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Synthesis and Electrochemical Study of an Original Copper(II)-Capped Salen–Cyclodextrin Complex

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A new metallocapped cyclodextrin (CD) was synthesized by the regioselective debenzylation, induced by diisobutylaluminium hydride (DIBAL-H), of perbenzylated cyclodextrins. This reaction allowed for the efficient preparation of an unprecedented CD–salen type copper(II) complex. The electrochemical behavior of both the bound and unbound CD–salen compounds was investigated by cyclic voltammetry. Notably, it was shown that the presence of *tert*-butyl groups at the *ortho*- and *para*-positions of the salen aromatic rings stabilized the copper(II) phenoxyl radical species that was generated upon the one-electron oxidation of the starting compound. Importantly, this stabilization remained effective when the salen-type ligand was covalently attached to the CD. This allowed for investigations of the reactivity of the copper(II) phenoxyl radical complex towards a primary alcohol to be performed by cyclic voltammetry. This reaction can be considered as mimicking the behavior of galactose oxidase. However, under these conditions, no reactivity was observed in the presence of benzyl alcohol. This may be due to distortion, either of the initially square planar salen ligand after its grafting to the CD primary face, and/or of the CD itself. On the other hand, the electrochemical reduction of the un-grafted copper(II) salen-type ligand led to a transient anionic species that exhibited significant stability on the time-scale of the slow cyclic voltammetry measurement in the absence of the CD, but was unstable in the presence of the CD. In the latter case, it was demonstrated that the anionic species was protonated by the CD. Importantly, this protonation was not fast enough to prevent catalytic activation of iodomethane by the electro-generated copper(I)-capped salen CD complex.

Introduction

Combining cyclodextrins (CDs) with transition metal salts or complexes has proven to be a very attractive way of designing new catalysts, enzyme mimics, sensors, and molecular wires.[1] Two main approaches are generally used to immobilize transition metals in the vicinity of CDs . In the first one, the CD acts as a second-sphere ligand binding noncovalently to the first ligand sphere of the metal center. This supramolecular approach, which relies on the ability of the CDs to include part of a metal complex in their internal hydrophobic cavities, is strongly dependent on the nature of the solvent. Indeed, the driving force for the complexation between a CD and a substrate involves several factors such as van der Waals forces, hydrophobic interactions, electronic effects, and steric factors, all of which may be too weak to enforce a strong association between the adduct partners.[2] Hence, when the metal ligands are hydrophobic, dissociation is favored in organic solvents and water appears to be the most suitable solvent for complexation.

The second approach involves covalently attaching one or more ligands of the transition metal complex to the primary or secondary face of the CD. In such a configuration, the metal center can be kept close to the CD cavity regardless of the solvent polarity. We recently used this approach to design a new cobalt(II)–CD complex, and to investigate the stability/reactivity duality of the corresponding low-valent cobalt(I) species that was electrochemically generated.[3] This cobalt-CD complex was prepared from CoX_2 (X = Br and BF_4) in the presence of 1 equiv. of 6-deoxy-*N*-(2-methyliminopyridine)-β-CD ligand. Under these conditions, we demonstrated for the first time, that the electrogenerated cobalt(I) species could be kinetically and thermodynamically stabilized by the presence of the CD. Importantly, this did not prevent the cobalt(I) species from remaining sufficiently reactive to enable it to activate aryl halides. We also used this approach to generate a Pd-capped CD, and demonstrated for the first time the inherent chirality of regioisomerically functionalized CDs.[1a]

Copper is an important transition metal in catalysis. Copper is used in organic synthesis,[4] but is also found in metalloenzymes such as galactose oxidase (GO) that catalyses the oxidation of primary alcohols to their corresponding aldehydes with concomitant reduction of molecular dioxygen to hydrogen peroxide.[5] Interestingly, this two-elec-

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tron oxidation process is promoted by a single copper atom acting in synergy with a tyrosyl radical from the protein. The fact that GO possesses a N_2O_2 coordination sphere has led to the preparation of numerous compounds that model its active site.[5] A wide number of copper(II) complexes of salen-type ligands have been prepared and investigated, but only a limited number of reports of functional models that exhibit activity towards the oxidation of primary alcohols are available. A functional model of GO was described in 1996 by Stack et al. involving the one-electron oxidized copper(II) phenolate complex of a salen-type ligand.[6] This model compound was able to catalyze the aerobic oxidation of benzyl alcohol to benzaldehyde with high turnover values. To achieve such reactivity, the phenolate moieties were *ortho*- and *para*-substituted with electron donating groups that had the effect of stabilizing the phenoxyl radical, furthermore a significant tetrahedral distortion was induced around the copper atom by the binaphthyl linker. However, oxidation of the initial copper(II)-phenolate complex to the catalytically active copper(II)-phenoxyl radical species required the use of a strong chemical oxidant. Alternatively, it was shown that the copper(II) complex of *N*,*N*′-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)-1,2-ethylenediamine was readily electrochemically oxidized, and allowed for the oxidation of primary alcohols to aldehydes but could not oxidize secondary alcohols under the same conditions.[7] Other copper(II) complexes of salen-type ligands have been prepared and tested, and have been found to oxidize primary alcohols with reasonable success.[8]

In this context, and taking advantage of our recent works on CDs,[1a,3,9] we decided to prepare and examine the reactivity of a complex in which the salen-type ligand would be covalently attached to the primary face of the CD. To the best of our knowledge, there is only one report dedicated to discussing the challenge of building of a salen-type ligand onto a cyclodextrin rim.[10] This report detailed the synthesis of a CD–salen-type ligand in which the two salen moieties were covalently attached to the A and B positions of the CD. This ligand was used to prepare the corresponding manganese(III) complex, a superoxide dismutase mimic.

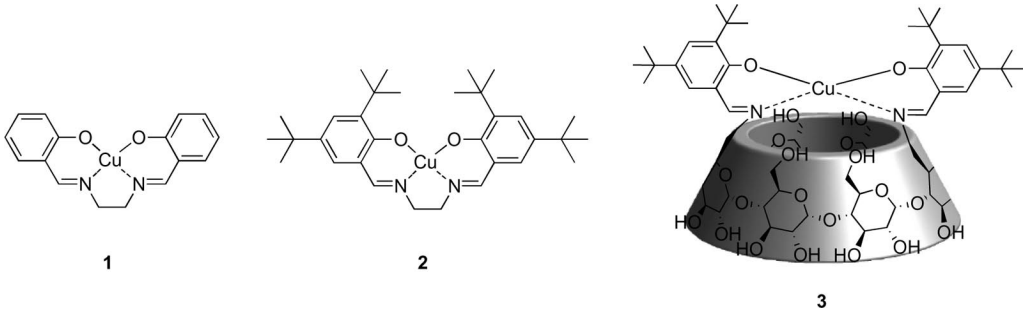
Our aim here is to observe the influence of the CD on the electrochemical behavior of a copper(II) complex; we therefore designed a CD-based salen ligand that would bring the metal center of the complex into close proximity with the cavity, hence forming a so-called metallocapped CD (see **3** in Scheme 1).[11] The presence of the CD cavity right under the metal center could enhance the selectivity of the catalyst towards oxidation reactions, and allow reactions to be performed in aqueous media. Moreover, combination of the rigid salen ligand with a less rigid cyclodextrin ligand could result in ligands that exhibit interesting chemical reactivity. Since tetrahedral distortion of the salen moiety was found to be of importance in aiding the oxidation of primary alcohols, 6^A,6^D-dideoxy-6^A,6^D-bis[(*tert*-butyl-*N*-salicylidene)imino]-α-cyclodextrin (**3**) has been designed to modify the initial geometry of the salen moiety, and most likely the CD itself.

Electrochemical investigations of both this new copper(II)–CD–salen complex and its parent complexes (Scheme 1) were useful, not only for probing the redox properties of this complex, but also for delineating the structure/reactivity relationship of the electro-generated transient species.

Results and Discussion

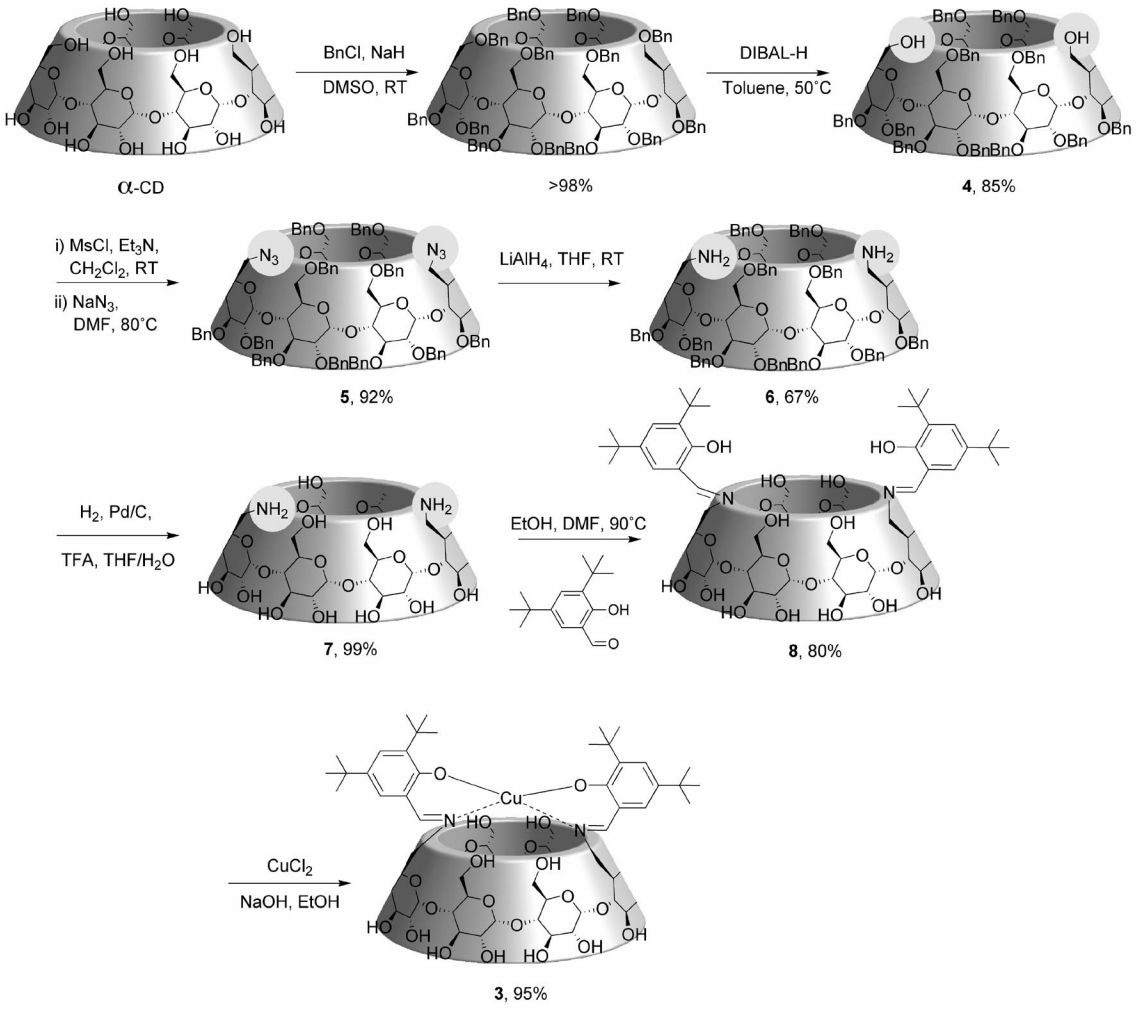
a) Synthesis of Complex (3)

In order to synthesize complex **3** (Scheme 2) two diametrically opposed primary hydroxyl groups of the CD ligand had to be selectively modified. Our strategy was based on the perbenzylation-debenzylation sequence developed by some of us[12] to regioselectively access a wide variety of functional CDs.[13] This gives access, in very high yield, to α-cyclodextrin **4**, which is selectively protected at all but the 6^A and 6^D positions. Amino groups were then introduced by mesylation, followed by substitution with an azido group to yield CD **5**. CD **5** was then reduced by $LiAlH_4$ to give CD **6**. Hydrogenolysis of the benzyl groups on CD **6** afforded the diamino-α-cyclodextrin **7** in 52% overall yield. It is worth noting that the azido groups had to be reduced prior to hydrogenolysis of the benzyl groups to avoid poisoning the catalyst. This route is also an improvement on a previously described synthesis method for **7** that gave only a 3.7% yield.[14] Copper salen complex **3** was then synthesized according to a classical procedure.[15] The condensation reaction involving 3,5-di-*tert*-butyl-2-hydroxybenzalde-



1 2 3

Scheme 1. The copper(II) complexes of salen-type ligands investigated in this work.



Scheme 2. Synthesis route for complex **3**.

hyde was performed in ethanol and DMF for solubility reasons. The final complex was obtained using $CuClO_4$ as a copper source, with an overall yield of 40% based on the native α-cyclodextrin. (Scheme 2).

b) Electrochemical Behavior of Complexes 1, 2, and 3

Cyclic voltammograms obtained during reduction or oxidation scans of the copper(II) salen complex **1** are shown in Figure 1. As already reported, the reduction of **1** proceeded through two distinct electron-transfer processes located at –1.22 V ($E°$ = –1.18 V) and –2.49 V (Figure 1, A).[16] The first wave corresponded to the electrochemically reversible Cu^{II}/Cu^{I} transition, whereas the second one certainly featured a reduction of Cu^{I} to the corresponding Cu^{0} complex, followed by removal of the metal center from the ligand (Scheme 3). Although no Cu^{0} deposit could be observed in the anodic range, which was explored, the reduction of the resulting free dianionic ligand could be observed at a more negative potential value (E = –2.95 V) (not shown in Figure 1).

The oxidation of **1** was poorly resolved at a glassy carbon electrode surface. Therefore, a platinum electrode was used to follow the oxidation process of **1** (Figure 1, B). Under these conditions an irreversible two-electrons oxidation wave was exhibited at +1.03 V, showing the low stability of the electro-generated copper phenoxyl radical species with respect to the time-scale of the slow cyclic voltammetry experiment.

Importantly, when the same experiment was run with **2** instead of **1** the oxidation process gained some reversibility ($E°$ = +0.88 V), and tended towards a one-electron process. This confirmed that a sterically bulky and electron-donating substituent at the *ortho*- and *para*-positions of the two aromatic rings thermodynamically and kinetically stabilized the phenoxyl radical (Figure 1, D). A similar effect involving an ethylenediamine linker substituting for an ethylenediimine linker has already been evidenced based on cyclic voltammetry and EPR studies.[7a] The reversible oxidation wave O'_2 may therefore be attributed to the oxidation of the μ-phenolato moiety to a μ-phenoxyl radical. In other words, the oxidation process involves the ligand rather than the metal (Scheme 3).

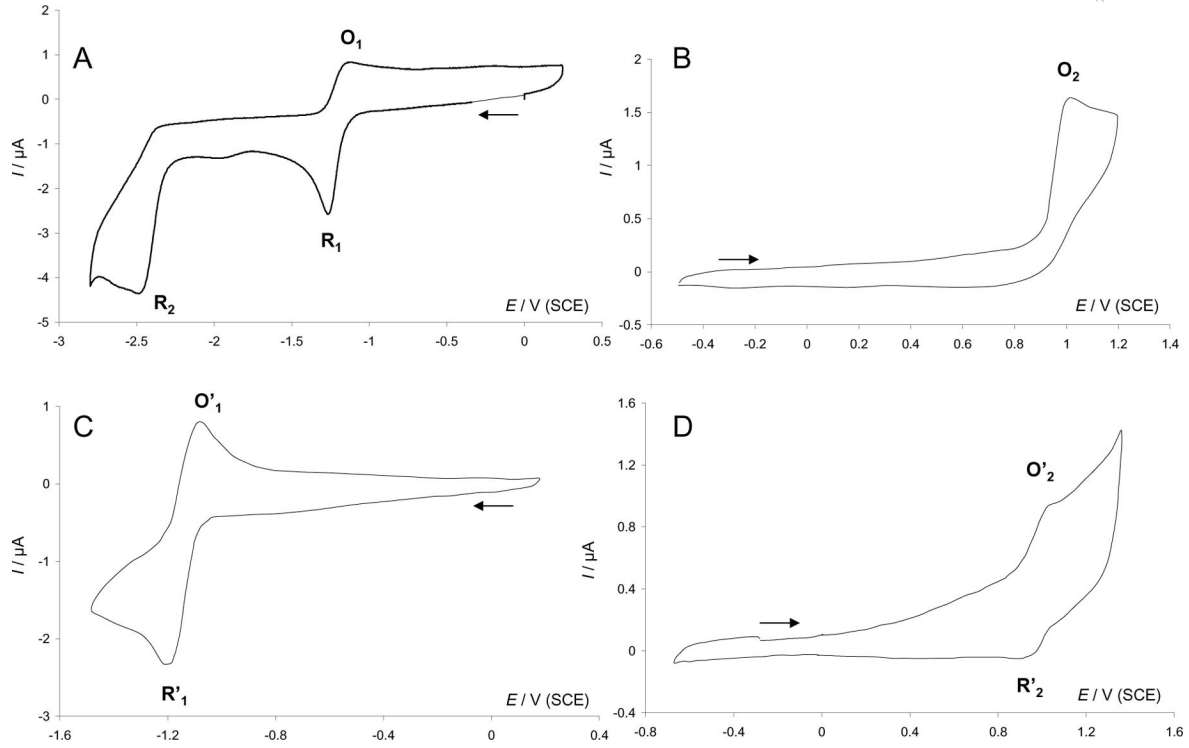
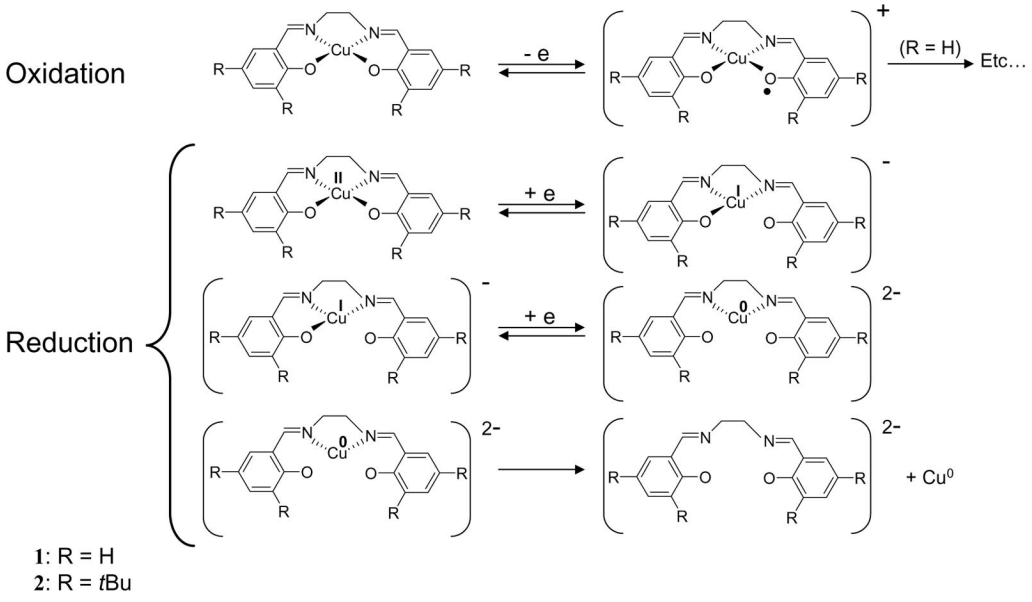


Figure 1. Voltammetry of **1** (2 mM) in DMF with $TBABF_4$ (0.1 M) as the supporting electrolyte, recorded at a scan rate of 200 $mV\,s^{-1}$. Reductive (**A**) and oxidative (**B**) directions for the initial scans were recorded at a glassy carbon electrode (1 mm diameter) and at a platinum electrode (0.5 mm diameter), respectively. Voltammetry of **2** in DMF with $TBABF_4$ (0.1 M) as the supporting electrolyte, recorded at a glassy carbon electrode (1 mm diameter), at a scan rate of 100 $mV\,s^{-1}$. Reductive (**C**) and oxidative (**D**) scans. The concentration of **2** was 2 mM for scan **C** and 1 mM for **D**.



Scheme 3. Oxidation and reduction processes of complexes **1** and **2**.

On the other hand, the presence of the four *tert*-butyl groups in complex **2** did not lead to a change in the reduction process when compared to **1**. The reduction still occurred at $E° = -1.18$ V and remained reversible. A second reduction wave was also observed at higher potentials (not shown in Figure 1, C) once again leading to a rapid expulsion of Cu^0.

The electrochemical behavior of complex **3** in which the salen-type ligand is covalently attached to the CD primary face, was significantly different from that of **1** and **2** (Fig-

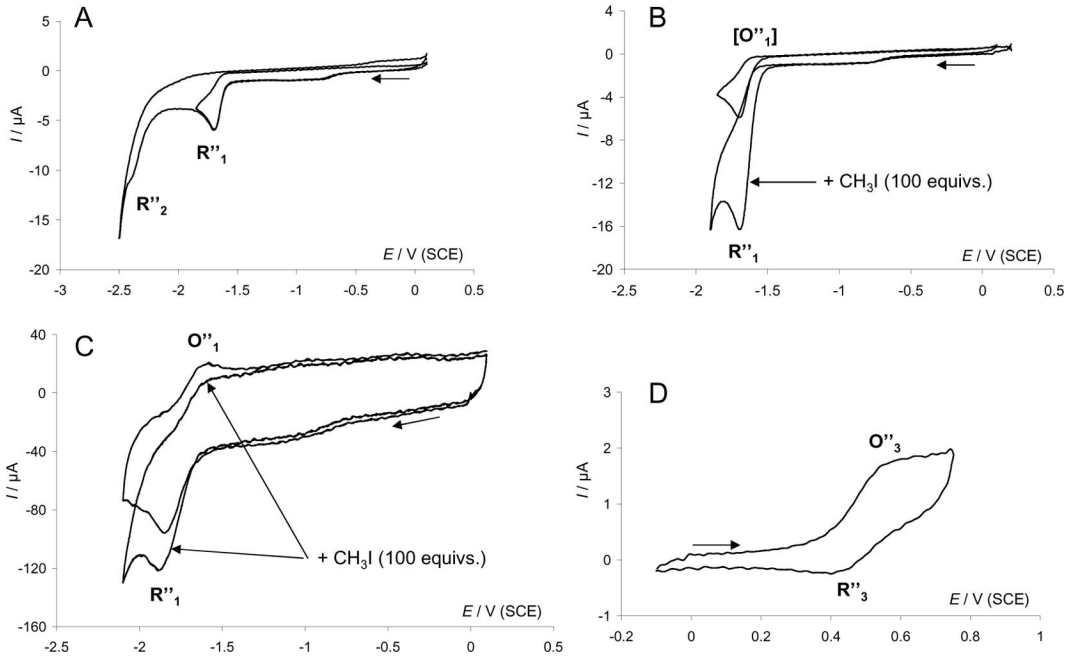


Figure 2. Voltammetry of **3** (1 mM) in DMF with $TBABF_4$ (0.1 M) as the supporting electrolyte, recorded at a scan rate of 200 $mV s^{-1}$ (**A**, **B**, **D**) and 30 $V s^{-1}$ (**C**). Reductive (**A, B**, **C**) and oxidative (**D**) scans recorded at a glassy carbon electrode (1 mm diameter) in the absence and the presence of iodomethane (**B**, **C**).

ure 2). Although the reduction of **3** proceeded through an irreversible wave R''_1 (–1.71 V) at slow scan rates, the process became reversible above 30 $V s^{-1}$ which is evidence for a rather slow follow up reaction involving the initial Cu^I species in the presence of the cyclodextrin (Figure 2, A and C). A second reduction wave R''_2 could be also observed at –2.40 V at slow scan rates (Figure 2, A), but again, and contrary to previous reported works,[16,17] no Cu^0 deposit could be observed despite the irreversibility of R''_1. Since CDs are known to be good proton donors, the irreversibility of the reduction wave may involve protonation of the anionic species produced in R''_1. To verify this point one molar equivalent of native α-CD was added to a solution containing complex **2**, and under these conditions the initially reversible reduction wave R'_1 became irreversible. On the other hand, R'_1 remained reversible after the addition of one molar equivalent of a per-benzylated α-CD. These results clearly established the feasibility of a reaction between the phenate moiety and a proton donated by a CD moiety, even under less favorable conditions than in the reaction incorporating **2** (bimolecular reaction with 1:1 concentration ratio). Such a reaction may then lead to the conversion of the initial Cu^I to the corresponding protonated form that is prone to being reduced in R''_2.

Importantly, over a short time-scale ($v \geq 30\ V s^{-1}$) the addition of increasing amounts of iodomethane led to the disappearance of the oxidation wave O''_1 and a slight increase in the peak current intensity of R''_1. This current peak increase was more pronounced when the same experiment was performed over a longer time-scale (v = 100 $mV s^{-1}$; compare Figure 2 , B and C). These results clearly showed a redox catalysis process occurring between the electro-generated copper(I)-capped salen–cyclodextrin and the alkyl halide. This process is faster than the protonation reaction.

Interestingly, and as observed with the nongrafted complex **2**, the oxidation of **3** appeared to be reversible at 0.2 $V s^{-1}$, confirming the stabilization of the electro-generated phenoxyl radical in the presence of the *tert*-butyl groups despite the presence of the cyclodextrin (Figure 2, D). This prompted us to investigate, by cyclic voltammetry, the reactivity of the phenoxyl radical towards a primary alcohol to examine its potential as a galactose oxidase mimic. Thus, increasing amounts of benzyl alcohol were added to a solution of **3** and voltammetric data were collected at slow scan rates. However, no changes were observed in the voltammograms when compared to the initial cyclic voltammogram of **3** showing that no reaction occurred over the voltammetric time-scale ($t < 1$ s). This lack of reactivity may be due to a distortion of the square planar salen-type ligand as previously observed when a binaphthyl linker was attached to the complex.[6] Indeed, the flexibility and degree of distortion required to shift from a square planar towards a tetrahedral geometry is certainly modulated by the nature of the linker between the salicylidene moieties.[5] Yet, other effects may also explain such lack of reactivity, such as a possible distortion of the CD itself due to its natural flexibility, or because of steric hindrance caused by the presence of the CD.

Conclusions

For the first time, a copper(II) salen-type complex was synthesized by covalent attachment of a salen ligand to the

primary face of an α-cyclodextrin at the A–D position. The preparation of this new complex was possible due to the remarkable ability of diisobutylaluminium hydride to regioselectively de-*O*-benzylate perbenzylated cyclodextrins.[12,13] The electrochemical behaviors of the grafted and nongrafted copper(II) salen-type ligands were investigated by cyclic voltammetry. It was shown that the presence of *tert*-butyl groups at the *ortho*- and *para*-positions of the salen aromatic rings stabilized the copper phenoxyl radical obtained by oxidation of the starting compound. A similar stabilization was obtained when the salen-type ligand was covalently attached to the CD. Similarly, the electrochemical reduction of the nongrafted copper(II) salen-type ligand led to an anionic species that appeared to be a little bit less stable in the presence of an added cyclodextrin, most probably because it was protonated by the CD. The reactivity of the electro-generated copper(I)-capped salen CD complex and of the corresponding copper phenoxyl radical were investigated towards iodomethane and benzyl alcohol, respectively. Iodomethane could be activated through a redox catalytic process which occurred faster than the protonation of the copper(I)-capped salen CD. On the other hand, no reactivity was observed between the copper bound phenoxyl radical and the primary alcohol. This lack of reactivity may be due to a possible distortion either of the initially square planar salen ligand after its grafting to the CD primary face, and/or of the CD itself.

These results clearly showed that grafting of a copper salen-type complex on to a CD led to intermediary species with new and interesting reactivity properties. This may lead to new methods for the design of new metal-based catalysts and enzyme mimics. A systematic study is in progress that involves grafting the salen-type ligand onto other CD positions with the purpose of tailoring the molecular distortions, and to test the catalytic ability of these new complexes towards the oxidation of primary alcohols.

Experimental Section

Chemicals: Tetrabutylammonium tetrafluoroborate ($TBABF_4$), which was dissolved in dimethylformamide (DMF) and used as the supporting electrolyte for electrochemical measurements, was prepared from $NaBF_4$ (Acros), and nBu_4NHSO_4 (Acros). The $TBABF_4$ was recrystallized from ethyl acetate/hexane (both solvents were purchased from Acros), and dried at 60 °C.

Solvents were freshly distilled from Na/benzophenone (THF, toluene) or P_2O_5 (CH_2Cl_2). Reactions were carried out under Ar. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck). Diisobutylaluminium was purchased from Aldrich as a 1.5 M solution in toluene. All other chemicals were purchased.

Complexes **1** and **2** were synthesized as described elsewhere by combining stoichiometric amounts of the appropriate salen ligand and copper(II) acetate.[16,18] These complexes were not prepared in-situ due to the possibility of the acetate ions reacting with the final Cu(salen) complex.[16]

Instrumentation: Cyclic voltammetry experiments were performed at room temperature under an argon atmosphere in a three-electrode cell with an Autolab potentiostat (PGSTAT 20). The reference electrode was a SCE (Tacussel), which was separated from the solution by a bridge compartment filled with the same solvent/supporting electrolyte solution that was used in the cell. The counter electrode was a gold wire, 1 cm in length. The glassy carbon (1 and 3 mm diameter; Goodfellow) and platinum (0.5 mm diameter; Goodfellow) working electrodes were prepared in-house.

Syntheses and Chemical Characterizations: Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) with detection permitted by charring with sulfuric acid. ^1H NMR [^{13}C NMR] spectra were recorded at room temperature with a 400 MHz [100 MHz] Bruker AVANCE 400 spectrometer. Chemical shifts are given in ppm, referenced to the residual resonances of the solvents (δ = 7.26 or 77.16 ppm, for $CDCl_3$). Coupling constants (J) are given in Hertz [Hz]. Assignments were aided by COSY, J-mod technique and HMQC. Optical rotations were determined with a Perkin–Elmer 343 polarimeter (c = g/100 mL, $CHCl_3$). Mass spectrometry experiments were carried out on a Micromass ZABSpecTOF or a Bruker microTOF.

α-CD–Disalen–Cu Complex 3: An ethanol solution of NaOH (0.24 mL, 5 g/L, 2 equiv.) and $CuCl_2$ (2.0 mg, 15 μmol, 1 equiv.) was added to a solution of disalen α-CD **8** (21 mg, 15 μmol, 1 equiv.) in ethanol (1.0 mL) at room temp. The reaction mixture was stirred under nitrogen for 12 h. Then the solvent was removed by evaporation under vacuum. The residue was washed with diethyl ether (2 × 3 mL) to give CD **3** (21 mg, 96%) as a green amorphous powder. $[a]_D^{20}$ = +104 (c = 0.05, methanol). HRMS (ESI) [M + Na]$^+$: calcd. for $C_{66}H_{100}N_2O_{30}CuNa$ 1486.5549; found 1486.5096.

6^A,6^D-Dideoxy-6^A,6^D-diazido-$2^{A–F}$,$3^{A–F}$,6^B,6^C,6^E,6^F-hexadeca-*O*-benzyl-α-cyclodextrin (5): NaN_3 (1.6 g, 25.2 mmol, 8 equiv.) was added to a solution of a known dimesylated α-CD[13a,13e] (8.1 g, 3.15 mmol, 1 equiv.) in DMF (45 mL) at room temp. under nitrogen. The reaction mixture was heated at 80 °C for 12 h, then cooled to room temp., and the DMF removed by evaporation. The residue was dissolved in EtOAc (20 mL) and washed with water (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. Silica gel flash chromatography of the residue (cyclohexane/EtOAc: 5:1 → 3:1) gave **5** (7.1 g, 92%) as an amorphous powder. $[a]_D^{20}$ = +52.0 (c = 1.0, $CHCl_3$); R_f = 0.50 (cyclohexane/AcOEt, 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.15 (m, 80 H, H arom.), 5.31 (d, ^2J = 10.7 Hz, 2 H, 2 × CHPh), 5.23 (d, $^3J_{1,2}$ = 3.5 Hz, 2 H, 2 × 1-H), 5.19 (d, ^2J = 11.0 Hz, 2 H, 2 × CHPh), 5.05 (d, ^2J = 11.4 Hz, 2 H, 2 × CHPh), 5.00 (d, $^3J_{1,2}$ = 3.1 Hz, 2 H, 2 × 1-H), 4.99 (d, $^3J_{1,2}$ = 3.1 Hz, 2 H, 2 × 1-H), 4.92 (d, ^2J = 11.0 Hz, 2 H, 2 × CHPh), 4.89 (d, ^2J = 11.4 Hz, 2 H, 2 × CHPh), 4.86 (d, ^2J = 10.7 Hz, 2 H, 2 × CHPh), 4.65 (d, ^2J = 12.3 Hz, 2 H, 2 × CHPh), 4.56 (d, ^2J = 11.8 Hz, 4 H, 4 × CHPh), 4.53 (d, ^2J = 12.7 Hz, 2 H, 2 × CHPh), 4.50 (d, ^2J = 12.4 Hz, 2 H, 2 × CHPh), 4.47 (d, ^2J = 13.6 Hz, 4 H, 4 × CHPh), 4.45 (s, 4 H, 2 × CH_2Ph), 4.43 (d, ^2J = 11.2 Hz, 2 H, 2 × CHPh), 4.18 (dd, $^3J_{2,3}$ = 8.3, $^3J_{3,4}$ = 9.7 Hz, 2 H, 2 × 3-H), 4.14–4.09 (m, 6 H, 4 × 3-H, 2 × 6-H), 4.05–3.99 (m, 8 H, 4 × 4-H, 2 × 5-H, 2 × 6-H), 3.95 (br. d, $^3J_{4,5}$ = 9.6 Hz, 2 H, 2 × 5-H), 3.89 (br. dd, $^3J_{4,5}$ = 9.4, $^3J_{5,6}$ = 2.9 Hz, 2 H, 2 × 5-H), 3.77 (br. d, ^2J = 11.0 Hz, 2 H, 2 × 6-H), 3.75 (dd, $^3J_{3,4}$ = 8.6, $^3J_{4,5}$ = 8.6 Hz, 2 H, 2 × 4-H), 3.65 (br. d, ^2J = 10.3 Hz, 2 H, 2 × 6-H), 3.59 (dd, $^3J_{5,6}$ = 2.0, ^2J = 10.5 Hz, 2 H, 2 × 6-H), 3.56 (dd, $^3J_{1,2}$ = 3.7, $^3J_{2,3}$ = 9.9 Hz, 2 H, 2 × 2-H), 3.53–3.49 (m, 4 H, 2 × 2-H, 2 × 6-H), 3.45 (dd, $^3J_{1,2}$ = 3.3, $^3J_{2,3}$ = 9.9 Hz, 2 H, 2 × 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.25 (2 C), 140.22 (2 C), 140.20 (2 C), 139.38 (2 C), 139.20 (2 C), 139.12

(2 C), 139.01 (2 C), 138.99 (2 C, 16× C arom. quat.), 128.38–126.88 (m, 80× C arom. tert.), 98.96 (2 C), 98.79 (2 C), 98.25 (2 C, 6× C-1), 80.87 (2 C), 80.81 (2 C), 80.68 (2 C, 6× C-3), 80.42 (2 C), 80.03 (2 C), 79.61 (2 C, 6× C-4), 79.32 (2 C), 78.99 (2 C), 78.44 (2 C, 6× C-2), 75.86 (2 C), 75.74 (2 C), 75.04 (2 C), 73.48 (2 C), 73.46 (2 C), 73.12 (2 C), 72.90 (2 C), 72.60 (2 C, 16× CH_2Ph), 71.86 (2 C), 71.64 (2 C), 70.78 (2 C, 6× C-5), 69.47 (2 C), 68.91 (2 C), 52.34 (2 C, 6× C-6) ppm. HRMS (ESI) $[M + 2Na]^{++}$: calcd. for $C_{148}H_{154}N_6O_{28}Na_2$ 1254.52978; found 1254.53318 (+2.8 ppm).

6^A,6^D-Dideoxy-6^A,6^D-diamino-$2^{A–F}$,$3^{A–F}$,6^B,6^C,6^E,6^F-hexadeca-*O*-benzyl-α-cyclodextrin (6): $LiAlH_4$ (92 mg, 2.44 mmol, 6 equiv.) was added to a solution of diazido α-CD **5** (1.0 g, 0.406 mmol, 1 equiv.) in dry THF (10 mL) at room temp. under nitrogen. The reaction mixture was heated at 60 °C for 2 h, then water was added, and THF was removed by evaporation. The residue was dissolved in EtOAc (15 mL) and washed with water (10 mL) and diluted HCl (1 mol·L^{-1} in water, 10 mL). Then the layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with NaOH (1 mol. L^{-1} in water, 10 mL), dried with $MgSO_4$, filtered, and concentrated under vacuum. Silica gel flash chromatography of the residue (CH_2Cl_2/MeOH, 40:1) gave **6** (807 mg, 82%) as an amorphous powder. $[\alpha]_D^{20}$ = +36.6 (*c* = 1.0, $CHCl_3$); R_f = 0.30 (CH_2Cl_2/MeOH, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–6.85 (m, 80 H, H arom.), 5.50 (d, $^3J_{1,2}$ = 3.6 Hz, 2 H, 2× 1-H), 5.31 (d, ^2J = 10.5 Hz, 2 H, 2× CHPh), 5.09 (d, ^2J = 10.8 Hz, 2 H, 2× CHPh), 4.85–4.60 (m, 18 H, 14× CHPh, 4× 1-H), 4.50–4.20 (m, 14 H, 10× CHPh, 4× 5-H), 4.11 (t, $^3J_{2,3}$ = 9.4 Hz, 2 H, 2× 3-H), 4.04–3.84 (m, 12 H, 4× 3-H, 4× 4-H, 4× 6-H), 3.82–3.65 (m, 8 H, 4× CHPh, 2× 4-H, 2× 5-H), 3.62 (d, $^3J_{5,6}$ = 10.4 Hz, 2 H, 2× 6-H), 3.54 (d, $^3J_{5,6}$ = 10.6 Hz, 2 H, 2× 6-H), 3.46 (dd, $^3J_{1,2}$ = 3.8, $^3J_{2,3}$ = 10.0 Hz, 2 H, 2× 2-H), 3.35 (dd, $^3J_{1,2}$ = 3.4, $^3J_{2,3}$ = 9.8 Hz, 2 H, 2× 2-H), 3.23 (dd, $^3J_{1,2}$ = 3.0, $^3J_{2,3}$ = 9.6 Hz, 2 H, 2× 2-H), 2.78 (br. d, $^3J_{5,6}$ = 13.4 Hz, 2 H, 2× 6-H), 2.77 (br. d, $^3J_{5,6}$ = 13.8 Hz, 2 H, 2× 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.35 (2 C), 139.32 (2 C), 139.31 (2 C), 138.57 (2 C), 138.36 (2 C), 138.21 (2 C), 138.10 (2 C), 138.02 (2 C, 16× C arom. quat.), 128.40–128.10, 128.05–127.85, 127.75–127.50, 127.17–126.93, 126.77, 126.39 (m, 80× C arom. tert.), 98.36 (2 C), 98.27 (2 C), 98.02 (2 C, 6× C-1), 81.38 (2 C), 80.98 (2 C), 80.92 (4 C), 80.76 (2 C), 80.66 (2 C, 6× C-3, 6× C-4), 79.89 (2 C), 79.10 (2 C), 77.99 (2 C, 6× C-2), 76.24 (2 C), 75.95 (2 C), 74.13 (2 C), 73.48 (2 C), 73.41 (2 C), 73.34 (2 C), 72.99 (2 C), 72.26 (2 C, 16× CH_2Ph), 71.98 (2 C), 71.90 (2 C), 71.06 (2 C, 6× C-5), 69.69 (2 C), 69.10 (2 C), 42.64 (2 C, 6× C-6) ppm. HRMS (ESI) $[M + H]^+$: calcd. for $C_{148}H_{159}N_2O_{28}$: 2412.1079; found 2412.1084 (+0.2 ppm).

6^A,6^D-Dideoxy-6^A,6^D-diamino-α-cyclodextrin (7): The diamine α-CD **6** (100 mg, 0.041 mmol, 1 equiv.) was dissolved in a mixture of H_2O (2 mL) and THF (6 mL) under nitrogen, then TFA (25 μL) and Pd/C 10% (50 mg) were added to the solution. The reaction mixture was stirred under an H_2 atmosphere for 12 h, filtered through a Celite pad, and concentrated under vacuum. The residue was washed with mixture of H_2O/MeOH (5 mL) and the solvents were removed by evaporation under vacuum. The residue was washed with $CHCl_3$ (5 mL) to give **7** (39 mg, 99%) as an amorphous powder. $[\alpha]_D^{20}$ = +76.2 (*c* = 0.5, methanol). ^{1}H NMR (400 MHz, MeOD): δ = 5.00 (d, $^3J_{1,2}$ = 3.1 Hz, 2 H, 2× 1-H), 4.97 (d, $^3J_{1,2}$ = 3.3 Hz, 2 H, 2× 1-H), 4.93 (d, $^3J_{1,2}$ = 3.1 Hz, 2 H, 2× 1-H), 4.17 (br. dd, ^3J = 8.0, ^3J = 8.8 Hz, 2 H, 2× 5-H), 4.02–3.68 (m, 18 H, 6× 3-H, 4× 5-H, 8× 6-H), 3.67–3.43 (m, 12 H, 6× 2-H, 6× 4-H), 3.17 (br. d, ^3J = 6.5 Hz, 2 H, 2× 6-H), 3.14 (br. d, ^3J = 7.9 Hz, 2 H, 2× 6-H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 103.80 (2 C), 103.70 (2 C), 103.20 (2 C, 6× C-1), 85.20 (2 C), 83.29 (2 C), 82.97 (2 C, 6× C-4), 75.02 (2 C), 74.89 (2 C), 74.61 (2 C, 6× C-3), 74.06 (2 C), 73.63 (2 C), 73.59 (2 C), 73.53 (2 C), 73.52 (2 C, 6× C-2, 4× C-5), 69.70 (2× C-5), 61.95 (2 C), 61.88 (2 C), 41.96 (2 C, 6× C-6) ppm. HRMS (ESI) $[M + H]^+$: calcd. for $C_{36}H_{63}N_2O_{28}$ 971.35619; found 971.35553 (–0.7 ppm).

α-CD–Disalen 8: 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (33 mg, 140 μmol, 3 equiv.) was added to a solution of diamine α-CD **7** (40 mg, 610 μmol, 1 equiv.) in ethanol (5.0 mL) and in DMF (1.0 mL) under argon at room temp. The reaction mixture was heated at 90 °C for 12 h, cooled to room temp., and the solvents removed by evaporation. The residue was washed with acetone to give **8** (47 mg, 80%) as a yellow amorphous powder. $[\alpha]_D^{20}$ = +89.0 (*c* = 1.0, methanol). ^{1}H NMR (400 MHz, MeOD): δ = 8.46 (s, 2 H, 2× N=C–H), 7.38 (d, ^4J = 2.1 Hz, 2 H, 2× H arom.), 7.19 (d, ^4J = 2.1 Hz, 2 H, 2× H arom.), 4.98 (d, $^3J_{1,2}$ = 2.8 Hz, 2 H, 2× 1-H), 4.95 (d, $^3J_{1,2}$ = 2.7 Hz, 4 H, 4× 1-H), 4.17 (br. dd, ^3J = 9.2, ^3J = 4.3 Hz, 2 H, 2× 5-H), 4.07–3.92 (m, 12 H, 4× 6-H, 2× 5-H, 6× 3-H), 3.88–3.72 (m, 10 H, 8× 6-H, 2× 5-H), 3.59–3.44 (m, 12 H, 6× 2-H, 6× 4-H), 1.41 (s, 18 H, *t*Bu), 1.31 (s, 18 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 170.06 (2× C=N), 159.45 (2 C), 141.29 (2 C), 137.55 (2 C), 119.54 (2 C, 8× C arom. quat.), 127.97 (2 C), 127.56 (2 C, 4× C arom. tert.), 104.01 (2 C), 103.84 (2 C), 103.57 (2 C, 6× C-1), 85.24 (2 C), 83.26 (2 C), 83.00 (2 C, 6× C-4), 75.27 (2 C), 75.21 (2 C), 75.07 (2 C, 6× C-3), 73.90 (8 C, 6× C-2, 2× C-5), 73.76 (2× C-5), 71.98 (2× C-5), 61.91 (2 C), 61.73 (2 C), 60.23 (2 C, 6× C-6), 35.91 (2 C), 35.01 (2 C, 4× C *t*Bu quat.), 31.93 (2 C), 30.03 (2 C, 4× CH_3) ppm. HRMS (ESI) $[M + Na]^+$: calcd. for $C_{66}H_{102}N_2O_{30}Na$ 1425.64096; found 1425.64119 (+0.2 ppm).

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