Tertiary : secondary : primary C–H bond relative reactivity in the one-electron oxidation of alkylbenzenes. A tool to distinguish electron transfer from hydrogen atom transfer mechanisms

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Data of tertiary : secondary : primary C–H bond relative reactivity (TSP selectivity) for a number of electron transfer (ET) and hydrogen atom transfer (HAT) reactions of alkylbenzenes have been critically reviewed and in a few cases supplemented by additional experiments. The resulting picture indicates that there are significant differences in TSP selectivity between ET and HAT reactions. When the HAT mechanism is operating the reactivity order tertiary > secondary > primary C–H bond is always observed. This order never holds in reactions occurring by an ET mechanism where, generally, the secondary C–H bond is the most reactive one and the tertiary centre can be either more or even less reactive than the primary one. Whatever the possible reasons for these differences, it turns out that TSP C–H bond selectivity determinations can afford useful information with respect to the distinction between ET and HAT mechanisms in the oxidations of alkylbenzenes. To check this conclusion a study of TSP selectivity in the oxidation of alkylbenzenes promoted by metalloporphyrins and by microsomal cytochrome P-450 has been carried out, which has allowed us to assign a HAT mechanism to these reactions, in full accord with previous attributions.

Introduction

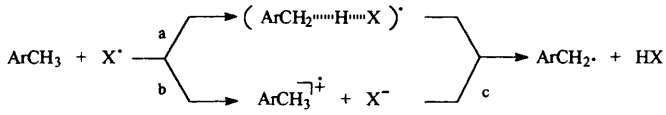
There has been a continuous interest in the side-chain oxidation of alkylbenzenes because of the many important theoretical and practical aspects associated with this process.[1] Particularly remarkable is the very broad scope of this reaction, which leads to a wide range of different products, some of them of relevant industrial interest and allows the use of a great variety of reactants including enzymatic systems (*e.g.* halogen atoms, alkoxy radicals, metal ions like Ce^{4+}, Mn^{3+}, Co^{3+}, excited states, cytochrome P-450).

The key step of the side-chain oxidation of alkylbenzenes generally involves the cleavage of a Cα–H bond (a β bond, with respect to the aromatic ring), with formation of a benzylic radical [eqn. (1), where X• is a generic one-electron reactant].

$$ArCH_3 + X^{\bullet} \longrightarrow ArCH_2^{\bullet} + HX \qquad (1)$$

For a long time, it has been widely accepted that reaction (1) is a *one-step* process involving a hydrogen atom transfer (HAT); over the last two decades, however, this view has changed considerably, since it has been recognized that electron transfer (ET) processes can also play a very important role.[2] Thus, nowadays, for these reactions the mechanistic dichotomy illustrated in Scheme 1 must be considered, where the HAT mechanism (path a) is in competition with a two-step mechanism, involving first an electron transfer (ET) step (path b) resulting in the formation of an aromatic radical cation, which is then deprotonated (path c) in the second step. The competition between the two mechanisms will be determined mainly by the relative redox potential of $ArCH_3$ and X•, as well as by the strength of the H–X bond and by the solvent. The reorganization energy associated with the electron transfer step can also play a significant role.

The distinction between HAT and ET mechanisms is a very important problem, from both theoretical and practical points of view. Indeed, this distinction is necessary for a correct prediction of reactivity and selectivity in the oxidations of aromatic substrates, since the relationship between structure



Scheme 1

and reactivity can be significantly different for the two mechanisms. Moreover, this distinction is very useful in the field of enzymatic oxidations, as it can provide an insight into the nature of the intermediates which may be involved in these reactions.

In the acquisition of information in this respect, reaction selectivity studies have been particularly valuable. In particular, substantial differences between ET and HAT reactions have been found in the competition between C–H and C–Si bond cleavage for the oxidation of benzyltrimethylsilanes,[3,4] and in the relative reactivity of non-equivalent methyl groups for the reactions of 5-substituted 1,2,3-trimethylbenzenes and 4-substituted 1,2-dimethylbenzenes.[5,6] Thus, these substrates can be employed as mechanistic probes to distinguish between ET and HAT mechanisms.

In studies of reaction mechanisms, the larger the number of criteria that can be applied, the more reliable will be any mechanistic conclusion. Thus, it is very surprising that no attempt has been made until now to use the relative reactivity of tertiary, secondary and primary C–H bonds (denoted TSP selectivity) as a mechanistic probe, in spite of the fact that it represents one of the most studied types of behaviour of the side-chain oxidations of alkylbenzenes.

We considered it of interest to address this problem and in this article we report a critical review of the available data of TSP selectivity for a number of HAT and ET side-chain oxidations of alkylbenzenes. A number of new determinations have also been carried out to acquire more information in this respect.

The results of this review have shown that HAT and ET reactions exhibit quite distinct TSP selectivity patterns, which

represent a suitable probe for the distinction between the two mechanisms. As a check of this conclusion a study of the TSP selectivity in biomimetic and enzymatic oxidations of alkylbenzenes has also been performed.

Intermolecular and intramolecular TSP selectivity

Generally, the TSP selectivity in the side-chain reactions of alkylbenzenes can be determined by measuring either the relative reaction rates of isopropylbenzene, ethylbenzene and toluene (intermolecular TSP selectivity) or the relative reactivity of Me and Pr^i in *p*-methylisopropylbenzene (*p*-cymene) and of Me and Et in *p*-ethyltoluene (intramolecular TSP selectivity). It is important to point out that, depending on the reaction mechanism, the two approaches may be non-equivalent. It should also be kept in mind that by using alkyl groups other than those above, as well variations in the aromatic ring, substantial variations in TSP selectivity are possible (*vide infra*). The presence of substituents in *ortho* to the alkyl groups can also play an important role in this respect. Thus, in this paper, we will restrict our discussion only to those data which refer to the relative reactivity of Cα-H bonds of Me, Et and Pr^i groups in mono- or *p*-di-substituted benzenes.

TSP selectivity in HAT reactions

There is little doubt that when the HAT mechanism is operating, the C–H bond relative reactivity should decrease in the order 3°C–H > 2°C–H > 1°C–H. This order, which has been verified for a large number of one-electron reactions, arises from the fact that in the transition state of this process, substantial breakage of the C–H bond occurs, and the C–H bond dissociation energy (BDE) increases in the progression from tertiary to secondary to primary C–H bonds, as shown by the Cα–H BDEs of isopropylbenzene, ethylbenzene and toluene[7] displayed in Table 1, together with the oxidation potentials of the same substrates.[8] Some charge separation in the transition state of HAT reactions is also possible (polar effects), as illustrated in structure **1** (R = H, Me); however, on

$$(ArCR_2^{\delta+} \cdots H \cdots X^{\delta-})^{\cdot}$$

1

the basis of the relative stability of the corresponding carbocations, these effects should act in the same direction as the enthalpic effect, thus reinforcing the expected 3°C–H > 2°C–H > 1°C–H reactivity order.

Values of TSP selectivity for a number of HAT reactions are collected in Table 2,[9–15] but further data can be found in an excellent review by Russell.[16] In *all cases* the reactivity order Pr^i > Et > Me is qualitatively observed, even though there are significant differences between the various reactions from a quantitative point of view. This is most likely due to the variation in the relevance of the role of polar effects, but differences in the degree of C–H bond breakage in the transition state may also have an important effect.

It should be noted that almost all data in Table 2 come from intermolecular TSP selectivity studies; however, since we are dealing with a one-step reaction, no significant difference is expected when the TSP selectivity is determined in intramolecular experiments, rate and product distribution being determined in the same step.† This expectation is confirmed by the 2°C–H:1°C–H reactivity ratio determined in the NBS-induced bromination, which is 25 when measured in terms of the ethylbenzene:toluene relative reactivity[9] and 23 when measured by the Et:Me relative reactivity in *p*-ethyltoluene[10] (Table 2, entry 1). Likewise, very similar values of intermolecular and intramolecular tertiary:primary C–H bond relative reactivity are observed in the reactions with $Bu^tO^{\cdot}$[11,12] (Table 2, entry 4) and benzophenone triplet[14,15] (Table 2, entry 7).

An important structural feature is that, for efficient stabilization of the incipient radical (or of the partial positive charge if polar effects are important) in the transition state, it is necessary for the C–H bond to be cleaved to be collinear with the aromatic system (stereoelectronic effect).[17] This collinearity is progressively more difficult to reach as the bulk of the alkyl group increases, thus the stereoelectronic effect can influence TSP selectivity in a direction exactly opposite to that predicted on the basis of the above-discussed polar and enthalpic effects. The data in Table 2, however, suggest that the role of stereoelectronic effects for HAT reactions of simple monoalkylbenzenes is not significant. However, we must be aware that these effects can become very important in more complex systems, such as neopentylbenzenes[18] or α-alkylnaphthalenes.[19] For example, in α-alkylnaphthalenes, the secondary C–H bond is more reactive than the tertiary one.

TSP selectivity in ET reactions

Whereas in the HAT reactions of alkylbenzenes, the order of TSP C–H bond reactivity is expected to be always qualitatively the same, a more complex situation may arise in ET reactions. Accordingly, when the two-step ET mechanism is operating,

Table 1 Cα–H bond dissociation energies and oxidation potentials for toluene, ethylbenzene and isopropylbenzene

	Toluene	Ethyl-benzene	Isopropyl-benzene
E_{BD} (Cα–H)/kJ mol^{-1} [a]	368.4	357.5	353.3
E°/V *vs.* NHE[b]	2.64	2.54	2.53

[a] Ref. 7. [b] In CF_3CO_2H, ref. 8.

† Differences might arise if the effects that the two groups to be compared exert on one another, when bonded to the same ring, are significantly different. Since we are dealing with alkyl groups, this possibility should be unlikely.

Table 2 Intermolecular TSP selectivity in HAT side-chain reactions of alkylbenzenes[a]

		C–H bond relative reactivity		
Entry	Reactant	Primary	Secondary	Tertiary
1	NBS[b]	1	25 (23)[c]	58
2	$Cl_3C^{\cdot}$[d]	1	50	260
3	$Ph^{\cdot}$[e]	1	4.4	9.7
4	$Bu^tO^{\cdot}$[d]	1	3.2	6.8 (6.8)[f]
5	Br_2–*hν*[d]	1	17	37
6	O_2(autoxidation)[g]	1	7.9	13
7	Benzophenone triplet[h]	1	4.6	9.9 (8.6)[i]

[a] Determined by the relative reactivity, statistically corrected, of toluene, ethylbenzene and isopropylbenzene. [b] *N*-Bromosuccinimide at 80 °C in CCl_4, ref. 9. [c] Intramolecular relative reactivity determined in *p*-ethyltoluene, ref. 10. [d] At 40 °C, ref. 11. [e] At 60 °C, ref. 11. [f] Intramolecular reactivity ratio determined in *p*-cymene, ref. 12. [g] At 90 °C, ref. 13. [h] Ref. 14. [i] Intramolecular reactivity ratio in *p*-cymene, ref. 15.

Table 3 Intramolecular TSP selectivity in ET side-chain oxidations of alkylbenzenes[a]

Entry	Oxidizing system	C–H bond relative reactivity		
		Primary	Secondary	Tertiary
1	$Co(OAc)_3$[b]	1	0.5	0.3
2	$(NH_4)_2Ce(NO_3)_6$[c]	1	5.2	3.0
3	Photoexcited methylacridinium ion[d]	1	7.8	4.0
4	$NO_3^{\bullet}$[e]	1	2.3	1
5	$S_2O_8^{2-}/Cu^{2+}$[f]	1	2.0	1.5
6	Triplet trifluoroacetophenone[g]	1		0.7

[a] Data obtained by product distribution, statistically corrected, in the side-chain reactions of *p*-ethyltoluene and *p*-cymene. [b] In AcOH at reflux, ref. 20. [c] In AcOH, ref. 21. [d] Ref. 22. [e] In MeCN; $NO_3^{\bullet}$ generated photochemically from $(NH_4)_2Ce(NO_3)_6$, ref. 23. [f] In AcOH at 100 °C; in MeCN the TSP selectivity is 1:4.8:4.8, ref. 24. [g] Ref. 25.

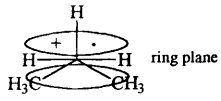
inter- and intra-molecular TSP selectivity can be significantly different since the latter is determined in the second step of the reaction (the deprotonation of the alkylbenzene radical cation, which is irreversible), whereas the former can be determined either in the first step (involving the transfer of the electron) or in the second step, depending on which one is rate-determining. Thus, the intra- and inter-molecular TSP selectivities of ET reactions of alkylbenzenes will be dealt with separately in the following discussion.

Intramolecular TSP selectivity. Data for the intramolecular TSP selectivity of a number of well behaved ET oxidations of alkylbenzenes are displayed in Table 3. The most significant observation is that the Pr^i group is *always* less reactive than the Et group, and in a few cases it is even less reactive than the Me group. Moreover, the relative reactivity ratios generally have a small value, particularly those involving the tertiary centre.

In ET side-chain reactions, TSP selectivity is determined in the radical cation deprotonation step, which, being irreversible, is also the step controlling the product distribution. Thus, the structural factors that are important with respect to the kinetic acidity of alkylbenzenes radical cations should also play a corresponding role with respect to the intramolecular TSP selectivity of ET reactions of the parent hydrocarbons.

Alkylbenzene radical cations are extremely strong carbon acids and the thermodynamic and kinetic aspects of this acidity have already been addressed in some detail.[26,27] From the thermodynamic point of view, the acidity depends on the oxidation potential of the neutral substrate as well as on the BDE of the C–H bond which is cleaved. Thus, when we compare different alkyl groups bonded to the same aromatic ring, as in the present case, the thermodynamic acidity should correlate with the values of the BDE and therefore decrease in the order Pr^i > Et > Me. However, the cleavage of the C–H bond must be accompanied by extensive electronic reorganization during which one of the electrons of the σ C–H bond has to be completely transferred to the aromatic π system. Thus, the ease of deprotonation can change with respect to the thermodynamic acidity because of the possible role played by stereoelectronic effects. Moreover, the steric requirements of the proton-abstracting base may also be important.

The predominant role of stereoelectronic effects in the deprotonation step was first proposed by Schulz and his associates[20] to explain the reactivity order Me > Et > Pr^i found in the oxidations effected by $Co(OAc)_3$ (Table 3, entry 1). It was suggested that for the deprotonation of an alkylbenzene radical cation a conformation must be assumed in which the C–H bond to be cleaved is collinear with the π system. This conformation, which is required to allow the above-mentioned intramolecular electron transfer from the C–H bond to the aromatic ring, should be more difficult to reach with Pr^i than with Et and Me, owing to the unfavourable interaction between the two isopropyl CH_3 groups with the *ortho* hydrogens of the benzene ring, as illustrated by structure **2**. Thus, the kinetic acidity of the alkyl groups should decrease in the order Me > Et > Pr^i, which is the reactivity order observed in the oxidation reaction.



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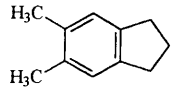
Doubts on the Schulz proposal and on the actual role of stereoelectronic effects were later raised.‡ Thus, an EPR study by Symons and coworkers,[30] has provided evidence indicating that in isopropylbenzene radical cations the Pr^i group can assume a conformation in which the tertiary C–H bond is perpendicular to the aromatic ring. Moreover, direct studies on the deprotonation of alkylbenzene cation radicals (supplemented now by the determination of the rate of deprotonation of 4-methoxyisopropylbenzene cation radical) have shown that, in contrast with Schultz suggestions, the order of kinetic acidity is often Pr^i > Et > Me (Table 4, entries 1–3). Thus, it would seem that the C–H BDE is also an important factor with respect to the heterolytic cleavage of this bond in the cation radical.

Nevertheless, though it now appears clear that stereoelectronic effects in the deprotonation of the alkylbenzene radical cations under investigation are less important than originally thought, there is little doubt that they must contribute to some extent to the levelling off of the reactivity ratios reported in Table 3. Unequivocal evidence for the role of stereoelectronic effects in the deprotonation of alkylbenzene radical cations comes from our recent observation that in the ET oxidation of 5,6-dimethylindane (**3**) the relative reactivity of the secondary:



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primary C–H bond is significantly higher than in the corresponding reaction of *p*-ethyltoluene, owing to the fact that in the former substrate the secondary C–H bonds are forced to be collinear with the aromatic π system.[33] Interestingly, this study has also shown that stereoelectronic effects are much more important in the deprotonation of

‡ Even the ET mechanism of the reactions induced by $Co^{III}(OAc)_3$ has been questioned since no C–C bond fragmentation was observed when the substrate is bicumyl;[28] this would be the expected outcome if a cation radical had been formed. However, later work has shown that oxidation of alkylaromatics by 12-tungstocobaltate(III) (a genuine ET reactant) are subject to base catalysis.[29] Thus, if the same holds for $Co(OAc)_3$ it may be that when no deprotonation is possible, back electron transfer becomes the predominant process and no reaction (*i.e.* C–C bond fragmentation[28]) is observed.

Table 4 Relative rates of deprotonation of $YC_6H_4CHR^1R^2$ cation radicals

Entry	Y	Relative rates[a]		
		$R^1 = R^2 = H$	$R^1 = H, R^2 = CH_3$	$R^1 = R^2 = CH_3$
1	OMe[b]	1	2.4	3.4
2	H[c]	1	3.5	6.0
3	H[d]	1	1.4	1.5
4	H[e]	1	2.7	1.8

[a] Statistically corrected. [b] Deprotonation induced by NO_3^- (laser flash photolysis), ref. 26 and this work; the rate constant for the deprotonation of 4-methoxytoluene radical cation is 4.1×10^7 dm^3 mol^{-1} s^{-1}. [c] Radical cations generated in pulse radiolysis experiments; reactions carried out in HCl 6 mol dm^{-3}, ref. 31. [d] In the gas phase, using pyridine as the base, ref. 32. [e] In the gas phase, using 2,6-dibromopyridine as the base, ref. 32.

alkylbenzene radical cations (and consequently in ET oxidations) than in HAT reactions,[18,33] thus accounting for the apparent lack of these effects in the latter reactions.

As anticipated above, the steric requirement of the proton abstracting base can also influence the kinetic acidity of alkylbenzene radical cations by acting in the same direction as the stereoelectronic effects. This is nicely shown by the observation that in the gas-phase deprotonation of alkylbenzene radical cations, the order Pr^i > Et > Me, followed when the base is pyridine, becomes Et > Pr^i > Me when the base is the bulkier 2,6-dibromopyridine[32] (compare entries 3 and 4 in Table 4).

Thus, the intramolecular TSP selectivity data for the oxidation of alkylbenzenes, reported in Table 3, are probably the result of various combinations of the effects discussed above. The steric requirements of the base may be the main factor determining the Me > Et > Pr^i reactivity order found in the oxidations effected by $Co(OAc)_3$ (Table 3, entry 1). Accordingly, in this case the base might be the reduced form of the oxidant, which is in dimeric form, and therefore characterized by high steric requirements.[34] Me is also more reactive than Pr^i in the photooxidation of *p*-cymene promoted by trifluoroacetophenone triplet[25] (Table 3, entry 6), but this might be a special case, owing to the relative orientation the two reactants have to assume in the CT complex which is the reaction intermediate.§ Finally, the reactivity order Et > Pr^i > Me, observed in the majority of cases, clearly indicates that the most common situation is that where the combination of steric and stereoelectronic effects makes Pr^i less reactive than Et, but still more reactive than Me.

Intermolecular TSP selectivity. When the ET step is rate-determining, the nature of the C–H bond (primary, secondary or tertiary) should play a very minor role with respect to the substrate reactivity. Accordingly, in this case, the reactivity ought to be determined mainly by the value of the oxidation potential of the substrate, which is almost the same for toluene, ethylbenzene and isopropylbenzene (Table 1). Thus, we should expect a very low intermolecular TSP selectivity. However, a different situation can arise when the second step also contributes to the reaction rate, due, as already discussed, to the differences in the kinetic acidity of tertiary, secondary and primary C–H bonds. In this second case, the intermolecular TSP selectivity may be very similar to the intramolecular selectivity.

§ This reaction has been suggested to involve a CT complex formed from the excited ketone and the substrate rather than lead to the fully formed radical ion of the substrate. The transfer of hydrogen should take place inside that complex in order to assume the partial character of proton transfer. Since the formation of the complex implies substantial electron transfer, it is difficult experimentally to distinguish this route from the ET pathway, since similar reactivity–structure relationships are expected. Thus, we feel it warranted to consider the oxidation induced by trifluoroacetophenone triplet as substantially an ET reaction.

Unfortunately, very few data concerning the TSP intermolecular selectivity in ET reactions are available. Thus, in order to have more information in this respect, we have carried out a kinetic study of the oxidations of *p*-methoxyisopropylbenzene, *p*-methoxyethylbenzene and *p*-methoxytoluene promoted by potassium 12-tungstocobaltate(III), a *bona fide* ET reactant.[29] The results of this study are reported in Table 5, together with those of previous investigations.

Even with this limited number of data, it quite clearly emerges that the intermolecular TSP selectivity in ET reactions of alkylbenzenes exhibits a pattern not substantially different from that found for the intramolecular selectivity (Table 3). Again the Et group is always the most reactive and relatively small reactivity ratios are observed. The Pr^i group is in all cases more reactive than Me, thus the reactivity order Et > Pr^i > Me is observed. This order should result from the combination of steric and stereoelectronic effects already discussed, as in the case of the intramolecular TSP selectivity.

TSP selectivity as a mechanistic criterion to distinguish HAT and ET reactions

The foregoing discussion has shown that, whatever the possible reasons, significant differences in TSP selectivity actually exist between HAT and ET reactions. In HAT reactions of alkylbenzenes the reactivity order Pr^i > Et > Me is *always* observed, both when the comparison is intermolecular and intramolecular. This reactivity profile, however, appears significantly modified in ET reactions, both for the intermolecular and intramolecular TSP selectivity, the main feature being the reduced relative reactivity of the Pr^i group, which is *always* less reactive than the Et group and in several cases even less reactive than the Me group.

We felt therefore that a careful inspection of inter- and intramolecular TSP selectivity data may provide useful information with respect to the problem of distinguishing between the occurrence of ET and HAT mechanisms in the one-electron oxidation of alkylbenzenes. Particularly in those cases where a significant deviation from the Pr^i > Et > Me reactivity order is observed, an ET mechanism can quite confidently be predicted. When instead the reactivity sequence is Pr^i > Et > Me, a HAT mechanism must be considered the most likely. In the latter case, however, some caution should be exercised if the selectivity is *very low*, since we feel that in such a situation an ET mechanism cannot be excluded with certainty. Under these circumstances, the use of additional mechanistic probes is necessary.

TSP selectivity in the enzymatic and biomimetic oxidation of alkylbenzenes

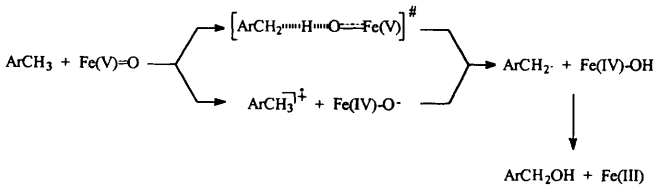
Hydroxylation of aliphatic C–H bonds is perhaps the most typical process effected by cytochrome P-450 isozymes.[37,38] A hydrogen atom transfer (HAT) route from the substrate to the perferryl group ($Por^{+\bullet}Fe^{IV}=O$, Por = porphyrin) of P-450, followed by fast rebound of $OH^\bullet$ to give an alcohol, appears to be the most likely mechanism in unactivated alkanes.[37–39]

Table 5 Intermolecular TSP selectivity in ET side-chain oxidations of alkylbenzenes[a]

Entry	Oxidizing system	C–H bonds relative reactivity[b]		
		Primary	Secondary	Tertiary
1	$Co^{III}W$ in AcOH–H_2O at 50 °C[c]	1	2.1	1.8
2	$Co(OAc)_3$ in AcOH at 65 °C[d]	1	1.96	1.1
3	$NO_3^{\bullet}$ in MeCN[e]	1	2.0	1.1
4	$NO_3^{\bullet}$ in MeCN[f]	1	3.0	1.2
5	Excited state of 10-methylacridinium ion[g]	1	6.3	4.0

[a] Relative reactivity of toluene, ethylbenzene and isopropylbenzene. [b] Statistically corrected. In ET reactions TSP selectivity, if determined in the ET step, should not depend on the number of removable hydrogen atoms. However, this is no longer valid if the deprotonation step (see the text) is also important. We have always applied the statistical correction, to make the data more easily comparable with those of HAT reactions. [c] Relative reactivity of 4-methoxy derivatives of toluene, ethylbenzene and isopropylbenzene with potassium 12-tungstocobaltate(III), obtained by measurements of initial rates; this work, see the Experimental. [d] Relative reactivity determined by rate measurements, ref. 35. [e] Relative rates determined in competition experiments, ref. 23. [f] Relative rates by direct rate measurements (laser flash photolysis), ref. 36. [g] Photoinduced electron transfer between toluene, ethylbenzene and isopropylbenzene and excited 10-methylacridinium ion; competitive experiments, ref. 22.

However, when the side-chain hydroxylation of alkylbenzene compounds is considered, an ET mechanism is also a possibility, as suggested in several cases,[3a,40] since in cytochrome P-450 the perferryl group is a strong oxidant, the strength of which has been roughly quantified to be 2.0–2.5 V (*vs.* NHE).[41] Thus a mechanistic dichotomy corresponding exactly to that depicted in Scheme 1, can also be envisaged for these enzymatic oxidations (Scheme 2). In the ET mechanism



Scheme 2

an electron is transferred from the substrate to the perferryl group, followed by H^+ loss and rebound of $OH^{\bullet}$, to give the hydroxylated product. The same mechanistic scheme applies to the hydroxylation reactions promoted by synthetic iron porphyrins which in the presence of a suitable oxygen donor are capable of efficiently mimicking the reactivity of the cytochrome P-450 enzymes. The reduction potential of the perferryl group in the iron porphyrin models is somewhat lower (*ca.* 1.5 V)[41,42] than in the enzymatic system but still sufficient to induce ET reactions with many aromatic compounds.

Another related point to be taken into consideration with respect to the ET route is the ease of oxidation of the substrate RH which, in connection with the strength of the oxidant, would contribute to make the ET pathway more or less accessible.

The problem of this mechanistic dichotomy in biomimetic and enzymatic oxidations of alkylbenzenes has already been addressed in our laboratory, using the intramolecular selectivity of polymethylbenzenes and benzyltrimethylsilanes as mechanistic probes.[3] Both probes have suggested an HAT mechanism in non-polar solvents. In the light of the previous discussion, we considered it of interest also to study the TSP selectivity of these reactions, to test whether the application of this criterion leads to the same conclusions previously reached.

We have determined the intramolecular TSP selectivity in a biomimetic process by measuring the isomeric product distribution in the side-chain oxidation of *p*-cymene and *p*-ethyltoluene catalysed by Fe^{III} and Mn^{III} tetraphenylporphyrin (indicated as FeTPP and MnTPP, respectively) with iodosylbenzene as the oxygen donor, and compared it with that of the enzymatic oxidation promoted by microsomal cytochrome P-450. For the case of the biomimetic oxidations the determination of the relative rates of isopropylbenzene, ethylbenzene and toluene allowed the intermolecular TSP selectivity to be determined as well. The relative reaction rates of the corresponding *para*-methoxy derivatives have also been measured to test the possible effect of the substrate oxidation potential on the TSP selectivity. No corresponding study of the intermolecular TSP selectivity of the enzymatic reaction has been performed, because of the possibility that in this case the relative rates are affected by differences in the binding of the substrates to the enzyme.[43]

Results and discussion

The data pertaining to the intermolecular TSP selectivity for the oxidations catalysed by FeTPP and MnTPP, obtained by the competitive method, are displayed in Table 6. The reactivity order tertiary > secondary > primary is qualitatively observed with the two oxidizing systems, when unsubstituted monoalkylbenzenes are the substrates (Table 6, entries 1, 2). From a quantitative point of view, FeTPP and MnTPP behave very similarly, both exhibiting high tertiary/primary and secondary/primary reactivity ratios, which is consistent with a radical reactivity profile; these results lead us to suggest quite confidently that a HAT mechanism is operating in the oxidation with both the metalloporphyrins, in agreement with previous conclusions.

When *p*-methoxy substituted alkylbenzenes are the substrates, the reactivity order tertiary > secondary > primary is again observed with both metalloporphyrins (Table 6, entries 3 and 4). Thus, also for these more easily oxidizable substrates, a HAT mechanism can be proposed. The finding of a TSP selectivity lower than that determined for the reactions of unsubstituted alkylbenzenes is probably due to the fact that, having the transition state some polar character, the extent of positive charge development on the α-carbon (see structure **1**) is lower in the methoxy-substituted substrates, where the charge can be delocalized on the methoxy group.

The results of the study of the isomeric distribution in the oxidation of *p*-cymene and *p*-ethylbenzene (intramolecular TSP selectivity) by metalloporphyrins and microsomal cytochrome P-450 are reported in Table 7. Again, FeTPP and MnTPP afford the reactivity order expected for a HAT mechanism, *i.e.*, tertiary > secondary > primary, in line with the results of the intermolecular TSP selectivity investigations.

The oxidations by microsomal cytochrome P-450 exhibit qualitatively the same behaviour as that of the porphyrin model compounds, but the reactivity ratios are very low. Thus, even though the reactivity order, Pr^i > Et > Me, suggests a HAT mechanism, we are in that situation where the conclusion should not be considered unambiguous. However, since the other probes that have been used in this respect[4] have indicated a HAT mechanism, the present TSP selectivity data can quite confidently be considered to be in accord with the previous

Table 6 Intermolecular TSP selectivity in the side-chain oxidation of alkylbenzenes and 4-methoxyalkylbenzenes by iodosylbenzene catalysed by metalloporphyrins[a]

Entry	Metalloporphyrin	Substrate	TSP selectivity		
			$R^1 = R^2 = H$	$R^1 = H, R^2 = Me$	$R^1 = R^2 = Me$
1	$Fe^{III}TPP$	$C_6H_5CHR^1R^2$	1	10	22
2	$Mn^{III}TPP$		1	15	20
3	$Fe^{III}TPP$	$4MeOC_6H_4CHR^1R^2$	1	5	11
4	$Mn^{III}TPP$		1	6	9

[a] Relative reactivity, statistically corrected, of toluene, ethylbenzene and isopropylbenzene and their 4-methoxy derivatives obtained in competition experiments.

Table 7 Intramolecular selectivity in the side-chain oxidation of alkylbenzenes promoted by iodosylbenzene–metalloporphyrins and by microsomal cytochrome P-450[a]

Metalloporphyrins or microsomes	TSP Selectivity		
	Me	Et	Pr^i
$Fe^{III}TPP$	1	8	11
$Mn^{III}TPP$	1	6	10
Microsomal P-450	1	3.1	3.8

[a] Data from the isomeric product distribution in the oxidations of *p*-ethyltoluene and *p*-cymene; statistically corrected.

conclusions. It is probable that the low reactivity ratios observed in the microsomal reactions are attributable to the very low selectivity of the perferryl group of cytochrome P-450 as the hydrogen abstracting species. Accordingly, in our previous study of the oxidation of 4-substituted *ortho*-xylenes, the positional selectivity of the microsomal oxidation turned out to be as low as that of Cl$^{\bullet}$.[3b] It is interesting that the low TSP selectivity of microsomal P-450 as an H-atom abstracting species is not exactly reproduced by its porphyrin models.

Conclusions

A careful analysis of the available data of TSP C–H bond relative reactivity, in few cases supplemented by new experiments, has shown that HAT and ET reactions exhibit a different reactivity profile. Therefore it seems possible to use TSP selectivity as a criterion to distinguish between the two reaction paths. The validity of this conclusion has been checked by a study of the TSP selectivity in the oxidations of alkylbenzenes induced by metalloporphyrins and by microsomal cytochrome P-450, which has allowed us to assign a HAT mechanism to these reactions, in full accord with previous findings.

Experimental

GC-analyses were performed on a Varian 3400 Star GC and a Varian 6000 GC using a silica capillary column (OV1701, 30 m × 0.25 mm) and a silica wide-bore column (OV5, 10 m × 0.53 mm). GC–MS analyses were performed on an HP5890 GC equipped with a 12 m × 0.2 mm silica capillary column coated with methylsilicone gum and coupled with an HP5970 MSD. Kinetic runs were followed with a Cary 1 UV–VIS spectrophotometer.

Materials

High purity commercial samples of cobaltous acetate tetrahydrate, potassium acetate, sodium tungstate dihydrate, potassium persulfate, toluene, ethylbenzene, iron(III) tetraphenylporphyrin chloride, manganese(III) tetraphenylporphyrin chloride, cerium(IV) ammonium nitrate and tetra(*n*-butyl)ammonium nitrate were used as received. 4-Methoxytoluene and 4-ethyltoluene required further purification and were distilled under reduced pressure. Isopropylbenzene and *p*-cymene were further purified by chromatography on a silica gel column with light-petroleum–chloroform (3:1). Potassium 12-tungstocobaltate(III) was prepared as described previously.[29a] 4-Methoxyethylbenzene was prepared from the corresponding ketone by the Huang–Minlon modification of the Wolff–Kishner reduction.[29b] 4-Methoxycumene was prepared by reaction of 4-isopropylphenol with methyl iodide and the product was distilled under reduced pressure (bp 116–117 °C at 45 mmHg, lit.,[44] 100 °C at 22 mmHg). Iodosylbenzene was prepared by hydrolysis of the corresponding diacetate with aqueous sodium hydroxide.[45]

Microsomal preparation

The liver microsomes were obtained from male Sprague–Dawley rats pre-treated with sodium phenobarbital (300 mg kg^{-1} of body weight, each day for 7 days) according to a procedure reported in the literature.[46]

Oxidation with potassium 12-tungstocobaltate(III)

All the kinetics studied were carried out in a 1.0 cm quartz cuvette; acetic acid and water were thoroughly purged with argon.[28b] A cuvette, containing the solution of the substrate (5×10^{-2} mol dm^{-3}) and AcOK (0.5 mol dm^{-3}) in AcOH–H_2O (70:30), was placed in a thermostated compartment of a UV–VIS spectrophotometer. After thermal equilibration at 50 °C, the reaction was started by rapid addition of the Co^{III} complex solution (1.5×10^{-2} mol dm^{-3}; 100 μl). The reactivity data were obtained by measuring the initial rates of disappearance of Co^{III} spectrophotometrically at 390 nm. Previous studies have already shown that reactions of potassium 12-tungstocobaltate(III) with alkylbenzenes under the above conditions lead to side-chain substituted products (benzyl alcohols and acetates).[29]

Biomimetic oxidation

All experiments were carried out under an argon atmosphere, employing benzene dried on sodium and purged with argon. Usually, 2 mmol of substrate, 40 μmol of PhIO and 4 μmol of $TPPM^{III}$ ($M^{III} = Fe^{III}$ or Mn^{III}) in 3 cm^3 of benzene were magnetically stirred for 90 min at room temperature.[47] At the end of the reaction an internal standard (either hexadecane or octadecane) was added, and the mixture directly analysed by GC. From the substrates investigated the following products were identified by comparison with authentic specimens: 4-$XPhCH_2OH$ and 4-XPhCHO (X = H, Et, Pr^i, OMe), 4-$YPhCH(CH_3)OH$, 4-$YPhCOCH_3$, 4-$YPhC(CH_3)_2OH$ and 4-$YPhC(CH_3)=CH_2$ (Y = H, Me, OMe). Thermal dehydration of the tertiary alcohols occurred extensively (*ca.* 20–40%) in the injection port of the GC, to yield an α-methylstyrene derivative, whenever a capillary column was employed for the separation; in contrast, when a wide-bore column was used, no dehydration of the tertiary alcohols occurred, as verified on pure (alkene free) samples.

In order to simplify the quantitative analyses it was considered convenient to convert the alcohols into the corresponding carbonyl compounds. Thus, pyridinium chlorochromate (PCC) (sufficient to cover the tip of a spatula) was added to the final reaction mixture, which was stirred for an additional hour before a sample was removed and injected into the GC. By this procedure, the TSP intramolecular selectivity in the oxidation of *p*-cymene was determined from the ratio between the substitution products at the Pr^i group [4-$MeC_6H_4C(CH_3)_2OH$ and 4-$MeC_6H_4C(CH_3)$=CH_2] and substitution product at the Me group (4-$Pr^iC_6H_4CHO$). In the oxidation of *p*-ethyltoluene the ratio was between 4-$MeC_6H_4COCH_3$ and 4-EtC_6H_4CHO. In all cases the results were corrected for the statistical factor. No change in selectivity was observed when, in some cases, the PCC treatment of the final mixture was omitted.

The intermolecular TSP selectivity data were obtained by the competitive method by measuring the amounts of products derived from two substrates in competition. The same analytical procedure described above was used.

Enzymatic oxidation

In the microsomal oxidation, phenobarbital-induced rat liver microsomes (40 mg of protein), NADPH generating system (5 μmol of $NADP^+$, 50 μmol of glucose 6-phosphate, 50 μmol of $MgCl_2 \cdot 6H_2O$, 40 units of glucose 6-phosphate dehydrogenase) and substrate (160 μmol) were incubated in 7 cm^3 of phosphate buffer (pH 7.4, 0.1 mol dm^{-3}) at 36 °C for 1 h. Reaction products were extracted as reported before[3b] and analysed by GC and GC–MS.

The oxidation of *p*-ethyltoluene and *p*-cymene gave the benzylic alcohols: 4-$EtC_6H_4CH_2OH$, 4-$MeC_6H_4CH(CH_3)OH$ and 4-$Pr^iC_6H_4CH_2OH$, 4-$MeC_6H_4C(CH_3)_2OH$ as the main products. Small amounts of 4-$MeC_6H_4COCH_3$ and 4-EtC_6H_4CHO were observed with *p*-ethyltoluene, while 4-$Pr^iC_6H_4CHO$ and 4-$MeC_6H_4C(CH_3)$=CH_2 were also observed with *p*-cymene. Intramolecular selectivity data were obtained as already described for the biomimetic oxidations.

Laser flash photolysis

Excitation wavelengths of 308 nm from an excimer laser (XeCl*-Lambda Physik, EMG150E) was used in the flash photolysis experiment (pulse width 20 ns and $E < 10$ mJ $pulse^{-1}$).[36] The 4-methoxyisopropylbenzene radical cation was generated by reaction of 4-methoxyisopropylbenzene with $NO_3^{\bullet}$ radical formed by photolysis of cerium(IV) ammonium nitrate.[26,36] The deoxygenated solution containing 4-methoxyisopropylbenzene (1 mmol dm^{-3}), cerium(IV) ammonium nitrate (0.2 mmol dm^{-3}) and tetra-(*n*-butyl)ammonium nitrate (0–0.5 mmol dm^{-3}) at room temperature was allowed to flow through the quartz photolysis cell at a rate of 3–5 cm^3 min^{-1}. The optical absorption signals were digitized with a Tektronix 7612 or 7912 transient recorder interfaced with a DEC LSI $11/73^+$ computer. The rate of deprotonation of the radical cation was followed at $\lambda_{max} = 450$ nm using NO_3^- as the base. A value of 1.4×10^8 dm^3 mol^{-1} s^{-1} was obtained for the second-order deprotonation rate constant.

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