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Mechanistic Aspects of β-Bond-Cleavage Reactions of Aromatic Radical Cations

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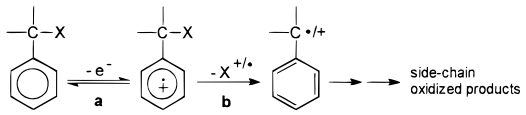
ABSTRACT
The mesolytic cleavage of a β-C−X bond ($ArCR_2-X^{\bullet+} \rightarrow ArCR_2^{\bullet/+} + X^{+/\bullet}$) is one of the most important reactions of alkylaromatic radical cations. In this Account, our group's results concerning some fundamental aspects of this process (cleavage mode, structural and stereoelectronic effects, competitive breaking of different β-bonds, nucleophilic assistance, possible stereochemistry, carbon vs oxygen acidity in arylalkanol radical cations) are presented and critically discussed for reactions where X = H, CR_3, SR, and SiR_3. Several examples illustrating how this information was exploited as a tool to detect electron-transfer mechanisms in chemical and enzymatic oxidations are also reported.

Introduction

The removal of an electron from an aromatic substrate leads to the formation of a radical cation, a species capable of undergoing a large variety of reactions (activation by electron transfer, ET).[1,2] Among these reactions, those involving the cleavage of a bond β to the aromatic ring (Scheme 1, step b) are prominent for generality and scope. Many different bonds can be involved (e.g., X = H, alkyl, SR, OR, SeR, SiR_3, SnR_3), and the cleavage is an essential step in the side-chain oxidation of alkylaromatics and related compounds, a process of great practical importance.

The side-chain reactivity of aromatic radical cations originates from the significant weakening of the β-bond caused by the overlap of its σ orbital with the SOMO in the aromatic ring. The cleavage of this bond is therefore

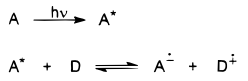
Scheme 1



a relatively facile process presenting several aspects of great theoretical interest. There are three major concerns: (a) The mode of cleavage, which can be (i) homolytic or heterolytic, depending on the way the bond electrons are apportioned between the two fragments,[3] or (ii) unimolecular or bimolecular, if the assistance of a nucleophile is required. (b) The kinetic and thermodynamic carbon acidity of the radical cation when X = H. (c) The competition between the rupture of different β-bonds and the factors which govern this competition.[4−8]

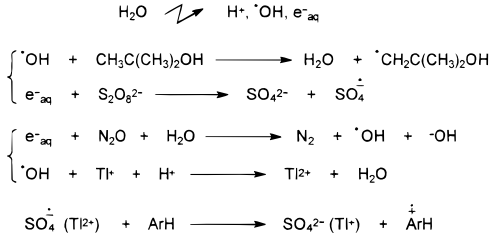
We have been interested in the side-chain reactivity of aromatic radical cations for a long time, with the main objective of obtaining fundamental information about the structure−reactivity relationships in reactions involving the cleavage of C−H, C−C, C−S, and C−Si bonds. This information was also successfully exploited as a mechanistic tool to detect the possible intermediacy of radical cations in organic and bioorganic reactions.[9] In this Account we will present and discuss the main results of our studies. First, however, it is appropriate to briefly summarize the different experimental approaches used in our work for the generation and the study of radical cations. These are the following: (a) Anodic oxidation of a substrate or its reactions with *genuine* one-electron chemical oxidants such as potassium 12-tungstocobalt(III)ate, $K_5Co^{III}W_{12}O_{40}$,[10] hereafter indicated as $Co^{III}W$, and study of the products formed by the intermediate radical cation. (b) Sensitized photochemical oxidation (Scheme 2 (A = substrate, D = sensitizer) leading to radical cations

Scheme 2



whose fate can be indirectly followed by products study (steady-state photolysis) or directly by UV−visible spectrophotometry (laser photolysis). (c) Oxidation of a substrate by $SO_4^{\bullet-}$ or Tl^{2+} generated in water by pulse or γ radiolysis (Scheme 3); in the former case the radical cation

Scheme 3



Enrico Baciocchi received the laurea in chemistry from the University "La Sapienza" in Rome in 1954 and carried out postdoctoral work at the same University with G. Illuminati and at Brown University, Providence, Rhode Island, with J. F. Bunnett. He then joined the Faculty of Science of the University "La Sapienza" as an Assistant Professor and became Professor of Organic Chemistry at the University of Perugia in 1970. He moved to the University "La Sapienza" in 1986.

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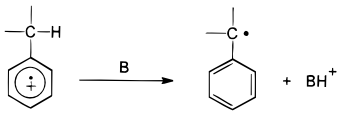
can be detected and its decay followed spectrophotometrically, while in the latter the reactivity of the radical cation is again inferred from product studies.

Reactions Involving C−H Bond Cleavage: Alkylaromatic Radical Cations as Carbon Acids

The simplest and most common side-chain reaction of alkylaromatic radical cations is the cleavage of a C_α−H (hereafter simply indicated as C−H) bond. Since in solution such a cleavage is generally heterolytic due to the very large solvation energy of the proton (Scheme 4,

Scheme 4



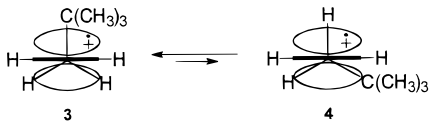
where B is a proton-accepting base including the solvent),[11] alkylaromatic radical cations behave as carbon acids, and accordingly their deprotonations exhibit intrinsic barriers as high as 0.5−0.6 eV, typical of these acids.[12] However, since a correlation was found between the intrinsic barrier and the homolytic C−H bond dissociation energy (BDE), it was suggested that C−H deprotonation of alkylaromatic radical cations can be better described as a concerted H atom electron transfer.[13,14]

The kinetic acidity of alkylaromatic radical cations is little influenced by the strength of the attacking base or the acid strength of the radical cation as shown by the quite low (0.2−0.3) values of the Brønsted coefficients (β and α, respectively) observed in the deprotonation of polymethylbenzene radical cations by substituted pyridines[15] and of α-substituted 4-methoxytoluenes by pyridine and NO_3^-.[16] A reactant-like transition state is suggested. In all cases, electron-releasing groups which stabilize the radical cation decrease the C−H deprotonation rate.

Spin and/or charge density at the scissible C−H bond also influences the kinetic acidity of alkylaromatic radical cations, which accordingly is very sensitive to the nature and position of ring substituents. Thus, in 1,2,3-trimethyl-5-methoxybenzene radical cation, deprotonation at the 2-methyl group (where there is the largest charge/spin density) occurs more than 100 times faster than that at the 1- and 3-methyl groups.[17] This has interesting consequences from the synthetic point of view. Thus, exclusive oxidation at the 2-methyl group is observed in the anodic and cerium ammonium nitrate (CAN)-promoted oxidations of 1,2,3-trimethyl-5-methoxybenzene.[17]

The deprotonation rate of an alkylaromatic radical cation is, moreover, affected by the relative orientation of the scissible C−H bond and the aromatic π system (stereoelectronic effect). Namely, the orientation most suited for the cleavage is the one where the C−H bond and the π system are collinear, allowing the best orbital overlap for intramolecular ET between the C−H σ orbital and the SOMO in the ring, required for the C−H bond cleavage. There is much evidence in this respect,[18−21] including our study of the anodic oxidation of *p*-neopentyltoluene (**1**) and 2,2,5,6-tetramethylindane (**2**).[20] $\mathbf{1}^{\bullet+}$ is almost exclusively deprotonated at the methyl group, which was attributed to the fact that its most stable conformation is **3**, where the orientation of the C−H bond is not suitable for the cleavage (Scheme 5).

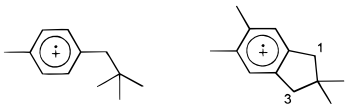
Scheme 5



3 **4**

A quantitative assessment of the great importance of stereoelectronic effects was obtained by comparing the CH_3/CH_2tBu reactivity ratio in $\mathbf{1}^{\bullet+}$ to that in $\mathbf{2}^{\bullet+}$, where the CH_2 groups in the positions 1 and 3 bear a substituent comparable to a *t*Bu group (Scheme 6). The CH_3/CH_2tBu

Scheme 6



$\mathbf{1}^{\bullet+}$ $\mathbf{2}^{\bullet+}$

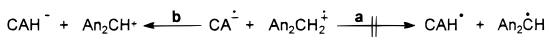
reactivity ratio was 100 in $\mathbf{1}^{\bullet+}$, but as small as 0.02 in $\mathbf{2}^{\bullet+}$, where the 1- and 3-C−H bonds are kept almost collinear with the aromatic system because of the rigidity imposed by the cyclopentane ring. Thus, the deprotonation rate from CH_2tBu drops by as much as 5000 times when stereoelectronic effects are operating!

The deprotonation of the intermediate radical cation is one of the key steps in the one-electron side-chain oxidation of alkylaromatics (Scheme 1, X = H), and it can therefore influence the rate of the entire process if the electron-transfer step is reversible (endergonic electron transfer). When this situation holds, however, no straightforward prediction about substituent effects would seem possible as substituents affect the electron transfer and the deprotonation step in opposite ways. For example, substituents which stabilize the radical cation make the electron-transfer easier but decrease the rate of deprotonation. This problem has been addressed in a detailed kinetic study of the side-chain oxidation of α-substituted 4-methoxytoluenes by $Co^{III}W$, which has allowed us to establish that, at least as far as the α-substituents are concerned, the electron-transfer step plays the major role with respect to the overall side-chain oxidation rate.[22]

As already mentioned, the preference of alkylaromatic radical cations for heterolytic C−H bond cleavage (Scheme 4) in solution also extends to the case in which the base is a radical anion, a situation often encountered in photoinduced electron-transfer reactions (Scheme 2). Very recently, however, the first evidence for a homolytic C−H bond cleavage was provided by a laser photolysis study of bis(4-methoxyphenyl)methane (An_2CH_2) in the presence of chloranil (CA) in MeCN.[23] In this system, the excited triplet chloranil, ^{3}CA*, forms, which reacts with An_2CH_2 by an ET process to produce $An_2CH_2^{\bullet+}$ and $CA^{\bullet-}$.

However, the reaction between the two radical ions led not to the semiquinone radical ($CAH^{\bullet}$) and the carbon radical ($An_2CH^{\bullet}$) expected for the deprotonation process (Scheme 7, path a), but to the formation of An_2CH^+,

Scheme 7



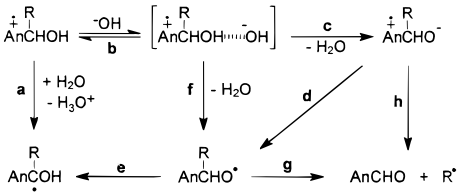
characterized by a strong absorption at 505 nm, and CAH^-, indicating the occurrence of a hydrogen atom-transfer (HAT) reaction (path b).

This result was very surprising, but actually it could be predicted, at least on a thermodynamic basis, as reaction b exhibits a more negative $\Delta G°$ value than reaction a (≤ -29 vs ≤ -16 kcal mol^{-1}). This thermodynamic advantage remains as long as the reduction potential of the arylmethyl cation is <0.7 V/NHE. Thus, homolytic C−H bond breaking from an alkylaromatic radical cation might be more frequent than hitherto thought.

Carbon vs Oxygen Acidity of 1-Arylalkanol Radical Cations

A major achievement in the study of the acidity of aromatic radical cations is the recent discovery that 1-arylalkanol radical cations in H_2O exhibit a pH-dependent mechanistic dichotomy whereby these species undergo C−H deprotonation at pH 3−5, but deprotonation at the alcoholic O−H group in basic medium. Evidence in this respect was provided by a pulse radiolysis study of 4-methoxybenzyl alcohol (**5**) and its methyl ether (**6**).[24] At pH 3−5, $\mathbf{5}^{\bullet+}$ and $\mathbf{6}^{\bullet+}$ decay at approximately the same rate ($k = 1.5 \times 10^4$ s^{-1}) by a H_2O-induced C−H deprotonation process, as also evinced by the sizable deuterium kinetic isotope effects ($k_H/k_D = 4-5$) measured with the α-deuterated counterparts of **5** and **6**. However, in the presence of $^-$OH, $\mathbf{5}^{\bullet+}$ reacted at a diffusion-controlled rate ($k_{-OH} = 1.2 \times 10^{10}$ M^{-1} s^{-1}) and was almost 50 times more reactive than $\mathbf{6}^{\bullet+}$. Both of these observations suggested the mechanistic dichotomy reported in Scheme 8 (R = H; An

Scheme 8



= 4-MeOC$_6$H$_4$). When H_2O is the base, $\mathbf{5}^{\bullet+}$ is C−H deprotonated (path a), whereas when the base is $^-$OH, the alcoholic O−H bond is deprotonated, the radical cation behaving as an oxygen acid. Proton transfer occurs in the encounter complex, formed in the rate-determining step (path b), leading either directly (path f) or via an intermediate radical zwitterion (paths c and d) to a benzyloxyl radical which eventually undergoes a formal 1,2-H atom shift (path e)[25] to form the same carbon radical as the one formed at pH 3−5. This mechanism also holds when R = Me, but for R = Et and *i*Pr, C−C bond cleavage (to be discussed in the next section) begins to compete (paths g and h).

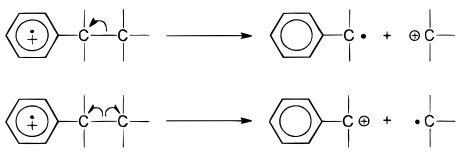
A possible explanation for this very remarkable shift from carbon to oxygen acidity may be attributed to the fact that C−H deprotonation is largely favored thermodynamically with respect to O−H deprotonation, but it has a significantly higher intrinsic barrier.[12−14] Thus, when a very weak base (H_2O) is involved, the effect of the much larger driving force predominates and C−H deprotonation is observed. However, when the base becomes strong ($^-$OH), both deprotonations are thermodynamically feasible, and O−H deprotonation, with the smaller intrinsic barrier, outruns C−H deprotonation.

C−C Bond Cleavage in Alkylaromatic and 1- and 2-Arylalkanol Radical Cations

The side-chain β-C−C bond cleavage in aromatic radical cations has been intensively investigated from both the practical and theoretical points of view. Such a cleavage can play a fundamental role in very important processes such as the oxidative degradation of lignin to lower and useful aromatics.

For the C−C bond, either the heterolytic or the homolytic mode of cleavage are possible (Scheme 9),[6]

Scheme 9



depending on the relative oxidation potentials of the two fragments formed,[26] and recently it was suggested[27] that the process may be reversible and that due to its small intrinsic barrier (0.1−0.2 eV)[27,28] the diffusion of the fragments from the solvent cage can be rate determining for endergonic cleavages. The smaller intrinsic barrier for the cleavage of the C−C bond than for the deprotonation process (see above) might explain the observation that in several instances the cleavage of the C−C bond successfully competes with that of the C−H bond, even when the latter is largely thermodynamically favored. For example, in MeCN/MeOH, C−C bond cleavage is the only fragmentation pathway for $Ph_2CH-CHPh_2^{\bullet+}$, although the BDE of this bond is 9 kcal mol^{-1}, whereas the C−H bond cleavage is exothermic by 17 kcal mol^{-1}.[26,29] Another factor might be that the C−H bond cleavage is generally strongly depressed by stereoelectronic effects since its steric requirements are much smaller than those of a C−C bond. Thus, the conformation with the latter bond collinear with the π system is generally the most favored one.

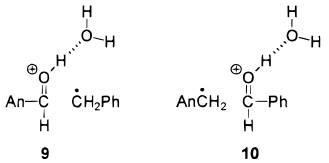
It should also be considered that C−C bond cleavage can be nucleophilically assisted, as observed by Dinnocenzo and his associates for the C−C bond cleavage in phenylcyclopropane radical cations,[30] which accordingly occurs with inversion of configuration at the β-carbon, thus suggesting that the most important orbital interaction is that between the HOMO of the nucleophile and the

LUMO of the radical cation.[31] Very recently, nucleophilic assistance has also been detected in the C−C bond fragmentation of 2-methyl-2-(4-methoxybenzyl)-1,3-dioxolane radical cation.[32]

Theoretical calculations suggest that a substantial amount of positive charge has to be transferred to the scissible bond in the transition state leading to C−C bond cleavage (through-bond delocalization).[33−35] Indeed, C−C bond cleavage appears to be favored by groups on C_α and/or C_β able to stabilize a positive charge.[35,36] It should be noted, however, that such groups can also decrease the BDE of the C−C bond, as they stabilize the formed fragments (thermodynamic effect).[26,29]

Through-bond delocalization is probably more important in the cleavage of the C−C bond than in that of the C−H bond since the former is disfavored, with respect to the latter, when ring substituents are present which stabilize the positive charge, making the side-chain-to-nucleus electron transfer more difficult. Thus, exclusive C−C bond cleavage was found in the $Co^{III}W$-induced oxidation of $PhCH_2CH(OMe)CH_3$, whereas only C−H deprotonation occurs in the 4-methoxyphenyl derivative.[37] Among the groups on C_α and/or C_β which can favor the breaking of the C−C bond, the OH group occupies a very special position, and accordingly it is well known that 1- and 2-arylalkanols undergo very efficient C−C bond-cleavage reactions when reacted with one-electron oxidants.[38,39]

Quantitative information on the role of the OH group was provided by a detailed pulse radiolysis study of 1- and 2-arylalkanol radical cations in water. The first observation was that OH is always more effective than OMe in promoting C−C bond cleavage. For example, in acid solution (pH = 3−5) the radical cation of 4-$MeOC_6H_4CH$(OH)*t*Bu (**7**$^{\bullet+}$) undergoes exclusive C−C bond cleavage with a rate ($k = 1.5 \times 10^5$ s^{-1}) which is about 4 orders of magnitude higher than that of its methyl ether **8**$^{\bullet+}$.[24b] This difference is remarkable, especially when it is considered that the C−C BDE is practically the same in the two radical cations. The position of the OH group, α or β, does not seem to play a significant role, as similar rates of C−C bond cleavage were observed for 4-$MeOC_6H_4CH(OH)CH_2C_6H_5^{\bullet+}$ and 4-$MeOC_6H_4^{\bullet+}CH_2CH(OH)C_6H_5$.[37] An explanation, based on the relatively small values (1.2−1.4) of the solvent deuterium kinetic isotope effect, $k(H_2O)/k(D_2O)$, is that when the OH group is present, the transition state for C−C bond cleavage may benefit from a strong stabilization by hydrogen bonding with the solvent water as shown by structures **9** and **10**. Other factors, however, might play a role in this respect.[37]



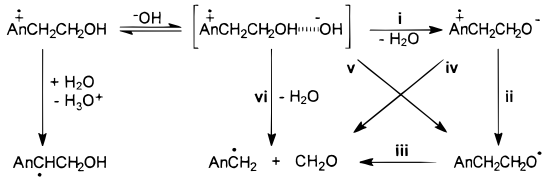
9 **10**

The second observation was that in both 1- and 2-arylalkanol radical cations, C−C bond cleavage is strongly favored by the presence of a base. For 1-arylalkanols, it was found that 4-$MeOC_6H_4CH(OH)CH(CH_3)_2^{\bullet+}$ (**11**$^{\bullet+}$) undergoes predominant C−H bond cleavage at pH = 4, but almost exclusive C−C bond cleavage in the presence of $^-$OH.[24b] With both **7**$^{\bullet+}$ and **11**$^{\bullet+}$ the C−C bond-cleavage reaction is diffusion controlled ($k_{-OH} = (1.2-1.3) \times 10^{10}$ M^{-1} s^{-1}), exactly like the base-induced deprotonation of **5**$^{\bullet+}$ (see above).[24b] Thus, under these conditions, **7**$^{\bullet+}$ and **11**$^{\bullet+}$ also display oxygen acidity (Scheme 8, R = *t*Bu, *i*Pr), forming a benzyloxyl radical by O−H deprotonation (path f or paths c and d), which undergoes C−C bond cleavage (path g) instead of the 1,2-H atom shift. Alternatively, in the zwitterion, the intramolecular ET might be concerted with C−C bond cleavage (path h).

Direct evidence for the formation of an intermediate oxyl radical was, indeed, obtained in a pulse radiolysis study of the $^-$OH-induced C−C bond cleavage of 4-methoxycumyl alcohol radical cation. The 4-methoxycumyloxyl radical is first formed, which then undergoes C−C bond cleavage leading to 4-methoxyacetophenone and Me$^\bullet$.[40] However, we cannot yet exclude path h, which might operate in reactions involving oxyl radicals that are less stable than 4-methoxycumyloxyl radical (see below).

For 2-arylalkanol radical cations (β-OH), C−H bond cleavage is observed at pH = 3−5, but in the presence of $^-$OH, exclusive C−C bond cleavage occurs at a rate very close to the diffusion limit. For example, 4-$MeOC_6H_4CH_2CH_2OH^{\bullet+}$ (**12**$^{\bullet+}$) in acid medium is C−H deprotonated ($k = 5.2 \times 10^2$ s^{-1}), but in basic medium it undergoes C−C bond cleavage with $k_{-OH} = 8.3 \times 10^9$ M^{-1} s^{-1}.[41] Thus, **12**$^{\bullet+}$ also displays carbon acidity in acid solution and oxygen acidity in basic solution. A mechanism similar to the one described in Scheme 8 for 1-arylalkanols can be proposed (Scheme 10, An = 4-$MeOC_6H_4$).

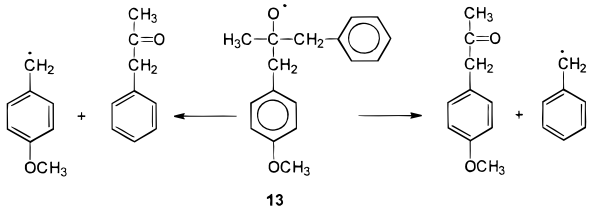
Scheme 10



In the encounter complex, the proton transfer from the O−H group might lead, either directly (path v) or via a radical zwitterion (paths i and ii), to an alkoxyl radical, which then undergoes C−C bond β cleavage (path iii). In this case, however, it is also possible that O−H deprotonation and C−C bond cleavage are concerted (Grob-type fragmentation, path vi) or that in the radical zwitterion C−C bond cleavage and intramolecular ET are concerted (path iv). Indeed, the latter two pathways have already been proposed by the groups of Whitten[5,42] and Schanze,[43] respectively, to rationalize the effect of the β-OH group upon C−C bond cleavage in the radical cations of 2-(4-*N*,*N*-dimethylaminophenyl)-1-phenylethanol and of a series of 2-(phenylamino)-1,2-diphenylethanols, where, however, the positive charge mainly resides on the nitrogen atom.

To get information in this respect we carried out a product study (steady-state γ-radioysis) of the $^-$OH-induced decay of 4-$MeOC_6H_4CH_2C(Me)(OH)CH_2Ph^{\bullet+}$.[41] In this case, if the alkoxyl radical **13** is a reaction intermediate, then both phenyl- and 4-methoxyphenylacetone should form, as similar activation energies can be predicted for the two possible fragmentation paths of **13** (Scheme 11).

Scheme 11

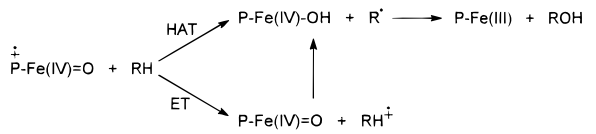


13

Since only 4-methoxyphenylacetone was observed, the intermediacy of the alkoxyl radical can be excluded, and the two mechanisms suggested by Whitten et al. and Schanze et al. (paths vi and iv in Scheme 10) are the most likely ones. Perhaps, in order to choose between the two pathways, it might be useful to determine whether the reaction is subject to specific or general base catalysis.

The fragmentation pattern of $\mathbf{7}^{\bullet+}$ (exclusive C−C bond cleavage in acidic and basic medium) suggested the use of **7** as a mechanistic probe for distinguishing an ET from a HAT mechanism in the side-chain hydroxylation of arylalkanes promoted by cytochrome P-450 (Scheme 12,

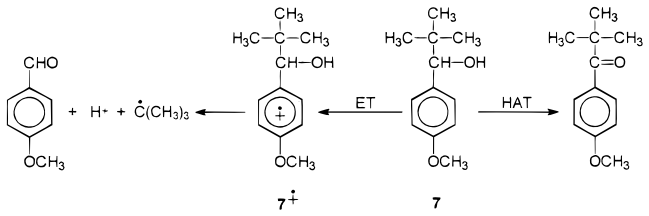
Scheme 12



where $P^{\bullet+}$—Fe(IV)═O is the protoporphyrin IX iron oxo complex, suggested to be the active oxidant in the enzyme).[44]

Accordingly, if particular effects related to some specific enzyme−substrate binding can be excluded, the ET mechanism should lead to products of C−C bond cleavage, whereas the HAT mechanism should lead to the corresponding ketone (Scheme 13).

Scheme 13

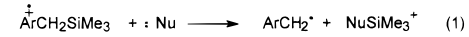


$\mathbf{7}^{\bullet+}$ **7**

Since the ketone was the only product observed in the microsomal oxidation of **7**,[45] the HAT mechanism appears to be the most likely one, a conclusion in line with previous proposals.[46]

C−Si Bond Cleavage in Benzyltrimethylsilane Radical Cations

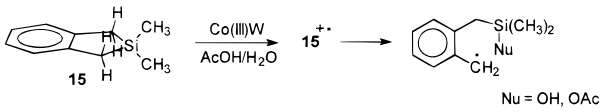
The cleavage of the C−Si bond is the most common pathway of benzyltrimethylsilane radical cations.[47] There is ample evidence that this cleavage is nucleophilically assisted and can be described as in eq 1.[48]



$$\dot{Ar}CH_2SiMe_3 + :Nu \longrightarrow ArCH_2^{\bullet} + NuSiMe_3^{+} \quad (1)$$

The cleavage of the C−Si bond is generally much faster than that of the C−H bond. For example, in MeCN, laser flash photolysis experiments have shown that desilylation of 4-methoxybenzyltrimethylsilane radical cation ($\mathbf{14}^{\bullet+}$) is >200 times faster than deprotonation of 4-$MeOC_6H_4CH_3^{\bullet+}$.[32] Likewise, 4-methylbenzyltrimethylsilane is oxidized by CAN to give exclusively products of desilylation.[47c] Interestingly, stereoelectronic effects do not play a significant role in C−Si bond-cleavage reactions, in contrast to what is observed with the C−H bond. Thus, the oxidation of 2,2-dimethyl-2-silaindane (**15**) with $Co^{III}W$ in AcOH/H_2O[49] led exclusively to products of C−Si bond cleavage (Scheme 14), even though in this substrate the C−Si bond

Scheme 14



15

Nu = OH, OAc

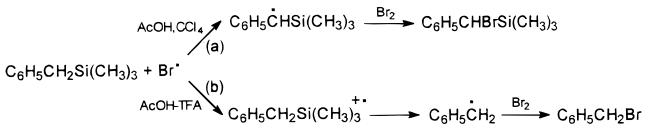
is almost coplanar with the benzene ring, as indicated by theoretical calculations.[50] Probably, C−Si bond cleavage is so fast that it remains the main process even when the bond and the aromatic π system cannot be collinear.

Because of the fast C−Si bond-cleavage rate, the formation of the radical cation is the rate-determining step in the oxidation of benzyltrimethylsilanes induced by $Co^{III}W$ in AcOH/H_2O, which accordingly exhibited clean second-order kinetics and no retarding effect by $Co^{II}W$.[47a] As expected, the rates of oxidation of benzyltrimethylsilanes are very sensitive to the electronic effects of ring substituents, and good correlations with the substituent σ^+ values were observed in the TiO_2-photocatalyzed oxidation in the presence of Ag_2SO_4 ($\rho^+ = -2.5$)[47b] and in the CAN-promoted oxidation ($\rho^+ = -5.4$).[47c]

Benzyltrimethylsilanes too were exploited as mechanistic probes to differentiate ET from HAT mechanisms in chemical and enzymatic oxidations since an ET step leads to products of C−Si bond cleavage (benzyl derivatives), whereas a HAT mechanism forms silicon-retaining α-substituted products or products derived therefrom (benzaldehydes) if further oxidation is possible. When applied to the photobromination reaction, this probe clearly evidenced a mechanistic dichotomy strongly influenced by substrate structure and solvent.[51]

As shown in Scheme 15, the reaction of benzyltrimethylsilane (**16**) with $Br_2/h\nu$, in CCl_4 or AcOH, forms (α-bromo)benzyltrimethylsilane certainly via a HAT mechanism (path a). However, in AcOH/TFA the mechanism changed to ET, and the major product was benzyl bromide formed upon C−Si bond cleavage in $\mathbf{16}^{\bullet+}$ (path b).

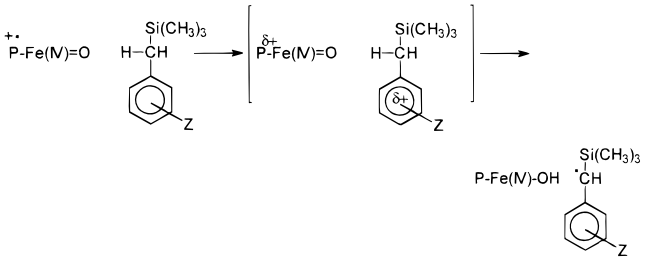
Scheme 15



Interestingly, with the more easily oxidizable 4-methoxybenzyltrimethylsilane (**14**), the ET mechanism was observed also in AcOH.

The benzyltrimethylsilane probe was also applied to the study of the mechanism of the benzylic hydroxylation catalyzed by iron(III) tetrakis(pentafluorophenyl)porphyrin [Fe^{III}(TPFPP)],[52] a model compound of cytochrome P-450 monooxygenases. For this biomimetic reaction, the same mechanism holds as that described for cytochrome P-450 (Scheme 12, where P is now TPFPP). When the iron-oxo complex [$P^{\bullet+}$—Fe(IV)═O], formed by reaction of the model compound with iodosylbenzene, reacted with ring-substituted benzyltrimethylsilanes in CH_2Cl_2, the corresponding benzaldehydes were formed, thus indicating a HAT mechanism with the hydrogen transfer probably occurring in a charge-transfer complex (Scheme 16).[52a] An

Scheme 16



increase in solvent polarity induced a mechanistic changeover. Thus **14** in CH_2Cl_2/MeOH/H_2O reacts by an ET mechanism forming 4-methoxybenzyl alcohol and 4-methoxybenzyl methyl ether.[52b]

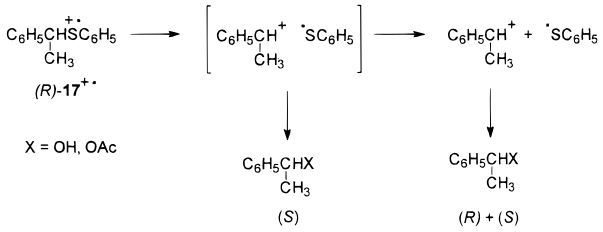
Interestingly, in the reaction of **14** with cytochrome P-450, only 4-hydroxybenzyltrimethylsilane was formed (O-demethylation).[53] This result confirms that radical cations are not involved in this reaction.[54]

C—S Bond Cleavage in Benzyl Phenyl Sulfide Radical Cations

The chemistry of aromatic sulfide radical cations is of great interest as a large variety of sulfur-containing functional groups, present in many important materials such as coal, organic polymers, biological macromolecules, and xenobiotics, are highly susceptible to one-electron oxidation.[56] In this area we have been concerned with the fragmentation reactions of benzyl phenyl sulfide radical cations, particularly with the cleavage of the C—S bond, which is one of the main reaction paths of these species. This cleavage always occurs to form a benzyl carbocation and an arylthiyl radical, as the reverse type of cleavage would lead to a very unstable sulfenylium cation. The mode of cleavage, heterolytic or homolytic, depends on whether the SOMO is on the sulfur atom or on the ring of the benzyl moiety, respectively. The former possibility appears to hold when no electron-releasing substituents are present in the benzyl ring.[57]

To establish whether C—S bond cleavage requires nucleophilic assistance, the stereochemistry of the reaction of (*R*)-1-phenylethyl phenyl sulfide [(*R*)-**17**] with $Co^{III}W$ in AcOH/H_2O was studied.[58] The C—S bond-cleavage products were 1-phenyl ethanol and 1-phenylethyl acetate, both with an *S*/*R* ratio of 1.4. Thus, the C—S bond cleavage in the intermediate radical cation occurs with racemization, accompanied by 16% of inversion. A unimolecular process was suggested, leading to a geminate radical—cation pair which in part undergoes attack from the solvent (with inversion) before dissociation to solvated species (Scheme 17). A competition between a

Scheme 17

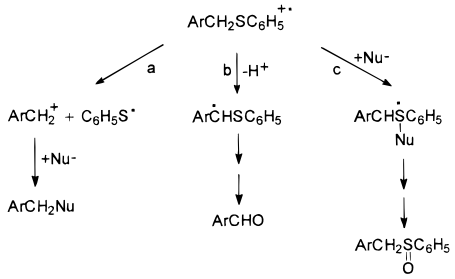


unimolecular and a nucleophilically assisted mechanism of cleavage was excluded in view of the very small effect of an added base (AcO^-) upon the reaction rate and the *S*/*R* ratios of both cleavage products.

This conclusion may appear surprising in light of the non-negligible BDE estimated for the C—S bond (16 kcal mol^{-1}) in $\mathbf{17}^{\bullet+}$ and the previous observations with C—C and C—Si bond-cleavage reactions. A tentative rationalization is that in this radical cation the SOMO is on the sulfur atom;[57] thus, no significant electronic reorganization is required for the C—S bond cleavage, which should result in a very low intrinsic barrier for this process.

In benzyl phenyl sulfide radical cations, C—S bond cleavage is in competition with C—H deprotonation and nucleophilic attack at sulfur (Scheme 18). The relative

Scheme 18



importance of these processes can easily be determined by the relative amounts of products deriving from the three pathways: benzyl derivatives, benzaldehydes, and sulfoxides, respectively.

C—S bond cleavage prevails in the benzyl phenyl sulfide radical cation ($\mathbf{18}^{\bullet+}$), unless a relatively strong base is present, which instead favors C—H deprotonation. Thus, $\mathbf{18}^{\bullet+}$, anodically generated, undergoes C—S bond cleavage in MeCN/$LiClO_4$ but predominant C—H deprotonation in

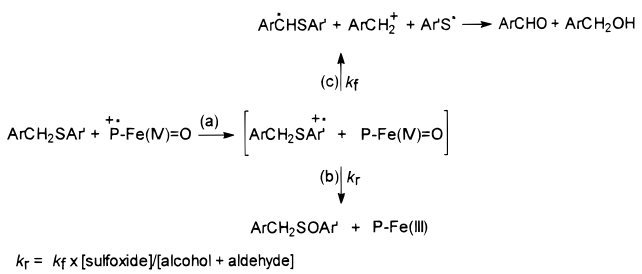
AcOH/AcO^-.[59] Likewise, mainly C−H deprotonation is observed in the TiO_2/Ag_2SO_4[60] and 9,10-dicyanoanthracene (DCA)/O_2[61] photosensitized oxidations of **18** in MeCN. In the former case, an active role of the oxygenated basic sites present on the TiO_2 surface can be envisaged. In the second, the basic species is probably $O_2^{\bullet-}$, produced upon ET from $DCA^{\bullet-}$ to O_2.

The C−S/C−H bond-cleavage ratio in MeCN is 0.7 in $\mathbf{18}^{\bullet+}$ and 1.0 in the 4-methoxybenzyl phenyl sulfide radical cation.[62] Thus, a *p*-OMe group in the benzylic ring does not significantly increase the contribution of the C−S bond-breaking channel, even though a more stable benzyl cation is formed, suggesting that very little charge is transferred from sulfur to carbon in the transition state of the C−S bond-cleavage pathway.

Quantitative information on the rate of fragmentation of benzyl phenyl sulfides in H_2O has been obtained by a pulse radiolysis study of water-soluble substrates such as $PhCH_2SC_6H_4CH_2SO_3K$ (**19**).[63] $\mathbf{19}^{\bullet+}$ decayed with formation of $PhCH^{\bullet}SC_6H_4CH_2SO_3K$ by deprotonation, and $^{\bullet}SC_6H_4CH_2SO_3K$ by C−S bond cleavage. The overall process took place with a rate constant of $2.6 \times 10^3\ s^{-1}$. Similar results were obtained with the *p*-OMe derivative.

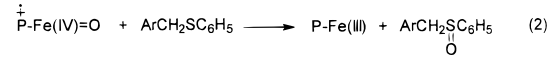
This information was applied to the study of the oxidation of aromatic sulfides to sulfoxides catalyzed by horseradish peroxidase (HRP),[9a,63] a hemoprotein whose active oxidant is the same iron oxo porphyrin complex as that involved in the cytochrome P-450-induced oxidations. The reaction mechanism involves the formation of a sulfide radical cation intermediate which then undergoes a fast oxygen rebound (Scheme 19, paths a and b) to form

Scheme 19



the sulfoxide. When **19** was oxidized by HRP the sulfoxide was obtained, but together with comparable amounts of benzyl alcohol and benzaldehyde. Clearly, $\mathbf{19}^{\bullet+}$ is formed, which partitions between oxygen rebound and C−S and C−H bond cleavage (path c in Scheme 19).

Knowing the rate of path c, it was possible to estimate the rate of the oxygen rebound step ($k = 6.3 \times 10^3\ s^{-1}$) from the relative amounts of sulfoxide and fragmentation products. However, no fragmentation products but only sulfoxides were obtained in the oxidation of benzyl sulfides by cytochrome P-450[9a,64] and chloroperoxidase,[9a,63] which would suggest that the reactions catalyzed by these enzymes involve non an ET step but a direct oxygen transfer (eq 2).



(2)

The possibility that with cytochrome P450 and chloroperoxidase the radical cation undergoes the oxygen rebound step at a much faster rate than the fragmentation reaction is unlikely since exclusive formation of sulfoxide is also observed with substrates, such as $3,4,5\text{-}(CH_3O)_3C_6H_2\text{-}CH_2SC_6H_5$, forming radical cations which should exhibit a relatively slow rate of oxygen rebound since the positive charge does not reside on the sulfur atom.[65]

Concluding Remarks

Particularly in the past decade, considerable progress has been made in our knowledge of the main features of β-bond-cleavage reactions in aromatic radical cations. Nevertheless, there are several important aspects of these processes that are still not fully understood. For example, little is known about the factors which determine the competition between the cleavage of different types of β-bonds. Moreover, the problem of the stereochemistry and molecularity of the cleavage requires further investigation, particularly aimed at extending the range of substrates and types of bonds taken into consideration. More work is also necessary to better define the mechanistic details and the scope of the recently discovered carbon−oxygen acidity dichotomy in arylalkanol radical cations. Finally, it is important to point out that, unfortunately, very few theoretical studies concerning the reactivity of aromatic radical cations are presently available. A strong development of these studies in the near future is highly desirable, as it would be of great help for the interpretation of the experimental results and the design of new experiments.

The side-chain reactivity of aromatic radical ions has also shown to be a very useful mechanistic tool for detecting ET mechanisms in chemical and biochemical reactions. It is not difficult to foresee that this aspect will continue to be intensively investigated with the design of new mechanistic probes.

The invaluable contribution of Prof. S. Steenken to our pulse radiolysis investigation is very gratefully recognized. We are also very grateful to all other co-workers whose names appear in the cited references and thank MURST and CNR for continued financial support.

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