Mechanistic Criteria for the Cation Radical vs Electrophilic Mechanistic Distinction

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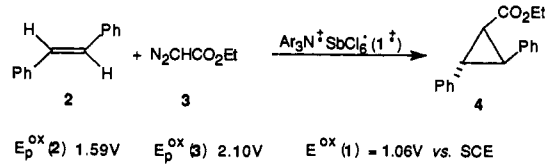
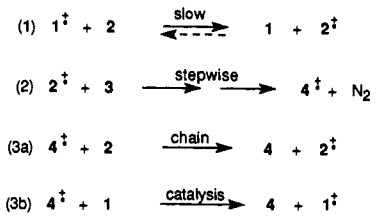
The elucidation of the chemistry of the cation radical intermediate continues at an impressive pace.[1] As interest in this area expands, it becomes increasingly important to clearly and rigorously distinguish the unique chemistry of the cation radical from that based on other reactive intermediates, especially carbocations. A simple test for distinguishing cation radical mechanisms from Bronsted acid catalyzed, carbocation-mediated mechanisms has been available for some time.[2] However, the rigorous distinction of cation radical mechanisms from general electrophile catalyzed carbocation-mediated mechanisms is more challenging. The importance of this distinction is underscored by the recent proposal[3] of an electrophilic mechanism for the triarylaminium salt catalyzed Diels–Alder cyclodimerization of 1,3-cyclohexadiene, a reaction widely considered to be a prototype cation radical process.[1] The purpose of this communication is to describe appropriate criteria for this mechanistic distinction and to rule out the electrophilic mechanism in one reaction system where a variety of these criteria are applicable. The tris(4-bromophenyl)aminium hexachlorantimonate ($\mathbf{1}^{\bullet+}$) catalyzed cyclopropanation of (*E*)-stilbene (**2**) by ethyl diazoacetate (**3**) was selected for the initial study.[4,5] An abbreviated version of the proposed cation radical mechanism of this reaction is given in Scheme 1, along with a hypothetical electrophilic mechanism which invokes Eberson's concept of the aminium salt as an electrophile.

A variety of electrophilic additions to (*E*)-stilbene and (*E*)-stilbene-d_2 consistently yield inverse kinetic secondary isotope effects in the range k_H/k_D = 0.8–0.9, as expected for an sp^2 to sp^3 rehybridization.[6] In contrast, the secondary isotope effect on rate-determining ionization of **2** appeared likely to be normal.[7] The deuterium isotope effect was obtained by accurately measuring the relative rate constant first for the competitive cyclopropanation of 4-methylstilbene vs stilbene (k_{rel} = 9.2) and then for the competition between 4-methylstilbene vs stilbene-d_2 (k_{rel} = 10.5) at 0 °C in dichloromethane. The isotope effect k_H/k_D = 1.14 is normal and decisively excludes the electrophilic mechanism.[8] The proposed cation radical mechanism involves hole transfer from $\mathbf{1}^{\bullet+}$ to **2**, yielding **1** (the hole conjugate of $\mathbf{1}^{\bullet+}$) along with the stilbene cation radical ($\mathbf{2}^{\bullet+}$). This mechanism is subject to strong rate retardation by added **1**, especially since the back hole transfer is exergonic.[9] Hole transfer from a benzylic carbocation intermediate to **1** is substantially endergonic and appears unlikely.[10] Experimentally, 100 mol % of added **1** slows the rate by a factor of ≥100. This criterion is made even more decisive when coupled with observations of selectivity enhancement. For example, the 4-methylstilbene/stilbene pair gives the enhanced value k_{rel} = 21 in the presence of 100 mol % of **1**. The Marcus equation predicts that substituent effects on rates of hole transfer (log k/k_0) should be about one-half those for the corresponding equilibrium (log K/K_0).[11] The addition of **1** converts a kinetically controlled hole transfer into one which is at least partly reversible.

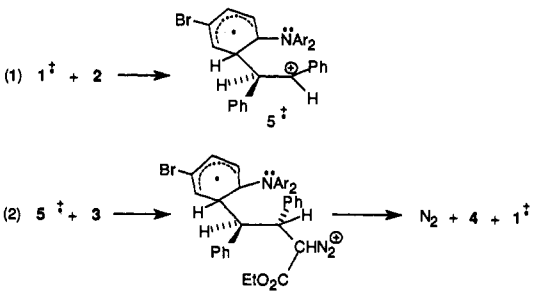
Scheme 1. Aminium Salt Catalyzed Cyclopropanation of (*E*)-Stilbene



I. Cation Radical Mechanism



II. Hypothetical Electrophilic Mechanism



The cation radical mechanism is permissive with respect to stereospecificity, depending upon whether addition is stepwise or concerted. Reactant isomerization is not expected. In contrast, the inherently stepwise electrophilic mechanism requires non-stereospecificity and also, where reversible, isomerization of reactants. Several pericyclic reactions catalyzed by $\mathbf{1}^{\bullet+}$ have, incidentally, already been found to be stereospecific and therefore presumably do not involve electrophilic mechanisms.[1] The cyclopropanation of (*Z*)- and (*E*)-stilbene, however, is nonstereospecific. The product stereochemical criterion is therefore inconclusive in this instance. In the absence of any **3**, the first

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(8) The isotope effect was also checked vs 3-methylstilbene (k_H/k_D = 1.11). The experimental error in these determinations is ca. 2%. The general experimental procedure for all of the competition runs including the isotope effect studies was as follows: Approximately 2–30 mol % of tris(4-bromophenyl)aminium hexachloroantimonate or 0.4–0.5 mol % of tris(2,4-dibromophenyl)aminium hexachloroantimonate was weighed into a 10 mL volumetric flask containing a magnetic stirrer. The flask was then capped with a septum, immersed in an ice–water bath, and purged with nitrogen. Methylene chloride (5 mL) was added, and the solution was stirred for 5 min. To this was then added (syringe) a solution containing equimolar amounts (ca. 0.12 mmol) of EDA in methylene chloride (5 mL). After an appropriate interval (timed so that the conversion is less than 10%), a 0.5 mL aliquot of the reaction mixture was quenched with 1 mL of saturated methanolic potassium carbonate. Water was added, and the organic layer was separated and dried ($MgSO_4$). The GC analyses were corrected for varying response factors. All cyclopropanes were isolated in synthetic runs and fully characterized (NMR, HRMS).
(9) The reaction $\mathbf{1}^{\bullet+}$ + **2** is 0.54 eV endergonic.
(10) The oxidation potential of **1** (1.05 V vs SCE) is greater than that of the benzyl radical (0.73 V) and much greater than that of 4-methylbenzyl (0.51 V): Sim, B. A.; Milne, P. H.; Griller, D.; Wayner, A. D. M. *J. Am. Chem. Soc.* **1990**, *112*, 6635–6638.
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step of the electrophilic mechanism is necessarily reversible, and reactant isomerization is required. In fact, (*Z*)-stilbene is completely stable toward isomerization under typical reaction conditions when **3** is omitted, as well as in the presence of **3**.

Whereas ionization of (*Z*)-stilbene (E_p^{ox} 1.70 V) is considerably more difficult than that of (*E*)-stilbene (E_p^{ox} 1.59 V),[12] the reactivity of the former toward electrophiles is substantially greater than that of the latter.[13] Experimentally, (*E*)-stilbene is at least 100 times as reactive as (*Z*)-stilbene toward cyclopropanation.

Additions to stilbene which proceed via unbridged carbocations are relatively insensitive to the presence of a single electron-withdrawing ring substituent since the carbocation site can be developed at the carbon benzylic to the unsubstituted ring.[14] A second EWG on the other ring then exerts a powerful rate retardation effect. The charge in monosubstituted stilbene cation radicals should be relatively more evenly distributed, allowing substituents to exert more nearly multiplicative effects. The relative rate constant for the 4-chlorostilbene/stilbene pair (k_{rel} = 0.25) is virtually identical to that for the 4,4′-dichlorostilbene/4-chlorostilbene pair (k_{rel} = 0.27). The value of k_{rel} for the 4,4′-dimethylstilbene/4-methylstilbene pair (6.0) is only modestly less than that for 4-methylstilbene/stilbene (9.2).

A Hammett–Brown plot of the data for stilbene and its 3-methyl, 4-methyl, and 4,4′-dimethyl derivatives (substrates for which the absolute reaction rates are essentially independent of the concentration of **3**) is linear (r^2 = 0.995) with slope ρ^+ = –2.74. This ρ^+ value is close to half that which correlates the oxidation potentials of 4,4′-disubstituted stilbenes (ρ^+ = –5.6),[15] as is appropriate for kinetically controlled ionization. With EWGs, rates are linearly dependent on [**3**], and the effective ρ value (ρ^+ = –5.32, r^2 = 1.000 for H, 4-Cl, and 4,4′-dichloro) suggests largely reversible ionization.

When the much more reactive hole catalyst tris(2,4-dibromophenyl)aminium hexachloroantimonate (**6**$^{\bullet+}$) is used to effect cyclopropanation, the ρ^+ value decreases to –2.17 (r^2 = 0.992). This indicates that the reactions as catalyzed by **1**$^{\bullet+}$ and **6**$^{\bullet+}$ cannot both be occurring via the chain mechanism, since this mechanism invokes ionization of the substrate (**2**) by the product cation radical (**4**$^{\bullet+}$), which is the same for both reactions. Since neutralization of **4**$^{\bullet+}$ by hole transfer to **1** (E_{ox} = 1.06 V) is undoubtedly much faster than the neutralization by **6** (E_{ox} = 1.50 V), the reaction as catalyzed by **1**$^{\bullet+}$, at least, must have a catalytic mechanism. This conclusion is further supported by the observation that the inclusion of 10 mol % of **1** or 50 mol % of naphthalene does not affect the substrate selectivity. If a chain mechanism involving ionization of the stilbenes by **4**$^{\bullet+}$ were the normal reaction mode, either small amounts of **1** or large amounts of naphthalene would be expected to substantially quench **4**$^{\bullet+}$, leading to a different species, either **1**$^{\bullet+}$ or naphthalene cation radical, as the species active in ionizing **1**. These less reactive cation radicals should then ionize stilbenes more selectively (corresponding to a large ρ^+). The relatively high ionization potential of **6** and the very small amounts of **6**$^{\bullet+}$ required for efficient catalysis (meaning very little **6** could be generated by the decomposition of **6**$^{\bullet+}$) suggest that the reaction as catalyzed by **6**$^{\bullet+}$ is probably occurring via the chain mechanism. The high exergonicity of the ionization of **2** by **4**$^{\bullet+}$ would correlate well with the relatively low ρ^+ value found for this reaction.

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