

MECHANISM OF ELECTROPHILIC AROMATIC SUBSTITUTIONS: COMMENTS ON A RECENT CRITICISM CONCERNING THE USE OF THE MESITYLENE/DURENE REACTIVITY RATIO AS A PROBE TO DISTINGUISH BETWEEN IONIC AND ET PATHWAYS

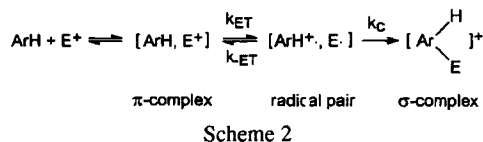
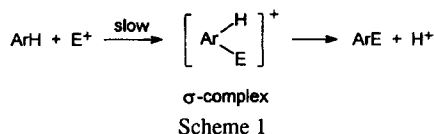
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As a rebuttal to recent criticisms aimed at the mechanistic significance of the determination of the mesitylene/durene relative reactivity, it is argued that this ratio does provide reliable information about the structure of the transition state of many S_EAr reactions, supporting the operation of the 'conventional' ionic mechanism, as opposed to the ET mechanism. Not even in the case of competitive experiments does it appear that the criticisms are justified.

The debate about the mechanism of electrophilic aromatic substitution reactions has continued in the recent literature. The 'conventional' ionic route of substitution via rate-limiting σ -complex formation (Scheme 1)¹ is challenged by another formulation, characterized by the transfer of an electron within the π -complex, which gives rise (k_{ET}) to a radical pair; collapse (k_c) to the σ -complex follows (Scheme 2).²

Although both mechanistic schemes involve the σ -complex as a key intermediate *en route* to products, they present substantial differences with respect to the structure of the transition state (TS) of the rate-determining step, which is similar to the σ -complex in Scheme 1 and to the radical pair in Scheme 2. A clear distinction between these two possibilities is not easy,



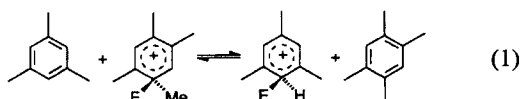
since in most cases the energy of the two transition states (both positively charged) responds in a similar way to structural effects.

Recently, however, it has been suggested that important information in this respect can be provided by the determination of the mesitylene-to-durene (MES/DUR) reactivity ratio.³ This pair of compounds presents a significant feature. In fact, since the σ -basicity of mesitylene is higher than that of durene, the former should be more reactive than the latter in an electrophilic aromatic substitution, if the structure of the TS resembles that of the σ -complex. Conversely, since the oxidation potential of durene is 0.28 V lower than that of mesitylene, a MES/DUR reactivity ratio of <1 is expected if the TS of the electrophilic aromatic substitution is structurally close to a radical pair.

When this probe was first applied to some of the most often studied electrophilic aromatic substitutions (chlorination, bromination),³ it was observed that these reactions exhibit MES/DUR reactivity ratios significantly >1 , which supports a structure similar to a σ -complex for their TSs, and consequently endorses the mechanistic pathway of Scheme 1. By contrast, MES/DUR ratios lower than one were found in reactions occurring by an ET mechanism^{3,4} (clearly, when substrates more easily oxidizable than the polyalkylbenzenes are employed, the electrophilic substitution pathway of Scheme 2 may take over³). Later, the same mechanistic criterion was applied to aromatic

iodination^{6,7} and acetylation⁸ reactions, the latter being studied both in solution and in the gas phase, which again gave MES/DUR ratios >1 ; consistently, the operation of the mechanism of Scheme 1 has been implied.

However, in a recent paper by Bockman and Kochi,⁹ the mechanistic conclusions deriving from the use of the MES/DUR probe were considered *generally* invalid. This is simply because the MES/DUR ratios, when obtained in competitive experiments, could be affected by a fast transfer of the electrophile from the more rapidly formed (but unstable) *ipso*-substituted durenium ion to mesitylene [equation (1)]. Thus, the MES/DUR reactivity ratios obtained would come out >1 only as the consequence of this artifact.



This criticism was presented in such a way that it led the reader to believe that: (i) *all* the mechanistic conclusions previously reached are based on MES/DUR ratios obtained from competitive experiments; and (ii) the equilibrium shown in equation (1) plays an important role in *all* electrophilic aromatic substitutions. Consequently, in no case could the MES/DUR probe have provided a reliable mechanistic insight. We therefore feel that a rebuttal is necessary, especially in view of the relevance of the problem under discussion; accordingly, in this paper we present a number of arguments which clearly show that neither point (i) nor (ii) above holds, and that the criticism to the application of the MES/DUR probe derives from inadequate consideration of the experimental data.

(a) First, and most important, there are four electrophilic aromatic substitution reactions (chlorination,³ bromination,³ thallation¹⁰ and mercuration¹⁰) where the MES/DUR reactivity ratios have been obtained by *absolute* rate measurements and *not* in *competitive* kinetic experiments; the latter two studies actually originate from Kochi's laboratory. For these data, no interference from the equilibration process in equation (1) can be envisaged, since the two substrates were not present together in the kinetic experiments. In addition, any significant contribution from *ipso* attack to the measured reactivity of durene can be excluded. In fact, the methyl-substituted positions of durene exhibit a reactivity towards electrophilic attack either lower than (halogens) or, at most, comparable (mercuration) with that of the unsubstituted positions; more in general, it has been shown that a methyl group exerts a rate-retarding effect (with respect to hydrogen) when the electrophile reacts at the *ipso* position of a polymethylbenzene.¹¹ Summing up, the MES/DUR ratios for the above four electrophilic reactions all being >1 , the conclusion that the substrate endowed with the higher

σ -basicity (i.e. MES) reacts faster, in agreement with the mechanistic formulation of Scheme 1, is accurate and cannot be questioned.

(b) Determination of the MES/DUR relative reactivity for the bromination, thallation and mercuration reactions has also been achieved in competition experiments.⁶ The ratios obtained (i.e. 57, 4.6 and 12) are in very good agreement with those above from the direct kinetic determinations (i.e. 66, 4.4 and 7.3),^{3,10} when allowance is made for the slightly different medium composition employed in the competitive experiments.⁶ Hence it appears that the equilibration in equation (1) exerts no major influence, if any, on the measured MES/DUR reactivity ratios. On the other hand, this conclusion could easily have been anticipated, in contrast to what has been suggested,⁹ on the basis of the directive effect of the substituents: electrophilic attack at the *ipso* positions of durene is *less* favoured (one *ortho*, one *meta* and one *para*-methyl groups) than that at the unsubstituted positions of mesitylene (two *ortho*- and one *para*-methyl groups).

(c) For the iodination reactions, the MES/DUR reactivity ratios have been obtained only in competitive experiments.^{6,7} However, even in this case a significant role of equation (1) appears highly unlikely. First, no variation of the MES/DUR ratio has been observed on changing the reactants concentration,⁶ contrary to the expectation that, if the equilibration process of equation (1) (a bimolecular process) plays a role, changes in the MES/DUR ratio would occur. Second, no traces of side-chain iodinated products have been observed,⁷ whereas side-chain functionalization is the typical outcome of an *ipso* electrophilic attack on polymethylbenzenes.¹² Hence the observed^{6,7} MES/DUR reactivity ratios of 50 ± 2 can be taken as a strong indication that Scheme 1 applies also to aromatic iodination.⁵

(d) Recently, and following the same criterion, another substrate pair (mesitylene and naphthalene) was taken into consideration as a mechanistic probe.⁶ Here again, the σ -basicity of mesitylene is (much) higher than that of naphthalene,⁶ while the latter is more easily oxidized. Hence a mesitylene-to-naphthalene (MES/NAPHT) reactivity ratio >1 is expected if the pathway of Scheme 1 holds, the reverse being expected if the reaction takes place according to Scheme 2. When this new probe was applied to the iodination case under competition conditions, a MES/NAPHT ratio of 2000 resulted, fully supporting the mechanistic conclusions based on the MES/DUR ratio.^{6,7} Of course, in this case no role of the equilibration in equation (1) is possible, since naphthalene is structurally unsuited to an *ipso*-adduct formation.

The above considerations clearly show that for a large number of electrophilic aromatic substitutions the determined MES/DUR ratios, even those obtained in competitive experiments, represents a genuine and reliable measure of the actual relative reactivity of the

two substrates. Based on these ratios, the conclusion that the mechanism of Scheme 1 is the most likely for these reactions appears unquestionable.

Of course, the possibility cannot be excluded that the equilibrium in equation (1) may represent a problem in other reactions. This is certainly the case in aromatic nitration, where *ipso* attack is often the major reaction path with several polymethylbenzenes, including durene.^{9,13} Indeed, nitration has its own peculiarities,¹ and even appears as a possible example of an aromatic substitution occurring according to Scheme 2,¹⁴ owing to the strong oxidizing properties of NO_2^+ . This possibility, however, is strongly disputed in the literature.¹⁵ When the MES/NAPHT probe was applied to the nitration reaction, MES was 20 times more reactive than naphthalene,⁶ in agreement with the σ -basicity trend; even though this result endorses the 'conventional' mechanism, one has to consider the additional complication that the nitration reactions occur close to the encounter limit,¹³ thus decreasing the reliability of intermolecular selectivity determinations in this case. Thus, extrapolations and generalizations from the behaviour of the nitration reaction to other electrophilic aromatic substitutions require caution and unambiguous experimental evidence.

Summing up, it seems fair to conclude that the study of intermolecular selectivity with selected pairs of substrates, determined whenever possible by absolute rate measurements, represents a good mechanistic tool, through which information on the TS structure of electrophilic aromatic substitutions can be obtained, and has to be regarded without undue prejudice.

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