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Environmentally Friendly Chemoselective Oxidation of Primary Aliphatic Amines by Using a Biomimetic Electrocatalytic System

Martine LARGERON^{*[a]}, Angèle CHIARONI^[b] and Maurice-Bernard FLEURY^[a]

Abstract: Environmentally friendly oxidation of primary aliphatic amines to imines has been successfully achieved, under metal-free conditions, by the use of diverse electrogenerated *o*-azaquinone mediators. High catalytic performance, together with high chemoselectivity, were observed with electron-poor *o*-azaquinone catalysts generated from 2-aminoresorcinol

derivatives. Similar to copper amine oxidases enzymes, these mediators exhibited lower reactivity with α -branched primary amines and no reactivity toward secondary amines. In the case of 3,4-aminophenol derivatives which lack the 2-hydroxyl group, the generated *o*-azaquinone species failed to catalyze the oxidation of the amine to the corresponding imine.

Further mechanistic considerations allowed to justify the crucial role of the 2-hydroxyl group to convert a catalytic inert species into a highly effective biomimetic catalyst.

Keywords: amines · chemoselectivity · enzyme models · electrocatalysis · oxidation

Introduction

The oxidation of amines to imines is of current and intense interest owing to the importance of imines as versatile synthetic intermediates. Especially, imines can act as electrophilic reagents in a plethora of reactions including reductions, additions, condensations and cycloadditions.^[1] In recent years, considerable efforts have been paid to develop new mild and general oxidation procedures for the synthesis of imines from secondary amines. Among them, the stoichiometric method using hypervalent iodine reagent (IBX) allowed the direct oxidation of diverse secondary amines to the corresponding imines under mild conditions and in excellent yields.^[2] Likewise, metal-catalyzed oxidation reactions were found to be efficient and widely applicable methods to convert various secondary amines into imines.^[3] A noteworthy example is the biomimetic catalytic aerobic oxidation of secondary amines that involves ruthenium-amine complexes as the key intermediates. This methodology, which tolerates important substrate classes, afforded both ketimines and aldimines in good yields with high selectivity.^[3c]

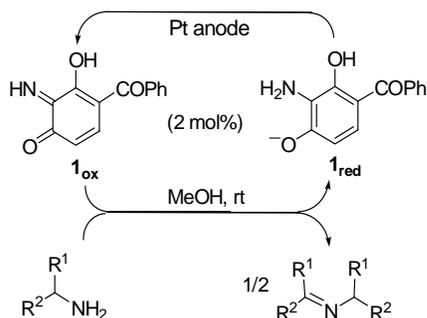
Comparatively, little attention has been devoted to the oxidation of primary amines, probably because the corresponding imines, in which a second α -amino hydrogen is available, usually constitute intermediate products which are rapidly dehydrogenated to nitriles.^[3b, 4] Furthermore, when primary amines were subjected to IBX, the resultant carbonyl species was isolated, even with the application of short reaction times, consecutively to hydrolysis of the initially formed imine product in situ.^[2] However, it was recently reported that a series of uracil-annulated heteroazulenes derivatives, and related compounds, were able to catalyze the oxidation of some primary amines to produce imines in situ, under aerobic and photo-irradiation conditions, while, except for benzylamine, no reaction took place under aerobic and thermal conditions.^[5]

The general interest in amine oxidation chemistry has also stimulated efforts to mimic the biological activity of amine dehydrogenases/oxidases toward the primary amines.^[6] In these systems, the amine is not dehydrogenated but reacts with a carbonyl group of a quinone cofactor leading to a Schiff base intermediate, which is then hydrolyzed to the corresponding aldehyde and the aminophenol products. The latter is oxidatively recycled to the starting quinone cofactor, after elimination of ammonia.^[7] Although this is not a suitable path as such to mimic the generation of imines, however, in the absence of water, the Schiff base intermediate can undergo a direct addition of the amine affording the condensation product *N*-alkylidenealkylamine instead of the aldehyde, together with the aminophenol product. Consequently, several synthetic models of naturally occurring quinones have been developed and good catalytic efficiency has been observed for the catalytic oxidation of benzylamine to *N*-benzylidenebenzylamine, in organic media, under metal-free conditions.^[8] However, these models failed to oxidize unactivated primary amines under the same experimental conditions, with the exception of a metal ion complex of the tryptophan tryptophylquinone model compound, which was able to oxidize aliphatic amines in anhydrous organic media. In contrast, no reaction took place in the absence of the metal ion.^[9]

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A few years ago, we showed that electrogenerated *o*-azaquinone **1_{ox}** (Scheme 1) acted as an effective biomimetic catalyst for the oxidation of benzylamine under metal-free conditions, through the pyridoxal-like transamination process reported for amine oxidases cofactors. The catalytic cycle produced the reduced catalyst **1_{red}** and *N*-benzylidenebenzylamine as the product of amine oxidation. Owing to its unstable nature, the presence in situ of *N*-benzylidenebenzylamine as the amine oxidation product was evidenced after subsequent electrochemical reduction of the exhaustively oxidized solution.^[10a] Further, we demonstrated that, in contrast to other existing amine oxidase mimics,^[8] **1_{ox}** was also active toward aliphatic amines in the absence of a metal ion. An expedient investigation of the performance of the biomimetic electrocatalytic system led to a preliminary communication.^[10b]



Scheme 1. Oxidation of primary amines mediated by the electrogenerated biomimetic catalyst **1_{ox}**.

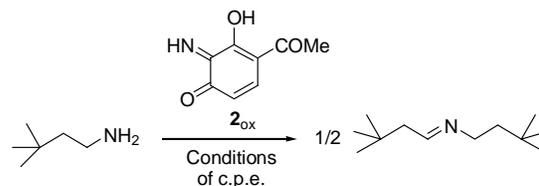
Then, we decided to explore further the potential of the biomimetic electrocatalytic system with two objectives. First, the **1_{ox}**-mediated catalytic oxidation of primary amines allowed the generation of unstable *N*-alkylidenealkylamine, without any stoichiometric reagents, under environmentally friendly conditions. These conditions are particularly favourable from a synthetic viewpoint, in particular for using the imine in situ for further reactions. Second, from a biological point of view, we thought that the design of small artificial catalysts, that closely approach the activity and specificity of amine oxidases enzymes, might provide important guidelines for designing inhibitors capable of regulating the human enzyme activity. In this paper, we present a full account of the biomimetic catalytic oxidation of primary amines to alkylimines. In particular, through the variation of the structure of the electrogenerated 3,4-azaquinone mediator, we disclose the specific role of 1-carbonyl substituent (COR) and 2-hydroxyl group in the development of the catalytic process.

Results and Discussion

Choice of the reaction conditions: First, we have performed optimization studies of the **2_{ox}**-mediated catalytic process using 3,3-dimethylbutylamine as the amine substrate (Table 1). Although the catalytic efficiency of **1_{ox}** and **2_{ox}** was equivalent (entries 1 and 2, Table 2), **2_{ox}** could be considered as the most attractive compound because the synthesis of the reduced form **2_{red}** only required two steps from commercially available 2-nitroresorcinol, whereas four steps were involved in the preparation of the previously used compound **1_{red}**.^[10b] For preparative scale controlled potential electrolysis (c.p.e.), the utilization of a platinum grid as the anode, methanol as the solvent, and tetraethylammonium hexafluorophosphate (TEAHFP) as the supporting electrolyte, gave optimal results (entry 3, Table 1). The Pt anode was more desirable from the consideration of green chemistry, though the Hg anode

could also be used without noticeable change (entry 1). MeCN (entry 4) and CH₂Cl₂ (entry 5) were not suitable solvents for the catalytic oxidation of the amine, probably because strong solvation of methanol to the *o*-azaquinone **2_{ox}** may be required to enhance the electrophilicity of the quinonoid moiety of **2_{ox}**, then favoring the nucleophilic attack of the amine. Among the supporting electrolytes tested, TEAHFP was preferred over the others (entries 6 and 7) owing to the potentially explosive hazard character of the perchlorate anions. Five mmol of 3,3-dimethylbutylamine together with 0.1 mmol of **2_{red}**, that corresponds to 2 mol % of the catalyst **2_{ox}**, were an ideal combination for the reaction.

Table 1: Representative screening conditions for the catalytic oxidation of 3,3-dimethylbutylamine.^[a]



Entry	Anode	Solvent	Supporting Electrolyte	Current Efficiency [%] ^[b]	Yield ^[c] [%]
1	Hg	MeOH	TEAHFP	98	45
2	Carbon	MeOH	TEAHFP	90	40
3	Pt	MeOH	TEAHFP	100	46
4	Pt	MeCN	TEAHFP	78	32
5	Pt	CH ₂ Cl ₂	TEAHFP	40	16
6	Pt	MeOH	TEAP	98	46
7	Pt	MeOH	LiClO ₄	100	46
8	Pt	MeOH	TEAHFP	63	30
9	Pt	MeOH	TEAHFP	74	35
10	Pt	MeOH	TEAHFP	92	40

[a] Reagents: (**2_{ox}**) = 0.4 mM (entries 1-8), 0.2 mM (entries 9 and 10); (3,3-dimethylbutylamine) = 20 mM (entries 1-7 and 9), 40 mM (entry 8), 10 mM (entry 10).

[b] The electrolysis time was 7 h and the controlled anodic potential was + 600 mV vs. SCE. [c] *N*-alkylidenealkylamine was isolated by converting to the corresponding 2,4-dinitrophenylhydrazone (DNPH), obtained upon workup of the oxidized solution with 2,4-dinitrophenylhydrazine under aqueous acidic conditions. TEAP: Tetraethylammonium perchlorate; TEAHFP: Tetraethylammonium hexafluorophosphate; c.p.e.: controlled potential electrolysis.

Under the optimized conditions, the cyclic voltammogram of compound **2_{red}** (0.4 mM), in deaerated MeOH, showed an oxidation peak Pa at + 500 mV vs. SCE, due to a two-electron process, the sweep rate being 0.1 V s⁻¹. The addition of 3,3-dimethylbutylamine (20 mM) had two effects: first, a shift of the peak Pa to 0 mV vs. SCE as a result of the ionization of the 4-hydroxyl group; second, a slight increase in the anodic peak intensity, which suggested that 3,4-azaquinone **2_{ox}** was protected from its succeeding polymerization reaction because it could act as a catalyst for the oxidation of amine. Similar effects have already been observed about the catalytic activity of close quinonoid species.^[11]

After the Pa potential was determined by cyclic voltammetry, controlled potential electrolysis was used as a preparative method

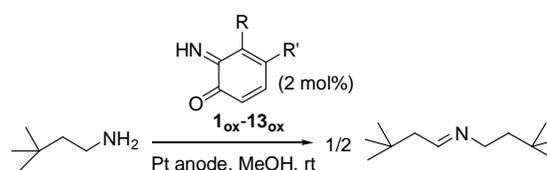
for the isolation of the products resulting from the catalytic oxidation of 3,3-dimethylbutylamine. When the controlled potential of the Pt anode was fixed at + 600 mV vs. SCE, the anodic current remained constant for a long time, and the current efficiency obtained by the electrolysis for 7h was 100%, indicating that no side reaction took place under the experimental conditions used (entry 3, Table 1). Note that a high potential value was intentionally chosen, because of the continuous shift of the peak Pa observed in the course of the electrolysis until + 500 mV vs. SCE, when the amine concentration was no more sufficient to ionize the 4-hydroxyl group of **2_{red}**. These results indicated that the **2_{red}**/**2_{ox}** system behaved as a redox mediator for the indirect electrochemical oxidation of 3,3-dimethylbutylamine to the corresponding *N*-alkylidenealkylamine, according to the ionic transamination mechanism previously reported.^[10a] After exhaustive controlled potential electrolysis, unstable alkylimine was isolated by converting to the 2,4-dinitrophenylhydrazone (DNPH), obtained upon workup of the oxidized solution with 2,4-dinitrophenylhydrazine under aqueous acidic conditions (See the Experimental Section). Note the yield could not exceed 50 %, because 5 mmol of 3,3-dimethylbutylamine only gave 2.5 mmol of the corresponding *N*-alkylidenealkylamine. Furthermore, control studies indicated that the amount of *N*-alkylidenealkylamine, produced either from simple autoxidation or from electrochemical oxidation of 3,3-dimethylbutylamine in the absence of catalyst **2_{ox}**, was negligible. Taken together, **2_{ox}** exhibited high catalytic efficiency toward the oxidation of this non-activated primary amine since the yield of DNPH reached 46 % (entry 3, Table 1). After exhaustive electrolysis, the catalyst **2_{ox}** was lost irreversibly, as corroborated by the anodic current, which remained negligible upon further addition of amine substrate. This result was in agreement with the fact that lowering the amount of catalyst **2_{ox}** from 2 mol % to 1 mol % decreased the yield of DNPH together with the current efficiency (entries 8 and 9, Table 1).

At this point, we suspected that the presence of both 1-acetyl group and 2-hydroxyl substituent was of overriding importance for the catalytic efficiency of **2_{ox}**. In this respect, it can be remembered that 5-hydroxyl proton of 2,4,5-trihydroxyphenylalanine quinone (TPQ), or 1-NH pyrrole proton of pyrroloquinoline quinone, were found to be a prerequisite for the catalytic activity of these quinonoid cofactors.^[12] So, to evaluate the specific role of each substituent in the development of the catalytic process, the oxidation of 3,3-dimethylbutylamine was examined using variously substituted *o*-azaquinone mediators.

Catalyst screening: With the reliable set of conditions in hand, we examined the catalytic efficiency of a variety of electrogenerated 3,4-azaquinone species toward the oxidation of 3,3-dimethylbutylamine. The results are summarized in Table 2. High catalytic performance was observed with electron-poor *o*-azaquinone entities, generated from substituted 2-aminoresorcinol reduced catalysts **1_{red}**-**4_{red}** bearing a carbonyl substituent (COR) at the 1-position, with high current efficiencies (90-100%) and yields of DNPH ranging from 42 to 46% (entries 1-4). Replacing COR by a nitro group decreased the yield to 29 % (entry 5), whereas anodic oxidation of 2-aminoresorcinol **6_{red}** generated a poor reactive *o*-azaquinone catalyst, which mainly decomposed to melanin-like polymers, giving only 6 % of DNPH (entry 6). In the specific case of 2-aminoresorcinol derivatives bearing a benzophenone framework **7_{red}**-**11_{red}** (entries 7-11), we sought to modulate the electrophilic properties of the 3,4-azaquinone catalyst by the attachment of substituents on the 1-benzoyl moiety. Surprisingly, the yield of DNPH was good regardless of the electronic and/or

steric effects of the substituents. In particular, the presence of an electron-donating group (entry 10) did not interfere with the catalytic process, except when an hydroxyl group was inserted in the 2'-position (entry 11). Then, the catalytic efficiency of 3,4-azaquinone **11_{ox}** markedly decreased, affording only 7 % of DNPH. This outcome could be rationalized from X-ray crystallographic analyses of the reduced catalysts **7_{red}**, **9_{red}** and **11_{red}**, which showed the presence of a hydrogen bond between the 2-hydroxyl substituent and the carbonyl group of the benzophenone skeleton (Figure 1).^[13] As a consequence, the substituted phenyl group twisted out of the plane, then affecting the transmission of the substituent effects. Similarly, a hydrogen bond could be expected on the 3,4-azaquinone oxidized form which would produce the same effects. However, in the case of compound **11_{red}** (entry 11), a second hydrogen bond was evidenced between the 2'-hydroxyl substituent and the carbonyl group of the benzophenone framework (Figure 1c). Although the intensity of both hydrogen bonds was almost the same, it could be expected that, in solution, the carbonyl group of the benzophenone skeleton of the oxidized form **11_{ox}** would bind preferentially with the 2'-phenolic group rather than with the more acidic 2-phenolic substituent of the *o*-azaquinone moiety.

Table 2: Choice of the organocatalyst^[a]



Entry	Reduced Catalyst	R	R'	Current Efficiency [%]	Yield ^[b] [%]
1	1_{red}	OH	COPh	100	46
2	2_{red}	OH	COMe	100	46
3	3_{red}	OH	CO <i>t</i> Bu	90	42
4	4_{red}	OH	COC ₆ H ₁₁	94	44
5	5_{red}	OH	NO ₂	74	29
6	6_{red}	OH	H	16	6
7	7_{red}	OH	CO(4-F-C ₆ H ₄)	100	46
8	8_{red}	OH	CO(4-SO ₂ Me-C ₆ H ₄)	98	44
9	9_{red}	OH	CO(2,6-diMe-C ₆ H ₃)	96	44
10	10_{red}	OH	CO(2-MeO-C ₆ H ₄)	100	46
11	11_{red}	OH	CO(2-HO-C ₆ H ₄)	20	7
12	12_{red}	H	COPh	— ^[c]	0
13	13_{red}	Me	COPh	— ^[c]	0

[a] Reagents and c.p.e. conditions: (**1_{ox}**-**13_{ox}**) = 0.4 mM, (3,3-dimethylbutylamine) = 20 mM, MeOH, rt, Pt anode (E = + 600 mV vs. SCE), 7h (entries 1-11), 2h (entries 12 and 13). [b] *N*-alkylidenealkylamine was isolated by converting to the corresponding DNPH, obtained upon workup of the oxidized solution with 2,4-dinitrophenylhydrazine under aqueous acidic conditions. [c] no comparison can be made because no catalytic process developed in this case.

Entries 12 and 13 in Table 2 deserve special note because the electrochemical oxidation of 3,4-aminophenol derivatives **12_{red}** and **13_{red}**, which lack the 2-hydroxyl substituent, generated 3,4-azaquinone species **12_{ox}** and **13_{ox}** which were devoid of catalytic efficiency toward the oxidation of 3,3-dimethylbutylamine. Under the aforementioned conditions, the cyclic voltammogram of compound **12_{red}** showed an oxidation peak Pa due to a two-electron process at +200 mV vs. SCE, the sweep rate being 0.1 Vs⁻¹, indicating that 3,4-aminophenol derivative **12_{red}** was less easily oxidizable than the corresponding 2-aminoresorcinol derivative **1_{red}**.

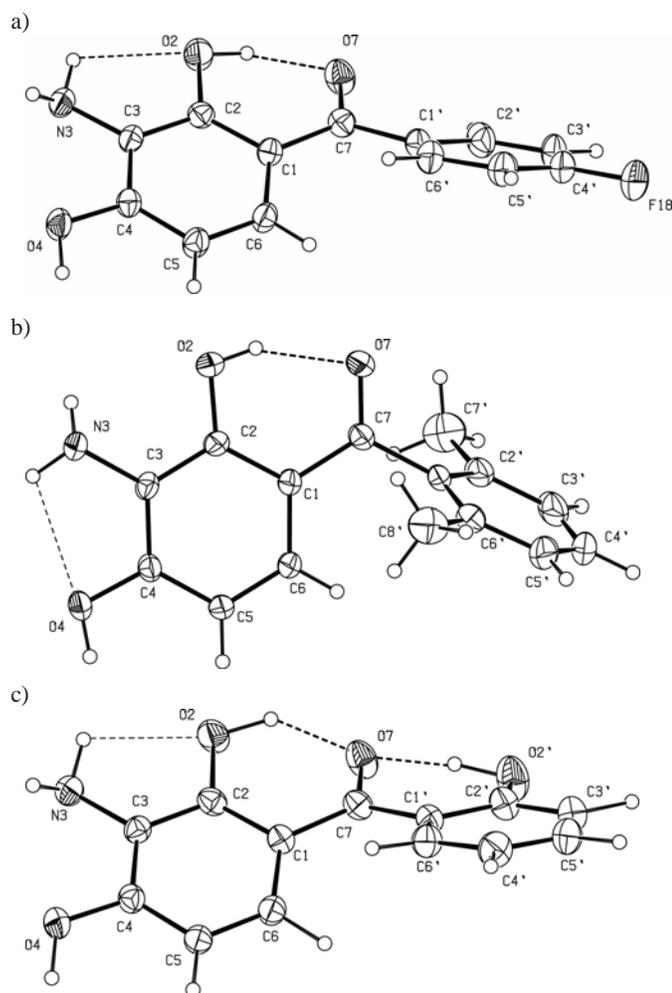


Figure 1. Ortep views of 2-aminoresorcinol reduced catalysts a) **7_{red}** b) **9_{red}** and c) **11_{red}**. Displacement ellipsoids are drawn at the 30% probability level.^[13]

When the controlled potential of the Pt anode was fixed at +600 mV vs. SCE, which is at a potential for which **12_{red}** could be oxidized to the 3,4-azaquinone form **12_{ox}**, a decrease in anodic electrolysis current was observed immediately while the solution became brown. At the end of the electrolysis, 4 electrons were transferred per molecule of **12_{red}**. These results indicated that the electrogenerated 3,4-azaquinone **12_{ox}** did not act as a catalyst but rather reacted with the amine to yield a Michael adduct which, after a subsequent two electron-oxidation reaction, spontaneously decomposed to melanin-like polymers. To confirm the ability of the 2-substituent to prevent the competing formation of Michael adduct, 3,4-aminophenol **13_{red}**, bearing a 2-methyl group, was used as the reduced catalyst (entry 13, Table 2). When treated under the same experimental conditions, the produced 3,4-azaquinone **13_{ox}** also failed to catalyze the oxidation of 3,3-dimethylbutylamine to the

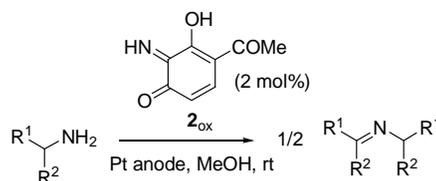
corresponding *N*-alkylidene alkylamine. Finally, the presence of the 2-hydroxyl substituent constituted a prerequisite to the development of the catalytic process. The exact role of the 2-hydroxyl group to convert a catalytic inert *o*-azaquinone species into a highly effective biomimetic catalyst will be disclosed below.

Given the high catalytic efficiency of *o*-azaquinone **2_{ox}** toward the oxidation of 3,3-dimethylbutylamine and the easy synthesis of its precursor **2_{red}** (only two steps), the synthetic potential of this biomimetic electrocatalytic system was then explored through the variation of the amine substrate.

Catalytic oxidation of various amines using *o*-azaquinone **2_{ox}**:

Results from the oxidation of representative amines, under conditions optimized for 3,3-dimethylbutylamine, are reported in Table 3. As expected, the **2_{ox}**-mediated oxidation of activated benzylamine gave the corresponding *N*-benzylidenebenzylamine in quantitative yield since the current efficiency and the yield of DNPH reached 100% and 50%, respectively (entry 1).

Table 3: Chemoselective oxidation of primary aliphatic amines mediated by the biomimetic electrocatalyst **2_{ox}**.^[a]

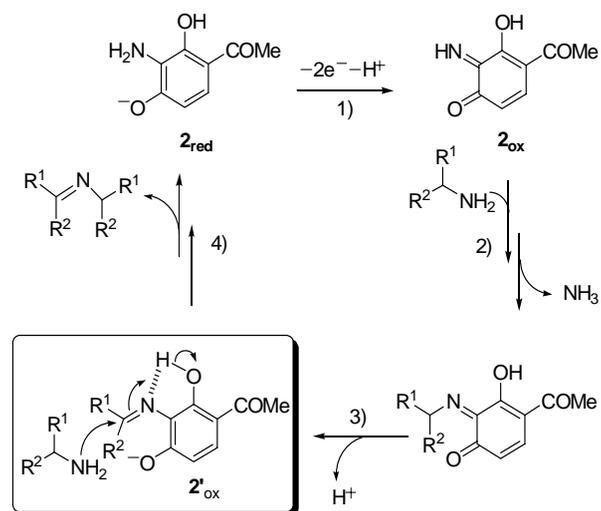


Entry	Amine Substrate	Current Efficiency [%]	Yield [%] ^[b]	
			(A)	(B)
1	Ph-CH ₂ -NH ₂	100	50	2500
2	Bu ^t -CH ₂ -NH ₂	100	46	2300
3	Pr ⁱ -CH ₂ -NH ₂	90	25 ^[c]	1250
4	Me, Et-CH ₂ -NH ₂	98	40	2000
5	Cyclopropyl-NH ₂	98	42	2100
6	Cyclohexyl-NH ₂	82	38	1900
7	HO-CH ₂ -CH ₂ -NH ₂	92	26 ^[c]	1300
8	Ph-CH ₂ -CH ₂ -NH ₂	60	22	1100
9	CH ₃ (CH ₂) ₆ -NH ₂	64	20	1000
10	Ph-CH(CH ₃)-NH ₂	54	25	1250
11	Cyclopentyl-NH ₂	24	7	350
12	Ph-CH ₂ -NHMe	— ^[d]	0	0
13	CH ₃ (CH ₂) ₆ -NHMe	— ^[d]	0	0

[a] Reagents and c.p.e. conditions: (**2_{ox}**) = 0.4 mM, (amine substrate) = 20 mM, MeOH, rt, Pt anode (E = +600 mV vs. SCE), 7h (entries 1-11), 2h (entries 12 and 13). [b] *N*-alkylidenealkylamine was isolated by converting the corresponding DNPH, obtained upon workup of the oxidized solution with 2,4-dinitrophenylhydrazine under aqueous acidic conditions; yields relative to the amine substrate (A) and to the mediator (B). [c] The yield of DNPH was lower than that expected from the current efficiency as a result of the partial conversion of unstable alkylimine into volatile aldehyde on the time scale of anodic electrolysis. [d] no comparison can be made because no catalytic process developed in this case.

Non-activated aliphatic primary amines were also good substrates for the catalyst 2_{ox} (entries 2-6), with yields of isolated DNPH ranging from 38 to 46% (1900 to 2300%, relative to the mediator). In the specific case of isopentylamine (entry 3) and ethanolamine (entry 7), the yield (25%) was lower than that expected from the high current efficiency, as a result of the partial conversion of unstable *N*-alkylidenealkylamine into volatile aldehyde on the time scale of anodic electrolysis. Interestingly, the presence of the alcohol group did not interfere with amine oxidation, indicating a high degree of functional group tolerance (entry 7). 3,4-Azaquinone 2_{ox} was less effective to oxidize more hydrophobic longer-chain amines such as phenylpropylamine or hexylamine, as shown by the lower current efficiency obtained (entries 8 and 9) and by the yield of DNPH which roughly decreased by half. Extended reaction times did not improve the yields of DNPH but, in contrast, produced a second product identified as the osazone (1,2-bis-DNPH), as previously observed with *o*-azaquinone catalyst 1_{ox} generated from 2-aminoresorcinol derivative 1_{red} .^[10b] Further investigations would be necessary to justify the formation of the osazone, which seems favoured when starting amines are not sterically encumbered by β and γ branching. Interestingly, as for the copper amine oxidases enzymes, α -branched amines (entries 10 and 11) were found to be lower substrates for the biomimetic organocatalyst 2_{ox} (for example, compare entry 1 with entry 10), whereas secondary amines (entries 12 and 13) were not reactive at all.

Mechanistic considerations: The above reported results indicated that high catalytic performance, together with high chemoselectivity, were observed with electron-poor *o*-azaquinone catalysts generated from 2-aminoresorcinol derivatives. Then, we questioned about the exact role of both 1-acetyl and 2-hydroxyl groups to convert a catalytic inert 3,4-azaquinone species into a highly effective electrocatalyst. For this purpose, we thoroughly re-examined the ionic transamination mechanism we have previously reported (Scheme 2).^[10]



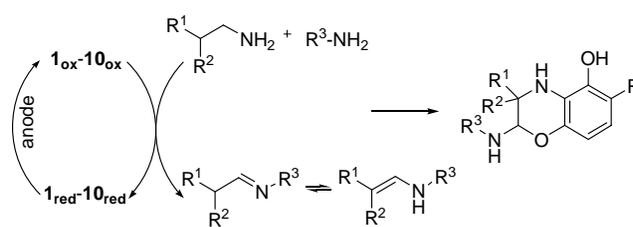
Scheme 2. Role of 2-hydroxyl group in the ionic transamination mechanism

Obviously, the presence of the 1-acetyl group (or another electron-withdrawing group) not only favoured the attack of the amine at the 3-position of the electrogenerated 3,4-azaquinone species (step 2, Scheme 2), but also, facilitated α -proton abstraction and the subsequent electron flow from the α -carbon to the *o*-azaquinone moiety, which aromatized to the Schiff base $2'_{ox}$ (step 3, Scheme 2). Accordingly, 3,4-azaquinone 6_{ox} , which was devoid of electron-

withdrawing group at C-1, together with 11_{ox} , in which the electron-withdrawing effect exerted by the carbonyl group of the benzophenone skeleton was partly lost because of its conjugation with the 2'-hydroxyphenyl group, acted as poor catalysts for the oxidation of amines, but rather were engaged in the competitive polymerization reaction.

More stringent again, the presence of the 2-hydroxyl group constituted a prerequisite to the development of the catalytic process. In fact, the activation of the imine function for further nucleophilic attack of amine leading to the extrusion of *N*-alkylidenealkylamine (step 4, Scheme 2) would be provided by an intramolecular hydrogen bond between the 2-hydroxyl group and the imine nitrogen, generating the highly reactive cyclic transition state $2'_{ox}$. This activated nucleophilic attack of amine, which leads to an amination intermediate (see scheme 2 in reference 10b), would constitute a driving force for the overall transamination mechanism, then preventing any competitive Michael addition reaction. Similar effects of 2-phenolic hydroxyl group on the reactivity of ketimine derivatives have been recently reported in the literature.^[14] Note, the activation of the imine function through intramolecular hydrogen bonding also supports the preference of the use of methanol over MeCN and CH_2Cl_2 as the solvent.

Synthetic applications: The biomimetic catalytic oxidation of primary aliphatic amines reported here produced chemically non-accessible alkylimines from amines, without any stoichiometric reagents, under environmentally friendly conditions. These conditions are particularly favourable for using the imine in situ for further reactions. To this end, we have recently shown that the tautomeric enamine form of the *N*-alkylidenealkylamine generated from the catalytic oxidation of a $R^1R^2CHCH_2NH_2$ amine (alone or in the presence of a second amine R^3-NH_2), could be efficiently engaged, under well-defined conditions, as the dienophile for inverse-electron-demand Diels-Alder (IEDDA) reaction with an *o*-azaquinone catalyst acting as the heterodiene (Scheme 3).^[15] This cascade reaction, wherein both cycloaddition partners were generated in situ, at room temperature, under metal-free conditions, allowed the one-pot regioselective synthesis of highly functionalized 2-alkylamino-1,4-benzoxazine derivatives which proved to be potent neuroprotective agents both in vitro and in vivo.^[15c]



Scheme 3. 3,4-Azaquinone-mediated cascade reaction affording highly functionalized 1,4-benzoxazine derivatives

Conclusion

New insights into the scope and mechanism of the biomimetic catalytic oxidation of primary aliphatic amines into alkylimines, under metal-free conditions, have been delineated through the variation of the structure of the *o*-azaquinone redox mediator. High catalytic performance was observed with electron-poor *o*-azaquinone catalysts electrogenerated from 2-aminoresorcinol derivatives, whereas *o*-azaquinone species electrogenerated from 3,4-aminophenol derivatives which lack the 2-hydroxyl group, were devoid of any catalytic efficiency. Given the easy synthesis of its

precursor **2_{red}** (only two steps) and its high catalytic efficiency, 3,4-azaquinone **2_{ox}**, bearing 1-acetyl and 2-hydroxyl substituents, was considered as the most promising biomimetic electrocatalyst of the studied series. Accordingly, **2_{ox}** exhibited the same substrate specificity as the copper amine oxidases enzymes, that is, poor reactivity with α -branched amines and no reactivity toward secondary amines. Finally, our biomimetic electrocatalytic system displayed two features that are most often associated with enzymatic systems. First, the reaction was enhanced through the participation of 1-acetyl and 2-hydroxyl substituents, as they prevented the competing formation of Michael adducts. Second, the presence of the active 2-hydroxyl group (analogous to 5-hydroxyl group of TPQ),^[12a] which was engaged in an intramolecular hydrogen bond with the imine nitrogen to form a highly reactive Schiff base cyclic transition state, constituted a prerequisite to the development of the catalytic process.

Experimental Section

General considerations: ¹H NMR spectra were recorded on a Bruker AC-300 spectrometer operating at 300 MHz. Chemical shifts, δ , are given in ppm relative to TMS and coupling constants, J , in hertz. The measurements were carried out using the standard pulse-sequences. Chemicals were commercial products of the highest available purity and were used as supplied. Reduced catalyst **1_{red}** was synthesized in four steps from commercially available 2-nitroresorcinol,^[16] while only two steps were involved in the synthesis of reduced catalysts **2_{red}**-**4_{red}**, **7_{red}** and **10_{red}** using the same starting material (See the supporting information of reference 15d). The synthesis of the reduced catalysts **8_{red}**, **9_{red}** and **13_{red}** is also described in reference 15d. Reduced catalysts **5_{red}**, **6_{red}** and **12_{red}** were synthesized through previously reported procedures.^[17] Reduced catalyst **11_{red}** was synthesized by demethylation of compound **10_{red}**, using 6 equiv of AlCl₃ in dry toluene heating at 50°C for 1h30 following a standard protocol.^[16] **(3-amino-2,4-dihydroxyphenyl)(2'-hydroxyphenyl)methanone 11_{red}**: Yellow solid (71 mg; 50%); m.p. 176 °C (petroleum ether/diethyl ether); ¹H NMR (300 MHz, DMSO D₆, 25°C): δ = 12.50 (bs, 1H), 9.86 (bs, 1H), 7.33 (t, J = 7.5, 1H), 7.18 (dd, J = 7.5, J = 1.5, 1H), 6.92 (m, 2H), 6.55 (d, J = 8.5, 1H), 6.31 (d, J = 8.5, 1H); **X-Ray analysis:** A little plate of 0.25 × 0.20 × 0.075 mm, was used. Empirical formula C₁₃H₁₁NO₄, M = 245.23, T = 293 K. Monoclinic system, space group P 2₁/a, Z = 4, a = 7.712(5), b = 7.712(6), c = 19.472(8) Å, β = 100.82(4)°, V = 1137.5(12) Å³, ρ_{calc} = 1.432 g cm⁻³, $F(000)$ = 512, μ = 0.108 mm⁻¹, $\lambda(\text{MoK}\alpha)$ = 0.71073 Å. A total of 8492 reflections was measured with a Nonius Kappa-CCD diffractometer of which 2073 were unique. Refinement of 178 parameters on F^2 led to $R_1(F)$ = 0.0475 calculated with 1367 observed reflections as $I > 2 \sigma(I)$ and $wR_2(F^2)$ = 0.1228 considering all the 2073 data. Goodness of fit = 1.048. CCDC deposition number: 649692

X-ray crystallographic analysis of 7_{red}: A little yellow plate of 0.50 × 0.50 × 0.025 mm, crystallized from a mixture petroleum ether/diethyl ether was used. Empirical formula C₁₃H₁₀FNO₃, M = 247.22, T = 293 K. Monoclinic system, space group P 2₁/a, Z = 4, a = 8.233(4), b = 7.179(3), c = 19.442(8) Å, β = 91.76(2)°, V = 1148.6(9) Å³, ρ_{calc} = 1.430 g cm⁻³, $F(000)$ = 512, μ = 0.113 mm⁻¹, $\lambda(\text{MoK}\alpha)$ = 0.71073 Å. 12461 intensity data were measured with a Nonius Kappa-CCD diffractometer giving 4725 monoclinic reflections, of which 2617 were unique. Refinement of 176 parameters on F^2 led to $R_1(F)$ = 0.0448 calculated with 1698 observed reflections as $I > 2 \sigma(I)$ and $wR_2(F^2)$ = 0.1255 considering all the 2617 data. Goodness of fit = 1.047. CCDC deposition number: 649690

X-ray crystallographic analysis of 9_{red}: A little orange prismatic crystal of 0.50 × 0.35 × 0.20 mm, crystallized from a mixture petroleum ether/diethyl ether was used. Empirical formula C₁₅H₁₃NO₃, M = 257.28, T = 293 K. Orthorhombic system, space group P 2₁2₁2₁, Z = 4, a = 9.256(3), b = 11.940(4), c = 12.006(4) Å, β = 90°, V = 1326.9 Å³, ρ_{calc} = 1.288 g cm⁻³, $F(000)$ = 544, μ = 0.090 mm⁻¹, $\lambda(\text{MoK}\alpha)$ = 0.71073 Å. A total of 11236 reflections was measured with a Nonius Kappa-CCD diffractometer of which 3027 were unique. Refinement of 187 parameters on F^2 led to $R_1(F)$ = 0.0425 calculated with 2440 observed reflections as $I > 2 \sigma(I)$ and $wR_2(F^2)$ = 0.1156 considering all the 3027 data. Goodness of fit = 1.044. CCDC deposition number: 649691

CCDC-649690-649692 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Electrochemistry: Cyclic voltammetry measurements were made with a Radiometer-Tacussel PRG 5 multipurpose polarograph, which was used only as a rapid-response potentiostat. Triangular waveforms were supplied by a Tacussel GSTP 4 function generator. Current-potential curves were recorded on a Schlumberger SI 8312 instrument. The cell was a Radiometer-Tacussel CPRA water-jacketed cell working at a

temperature of 25°C. The working electrode was a platinum disk, carefully polished before each voltammogram with an aqueous alumina suspension. The counter electrode was a platinum electrode Tacussel Pt 11. The reference electrode to which all potentials quoted are referred, was an aqueous saturated calomel electrode (SCE), which was isolated from the bulk solution in a glass tube with a fine-porosity frit.

General procedure for the *o*-azaquinone-mediated autorecycling oxidation of amines: Controlled-potential electrolysis was carried out in a cylindrical, three-electrode divided cell (9 cm diameter), using an electronic potentiostat. In the main compartment, a platinum grid (60 cm² area) served as the anode (working electrode). A platinum sheet was placed in the concentric cathodic compartment (counter electrode), which was separated from the main compartment with a glass frit. The SCE electrode was as above mentioned. The electrolyte solution (0.02 mol L⁻¹ tetraethylammonium hexafluorophosphate in methanol) was poured into the anodic and the cathodic compartments, as well as into the glass tube that contained the SCE electrode. Reduced catalyst (0.1 mmol) and an excess of primary aliphatic amine (5 mmol) were added to the solution in the main compartment (250 mL), and the resulting solution was then oxidized under nitrogen, at room temperature, at + 600 mV vs SCE (initial current 30-40 mA). After exhaustive electrolysis that is, when a negligible value of the current was recorded (0.5-1.0 mA), the solution was worked up by addition of 2.5 mmol of 2,4-dinitrophenylhydrazine reagent (in 5 mL of H₂SO₄, 15 mL of EtOH and 5 mL of water)^[18] because 5 mmol of primary amine only gave 2.5 mmol of *N*-alkylidenealkylamine. After 1h, the resulting solution was concentrated to 40 mL. The solid was collected by filtration, washed with water, and dried in a vacuum dessicator. The identity and purity of the 2,4-dinitrophenylhydrazone (DNPH) was confirmed by TLC and ¹H NMR, after comparison with an authentic sample.

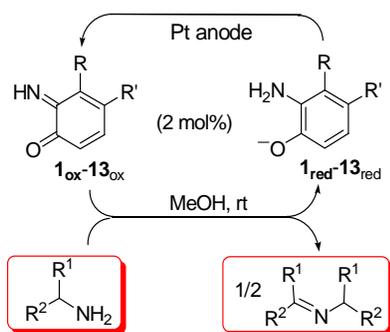
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- [13] It can be noted that, in the three analyzed compounds, all the hydrogen atoms belonging to the nitrogen atom N3 and to the different hydroxyl groups are engaged either in inter- or in intramolecular hydrogen bonds. As shown in Figure 1, a strong intramolecular hydrogen bond is established between the

- hydroxyl group O2-H and the carbonyl-oxygen atom O7 with the following characteristics: for **7_{red}**, distances O2...O7 = 2.524(2) Å, O2-H = 0.92, H...O7 = 1.68 Å, angle O2...H...O7 = 151.4°; for **9_{red}**, distances O2...O7 = 2.573 (2) Å, O2-H = 0.84, H...O7 = 1.81 Å, angle O2...H...O7 = 151.5°; for **11_{red}**, distances O2...O7 = 2.562 (2) Å, O2-H = 0.82, H...O7 = 1.80 Å, angle O2...H...O7 = 153.4° and in this compound, a second one appears built between the hydroxyl group O2'-H and the oxygen atom O7, with the respective geometry: distances O2'...O7 = 2.584(2) Å, O2'-H = 0.93, H...O7 = 1.76 Å, angle O2'...H...O7 = 145.9° aligning the three oxygen atoms (angle O2...O7...O2' = 178.2°). In the three compounds **7_{red}**, **9_{red}** and **11_{red}** the two phenyl rings are tilted by 43.9°, 72.6° and 42.3°, respectively.
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Oxidation of Primary Amines

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Environmentally Friendly Chemoselective Oxidation of Primary Aliphatic Amines by Using a Biomimetic Electrocatalytic System



Chemoselective oxidation of primary aliphatic amines to imines has been successfully achieved under metal-free conditions by using diverse electrogenerated *o*-azaquinone mediators. The catalytic efficiency of these amine oxidase mimics strongly depends on the nature of the substituents R and R'.