CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200700876

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 oxidase enzymes, these mediators exhibited lower reactivity toward α-branched primary amines and no reactivity toward secondary amines. In the case of 3,4-aminophenol derivatives lacking a 2-hydroxy group, the generated *o*-azaquinone species failed to catalyze the oxidation of the amine to the corresponding imine. Further mechanistic considerations allowed a rationalization of the crucial role of the 2-hydroxy group in converting a catalytically inert species into a highly effective biomimetic catalyst.

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

Introduction

The oxidation of amines to imines is of current and intense interest owing to the importance of imines as versatile synthetic intermediates. In particular, 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 directed towards the development of new, mild, and general oxidation procedures for the synthesis of imines from secondary amines. Among such procedures, the stoichiometric method using the hypervalent iodine reagent 2-iodoxybenzoic acid (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 for converting various secondary amines into imines.[3] A noteworthy example is the biomimetic catalytic aerobic oxidation of secondary amines involving ruthenium amine complexes as key intermediates. This methodology, which tolerates important substrate classes, affords both ketimines and aldimines in good yields and with high selectivity.[3c]

In contrast to the extensive work on secondary amines, 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 that are rapidly dehydrogenated to nitriles.[3b,4] Furthermore, when primary amines are treated with IBX, the corresponding carbonyl species is isolated, even with the application of short reaction times, following hydrolysis of the initially formed imine product in situ.[2] However, it has recently been reported that a series of uracil-annulated heteroazulene derivatives, as well as some related compounds, were able to catalyze the oxidation of some primary amines to produce imines in situ, by photo-irradiation under aerobic conditions, whereas, except in the case of benzylamine, no reaction took place under aerobic and thermal conditions.[5]

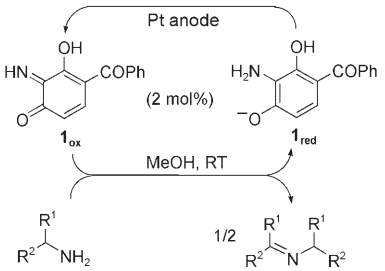
The general interest in amine oxidation chemistry has also stimulated efforts to mimic the biological activities of amine dehydrogenases/oxidases toward primary amines.[6] In these systems, the amine is not dehydrogenated but reacts with a carbonyl group of a quinone cofactor leading to a Schiff-base intermediate, which is then hydrolyzed to the corresponding aldehyde and aminophenol products. The

[a] Dr. M. Largeron, Prof. Dr. M.-B. Fleury
UMR 8638 CNRS-Université Paris Descartes
Faculté des Sciences Pharmaceutiques et Biologiques
4, avenue de L'Observatoire, 75270 Paris Cedex 06 (France)
Fax: (+33) 01-4407-3588
E-mail: martine.largeron@univ-paris5.fr

[b] Dr. A. Chiaroni
Laboratoire de Cristallochimie
Centre National de la Recherche Scientifique
Institut de Chimie des Substances Naturelles
1, avenue de la Terrasse
91198 Gif-sur-Yvette Cedex (France)

latter is oxidatively recycled to the starting quinone cofactor with the elimination of ammonia.[7] Although this is not in itself a suitable path to mimic the generation of imines, in the absence of water, the Schiff-base intermediate can undergo a direct addition of the amine affording the *N*-alkylidenealkylamine condensation product 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 in the catalytic oxidation of benzylamine to *N*-benzylidenebenzylamine in organic media under metal-free conditions.[8] However, these model systems failed to oxidize unactivated primary amines under the same experimental conditions, with the exception of the metal ion complex of a 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]

A few years ago, we showed that electrogenerated *o*-azaquinone $\mathbf{1_{ox}}$ (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 oxidase cofactors. The catalytic cycle produced the reduced catalyst $\mathbf{1_{red}}$ 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] $\mathbf{1_{ox}}$ was also active toward aliphatic amines in the absence of a metal ion. An expedient investigation of the performance of this biomimetic electrocatalytic system led to a preliminary communication.[10b]



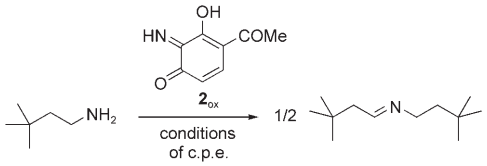
Scheme 1. Oxidation of primary amines mediated by the electrogenerated biomimetic catalyst $\mathbf{1_{ox}}$.

Then, we decided to explore further the potential of the biomimetic electrocatalytic system with two objectives. First, the $\mathbf{1_{ox}}$-mediated catalytic oxidation of primary amines allowed the generation of unstable *N*-alkylidenealkylamines, without any stoichiometric reagents, under environmentally friendly conditions. These conditions are highly favorable 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 oxidase enzymes, might provide important guidelines for designing inhibitors capable of regulating human enzyme activity. In this paper, we present a full account of the biomimetic catalytic oxidation of primary amines to alkylimines. In particular, through variation of the structure of the electrogenerated 3,4-azaquinone mediator, we disclose the specific role of the 1-carbonyl substituent (COR) and the 2-hydroxy group in facilitating operation of the catalytic process.

Results and Discussion

Choice of the reaction conditions: First, we performed optimization studies of the $\mathbf{2_{ox}}$-mediated catalytic process using 3,3-dimethylbutylamine as the amine substrate (Table 1). Although the catalytic efficiencies of $\mathbf{1_{ox}}$ and $\mathbf{2_{ox}}$ were equivalent (entries 1 and 2, Table 2), $\mathbf{2_{ox}}$ was considered to be the more attractive compound because the synthesis of the reduced form $\mathbf{2_{red}}$ required only two steps from commercially available 2-nitroresorcinol, whereas four steps were involved in the preparation of the previously used compound $\mathbf{1_{red}}$.[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

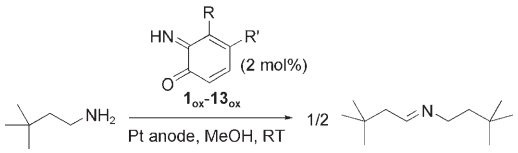
Table 1. Representative screening conditions for the catalytic oxidation of 3,3-dimethylbutylamine.[a]



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_2Cl_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: ($\mathbf{2_{ox}}$) = 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] The *N*-alkylidenealkylamine was isolated by conversion to the corresponding 2,4-dinitrophenylhydrazone (DNPH) by aqueous acidic work-up of the oxidized solution with 2,4-dinitrophenylhydrazine. TEAP: tetraethylammonium perchlorate; TEAHFP: tetraethylammonium hexafluorophosphate; c.p.e.: controlled potential electrolysis.

Table 2. Choice of the electrocatalyst.[a]



Entry	Reduced catalyst	R	R′	Current efficiency [%]	Yield[b] [%]
1	$\mathbf{1}_{red}$	OH	COPh	100	46
2	$\mathbf{2}_{red}$	OH	COMe	100	46
3	$\mathbf{3}_{red}$	OH	CO*i*Bu	90	42
4	$\mathbf{4}_{red}$	OH	COC_6H_{11}	94	44
5	$\mathbf{5}_{red}$	OH	NO_2	74	29
6	$\mathbf{6}_{red}$	OH	H	16	6
7	$\mathbf{7}_{red}$	OH	CO(4-F-C_6H_4)	100	46
8	$\mathbf{8}_{red}$	OH	CO(4-SO_2Me-C_6H_4)	98	44
9	$\mathbf{9}_{red}$	OH	CO(2,6-diMe-C_6H_3)	96	44
10	$\mathbf{10}_{red}$	OH	CO(2-MeO-C_6H_4)	100	46
11	$\mathbf{11}_{red}$	OH	CO(2-HO-C_6H_4)	20	7
12	$\mathbf{12}_{red}$	H	COPh	–[c]	0
13	$\mathbf{13}_{red}$	Me	COPh	–[c]	0

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

more desirable from the point of view of green chemistry, though an Hg anode could also be used without noticeable change (entry 1, Table 1). MeCN (entry 4, Table 1) and CH_2Cl_2 (entry 5, Table 1) proved not to be suitable solvents for the catalytic oxidation of the amine, probably because strong solvation of the *o*-azaquinone $\mathbf{2}_{ox}$ by methanol may be required to enhance the electrophilicity of its quinonoid moiety, thereby favoring the nucleophilic attack of the amine. Among the supporting electrolytes tested, TEAHFP was preferred over the others (entries 6 and 7, Table 1) owing to the potential explosion risk associated with perchlorate anions. A combination of 5 mmol of 3,3-dimethylbutylamine with 0.1 mmol of $\mathbf{2}_{red}$, which corresponds to 2 mol% of the catalyst $\mathbf{2}_{ox}$, was found to be ideal for the reaction.

Under the optimized conditions, the cyclic voltammogram of compound $\mathbf{2}_{red}$ (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, the peak Pa was shifted to 0 mV vs SCE as a result of ionization of the 4-hydroxy group; second, a slight increase in the anodic peak intensity was noted, which suggested that 3,4-azaquinone $\mathbf{2}_{ox}$ was protected from its subsequent polymerization reaction because it could act as a catalyst for the oxidation of the amine. Similar effects have previously been observed in relation to the catalytic activity of similar quinonoid species.[11]

After determining the Pa potential by cyclic voltammetry, controlled potential electrolysis was used as a preparative method for 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 electrolysis for 7 h 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 to +500 mV vs SCE, when the amine concentration was no longer sufficient to ionize the 4-hydroxy group of $\mathbf{2}_{red}$. These results indicated that the $\mathbf{2}_{red}/\mathbf{2}_{ox}$ 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, the unstable alkylimine was isolated by converting it to the 2,4-dinitrophenylhydrazone (DNPH) by aqueous acidic work-up of the oxidized solution with 2,4-dinitrophenylhydrazine (see the Experimental Section). Note that the yield could not exceed 50%, because 5 mmol of 3,3-dimethylbutylamine gave only 2.5 mmol of the corresponding *N*-alkylidenealkylamine. Furthermore, control studies indicated that the amount of *N*-alkylidenealkylamine produced either by simple autoxidation or by electrochemical oxidation of 3,3-dimethylbutylamine in the absence of catalyst $\mathbf{2}_{ox}$ was negligible. Taken together, the results indicate that $\mathbf{2}_{ox}$ exhibited high catalytic efficiency in the oxidation of this non-activated primary amine since the yield of DNPH reached 46% (entry 3, Table 1). After exhaustive electrolysis, the catalyst $\mathbf{2}_{ox}$ was irreversibly consumed, as corroborated by the anodic current, which remained negligible upon further addition of the amine substrate. This result was in agreement with the fact that lowering the amount of catalyst $\mathbf{2}_{ox}$ from 2 mol% to 1 mol% decreased the current efficiency as well as the yield of DNPH (entries 8 and 9, Table 1).

At this point, we suspected that the presence of both the 1-acetyl group and the 2-hydroxy substituent was of overriding importance for the catalytic efficiency of $\mathbf{2}_{ox}$. In this context, it may be noted that the 5-hydroxy proton of 2,4,5-trihydroxyphenylalanine quinone (TPQ) and the 1-NH pyrrole proton of pyrroloquinoline quinone were found to be prerequisites for the catalytic activity of these quinonoid cofactors.[12] So, to evaluate the specific role of each substituent in the course of the catalytic process, the autorecycling oxidation of 3,3-dimethylbutylamine was examined using variously substituted *o*-azaquinone mediators.

Catalyst screening: Having established a reliable set of conditions, we examined the catalytic efficiency of a variety of electrogenerated 3,4-azaquinone species for 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 $\mathbf{1}_{red}$–$\mathbf{4}_{red}$ 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, Table 2). Replacing COR by a nitro group decreased the yield to 29% (entry 5, Table 2), whereas anodic oxidation of 2-aminoresorcinol $\mathbf{6}_{red}$ generated a poorly reactive *o*-azaquinone catalyst, which mainly decomposed to melanin-like polymers, giving only 6% of DNPH (entry 6, Table 2). In the specific case of 2-aminoresorcinol derivatives bearing a benzophenone framework $\mathbf{7}_{red}$–$\mathbf{11}_{red}$ (entries 7–11, Table 2), we sought to modulate the electrophilic properties of the 3,4-azaquinone catalyst by the attachment of substituents to 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, Table 2) did not interfere with the catalytic process, except when a hydroxy group was introduced at the 2′-position (entry 11, Table 2). In this case, the catalytic efficiency of 3,4-azaquinone $\mathbf{11}_{ox}$ decreased markedly, and only 7% of DNPH was obtained. This outcome could be rationalized by X-ray crystallographic analyses of the reduced catalysts $\mathbf{7}_{red}$, $\mathbf{9}_{red}$, and $\mathbf{11}_{red}$, which showed the presence of a hydrogen bond between the 2-hydroxy substituent and the carbonyl group of the benzophenone skeleton (Figure 1).[13] As a consequence, the substituted phenyl group was twisted out of the plane, thereby affecting the transmission of the substituent effects. Similarly, a hydrogen bond could be expected for the 3,4-azaquinone oxidized form, which would produce the same effects. In the case of compound $\mathbf{11}_{red}$ (entry 11, Table 2), a second hydrogen bond was evidenced between the 2′-hydroxy substituent and the carbonyl group of the benzophenone framework (Figure 1(c)). Although the strengths of these two hydrogen bonds were almost the same, it could be expected that, in solution, the carbonyl group of the benzophenone skeleton of the oxidized form $\mathbf{11}_{ox}$ would bind preferentially to the 2′-phenolic group rather than to the more acidic 2-phenolic substituent of the *o*-azaquinone moiety.

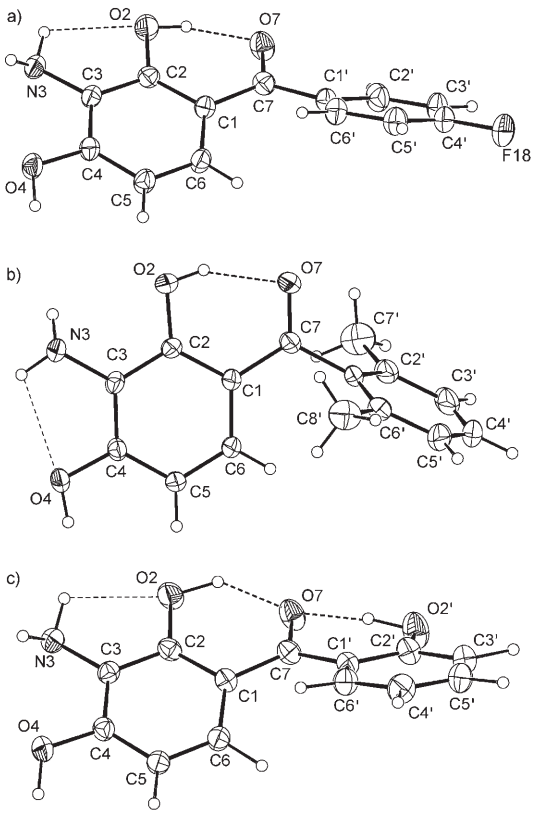


Figure 1. ORTEP views of 2-aminoresorcinol reduced catalysts: a) $\mathbf{7}_{red}$, b) $\mathbf{9}_{red}$, and c) $\mathbf{11}_{red}$. Displacement ellipsoids are drawn at the 30% probability level.[13]

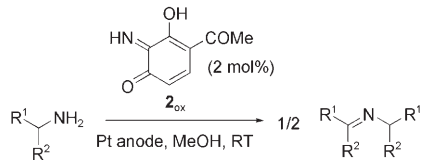
Entries 12 and 13 in Table 2 deserve special note because the electrochemical oxidation of 3,4-aminophenol derivatives $\mathbf{12}_{red}$ and $\mathbf{13}_{red}$, which lack the 2-hydroxy substituent, generated 3,4-azaquinone species $\mathbf{12}_{ox}$ and $\mathbf{13}_{ox}$ that were devoid of catalytic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

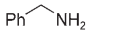
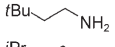
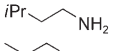
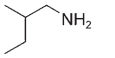
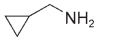
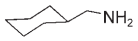
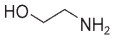
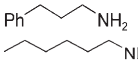
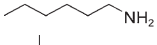
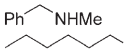
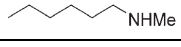
When the controlled potential of the Pt anode was fixed at +600 mV vs SCE, a potential at which $\mathbf{12}_{red}$ could be oxidized to the 3,4-azaquinone form $\mathbf{12}_{ox}$, a decrease in anodic electrolysis current was observed immediately while the solution became brown. At the end of the electrolysis, four electrons had been transferred per molecule of $\mathbf{12}_{red}$. These results indicated that the electrogenerated 3,4-azaquinone $\mathbf{12}_{ox}$ 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 competing formation of the Michael adduct, 3,4-aminophenol $\mathbf{13}_{red}$, bearing a 2-methyl group, was used as the reduced catalyst (entry 13, Table 2). When subjected to the same experimental conditions, the produced 3,4-azaquinone $\mathbf{13}_{ox}$ also failed to catalyze the oxidation of 3,3-dimethylbutylamine to the corresponding *N*-alkylidenealkylamine. It was thus concluded that the presence of the 2-hydroxy substituent was an essential requirement for successful operation of the catalytic process. The precise role of the 2-hydroxy group in converting a catalytically inert *o*-azaquinone species into a highly effective biomimetic catalyst will be disclosed below.

In view of the high catalytic efficiency of *o*-azaquinone $\mathbf{2}_{ox}$ in the oxidation of 3,3-dimethylbutylamine and the facile synthesis of its precursor $\mathbf{2}_{red}$ (only two steps), the synthetic potential of this biomimetic electrocatalytic system was subsequently explored through variation of the amine substrate.

Catalytic oxidation of various amines using *o*-azaquinone $\mathbf{2}_{ox}$: Results relating to the oxidation of representative amines, under conditions optimized for 3,3-dimethylbutylamine, are reported in Table 3. As expected, the $\mathbf{2}_{ox}$-mediated oxidation of activated benzylamine gave the correspond-

Table 3. Chemoselective oxidation of primary aliphatic amines mediated by the biomimetic electrocatalyst $\mathbf{2}_{ox}$.[a]



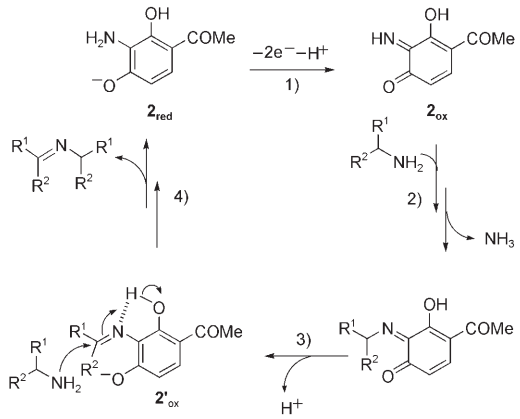
Entry	Amine substrate	Current efficiency [%]	Yield [%][b]	
			A	B
1		100	50	2500
2		100	46	2300
3		90	25[c]	1250
4		98	40	2000
5		98	42	2100
6		82	38	1900
7		92	26[c]	1300
8		60	22	1100
9		64	20	1000
10		54	25	1250
11		24	7	350
12		–[d]	0	0
13		–[d]	0	0

[a] Reagents and c.p.e. conditions: ($\mathbf{2}_{ox}$) = 0.4 mM, (amine substrate) = 20 mM, MeOH, RT, Pt anode (E = +600 mV vs SCE), 7 h (entries 1–11), 2 h (entries 12 and 13). [b] The *N*-alkylidenealkylamine was isolated by conversion to the corresponding DNPH by aqueous acidic work-up of the oxidized solution with 2,4-dinitrophenylhydrazine; 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 partial conversion of the 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.

ing *N*-benzylidenebenzylamine in quantitative yield since the current efficiency and the yield of DNPH reached 100% and 50%, respectively (entry 1, Table 3).

Non-activated aliphatic primary amines also proved to be good substrates for the catalyst $\mathbf{2}_{ox}$ (entries 2–6, Table 3), with isolated yields of DNPH ranging from 38 to 46% (1900 to 2300% relative to the mediator). In the specific cases of isopentylamine (entry 3, Table 3) and ethanolamine (entry 7, Table 3), the yields (25% and 26%) were lower than those expected on the basis of the high current efficiencies as a result of partial conversion of the unstable *N*-alkylidenealkylamines into volatile aldehydes 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, Table 3). 3,4-Azaquinone $\mathbf{2}_{ox}$ was less effective in oxidizing more hydrophobic longer-chain amines such as phenylpropylamine or hexylamine, as shown by the lower current efficiencies obtained (entries 8 and 9, Table 3) and by the yields of DNPH, which were roughly halved. Extended reaction times did not improve the yields of DNPH, but rather led to the generation of a second product identified as the osazone (1,2-bis-DNPH), as previously observed with *o*-azaquinone catalyst $\mathbf{1}_{ox}$ generated from 2-aminoresorcinol derivative $\mathbf{1}_{red}$.[10b] Further investigations would be necessary to rationalize the formation of the osazone, which seems to be favored when the starting amine is not sterically encumbered by β- or γ-branching. Interestingly, as for the copper amine oxidase enzymes, α-branched amines (entries 10 and 11, Table 3) were found to be inferior substrates for the biomimetic electrocatalyst $\mathbf{2}_{ox}$ (compare, for example, entry 1 with entry 10), whereas secondary amines (entries 12 and 13, Table 3) were not reactive at all.

Mechanistic considerations: The above reported results indicate that high catalytic performance, together with high chemoselectivity, were observed with electron-poor *o*-azaquinone catalysts generated from 2-aminoresorcinol derivatives. The question then arose as to the exact role of the 1-acetyl and 2-hydroxy groups in converting a catalytically inert 3,4-azaquinone species into a highly effective electrocatalyst. For this purpose, we thoroughly re-examined the ionic transamination mechanism that we reported previously (Scheme 2).[10]

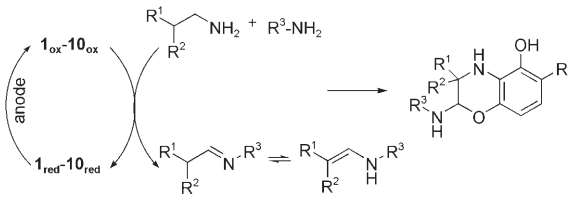


Scheme 2. Role of the 2-hydroxy group in the ionic transamination mechanism.

Obviously, the presence of the 1-acetyl group (or another electron-withdrawing group) not only favors attack of the amine at the 3-position of the electrogenerated 3,4-azaquinone species (step 2, Scheme 2), but also facilitates α-proton abstraction and the subsequent electron flow from the α-carbon to the *o*-azaquinone moiety, which aromatizes to the Schiff base $\mathbf{2'}_{ox}$ (step 3, Scheme 2). Accordingly, 3,4-azaquinone $\mathbf{6}_{ox}$, which is devoid of an electron-withdrawing group at C-1, as well as $\mathbf{11}_{ox}$, in which the electron-withdrawing effect exerted by the carbonyl group of the benzophenone skeleton is attenuated because of the conjugation of this group with the 2′-hydroxyphenyl group, were found to be poor catalysts for the oxidation of amines, promoting instead the competitive polymerization reaction.

Even more crucially, the presence of the 2-hydroxy group proved to be an essential requirement for the successful operation of the catalytic process. In fact, the activation of the imine function for further nucleophilic attack by the amine, leading to the extrusion of *N*-alkylidenealkylamine (step 4, Scheme 2), is provided by an intramolecular hydrogen bond between the 2-hydroxy group and the imine nitrogen, generating the highly reactive cyclic transition state $\mathbf{2'_{ox}}$. This activated nucleophilic attack of amine, which leads to an aminal intermediate (see Scheme 2 in ref. [10b]), would constitute a driving force for the overall transamination mechanism, thereby preventing any competitive Michael addition reaction. Similar effects of a 2-phenolic hydroxy group on the reactivity of ketimine derivatives have recently been reported in the literature.[14] Note that the activation of the imine function through intramolecular hydrogen bonding also supports the preference for 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 inaccessible alkylimines from amines, without any stoichiometric reagents, under environmentally friendly conditions. These conditions are particularly favorable 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 by the catalytic oxidation of an $R^1R^2CHCH_2NH_2$ amine (alone or in the presence of a second amine, R^3-NH_2), could be efficiently deployed, under well-defined conditions, as the dienophile in an inverse-electron-demand Diels–Alder (IEDDA) reaction with an *o*-azaquinone catalyst acting as the heterodiene (Scheme 3).[15]



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

This cascade reaction, for which both cycloaddition partners were generated in situ at room temperature under metal-free conditions, allowed the one-pot regiospecific synthesis of highly functionalized 2-alkylamino-1,4-benzoxazine derivatives, which proved to be potent neuroprotective agents both in vitro and in vivo.[15c]

Conclusion

New insights into the scope and mechanism of the biomimetic catalytic oxidation of primary aliphatic amines to alkylimines under metal-free conditions have been obtained through variation of the structure of the *o*-azaquinone redox mediator. High catalytic performance has been observed with electron-poor *o*-azaquinone catalysts electrogenerated from 2-aminoresorcinol derivatives, whereas *o*-azaquinone species electrogenerated from 3,4-aminophenol derivatives lacking the 2-hydroxy group proved to be devoid of any catalytic efficiency. Given the facile synthesis of its precursor $\mathbf{2_{red}}$ (only two steps) and its high catalytic efficiency, 3,4-azaquinone $\mathbf{2_{ox}}$, bearing 1-acetyl and 2-hydroxy substituents, is considered to be the most promising biomimetic electrocatalyst of the studied series. Accordingly, $\mathbf{2_{ox}}$ exhibited the same substrate specificity as copper amine oxidase 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-hydroxy substituents, as they prevented the competing formation of Michael adducts. Second, the presence of the active 2-hydroxy group (analogous to the 5-hydroxy group of TPQ),[12a] which is engaged in an intramolecular hydrogen bond with the imine nitrogen to form a highly reactive Schiff-base cyclic transition state, proved to be an essential requirement for successful operation of the catalytic process.

Experimental Section

General considerations: ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer operating at 300 MHz. Chemical shifts, δ, are given in ppm relative to TMS; coupling constants, *J*, are given in hertz. The measurements were carried out using standard pulse sequences. Chemicals were commercial products of the highest available purity and were used as supplied. Reduced catalyst $\mathbf{1_{red}}$ was synthesized in four steps from commercially available 2-nitroresorcinol,[16] while only two steps were required for the synthesis of reduced catalysts $\mathbf{2_{red}}$–$\mathbf{4_{red}}$, $\mathbf{7_{red}}$, and $\mathbf{10_{red}}$ using the same starting material (see the supporting information of ref. [15d]). The synthesis of the reduced catalysts $\mathbf{8_{red}}$, $\mathbf{9_{red}}$, and $\mathbf{13_{red}}$ is also described in ref. [15d]. Reduced catalysts $\mathbf{5_{red}}$, $\mathbf{6_{red}}$, and $\mathbf{12_{red}}$ were synthesized according to previously reported procedures.[17] Reduced catalyst $\mathbf{11_{red}}$ was synthesized by demethylation of compound $\mathbf{10_{red}}$ by heating at 50 °C for 1.5 h with 6 equiv of $AlCl_3$ in dry toluene according to a standard protocol.[16]

(3-Amino-2,4-dihydroxyphenyl)(2′-hydroxyphenyl)methanone ($\mathbf{11_{red}}$): Yellow solid (71 mg; 50 %); m.p. 176 °C (petroleum ether/diethyl ether); ^{1}H NMR (300 MHz,[D$_6$]DMSO, 25 °C, TMS): δ = 12.50 (br s, 1H), 9.86 (br s, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.18 (dd, J = 7.5, 1.5 Hz, 1H), 6.92 (m, 2H), 6.55 (d, J = 8.5, 1H), 6.31 ppm (d, J = 8.5 Hz, 1H).

X-ray analysis: A small plate of dimensions 0.25 × 0.20 × 0.075 mm was used. Empirical formula $C_{13}H_{11}NO_4$, M = 245.23, T = 293 K; monoclinic system, space group $P2_1/a$, Z = 4, a = 7.712(5), b = 7.712(6), c = 19.472(8) Å, β = 100.82(4)°, V = 1137.5(12) Å^3, ρ_{calcd} = 1.432 g cm^{-3}, F(000) = 512, μ = 0.108 mm^{-1}, λ(Mo$_{K\alpha}$) = 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 against F^2 led to $R_1(F)$ = 0.0475 calculated from 1367 observed reflections as $I > 2\sigma(I)$, and $wR_2(F^2)$ = 0.1228 considering all 2073 data. Goodness of fit = 1.048.

X-ray crystallographic analysis of $\mathbf{7_{red}}$: A small yellow plate of dimensions 0.50 × 0.50 × 0.025 mm, crystallized from a mixture of petroleum ether/diethyl ether, was used. Empirical formula $C_{13}H_{10}FNO_3$, M = 247.22, T = 293 K; monoclinic system, space group $P2_1/a$, Z = 4, a = 8.233(4), b = 7.179(3), c = 19.442(8) Å, β = 91.76(2)°, V = 1148.6(9) Å^3, ρ_{calcd} =

1.430 g cm^{-3}, $F(000)=512$, $\mu=0.113$ mm^{-1}, $\lambda(Mo_{K\alpha})=0.71073$ 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 against F^2 led to $R_1(F)=0.0448$ calculated from 1698 observed reflections as $I>2\sigma(I)$, and $wR_2(F^2)=0.1255$ considering all 2617 data. Goodness of fit = 1.047.

X-ray crystallographic analysis of 9_{red}: A small orange prismatic crystal of dimensions $0.50\times0.35\times0.20$ mm, crystallized from a mixture of petroleum ether/diethyl ether, was used. Empirical formula $C_{15}H_{15}NO_3$, $M=257.28$, $T=293$ K; orthorhombic system, space group $P2_12_12_1$, $Z=4$, $a=9.256(3)$, $b=11.940(4)$, $c=12.006(4)$ Å, $\beta=90°$, $V=1326.9$ Å^3, $\rho_{calcd}=1.288$ g cm^{-3}, $F(000)=544$, $\mu=0.090$ mm^{-1}, $\lambda(Mo_{K\alpha})=0.71073$ Å. A total of 11236 reflections was measured with a Nonius Kappa-CCD diffractometer, of which 3027 were unique. Refinement of 187 parameters against F^2 led to $R_1(F)=0.0425$ calculated from 2440 observed reflections as $I>2\sigma(I)$, and $wR_2(F^2)=0.1156$ considering all 3027 data. Goodness of fit = 1.044.

CCDC 649690 ($\mathbf{11_{red}}$), 649691 ($\mathbf{7_{red}}$), and 649692 ($\mathbf{9_{red}}$) 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 with a Schlumberger SI 8312 instrument. The cell was a Radiometer-Tacussel CPRA water-jacketed cell operating at a temperature of 25 °C. The working electrode was a platinum disk, which was carefully polished with an aqueous suspension of alumina before acquiring each voltammogram. The counter electrode was a Tacussel Pt 11 platinum electrode. The reference electrode, to which all quoted potentials are referred, was an aqueous saturated calomel electrode (SCE), which was isolated from the bulk solution in a glass tube by 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 cm^2 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 by a glass frit. The SCE was as described above. The electrolyte solution (0.02 mol L^{-1} tetraethylammonium hexafluorophosphate in methanol) was poured into the anodic and cathodic compartments, as well as into the glass tube that contained the SCE. Reduced catalyst (0.1 mmol) and an excess of primary aliphatic amine (5 mmol) were then added to the solution in the main compartment (250 mL), and the resulting solution was oxidized under nitrogen at room temperature at +600 mV vs SCE (initial current 30–40 mA). After exhaustive electrolysis, that is, when a negligible current was recorded (0.5–1.0 mA), the solution was worked-up by the addition of 2,4-dinitrophenylhydrazine reagent (2.5 mmol in 5 mL of H_2SO_4, 15 mL of EtOH, and 5 mL of water),[18] the stoichiometry reflecting the fact that 5 mmol of the primary amine gave only 2.5 mmol of the *N*-alkylidenealkylamine. After 1 h, the resulting solution was concentrated to a volume of 40 mL. The solid was collected by filtration, washed with water, and dried in a vacuum desiccator. The identity and purity of the 2,4-dinitrophenylhydrazone (DNPH) was confirmed by TLC and ^{1}H NMR, after comparison with an authentic sample.

[1] For a review on the synthetic use of imines, see: J. P. Adams, *J. Chem. Soc. Perkin Trans. 1* **2000**, 125–139.

[2] a) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem.* **2003**, *115*, 4111–4117; *Angew. Chem. Int. Ed.* **2003**, *42*, 4077–4082; b) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.

[3] For selected recent examples, see: a) A. H. Ell, J. S. M. Samec, C. Brasse, J. E. Bäckvall, *Chem. Commun.* **2002**, 1144–1145; b) K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2003**, *115*, 1518–1521; *Angew. Chem. Int. Ed.* **2003**, *42*, 1480–1483; c) J. S. M. Samec, A. H. Ell, J. E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 2327–2334; d) J. R. Wang, Y. Fu, B.-B. Zhang, X. Cui, L. Liu, Q.-X. Guo, *Tetrahedron Lett.* **2006**, *47*, 8293–8297; e) H. Choi, M. P. Doyle, *Chem. Commun.* **2007**, 745–747.

[4] For recent examples, see: a) K. Mori, K. Yamaguchi, T. Mizugaki, K. Ebitani, K. Kaneda, *Chem. Commun.* **2001**, 461–462; b) Y. Maeda, T. Nishimura, S. Uemura, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399–2403; c) K. Yamaguchi, N. Mizuno, *Chem. Eur. J.* **2003**, *9*, 4353–4361; d) S. Kamiguchi, A. Nakamura, A. Suzuki, M. Kodomari, M. Nomura, Y. Iwasawa, T. Chihara, *J. Catal.* **2005**, *230*, 204–213, and references therein.

[5] a) Y. Mitsumoto, M. Nitta, *J. Org. Chem.* **2004**, *69*, 1256–1261; b) S.-I. Naya, M. Nitta, *Tetrahedron* **2004**, *60*, 9139–9148; c) M. Nitta, D. Ohtsuki, Y. Mitsumoto, S.-I. Naya, *Tetrahedron* **2005**, *61*, 6073–6081; d) S.-I. Naya, Y. Yamaguchi, M. Nitta, *Tetrahedron* **2005**, *61*, 7384–7391.

[6] M. Mure, *Acc. Chem. Res.* **2004**, *37*, 131–139, and references therein.

[7] M. Mure, S. A. Mills, J. P. Klinman, *Biochemistry* **2002**, *41*, 9269–9278, and references therein.

[8] a) M. Mure, J. P. Klinman, *J. Am. Chem. Soc.* **1995**, *117*, 8707–8718; b) Y. Lee, L. M. Sayre, *J. Am. Chem. Soc.* **1995**, *117*, 11823–11828, and references therein; c) S. Itoh, N. Tanaka, S. Haranou, T. Ando, M. Komatsu, Y. Ohshiro, S. Fukuzumi, *J. Org. Chem.* **1996**, *61*, 8967–8974, and references therein; d) A. C. Rinaldi, A. Rescigno, A. Rinaldi, E. Sanjust, *Bioorg. Chem.* **1999**, *27*, 253–288, and references therein; e) K. Q. Ling, J. Kim, L. M. Sayre, *J. Am. Chem. Soc.* **2001**, *123*, 9606–9611.

[9] S. Itoh, M. Tanaguchi, N. Takada, S. Nagatomo, T. Kitagawa, S. Fukuzumi, *J. Am. Chem. Soc.* **2000**, *122*, 12087–12097.

[10] a) M. Largeron, M.-B. Fleury, *J. Org. Chem.* **2000**, *65*, 8874–8881; b) M. Largeron, A. Neudörffer, M.-B. Fleury, *Angew. Chem.* **2003**, *115*, 1056–1059; *Angew. Chem. Int. Ed.* **2003**, *42*, 1026–1029.

[11] K. Kano, M. Nakagawa, K. Takagi, T. Ikeda, *J. Chem. Soc. Perkin Trans. 2* **1997**, 1111–1119, and references therein.

[12] a) M. Mure, J. P. Klinman, *J. Am. Chem. Soc.* **1993**, *115*, 7117–7127; b) S. Itoh, M. Mure, M. Ogino, Y. Ohshiro, *J. Org. Chem.* **1991**, *56*, 6857–6865.

[13] It may be noted that, in the three analyzed compounds, all the hydrogen atoms belonging to the nitrogen atom N3 and to the different hydroxy groups are engaged in either inter- or intramolecular hydrogen bonds. As shown in Figure 1, a strong intramolecular hydrogen bond is established between the hydroxy group O2-H and the carbonyl oxygen atom O7, with the following characteristics: for $\mathbf{7_{red}}$, distances O2···O7 = 2.524(2) Å, O2–H = 0.92 Å, H···O7 = 1.68 Å, angle O2···H···O7 = 151.4°; for $\mathbf{9_{red}}$, distances O2···O7 = 2.573(2) Å, O2–H = 0.84 Å, H···O7 = 1.81 Å, angle O2···H···O7 = 151.5°; for $\mathbf{11_{red}}$, distances O2···O7 = 2.562(2) Å, O2–H = 0.82 Å, H···O7 = 1.80 Å, angle O2···H···O7 = 153.4°, and in this last compound, there is a second hydrogen bond between the hydroxy group O2′–H and the oxygen atom O7, with the respective geometry as follows: distances O2′···O7 = 2.584(2) Å, O2′–H = 0.93 Å, 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 $\mathbf{7_{red}}$, $\mathbf{9_{red}}$, and $\mathbf{11_{red}}$, the two phenyl rings are tilted by 43.9, 72.6, and 42.3°, respectively.

[14] a) H. Miyabe, Y. Yamaoka, Y. Takemoto, *Synlett* **2004**, 2597–2599; b) H. Miyabe, Y. Yamaoka, Y. Takemoto, *J. Org. Chem.* **2006**, *71*, 2099–2106.

[15] a) M. Largeron, A. Neudörffer, M. Vuilhorgne, E. Blattes, M.-B. Fleury, *Angew. Chem.* **2002**, *114*, 852–855; *Angew. Chem. Int. Ed.* **2002**, *41*, 824–827; b) E. Blattes, M.-B. Fleury, M. Largeron, *J. Org. Chem.* **2004**, *69*, 882–889; c) E. Blattes, B. Lockhart, P. Lestage, M.-B. Fleury, M. Largeron, *J. Med. Chem.* **2005**, *48*, 1282–1286; d) D. Xu, A. Chiaroni, M.-B. Fleury, M. Largeron, *J. Org. Chem.* **2006**, *71*, 6374–6381.

[16] R. Larget, B. Lockhart, B. Pfeiffer, A. Neudörffer, M.-B. Fleury, M. Largeron, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2929–2934.

[17] a) H. Lindner, *Chem. Ber.* **1923**, *56*, 1870–1871; b) P. Piateck, J. Kalisiak, J. Jurcka, *Tetrahedron Lett.* **2004**, *45*, 3309–3311; c) G. M. Tseiltlin, B. V. Tokarev, V. N. Kulagin, *J. Org. Chem. USSR (Engl. Transl.)* **1982**, 931–934.

[18] P. Lue, W.-Q. Fan, X.-J. Zhou, *Synthesis* **1989**, 692–693.

Received: June 8, 2007
Revised: August 23, 2007
Published online: November 8, 2007

