Corrole-based applications

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Despite of the many similarities between corroles and porphyrins, the chemistry of the former remained undeveloped for decades because of severe synthetic obstacles. The recent discoveries of facile methodologies for the synthesis of triarylcorroles and the corresponding metal complexes allowed for their utilization in various fields. This survey reveals many examples where corroles were used as the key components in catalysis, sensing of gaseous molecules and medicine-oriented research. The focus in all these cases was on the special features of corroles: stabilization of high valent transition metal ions, unique photophysical properties, large NH acidity, facile synthetic manipulation and distinct catalytic properties. The latter aspect includes several examples of reactions that are not catalyzed by any non-corrole metal complex, such as the iron-based aziridination by Chloramine-T, the clean disproportionation of peroxynitrite, and the very facile N–H activation of amines.

1 Introduction

Corroles are tetrapyrrolic macrocycles who owe their name to the cobalt-chelating corrin of vitamin B_{12} with whom they share an identical skeleton. Nevertheless, corroles are fully unsaturated and actually more closely related to the iron-chelating porphyrins of heme enzymes and proteins. The chemistry of corroles may be divided into two periods that are separated by the year of 1999. Three important reviews cover the first part that started with the 1964 synthesis of a corrole by Johnson and Kay and the first crystallography of a free-base corrole by Hodgkin and co-workers.[1] Chapter 2 in the Sessler and Weghorn book (1997) is most critical, not at least because it focused on correcting many wrong structural and/or electronic descriptions that were published in the literature during the years.[2] The *Porphyrin Handbook* series contains two chapters about corroles: the one written by Paolesse describes all approaches that were applied for the synthesis of corroles, while that of Erben, Will and Kadish concentrates on the coordination chemistry of the corresponding metal complexes.[3,4] Examination of the corrole literature until 1999 reveals that there were no reports or patents about corrole-based applications and that corrole analogs of tetraarylporphyrins were not prepared (Scheme 1). This is in remarkable contrast with porphyrins: they are used in numerous applications and tetraarylporphyrins play a dominant rule therein.

The 1999 disclosers of facile synthetic methodologies for the preparation of corroles with aryl groups on the three

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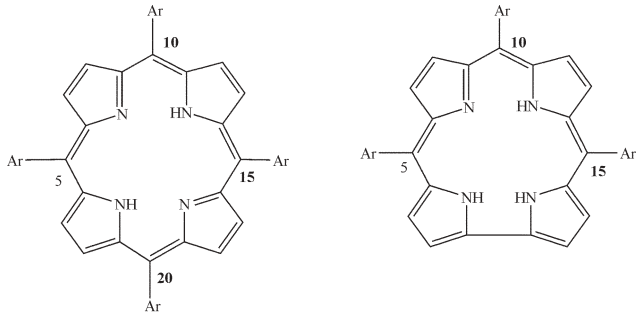
Iris Aviv was born in 1978 in Haifa, Israel. She received her BA (2001) from the Department of Chemistry at the Technion – Israel Institute of Technology. She is currently a graduate student at the final stage of the PhD program of the Technion under the supervision of Prof. Zeev Gross. Her research focuses on metal-catalyzed carbene insertion reactions, with the parts of her thesis that were published so far revealing the big advantages of corrole and porphyrin iron complexes for catalytic activation of amines and ammonia.

Zeev Gross completed his PhD degree in 1988 at Bar-Ilan University under the direction of Professor S. Hoz in the field of Physical Organic Chemistry. He then spent two years as a Fulbright postdoctoral fellow in Professor J. T. Groves' group at Princeton University, working on several aspects regarding the chemistry of porphyrins and their metal complexes. In 1990 he accepted a position at the Technion, where he is currently Professor of Chemistry and the incumbent of the Reba May & Robert D. Blum Academic Chair. Since 1999, when his group discovered the first facile synthesis of corroles from obvious starting materials, the focus of his research is on disclosing unique features of corroles and utilization of their metal complexes in many applications.



Scheme 1 General structures of tetraarylporphyrins such as H_2(tpp) (Ar = C_6H_5) and triarylcorroles such as H_3(tpc) (Ar = C_6H_5) and H_3(tpfc) (Ar = C_6F_5, **1**).

meso-carbon atoms (5,10,15-triarylcorroles) were highly influential regarding applications for the following reason.[5] Similar to porphyrins, the *meso*-carbon atoms are very reactive and most sensitive to oxidation and hence, *meso*-substituted derivatives of both macrocycles are much more stable and robust. This is particularly important for corroles whose π-system is much more electron-rich than that of porphyrins.[4,6] Indeed, 5,10,15-tris(pentafluorophenyl)corrole (**1**: abbreviated as H_3(tpfc), where tpfc stands for the trianionic macrocycle) with its electron-withdrawing substituents appears to be the most stable free-base corrole reported to date.[7] This particular derivative and a very large variety of its metal complexes were fully characterized by a combination of X-ray crystallography, electrochemistry, and diverse spectroscopic methods. For transition metal complexes this includes various oxidation and coordination states.[5b,8] The renewed attention to corroles is evident in the largely increased number of scientific publications (Fig. 1; 61 articles between 1964–1998 *vs.* 241 articles since 1999) and the several short reviews that were written about the developments since 1999.[9] While these mini-reviews mainly concentrated on the synthesis of the new corroles, this article focuses on their versatile applications in quite a variety of fields.

2 Oxidation catalysis

The first reported utilization of corroles was published in issue 7 of *Chemical Communications* of 1999, even before the syntheses of the free-base corroles **1** and H_3(tpc) (tpc = the trianionic form of 5,10,15-triphenylcorrole) were published.[10] Three examples for corrole-based catalysis were disclosed in that publication, of which two were oxidation reactions.

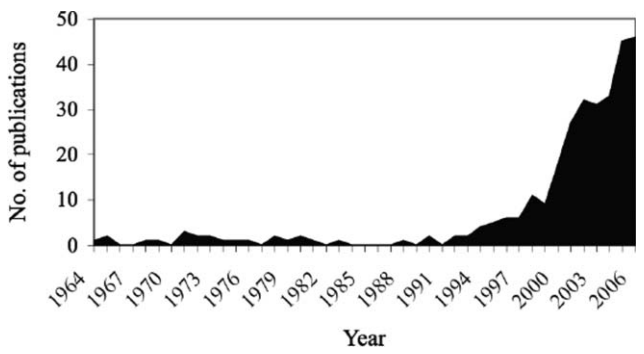
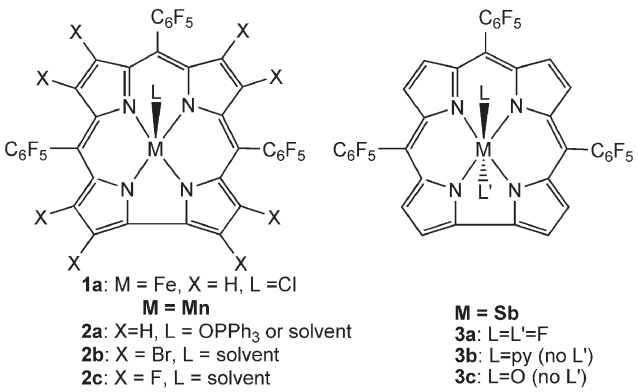


Fig. 1 Annual publications about corroles since the first report of 1964.

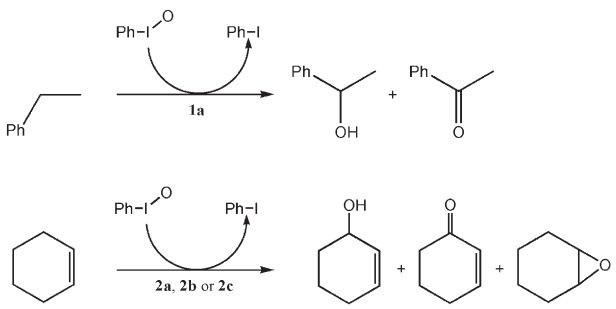
2.1 Hydroxylation of alkanes by iodosylbenzene

The iron corrole Fe(tpfc)Cl **1a** (Scheme 2) was found to catalyze the hydroxylation of ethylbenzene by iodosylbenzene (PhIO), providing 6.6% yield of the corresponding alcohol and 4.2% yield of the ketone (Scheme 3).[10] While this result served well as a proof of principle, the analogous porphyrin [Fe(tpfp)Cl, where tpfp stands for the dianionic form of 5,10,15,20-tetra(pentafluorophenyl)porphyrin] appeared as a more efficient catalyst for this reaction with 15.7% yield of alcohol and 8.9% yield of the ketone. In addition, the iron corrole was completely bleached at the end of the reactions and the porphyrin complex was not.

In later work, the manganese(III) complex Mn(tpfc) **2a** and the β-pyrrole-halogenated analogs Mn(Br_8-tpfc) **2b** and Mn(F_8-tpfc) **2c** (Scheme 2) were used for catalyzing the oxidation of cyclohexene by iodosylbenzene (Scheme 3).[11] The two latter complexes were much better catalysts than the former regarding all important terms: chemical yields (quantitative *vs.* low), reaction times (minutes *vs.* hours) turnover frequency (30 times larger) and stability (no bleaching during the reaction). However, there was no selectivity for one particular product: an almost equimolar mixture of alcohol, ketone and epoxide was produced. For all these reasons no extensive work was done regarding catalytic C–H activation



Scheme 2 Metallocorroles used as catalysts for oxidation of C–H bonds (and other catalytic processes).



Scheme 3 Metallocorrole catalyzed hydroxylation reactions.

via oxygen atom transfer from exogenous oxidants. However, investigations by Newcomb's group under non-catalytic reaction conditions revealed that the rates of oxygen atom transfer from oxo-metal corroles (the proposed intermediates in catalysis by **1a** and **2a**) to alkanes are much larger than that of analogous oxo-metal porphyrins (*vide infra*).[12] The challenge of exploring if these results may be confirmed and applied to catalytic hydroxylation reactions remains open. Finally we note that C–H oxygenation products were obtained in high efficiency and selectivity by a completely different approach: from singlet oxygen that was produced by photo-excitation of diamagnetic corrole metal complexes.[13]

2.2 Hydroperoxidation of alkanes by singlet oxygen

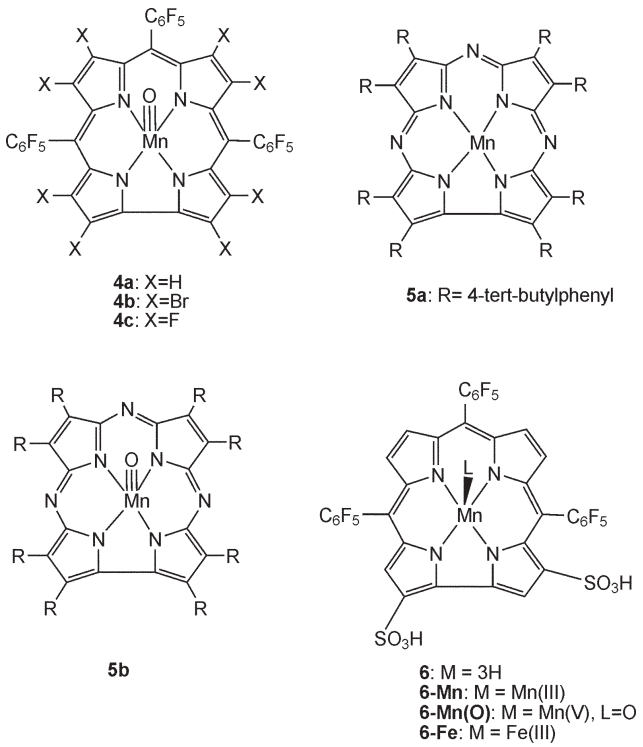
A recent publication by Lubeznova *et al.* disclosed that antimony corroles are very efficient catalysts for promoting photo-assisted aerobic oxygenation of organic molecules in a highly selective fashion.[13] The *trans*-difluoroantimony(V) corrole **3a** (Scheme 2) displayed particularly high activity and selectivity for the aerobic oxidation of hydrocarbons to the corresponding hydroperoxides. This photocatalytic system exhibited an absolute selectivity toward CH *vs.* C=C bonds: styrene was inert under the reaction conditions and only the allylic CH bonds of cyclohexene and cyclooctene were oxidized. Of the three non-olefin-containing substrates – ethylbenzene, adamantane and cumene – only the latter was oxidized. These results, as well as the non-reactivity of a sulfide known to be inert to singlet oxygen, are fully consistent with the following mechanism. The corrole is transformed by visible light to its excited singlet state, from which it efficiently decays into the excited triplet that converts ground-state molecular oxygen to the highly reactive singlet oxygen, which acts as the oxidizing agent. The antimony(III) and (oxo)antimony(V) corroles (Scheme 2: **3b** and **3c**, respectively) also displayed catalytic activity, but not as high as that of the *trans*-difluoroantimony(V) corrole. The most efficient catalyst also displayed the longest triplet lifetime,[14] which is one crucial factor for assuring a high yield of singlet oxygen. From the synthetic point of view, alcoholic solutions obtained from these reactions contained the hydroperoxides as the sole solute in concentrations that were high enough for NMR characterization without solvent evaporation. Taken together, this study clearly calls for more applications that rely on the tunable photophysical properties of metallocorroles.

2.3 Epoxidation

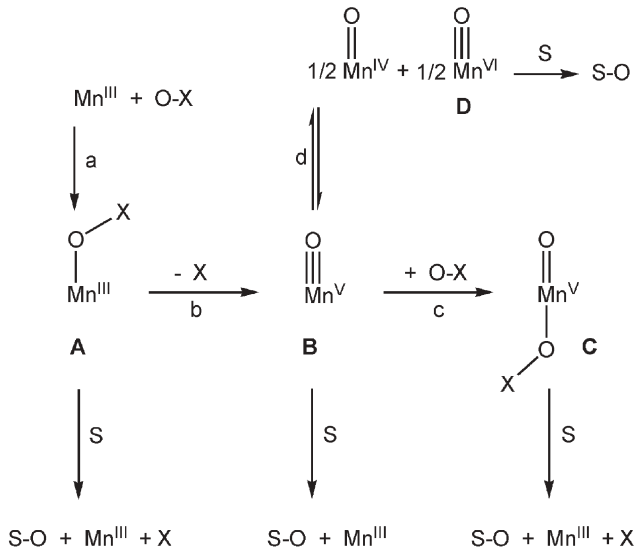
The first epoxidation catalyzed by a corrole metal complex was reported in 1999:[10] styrene was converted by PhIO to a mixture of styrene oxide (66% yield) and phenylacetaldehyde (21% yield), with 1% mol of Fe(tpfc)Cl **1a** (Scheme 2) as catalyst. Nevertheless, better results were obtained under identical reaction conditions by catalysis with the analogous porphyrin, Fe(tpfp)Cl: 90% yield of the epoxide and only 10% of the aldehyde. More interesting phenomena were obtained under catalysis by the manganese(III) complex Mn(tpfc) (**2a**, Scheme 2), as the first investigation revealed a puzzle that attracted the attention of several research groups.[11,12,15] Epoxidation of styrene by PhIO yielded the expected products, but: the reaction was very slow, the solution color changed from green (characteristic of the manganese(III) complex) to red, and this color persisted until all PhIO was consumed.[15a] Based on the well established reaction mechanisms for catalysis by iron(III) and manganese(III) porphyrins, all observations could be consistent with the rate-limiting step in the corrole-based system being oxygen atom transfer from PhIO to the catalyst and not from the oxo-metal intermediate to the substrate. In accord with this proposal and the indications for an apparently long-lived reaction intermediate, the red-colored complex was successfully isolated and characterized by NMR as an authentic (oxo)manganese(V) corrole, Mn(tpfc)(O) (**4a**, Scheme 4). However, the *isolated* Mn(tpfc)(O) did not transfer its oxygen atom to olefins under stoichiometric conditions and, accordingly, was concluded not to be the true reactive intermediate in the catalytic process.[15a]

One possible explanation for all the observations (*styrene being oxidized in the catalytic reaction, clear evidence for the formation of oxo-manganese during catalysis and the inertness of isolated Mn(tpfc)(O) toward styrene*) is that the reactive intermediate is a higher valent complex formed by disproportionation of Mn(tpfc)(O) (route **d** in Scheme 5). This was the hypothesis introduced in the original finding,[15a] since it was also consistent with a decreased stability of Mn(tpfc)(O) as a function of increased concentration. Stronger and independent evidence for the reasonability of a corrole-coordinated manganese(VI) center (such as **D** in Scheme 5) was provided much later, with the characterization of (nitrido)manganese(VI) corroles.[16]

Two other mechanistic proposals for the above-mentioned puzzles originate from investigations by the groups of Collman



Scheme 4 Manganese and iron complexes used for as catalysts for epoxidation and sulfoxidation reactions.



Scheme 5 Proposed reaction mechanisms for oxidation reactions catalyzed by manganese corroles (O–X = H_2O_2 or PhIO; X = H_2O or PhI; S = substrate (olefin or sulfide); S–O = oxidized substrate).

and Goldberg. The former demonstrated differences in competitive **2a**-catalyzed epoxidation of styrene and cyclooctene as a function of the exogenous oxidant; clearly indicative of an oxygen transferring intermediate that still contains the oxidant. The most obvious and reasonable candidate is the precursor of **B**, the iodosylarene-coordinated complex **A** (X = iodoarene) (Scheme 5).[15b] A different intermediate was proposed by Goldberg and co-workers who used the manganese(III) complex of a triazacorrole (corrolazine, **5a** Scheme 4) for the catalytic oxidation of *cis*-stilbene by PhIO (29% yield of a 2 : 1 mixture of *cis*- and *trans*-epoxide).[15d] The *isolated* (oxo)Mn(V) corrolazine **5b** was even more stable than the corrole analog **4a** and was easily ruled out as the reactive intermediate. Instead, these authors proposed that **5b** reacts with another PhIO to form a coordination complex (**B** to **C** in Scheme 5). The coordinated PhIO in **C** then directly transfers its oxygen atom to the substrate in what may be viewed as Lewis acid activation of PhIO by the (oxo)Mn(V) complex.

Additional insight was provided by Newcomb and co-workers from kinetic experiments, using laser flash photolysis methods to create and investigate the reactivity of (oxo)Mn(V) corroles toward organic substrates.[12] They showed that most of their results could be explained by either one of the two following mechanisms: oxidation by (oxo)Mn(VI), produced at low concentrations *via* disproportionation of (oxo)Mn(V) (route **d** of Scheme 5), or oxidation by "free" (oxo)Mn(V) that equilibrates with inactive "sequestered" forms. The most illuminating result described in that study is that an increase in the electron-withdrawing effects of the corrole ligand provided (oxo)Mn(V) species that were *less* reactive. Both models are consistent with this finding because the populations of active oxidants may be expected to be smaller for the electron-poor complexes. It also provides a rationalization for the stability of the high-electron demand corrolazine (oxo)Mn(V) species observed by Goldberg and co-workers. Newcomb's conclusion was that while multiple oxidant forms might be involved under catalytic turnover conditions, a single oxidant form appears to be involved when the (oxo)metal species are formed photochemically.

The above mechanistic discussion is apparently only relevant to cases where the (oxo)Mn(V) intermediate is a sluggish oxidant. Halogenation of the β-pyrrole positions leads to very efficient corrole-based catalysts: reactions with either Mn(Br_8-tpfc) or Mn(F_8-tpfc) led to quantitative reaction yields within minutes under conditions where the Mn(tpfc) catalyzed reactions provided limited yields and required many hours for completion.[11,15a] Importantly, the chemical reactivity must not be confused with thermal stability: a very good NMR spectrum of Mn(Br_8-tpfc)(O) can be obtained at room temperature (Fig. 2, unpublished results) despite of its very fast reaction with olefins. Preliminary results obtained from comparison of stoichiometric oxygen atom transfer from Mn(tpfc)(O) and Mn(Br_8-tpfc)(O) *vs.* catalysis by Mn(tpfc) and Mn(Br_8-tpfc) enforce all these conclusion: a variety of pathways with a major contribution from disproportionation (**D** in Scheme 5) in catalysis by Mn(tpfc)(O) *vs.* the dominance of Mn(Br_8-tpfc)(O) as the main reactive intermediate (**B** in Scheme 5) in the other case.[17]

Another intriguing point is that the Newcomb group also found experimental evidence for an (oxo)iron(V) corrole as an intermediate of truly unprecedented reactivity.[18] This was soon followed by computational support for the existence of such compounds for both corrole and corrolazine, but not for porphyrins which form only (oxo)iron(IV) porphyrin radical complexes.[19] It will be interesting to see if unambiguous spectroscopic evidence characteristic of (oxo)iron(V) corroles will be provided and if such data will be fully accepted by the scientific community.

2.4 Sulfoxidation

Goldberg and co-workers used 0.2 mol% of the manganese(III) corrolazine (**5a** in Scheme 4) for the catalytic oxidation of thioanisole by either iodosylbenzene or *p*-cyanodimethylaniline *N*-oxide (CDMANO).[15d] The very different catalytic rates observed with the two exogenous oxidants, as well as the very slow stoichiometric reaction between thioanisole and the *isolated* (oxo)Mn(V) complex (**5b** in Scheme 4) clearly ruled out the latter as key reaction intermediate in catalysis. Another observation was obtained by starting with 84% ^{18}O-labeled

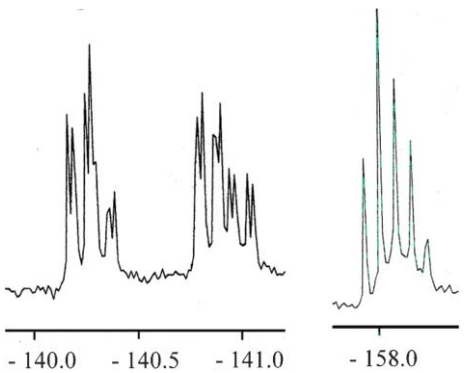


Fig. 2 ^{19}F NMR spectrum of the *ortho*-F (−140 to −141 ppm) and *para*-F (around −158 ppm) atoms of complex **4b**, recorded in $CDCl_3$ at 300 K.

(oxo)Mn(V); the extent of ^{18}O-labeled sulfoxide obtained from the reaction with excess thioanisole decreased from 61 to 4% when carried out in the presence of 5 equivalents of iodosylbenzene. The highest level of ^{18}O-incorporation (82%) was from $H_2{}^{18}O$ and, based on previous work by other groups, the authors suggested that this is indicative of oxygen exchange between water and metal bound PhIO. The authors proposed a mechanism in which the (oxo)Mn(V) species (**B** in Scheme 5) serves as a Lewis acid catalyst for the activation of PhIO, and that the oxygen atom in the coordinated PhIO is preferentially transferred to the substrate. We note, however, that the results may possibly been explained equally well by the most recent findings of Nam and co-workers, who showed that step **b** of Scheme 5 (in porphyrin chemistry) is reversible.[20] In other words, the (oxo)Mn(V) corrole might react with iodobenzene (produced during catalysis) as to provide managnese(III)-coordinated iodosylbenzene (**A** in Scheme 5) and that complex could be the actual oxygen-transferring intermediate (as proposed by Collman in the epoxidation studies).[15b]

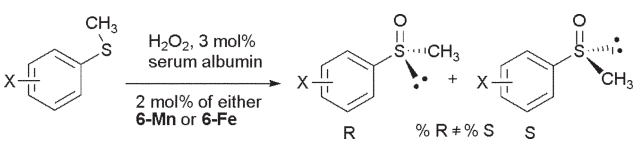
Catalytic sulfoxidation was also reported in what presents a much more interesting and potentially important approach. The amphiphilic bis-sulfonated corrole (**6** in Scheme 4) and its gallium, iron, and manganese complexes were shown to form tightly bound non-covalent conjugates with serum albumins,[21] which was used for affecting catalysis in a biomimetic fashion:[22] enantioselective oxidation of prochiral sulfides by hydrogen peroxide (Scheme 6). Control experiments clearly showed that catalysis relied on the corrole complexes and enantiomeric excesses on the chiral environment provided by the albumin. The examinations included ten different aryl-methyl sulfides and five albumin sources (HSA, BSA, PSA, RSA and SSA),[23] with each combination providing different ee values. The generally best results were obtained with the BSA-conjugated manganese corrole (51.4% ee for the average of 10 substituted sulfides). Throughout the series, the results obtained with the manganese corrole were superior of those with iron (**6-Fe** and **6-Mn** in Scheme 4) regarding all three important aspects: enantioselectivity, chemical yield, and stability of the catalyst. The highest ee's for all albumins except of HSA were obtained with *meta*- and/or *ortho*-substituted sulfides, with up to 74% ee for the **6-Mn**/BSA catalyzed sulfoxidation of 2-bromothioanisole by H_2O_2. This suggested that the substrate effect is mostly steric and less electronic in its origin.

Interestingly, this application-driven research also provided quite novel mechanistic information. Very significant differences – the color of the medium during reaction, chemical yield, ee values, and the extent of catalyst bleaching (none for H_2O_2 with any of the substrates) – were noted when the same reactions were performed with either hydrogen peroxide or PhIO as exogenous oxidants. What is more, independently prepared BSA/**6-Mn(O)** solutions were reduced very fast to BSA/**6-Mn** by hydrogen peroxide, but not by thioanisole (Scheme 7, k_3 and k_4, respectively). All the results with H_2O_2 as oxidant emphasized the importance of hydrogen-peroxide-coordinated manganese(III) corrole (**A** in Schemes 5 and 7) as the prime intermediate for efficient and enantioselective oxygen-atom transfer to the sulfides. The reaction mechanism for this particular case, where disproportionation may safely be ruled out due to the isolation of the catalyst by albumin, is drawn in Scheme 7. Nevertheless, it is apparently also relevant for the earlier described epoxidation catalysis by manganese corroles and sulfoxidation catalysis by manganese corrolazines. Another advantage of the manganese-catalyzed reactions is the stability of the system, reflected in the absence of catalyst bleaching and/or protein oxidation even when less reactive substrates (such as the 2-halogenothioanisoles) were employed. The reasons behind this phenomenon and its consequences are outlined in Section 3.3.

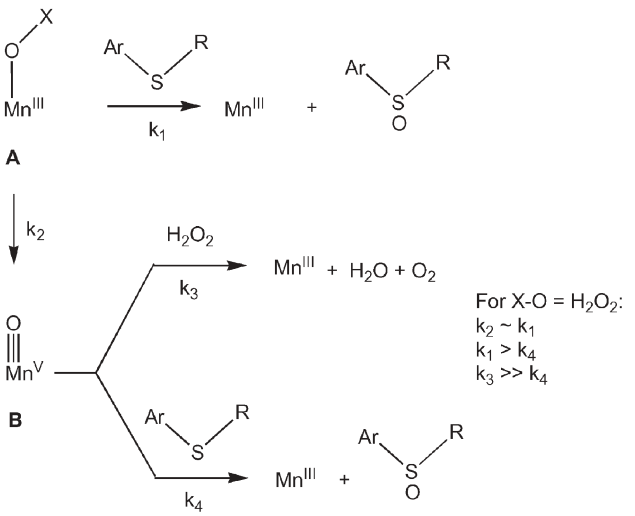
A completely different sulfoxidation system was developed with the aid of the earlier mentioned antimony corrole complexes– Sb(tpfc)$(F)_2$, Sb(tpfc)(py) and Sb(tpfc)(O) (**3a**, **3b** and **3c**, respectively, Scheme 2).[13] All displayed high catalytic activity for the photo-induced oxygenation of thioanisole by molecular oxygen, with the best results achieved in alcoholic solvents. The corresponding sulfoxide was the only product and no further oxidation to the sulfone was obtained. The catalytic efficiency was in the order of Sb(tpfc)$(F)_2$ > Sb(tpfc)(O) > Sb(tpfc)(py). Full conversion of thioanisole to its sulfoxide was obtained with as little as 0.02 mol% of Sb(tpfc)$(F)_2$, corresponding to 5000 catalytic turnovers, without any sign of catalyst bleaching. In contrast (and supportive of the earlier described reaction mechanism), no reaction took place when thioanisole was replaced by diphenylsulfide which is known to be inert toward oxidation by singlet oxygen.

3 Reduction catalysis

By virtue of the ability of corroles to stabilize metal ions in high oxidation states, low valent metallocorroles should be



Scheme 6 Biomimetic sulfoxidation by albumin-conjugated metallocorroles.



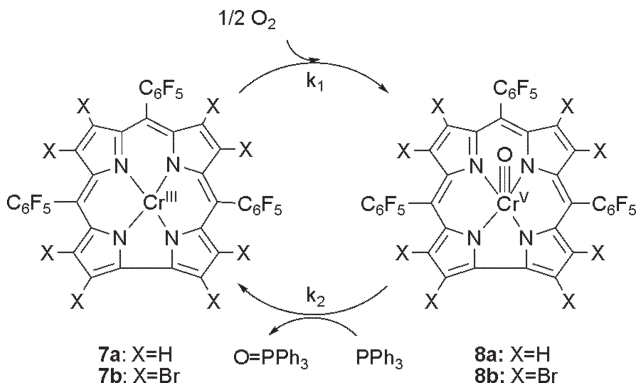
Scheme 7 Proposed reaction mechanism for the **6-Mn**/BSA-catalyzed oxidation of sulfides by H_2O_2.

very reactive. They might be expected to display unique properties regarding the activation of small reducible molecules, an aspect of very large interest and importance. However, this field is much less developed regarding corrole-based metal complexes.

3.1 O_2

Chromium complexes of corroles were isolated in four different oxidation states by Meier-Callahan *et al.* who found that the chromium(III) complex **7a** is oxidized by air to the oxo-chromium(V) complex **8a** (Scheme 8).[24] This significant finding of dioxygen activation by chromium(III) (normally achieved only by chromium(II) complexes) encouraged Mahammed *et al.* to use chromium corroles as catalysts for aerobic oxidations of organic substrates (Scheme 8).[25] Triphenylphosphine was aerobically oxidized to Ph_3PO by the (oxo)Cr(V) corrole **8a** which was reduced to the chromium(III) complex **7a**. Up to 33 catalytic turnovers, with >95% incorporation of labeled oxygen from $^{18}O_2$ into the phosphine, were obtained in acetonitrile without any external oxidizing or reducing agents. An important observation was the operation of a very significant solvent effect of acetonitrile on the kinetics of the two crucial oxygen-atom-transfer steps shown in Scheme 8, from dioxygen to catalyst (k_1: more than tenfold faster than in THF) and from (oxo)Cr(V) to substrate (k_2: minutes in CH_3CN *vs.* weeks in THF). The reactivity of the (oxo)Cr(V) complex could be increased to the level required for epoxidation of a reactive olefin (norbornene) *via* substitution of the corrole β-pyrrole carbon atoms by bromine. However, the chromium(III) complex of that corrole (**7b**) was not readily reoxidized by dioxygen to the (oxo)Cr(V) state **8b**. Although there is no obvious applicability concerned with this process, it is still the first example of aerobic oxidation catalysis in which both the reduced and the oxidized 3d metal complexes were fully characterized at ambient conditions.

Goldberg and co-workers also demonstrated oxygen activation,[26] albeit in that case the cobalt(III) corrolazine had to be reduced to the divalent oxidation state. Nevertheless, the reversible O_2 binding and the low temperature characterization of a Co^{III}-superoxo adduct are remarkable. Another long-standing effort regarding the activation of small molecules is to use bimetallic complexes such as porphyrin–porphyrin, porphyrin–corrole and corrole–corrole dyads and this



Scheme 8 Activation of molecular oxygen by chromium(III) corroles.

approach continues to gain significant interest.[27] In this respect, the work of Collman *et al.* on mononuclear cobalt and iron corroles is quite outstanding.[28] In a series of detailed electrochemical experiments, they have shown that the reduction of molecular oxygen proceeds all the way (the four-electron process) to water, without accumulation of the less reduced intermediates. This is in line with our independently acquired results regarding the very large efficiency of metallocorroles as catalysts for disproportionation of hydrogen peroxide (*vide infra*).[22]

3.2 CO_2

With CO_2 being one molecule of major environmental concern,[29] as well as a desirable component for "clean energy",[30] the importance of finding catalysts for its conversion into more useful molecules cannot be underemphasized. The single publication about this aspect in corrole chemistry revealed that the heavily reduced metal complexes perform about as well as porphyrins with the same metal ions (Fe and Co).[31] But, the formal metal oxidation state was higher by one unit in corroles than in porphyrins and the potentials required for catalysis were somewhat less negative. The catalytic reduction of CO_2 by the metallocorroles, confirmed in both electrochemical and photochemical systems, suggests that this approach has a yet to be developed future.

3.3 Reactive oxygen species (ROS)

One important observation in the earlier described metallocorrole-catalyzed biomimetic sufoxidation is concerned with the significant differences in results obtained with either hydrogen peroxide or PhIO as exogenous oxidant.[22] Specifically, quite significant catalyst bleaching and protein oxidation was obtained when less reactive substrates were oxidized by PhIO, but not by H_2O_2. The most obvious explanation for this difference is that only the latter can play a dual role, oxidant and reducible substrate. The first supportive indication regarding efficient disproportionation catalysis by metallocorroles was the formation of O_2 bubbles when the catalyst and H_2O_2 were combined with electron-poor and hence less reactive sulfides. Strong confirmation of this hypothesis came from the reaction of 30% H_2O_2 with 0.027 mol% manganese corrole **6-Mn** in the absence of any other potential substrate: the measured yield of O_2 was 10%, with only partial catalyst bleaching despite of the very high hydrogen peroxide concentration ($[H_2O_2]/[\mathbf{6\text{-}Mn}] > 3700$).

The above-mentioned pronounced catalase-like activity led to the investigation of metallocorroles as catalysts for decomposition of another ROS: peroxynitrite (PN), the nitrogen-containing analog of hydrogen peroxide (HO–ONO *vs.* HO–OH). PN may be considered as the most damage-causing ROS, mainly because of its spontaneous decay *via* homolytic bond cleavage to $^{\bullet}OH$ and $^{\bullet}NO_2$ (eqn (1)).

$$HOONO \rightarrow {}^{\bullet}OH + {}^{\bullet}NO_2 \qquad (1)$$

Accordingly, PN is both an ROS and a RNS (reactive nitrogen species); and it has become increasingly more evident that PN is heavily involved in many biological malfunctions initiated

by oxidative stress and the same holds for neurodegenerative disorders that (among many others) include Alzheimer's, Parkinson's and Huntington's diseases.[32] Another most important aspect is that in sharp contrast with other ROS, there are no specific enzymes for preventing the decomposition of PN. This highlights the urgent need for developing effective bio-available compounds that will catalyze the transformation of PN into biologically benign products.

The investigations of PN decomposition by the same corroles that were previously used for different purposes revealed that they are excellent catalysts.[33] In particular, the half life time of peroxynitrite was dramatically shortened from 1.8 s to 0.31 and 0.025 s with 4 mol% of **6-Mn** and **6-Fe** (Scheme 4), respectively. The catalytic rate reported for **6-Fe** is significantly larger than of all negatively-charged porphyrins and second only to the most optimized positively-charged iron porphyrin. Quantification of the NO_3^- yield suggested that, similar to iron porphyrins, the main catalytic action induced by **6-Fe** is isomerization of PN to HNO_3 (eqn (2)).

$$HOONO \rightarrow H^+ + NO_3^- \quad (2)$$

$$2\ HOONO \rightarrow 2\ H^+ + 2\ NO_2^- + O_2 \quad (3)$$

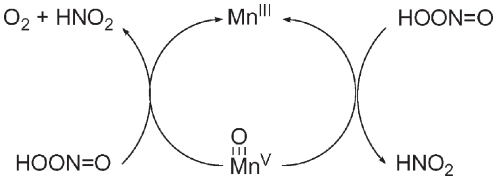
Despite of the lower catalytic rate, the results obtained with **6-Mn** were apparently more novel. It is the first manganese complex to display true (without exogenous reducing agent) catalytic activity; and product quantification (NO_2^- and O_2) showed that it operates through a genuine disproportionation process (eqn (3)). The proposed catalytic cycle is drawn in Scheme 9, emphasizing that the elementary steps do not create any radical species. Strong evidence for involvement of the (oxo)manganese(V) intermediate **6-Mn(O)** was provided by simultaneous monitoring of spectral changes in both the UV (PN) and the visible (**6-Mn(O)** and **6-Mn**) parts of the electronic spectrum at various reaction conditions and pH.

These results, together with independent demonstrations about the low cytotoxicity of these corroles and their facile non-covalent conjugation to targeting proteins (*vide infra*),[34] highlight the large potential of these compounds as catalysts for prevention of peroxynitrite-induced damage to biological molecules.

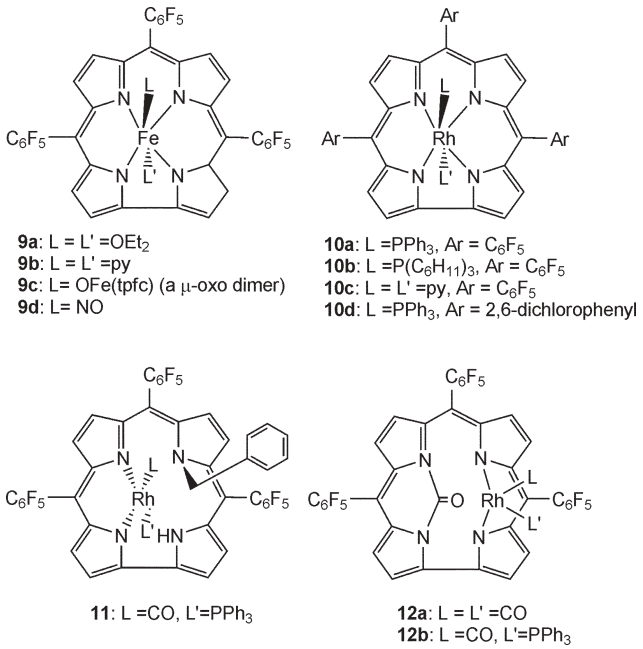
4 Group transfer catalysis

4.1 Carbene transfer to olefins (cyclopropanation)

The iron corroles **1a** (Scheme 2) and **9a–c** (Scheme 10), as well as the rhodium complexes of quite different corroles (**10–12** in Scheme 10), were found to be good catalysts for cyclopropanation of styrene by ethyl diazoacetate (EDA, Scheme 11).

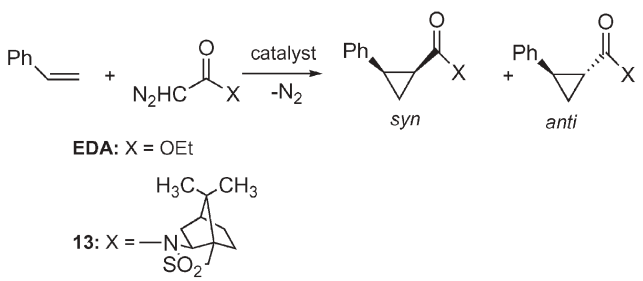


Scheme 9 Proposed reaction mechanism for **6-Mn**-catalyzed disproportionation of peroxynitrite.

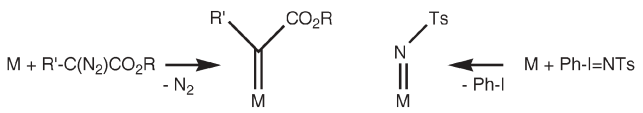


Scheme 10 The iron and rhodium corroles that were used as cyclopropanation catalysts (and other catalytic processes).

The first observation was that corrole-catalyzed reactions are more effective than those catalyzed by analogous porphyrins.[10] The chemical yields for **1a**-catalyzed cyclopropanation of styrene by EDA and the much larger unichiral diazo compound **13** (Scheme 11) were 71 and 41%, respectively, but only 24 and 10%, respectively, when the iron(III) porphyrin with four *meso*-C_6F_5 groups was applied instead of **1a**. This and the smaller *trans* : *cis* ratio of the cyclopropanation products in corroles than in porphyrins were attributed to the absence of the fourth aryl group in **1a** as being favorable for formation of the relatively large metal–carbene intermediates (Scheme 12). Another elucidated difference was that the metal oxidation states required for activating EDA were different. While iron(III) porphyrins are pre-catalysts requiring reduction to iron(II), iron(III) corroles were found to be the



Scheme 11 Catalytic cyclopropanation reactions.



Scheme 12 Commonly proposed intermediates in metal-catalyzed carbene- and nitrene-transfer reactions.

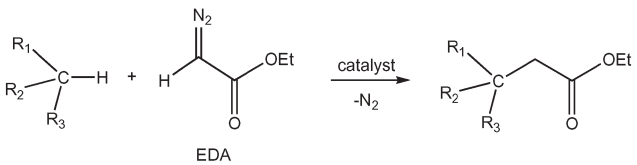
true catalysts. This conclusion was reached based on the almost complete invariance of results obtained with all catalysts, regardless of the oxidation state of iron and its ligands. For the iron(IV) corroles **1a** and **9d** (a binuclear μ-oxo complex), EDA was considered to act as a reducing agent to iron(III), similar to its role in porphyrin-catalyzed reactions (Fe^{III} to Fe^{II}). One shortcoming of all iron-based catalysts is that EDA dimerization products (mainly diethyl maleate) were observed as well.

The last mentioned limitation was much less significant for catalysis by the rhodium complexes,[8b] where much less diethyl maleate was obtained. Consistent with the conclusions drawn from the work with iron corroles about the disadvantage of steric crowding, **10d** with its *meso*-2,6-dichlorophenyl groups was a less effective catalyst than **10a** with the C_6F_5 groups instead (Scheme 10). In fact, **10d** was not able to catalyze the reaction of styrene with the large carbenoid **13** under conditions were the **10a**-catalyzed reaction provided a 56% yield (258 catalytic turnovers, *trans* : *cis* = 1) and 61% de for the *trans*-isomer. With all rhodium corroles, except of **12a** which was almost inert due to its two carbonyl groups, 0.2 mol% of catalyst were found to be sufficient for providing high yields of cyclopropanation products. The *trans* : *cis* ratio was smaller than with iron corroles, resembling similar trends found in porphyrins. Complexes **11** and **12a–b** are chiral and hence of potential for asymmetric catalysis. This was checked in a single case only: the reaction of styrene with EDA under catalysis by racemic **12b**, with and without a unichiral amine.[8e,g] The presence of amine lowered the chemical yield, indicative of coordination of the amine to the metal, but the ee or product ratio were not affected; thus ruling out the desired *in situ* resolution of **12b**.

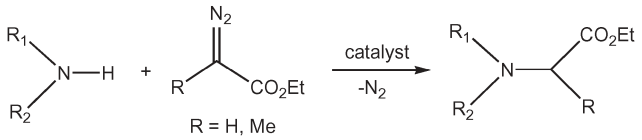
4.2 C–H insertion of carbenes

The results above and the large interest in intermolecular C–H insertions by metal-stabilized carbenoids[35] suggests that it would be interesting to determine if metallocorroles are capable of inserting the carbene moiety of ethyl diazoacetate (EDA) into the allylic C–H bonds of cyclohexene, dihydronaphthalene and indene (Scheme 13).

In yet unpublished results with Rh(tpfc)(PPh_3) (**10a** Scheme 10) as catalyst,[36] we found that the yields of the desired products were quite low and that the main products were the corresponding cyclopropanes from C=C activation. The rhodium complex was more suitable for this application, as only EDA dimerization products were obtained when the iron corroles Fe(tpfc)Cl (**1a**) and Fe(tpfc)(OEt_2)$_2$ (**9a**, Scheme 10) were used for attempted activation of the C–H bond of cyclohexene by EDA. More C–H activation was obtained when THF was used as both solvent and substrate,



Scheme 13 Catalytic C–H insertion reactions.



Scheme 14 Insertion of the carbene moiety into N–H bonds, where R_1 and R_2 represent alkyl, aryl or H.

but the EDA coupling products were produced with preference even in the **10a**-catalyzed reaction. The situation could only be reversed when the same approach was applied to 2,5-dihydrofuran. Utilization of other diazoacetates, which are usually much more relevant for the application,[37] was not yet reported.

4.3 N–H insertion of carbenes

Fe(tpfc)Cl (**1a** Scheme 2) and Fe(tpfc)(OEt_2)$_2$ (**9a** Scheme 10) were found to catalyze the insertion of ethyl diazoacetate (EDA) into the NH bonds of amines (Scheme 14).[38] The iron corroles catalyzed this reaction much better than other metallocorroles and, in fact, all other previously reported catalysts. Complete, fast, and full conversion into the corresponding *N*-substituted glycine ethyl esters was obtained by adding both the EDA and the amine in one portion to catalyst-containing solutions. In addition, only the iron corroles displayed absolute selectivity in favor of N–H *vs.* C=C activation in amine/olefin competition reactions. This selectivity was found to be shared only with iron(III) porphyrins, albeit the porphyrins were somewhat less selective in the case of primary amines (traces of the di-substituted product were obtained as well).

Regarding mechanism, metal catalyzed carbene transfer reaction are usually analyzed in terms of rate-limiting formation of a metallo-carbene, from which the corresponding products are formed. This would include the desired compounds (cyclopropane from olefin, ether from alcohol, *etc.*), as well as the EDA coupling products. However, the very large differences between the corrole-catalyzed reactions of EDA with amines and olefins (the latter proceeding much slower and with lower selectivity to desired *vs.* EDA-coupling products) suggested that the mechanism for NH insertion and C=C addition do not proceed *via* a common metallocarbene intermediate. A stronger indication pointing towards the same direction is that the emission of dinitrogen is very fast only when amines are used (Fig. 3). An extreme case is Fe(tpp)Cl,

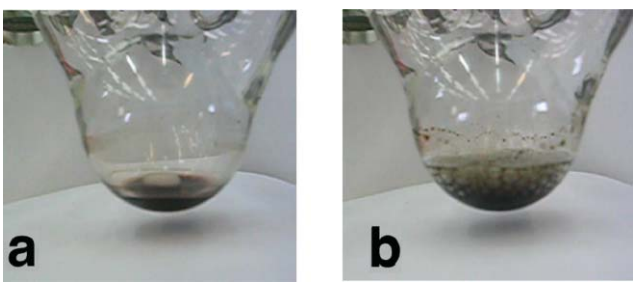


Fig. 3 Pictures taken (a) before and (b) 7 s after the addition of EDA to an ethereal solution of *p*-chloroaniline and catalyst **9a**, demonstrating the very fast emission of N_2.

which appeared to be an excellent catalyst for the NH insertion, while it does not catalyze cyclopropanation of olefins by EDA to any extent. All these results clearly point against metallocarbene intermediates, but an alternative reaction mechanism has not been proposed yet.

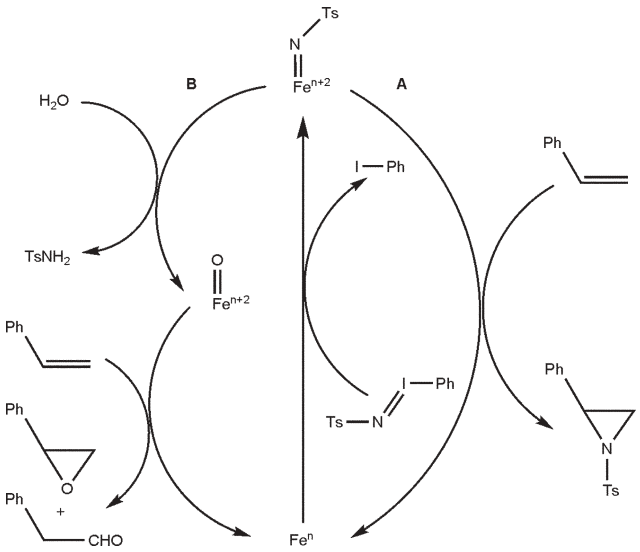
Based on the superior results with amines, the iron(III) corrole and porphyrin complexes were tested as catalysts of a much more challenging reaction:[39] the use of ammonia as the nitrogen atom source (Scheme 14, $R_1 = R_2 = H$). At least formally, this would by a NH activation process for the synthesis of *N*-free amino acid esters. The iron corrole catalyzed reaction of EDA with ammonia provided only trace amounts of the desired NH activation product; diethyl maleate was produced almost exclusively. Excellent results were however obtained with Fe(tpp)Cl as catalyst: ammonia reacted with both EDA and methyl-substituted EDA (Scheme 14, R = CH_3) as to provide a novel route to the ethyl esters of glycine and alanine, respectively. This process is very different from the approaches utilized by nature or in industry and has the potential of leading to a very convenient route to non-natural amino acids.

4.4 Nitrene transfer to olefins (aziridination)

Aziridination of olefins has been pioneered by the groups of Breslow and Mansuy who showed that heme enzymes and synthetic metalloporphyrins are efficient catalysts for transferring the NTs moiety from PhI=NTs into C–H and C=C bonds (Ts = tosylate). The reactive intermediate is considered to be a high valent metallonitrene complex, similar to metallocarbenoids in the reactions with diazo compounds (Scheme 12).

A comparison between the iron corroles **1a** and **9a–d** with analogous porphyrins revealed that the corrole-based complexes are better catalyst for aziridination of styrene by PhI=NTs.[40] The most important advantage is the larger selectivity toward the desired aziridine (up to 11.4 : 1 for **9a**) at the expense of oxygenation byproducts styrene oxide and phenylacetaldehyde. The results within the corrole series and the differences with those obtained with iron porphyrins were analyzed in terms of the accepted mechanisms for metal-catalyzed oxo- and nitrene-transfer reactions (Scheme 15). Apparently, the superior results and the relatively small amounts of oxygenation products obtained for corroles are related to the ease of formation and the hydrolytic stability of the metal–nitrene intermediate, respectively. In other words, the part of reaction proceeding *via* route **A**: iron–nitrene reacting with the olefin to produce the aziridine *vs.* **B**: hydrolysis of the iron–nitrene to the (oxo)iron complex that oxidizes the olefin, is larger for the corrole-catalyzed reaction. This was attributed to a less crowded environment of the corrole-based iron–nitrene complex.

A significantly larger challenge was met by replacing PhI=NTs by Chloramine-T (NaTsN–Cl) as the nitrogen atom source, which among other advantages also leads to NaCl and not iodobenzene as byproduct. Examination of all the iron corroles and porphyrins complexes used in the reaction with PhI=NTs, exposed the iron(IV) corrole Fe(tpfc)Cl (**1a** Scheme 2) as the only active catalyst. This is one indication that served for proposing a reaction mechanism for activation



Scheme 15 Plausible catalytic cycle for the Fe-catalyzed reaction of styrene with PhI=NTs.

of Chloramine-T that is quite different from that shown in Scheme 15. Another clue was that no oxygenation by-products were obtained; and suggesting the previous mechanism for iron(IV) corrole would require an unreasonable iron(VI) intermediate. The Fe(tpfc)Cl-catalyzed reaction remains the only example for aziridanation of olefins by chloramine-T with a transition metal catalyst other than copper.[41] A common feature of both systems could be the mechanism of action: umpolung of the Chloramin *N*-atom from nucleophilic when charge-balanced by Na^+ to electrophilic when coordinated to Fe^{IV} or Cu.

5 Corrole-based sensors

Cobalt(III) corroles were shown to be capable of binding carbon monoxide, which normally occurs only for cobalt(II) complexes.[42] In addition, the former were inert to O_2, which is not true for the latter. Accordingly, this selectivity could allow for the utilization of cobalt(III) corroles as sensors of CO gas. Six corrole complexes were investigated to examine their affinity to CO, *i.e.* their Lewis acid strength. The initial hypothesis (the larger the electron density on the metal, the lower the Lewis acid character and the lower the affinity to CO) was supported by the results; the cobalt(III) complex of octaethylcorrole did not adsorb CO at all, while that of tris(pentafluorophenyl)corrole (**1**) exhibited the largest affinity to CO.[43] The comparison with the iron(II) complex of picket fence porphyrin served to emphasize the absolute selectivity of cobalt(III) corroles to CO *vs.* O_2, which cannot be achieved by other complexes. These findings were soon applied to sol–gel encapsulated cobalt(III) corroles, although we note that a quite electron-rich corrole was employed.[44,45] Nevertheless, the results showed that the selectivity of CO adsorption compared to those of O_2 and N_2 are about 470 and 5600, respectively.

Optical pH sensors (optodes) are of large interest because of their advantages (size, electrical safety, costs, absence of reference elements, and more) relative to conventional pH meters. Corroles could be excellent candidates for such

applications since they exist in three protonation states at different aqueous pH values ($[H_4(cor)]^+$, $[H_3(cor)]$, $[H_2(cor)]$ that differ very much in fluorescence intensity (explicitly revealed for corrole **6**).[46] This phenomenon was demonstrated to be useful indeed for the developments of an fluoresence-based optical pH sensor (sol–gel encapsulated).[47] Specifically, a 10-(4-aminophenyl)-5,15-dimesitylcorrole based optode membrane displayed a linear response in the pH range of 2.2–10.3 and co-existing inorganic ions did not show obvious interference to the pH measurement. The optode could be stored under wet conditions without substantial change of the fluoresence intensity, showed good reproducibility and reversibility, and the photostability was reported to be excellent. The pH response range of that particular corrole was also significantly wider than that of corrole **1** (5.0–9.2) and tetraphenylporphyrin (3.3–5.0).

The same group also used a PVC [High molecular weight poly(vinyl chloride)] membrane with corrole **1** as the electroactive material for the construction of a silver(I) electrode.[48] The corrole-based material displayed better response characteristics than one based on tetraphenylporphyrin, with linear response concentration range of 5.1×10^{-6} to 1.0×10^{-1} silver ions, a slope of 54.8 mV decade^{-1}, with a working pH range from 4.0 to 8.0, and fast response time of <30 s. The electrode exhibited high selectivity and was easy to prepare and use. This electrode was used successfully in the determination of silver in real ore samples. In a later paper, the same electrode was also used for detection of mercury(II).[49]

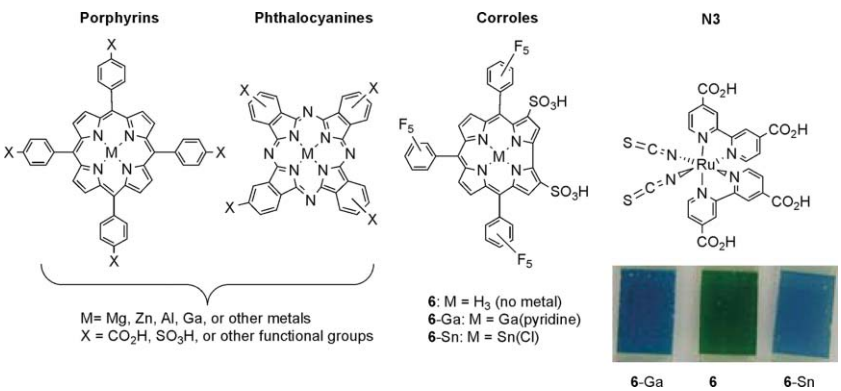
The incorporation of corroles into liquid membrane electrodes was also used for potentiometric discrimination of phenol isomers.[50] The uniquely high NH acidity of corroles was the key factor for recognizing phenol derivatives at the aqueous–organic interface. The response sensitivity of corrole-incorporated PVC membranes were *para* > *meta* > *ortho*-nitrophenol and 2,4- > 2,5- > 2,6-dinitrophenol; and corrole **1** displayed a slightly stronger potentiometric response than analogs that contained 2,6-dichloro or 4-nitro rather than pentafluoro substituents in the *meso*-aryl groups. The phenols were recognized in their non-ionized form, suggesting that the potentiometric signals reflect the formation of a supramolecular complex between them and the corrole host at the organic–aqueous interface. Further information about the molecular recognition phenomenon was obtained by investigating the influence of lipophilic, anionic or cationic salts, as well as the relationship between the acid–base properties of the phenolic guests and the hydrogen bond donor activity of the corrole host.[51]

An additional report refers to the application of corrole-incorporated ISEs (ion selective electrodes).[52] The authors emphasized that this is apparently the first potentiometric sensor that is sensitive to both salicylic acid and salicylate. The good detection limit of about 10^{-5} M obtained for the corrole-incorporated membranes makes them suitable for the analysis of salicylate in human serum (about 3×10^{-4} M). The corrole-ISEs also displayed a wide linear range (4.0×10^{-5} to 5.3×10^{-3} M) and low interference *vs.* other common anions, important for salicylate determination in real samples.

6 Dye sensitized solar cells (DSSCs)

Dye-sensitized solar cells (DSSCs) that can efficiently convert solar energy to electricity are of great promise regarding this important subject. The most popularly used dyes in this application are derivatives of Ru(II) bipyridines and porphyrinoids. The latter are attractive because their photophysical properties can be readily tuned by selective substitutions on their molecular frameworks and/or *via* variation of the central metal ion. Since the corrole frontier orbitals are at higher energy than those of analogous porphyrins,[6] their application as sensitizers in DSSCs was examined. The bis-sulfonated trispentaflourophenyl corrole (**6** in Scheme 4) and its gallium(III) (**6**-Ga) and (chloro)tin(IV) (**6**-Sn) complexes were chosen because of their structural similarity to the best performing dyes (Scheme 16).[53]

All the new complexes were found to bind to nanoporous TiO_2 electrodes and the incident photon to current efficiency (IPCE) spectra of the corroles on nanoporous TiO_2 revealed substantial differences in the efficiencies of the dyes: **6**-Ga ~ **6** ≫ **6**-Sn. The absorbed photon to current efficiency (APCE) plots were in the same order as their IPCEs, revealing that the variations in efficiencies of these dyes is apparently not due to differences in light absorption. The results suggested that the low efficiency of the **6**-Sn based DSSC is a consequence of the inability of the excited state to inject electrons into the TiO_2 film. Since the reduction potential of the **6**-$Sn^{+/0}$ couple is over half a volt more positive than those



Scheme 16 Metal complexes used in dye-sensitized solar cells and pictures of the corroles-bound nanoporous TiO_2 electrodes.

of **6**-Ga$^{+/0}$, **6**$^{+/0}$ and **N3**$^{+/0}$, the **6**-Sn excited state was not nearly as potent a reductant as the other.

These original results demonstrated that certain selectively substituted corroles perform well as components of DSSCs. Under identical conditions, they displayed cell efficiencies under 1.5 sun illumination up to half that of an **N3**-sensitized solar cell and larger than typical values for cells with other tetrapyrrolic sensitizers. The results revealed factors that if optimized could dramatically enhance the performance of corrole-based DSSCs. The driving force for electron injection is one critical factor: corroles (and also other porphyrinoids) with excited-state reduction potentials substantially more positive than roughly −1.0 V likely will not perform well in DSSCs based on TiO_2. The large advances in corrole synthesis assures that many other derivatives will be available for such research, as for example corroles bearing carboxylate rather than sulfonate head groups,[54] for assuring tighter binding and likely also more efficient electron transfer rates.

7 Medicinal applications

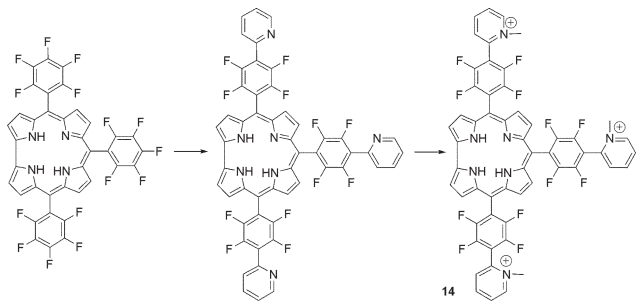
Despite of the limited information released in scientific journals so far,[55] corroles may be expected to play a big role in medicinal applications. The most obvious candidates for that purpose would be water-soluble and/or amphiphilic derivatives. The first corrole meeting these criteria was actually reported in the seminal publication about the synthesis of triarylcorroles.[5a] Replacement of the *para*-F atoms in (H_3)tpfc by *via* C-alkylation by pyridine and N-alkylation of that product led to the first water-soluble corrole (**14**), which due to its C_{2v} symmetry is also amphiphilic (Scheme 17). In fact, **14** was utilized in what appears to be the first corrole-based medicinal investigation and it fulfilled expectations.[56] Compared with quite a large variety of porphyrins, **14** was more efficient in terms of inhibiting endothelial cell proliferation, tumor progression, and metastasis in what remains the only *in vivo* investigation reported to date.

Other investigations focused on the most accessible **6** (Scheme 4)[57] whose sulfonate groups serve for inducing water-solubility as well as amphiphilicity in a fashion that is distinctively different from that of the common porphyrins: location of the polar groups on the macrocycle's skeleton and not on the symmetrically distributed aryl groups. Corrole **6** and its metal complexes were shown to bind tightly to serum albumins,[21] a phenomenon that could be either beneficial or troublesome for medicinal applications. Relying on the intense fluoresence of corroles and applying confocal fluorescence microscopy for the examinations, advantages were deduced in an *in vitro* investigation.[34] The negatively charged corroles did not penetrate the cell membranes in protein-free medium, but spontaneously (*in situ*) formed protein conjugates served very well for inducing cellular uptake and accumulation in the cytoplasm. Uptake was assisted by both serum albumins and specifically designed cell-targeting proteins. In the latter case, receptor-specific cell binding and cell entry was confirmed by inhibition studies. The most important demonstration was obtained with corroles conjugated to HerPBK10, a heregulin-targeted protein that specifically binds to heregulin receptors that are amplified on the cell surface of ErbB2+ human breast cancer cells and undergoes receptor-mediated cell entry. Indeed, the **6**-Ga/HerPBK10 conjugate was cytotoxic to ErbB2-positive (Fig. 4) but not ErbB2-negative breast cancer cells.

Taken together, these results seem encouraging enough as to safely predict that corroles will soon be used for many other medicinal applications. This will probably include approaches that will take advantage of the already uncovered photophysical properties of corroles,[8i,8o,14,58] as well as the catalytic decomposition of hydrogen peroxide and peroxynitrite by the iron and manganese complexes.[22,33]

8 Conclusions and Future Outlook

The chemistry of corroles remained in its infancy for many decades following the first reported derivative in 1964. Facile syntheses of triarylcorroles from commercially available reagents were disclosed as late as 1999, which coincided with the first ever reported application of corroles. We have shown that corroles are superior to porphyrins and related macrocycles in many cases, most especially in affecting stability and reactivity of high valent transition metals: corroles also have very favorable photophysical properties and NH acidity; their syntheses can be readily tuned; and they possess distinct catalytic properties. Importantly, research has revealed several examples of reactions that are not catalyzed by any non-corrole metal complex, such as the iron-based aziridination by Chloramine-T, disproportionation of peroxynitrite, and N–H activation of ammonia (shared by iron porphyrins). In terms of future outlook, we note that while past emphasis was on corrole-stabilization of metals in high oxidation states, the



Scheme 17 Synthesis of the first water-soluble corrole (**14**), used in the first and only reported *in vivo* medicinal investigation.

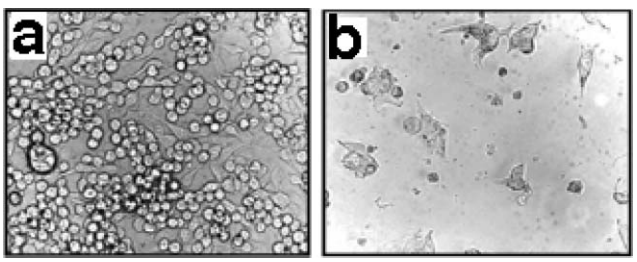


Fig. 4 Photomicrographs of breast cancer cells that were either (a) untreated or (b) treated by **6**-Ga conjugated to HerPBK10, showing that treatment results in a lower cell number and cytopathicity (shrinkage and lysis).

chemistry of low-valent metal corrole complexes has been relatively neglected, a situation that must be addressed, since the reductive activation of small molecules (O_2, CO, CO_2 and more) is of tremendous importance. We also believe that there are exciting opportunities for research on corrole-based sensors for both environmental and medicinal purposes. We predict that medicinal applications, such as tumor detection and/or destruction, and decomposition of reactive oxygen species will be another area where corroles will play a major role. It also is likely that corroles will be increasingly utilized in light-driven processes, including applications in both medical and alternative energy areas. Corrole chemistry has a very bright future!

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