of lumichrome (7,8-dimethylalloxazine).<sup>20</sup>



**Supplementary Figure 13.** (a) UV-Vis spectra of ACA at different concentration. (b) Standard calibration curve of ACA absorbance at  $\lambda = 287$  nm vs. concentration. This calibration curve was interpolated to determine the concentration of ACA in diluted aliquots of a saturated solution, from which the saturation concentration of ACA was calculated.

**Supplementary Table 1.** Substitution patterns and predicted standard reduction potential ( $E^{\circ}$ ) and logarithmic hydration equilibrium constant ( $\log K_{\text{hyd}}$ ) for alloxazines.



**alloxazine derivatives**

Position				B3LYP 6-311+G** CPCM											
6	7	8	9	$E^{\circ}$ (V)	$\log K_{\text{hyd}}$	$E^{\circ}$ (V)	$\log K_{\text{hyd}}$	$E^{\circ}$ (V)	$\log K_{\text{hyd}}$	$E^{\circ}$ (V)	$\log K_{\text{hyd}}$	$E^{\circ}$ (V)	$\log K_{\text{hyd}}$	$E^{\circ}$ (V)	$\log K_{\text{hyd}}$
<b>1 substituent</b>				R = -PO <sub>3</sub> H <sub>2</sub>		R = -SO <sub>3</sub> H		R = -COOH		R = -F		R = -OCH <sub>3</sub>		R = -CH <sub>3</sub>	
<b>H</b>	H	H	R	-0.62	-9.4	-0.67	-7.7	-0.53	-6.1	-0.63	-8.1	-0.54	-8.3	-0.67	-8.5
<b>H</b>	H	R	H	-0.57	-8.0	-0.52	-7.9	-0.56	-7.9	-0.66	-8.2	-0.71	-8.2	-0.68	-8.6
<b>H</b>	R	H	H	-0.59	-7.2	-0.57	-7.7	-0.60	-8.2	-0.64	-8.3	-0.70	-8.6	-0.67	-8.6
R	H	H	H	-0.59	-7.9	-0.63	-8.1	-0.59	-10.0	-0.63	-8.2	-0.57	-8.3	-0.67	-8.5
<b>2 substituents</b>															
R	R	H	H	-0.52	-9.0	-0.47	-9.4	-0.56	-8.2	-0.63	-8.0	-0.61	-7.7	-0.68	-8.6
R	H	R	H	-0.64	-7.7	-0.54	-7.8	-0.49	-10.4	-0.64	-8.1	-0.63	-8.9	-0.70	-8.8
R	H	H	R	-0.63	-7.3	-0.63	-7.4	-0.45	-7.8	-0.61	-7.9	-0.49	-8.1	-0.69	-8.6
<b>H</b>	R	R	H	-0.55	-7.3	-0.50	-7.2	-0.57	-7.9	-0.65	-8.0	-0.76	-8.3	-0.70	-8.7
<b>H</b>	R	H	R	-0.56	-7.5	-0.62	-7.1	-0.48	-7.8	-0.61	-7.9	-0.58	-9.2	-0.69	-8.7
<b>H</b>	H	R	R	-0.55	-8.0	-0.47	-7.0	-0.56	-7.7	-0.62	7.9	-0.66	-8.9	-0.69	-8.6
<b>3 substituents</b>															
R	R	R	H	-0.60	-7.4	-0.41	-6.9	-0.44	-7.9	-0.63	-7.9	-0.64	-8.1	-0.71	-8.6
R	R	H	R	-0.61	-7.1	-0.40	-7.1	-0.43	-7.4	-0.59	-7.8	-0.51	-8.2	-0.70	-8.7
R	H	R	R	-0.57	-8.2	-0.38	-6.1	-0.47	-10.1	-0.62	-7.8	-0.58	-8.8	-0.71	-8.9
<b>H</b>	R	R	R	-0.56	-6.8	-0.43	-6.7	-0.51	-7.4	-0.63	-7.9	-0.64	-8.9	-0.72	-8.8
<b>4 substituents</b>															
R	R	R	R	-0.52	-9.7	-0.35	-6.3	-0.43	-7.8	-0.61	-7.7	-0.62	-8.7	-0.77	-8.8

**Supplementary Table 2.** Predicted error in standard reduction potential ( $E^0$ ) values for (iso)alloxazine molecules at pH = 7.4 and in logarithmic hydration equilibrium constant ( $\log K_{\text{hyd}}$ ) values.

Method	$E^0$ (V)		$\log K_{\text{hyd}}$	
	$R^2$	Mean Error (meV)	$R^2$	Mean Error (log units)
PM7	0.86	23	0.79	1.5
PM7 COSMO	0.90	24	0.88	1.3
PBE 6-31G*	0.90	24	0.88	1.2
B3LYP 6-31G*	0.87	27	0.89	1.1
B3LYP 6-311+G**	0.89	25	0.85	1.2
B3LYP 6-311+G** CPCM	0.97	8	0.90	1.0