Reactivity of Radical Cations. Absolute Kinetic Data for Cycloaddition Reactions of Styrene Radical Cations to Alkenes[1]

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Received July 1, 1994

Cycloaddition reactions of radical cations to alkenes provide useful alternatives to conventional cyclobutanation and Diels–Alder reactions of the neutral substrates.[2-4] These reactions have low activation energies and frequently occur with high stereoselectivity and regioselectivity. They are thus of considerable utility as carbon–carbon bond-forming reactions in synthetic strategies[5] and have also recently been used as the basis for intramolecular radical cation probe reactions.[6,7] The radical cation Diels–Alder reaction is of particular interest from a synthetic point of view since electron-rich substrates, which are typically ineffective as dienophiles in the normal Diels–Alder reaction, are readily converted to radical cations. Despite the recognized importance of radical cation-mediated cycloaddition reactions, there is currently little absolute kinetic data for these important processes. We have recently used laser flash photolysis techniques to generate styrene radical cations and to measure their reactivity with a series of anionic nucleophiles and examine their dimerization reactions.[8-10] We now report the first direct kinetic measurements for cross additions of these radical cations to a variety of alkenes.[11] Such kinetic data are obviously essential for the appropriate design of synthetic strategies and probe techniques based on radical cation chemistry.

Our initial experiments in this area have focused on reactions of 4-methoxystyrene and 4-methoxy-β-methylstyrene radical cations with a representative group of substituted alkenes. Both styrenes undergo efficient [2 + 1] and [4 + 1] cycloadditions under hole transfer catalysis conditions using triarylaminium salts.[3,17-19] In addition, 4-methoxy-β-methylstyrene has recently been used as the basis for intramolecular radical cation probes to investigate the possibility of electron transfer chemistry in metalloporphyrin-catalyzed epoxidations.[6,7]

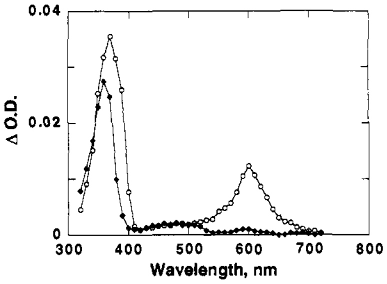

Figure 1. Transient absorption spectra of the 4-methoxy-β-methylstyrene radical cation (○) generated by 308 nm irradiation of the parent styrene and the radical cation of diene **16** (◆) generated by electron transfer quenching of the 4-methoxy-β-methylstyrene radical cation in acetonitrile.

Photoionization of 4-methoxystyrene and 4-methoxy-β-methylstyrene (ca. 1×10^{-4} M) in aerated acetonitrile using 308 nm laser irradiation leads to the formation of the radical cations with characteristic absorptions in the 600 and 300 nm regions (Figure 1).[8] The lifetimes of the 4-methoxystyrene and the β-methyl-4-methoxystyrene radical cations are 1 and 25 μs, respectively. Both radical cations are quenched in the presence of a variety of simple alkenes, enol ethers, styrenes, and dienes with the second-order rate constants summarized in Table 1. The rate constants cover a range of approximately 5 orders of magnitude, with the 4-methoxystyrene radical cation reacting, on average, 1–2 orders of magnitude faster than the β-methyl derivative. The two most likely mechanisms for reaction between the styrene radical cations and the substrates (**1–16**) listed in Table 1 are (1) electron transfer to generate alkene radical cations and the starting styrene and (2) cycloaddition to give cyclobutane or Diels–Alder products. A comparison of the oxidation potentials for the two styrenes with those for the quenchers used indicates that electron transfer is exoergonic for diene **16** and may also be a viable pathway for enol ether **5** and 1,3-cyclohexadiene.[20] However, it is obvious that electron transfer is endergonic for the remaining substrates and cannot occur at anything approaching the diffusion-controlled limit. Product studies also support our hypothesis that cycloaddition is the main reaction pathway for most of the substrates in Table 1. For example, aminium salt-catalyzed additions of 4-methoxy-β-methylstyrene to dihydropyran, 1,3-cyclohexadiene, and dienes **10**, **11**, and **13** have been reported to yield Diels–Alder adducts, whereas addition to diene **14** gives a cyclobutane product. Diels–Alder addition of the 4-methoxystyrene radical cation to 1,3-cyclohexadiene has also been observed, albeit with a substantially lower yield than the same reaction for 4-methoxy-β-methylstyrene. Radical cation-initiated cycloaddition to yield cyclobutane or dihydronaphthalene products is also well-documented for a variety of styrenes.[4,14,23,24]

Transient spectra were measured after complete quenching of the radical cations by a selection of the alkenes in order to substantiate our mechanistic conclusions. Quenching of either radical cation by diene **16** shows the clear production of a new transient that has a strong absorption band at 360 nm and a

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[1] Issued as NRCC-37283.

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[11] To the best of our knowledge, the only direct kinetic data for radical cation initiated dimerizations have been measured by laser flash photolysis or pulse radiolysis for substituted styrenes or dienes.[10,12,13] Calculated rate constants based on Stern–Volmer quenching for the same reactions,[14] as well as for the dimerization of dianisylethylene[15] and 1,3-cyclohexadiene[16] and the intramolecular dimerization and diene cycloaddition of anethole-based probe molecules,[6,7] have also been reported.

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[20] Peak potentials (irreversible oxidations, vs. SCE in acetonitrile) of 1.4, ≤1.3, 1.9, 1.7, and 1.7 have been reported for 4-methoxystyrene, 4-methoxy-β-methylstyrene, styrene, α-methylstyrene, and β-methylstyrene, respectively.[4,21] Those for **3**, **4**, **13**, and **15** are 1.62, 1.6, 1.59, and 1.53, respectively, whereas those for dienes **10–12** and alkenes **1–3** are all >1.7.[4,22]

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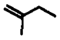
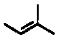
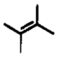
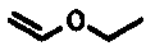
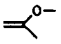
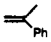
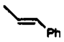
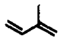
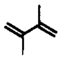
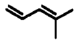
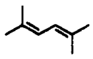
0002-7863/94/1516-10330$04.50/0 Published 1994 by the American Chemical Society

Table 1. Rate Constants for Reaction of 4-Methoxystyrene and 4-Methoxy-β-methylstyrene Radical Cations with Alkenes **1–16** in Acetonitrile

	k_q (M^{-1} s^{-1})	
quencher	4-methoxystyrene$^{\bullet+}$	4-methoxy-β-methylstyrene$^{\bullet+}$
1 	$(1.5 \pm 0.1) \times 10^6$	$<1 \times 10^5$
2 	$(1.4 \pm 0.3) \times 10^6$	$<1 \times 10^5$
3 	$(1.6 \pm 0.5) \times 10^7$	$<1 \times 10^5$
4 	$(7.2 \pm 1.1) \times 10^7$	$(5.0 \pm 1.0) \times 10^5$
5 	$(4.6 \pm 0.3) \times 10^8$	$(3.6 \pm 0.3) \times 10^6$
6 	$(1.3 \pm 0.1) \times 10^7$	$<1 \times 10^5$
7 	1.4×10^9 [a]	$(4.0 \pm 0.3) \times 10^6$
8 	$(1.2 \pm 0.2) \times 10^8$	$<1 \times 10^5$
9 	$<2 \times 10^5$	$<1 \times 10^5$
10 	*b*	$(1.9 \pm 0.2) \times 10^5$
11 	$(2.8 \pm 0.5) \times 10^7$	$(7.4 \pm 1.8) \times 10^4$
12 	$(1.8 \pm 0.2) \times 10^7$	$(1.5 \pm 0.5) \times 10^5$
13 	$(2.6 \pm 0.4) \times 10^7$	$(6 \pm 1) \times 10^5$
14 	$(2.7 \pm 0.2) \times 10^7$	$<1 \times 10^5$
15 	$(7.0 \pm 1.1) \times 10^8$	$(5.6 \pm 0.9) \times 10^6$
16 	$(8.3 \pm 0.6) \times 10^9$	$(7.2 \pm 0.9) \times 10^9$

[a] Calculated number from ref 10; reaction is reversible. [b] The decay of the 4-methoxystyrene radical cation is not first-order in the presence of **10**.

weaker band between 400 and 500 nm (Figure 1) and decays over a period of several microseconds. This species can be readily identified as the diene radical cation on the basis of its spectral similarity to the same species generated in a matrix at low temperature[25] and by chloranil-sensitized electron transfer.[26] Thus, there is no doubt that diene **16** reacts largely by electron transfer, although our results do not preclude some addition as well. In contrast, spectra obtained after reaction of the other alkenes show only very weak residual absorptions in the 300–330 nm region which are partially quenched by oxygen and are not particularly diagnostic. There is no evidence for the formation of alkene radical cations or for recovery of the bleaching of the starting material, as would be expected for an electron transfer reaction. Although in many cases the quencher radical cations may be difficult to detect due to their high reactivity or unfavorable absorption properties (i.e., weak extinction coefficients or short wavelength absorption), recent results have shown that radical cations of 1,3-dienes and enol ethers are observable under experimental conditions that are similar to those used herein.[13,26,27] In the case of reaction with styrenes **6–9**, the transient spectra are similar to those observed previously for the radical cation-mediated dimerization of 4-methoxystyrene and are consistent with similar addition reactions. The above evidence, in combination with the redox potential data and product studies, thus leads to the conclusion that the rate constants listed in Table 1, with the exception of diene **16**, are those for [2 + 1] or [4 + 1] cycloaddition of the radical cation to the alkene.

The results in Table 1 indicate that the 4-methoxystyrene radical cation adds to alkyl-substituted alkenes and dienes with rates on the order of 10^6–10^9 M^{-1} s^{-1}, with alkyl substitution leading to modest rate enhancements. A comparison of the data for substrates **1**, **11**, **5**, and **8** indicates that vinyl substitution leads to approximately an order of magnitude increase in rate constant over alkyl substitution, whereas phenyl and alkoxy substitutions lead to 100- and 300-fold increases, respectively. The results for styrenes **6**, **8**, and **9** indicate that an α-methyl group activates the styrene toward addition, whereas β-methyl-substitution leads to a decrease of at least 2 orders of magnitude in rate constant. These trends are in qualitative agreement with, although of lesser magnitude than, the relative rate constants measured for addition of diarylcarbocations to similar alkenes, a reaction which has been suggested to proceed via a partially bridged transition state.[28] It has been postulated on the basis of stereochemical and theoretical arguments that the cycloaddition of radical cations and alkenes occurs via a concerted but nonsynchronous mechanism to give a cyclic radical cation intermediate.[3,4,29] The present results are consistent with that hypothesis, as are our recent results on the dimerization of 4-methoxystyrene.[10]

The data in Table 1 demonstrate that the 4-methoxy-β-methylstyrene radical cation is substantially less reactive toward alkenes than the 4-methoxystyrene analogue. For example, simple alkenes **1–3** were too unreactive to be measured, and the enol ethers and most of the dienes were 1–2 orders of magnitude less reactive for the β-methyl-substituted radical cation. Note that the only exception is diene **16**, which as demonstrated above reacts by electron transfer rather than addition. In fact, the differences between the rate constants for the two radical cations are in line with our previous observations of substantial decreases in rates of nucleophilic addition upon β-methyl substitution[8] and provide further support for a reaction pathway involving addition rather than electron transfer.

The addition of the two radical cations to 1,3-cyclohexadiene provides an interesting system for comparison of the kinetic results with product studies.[3] The cycloaddition of 4-methoxystyrene was reported to give a 21% yield of the Diels–Alder adduct, whereas 4-methoxy-β-methylstyrene gave an 80% yield. Although at first glance these results suggest a more efficient reaction in the latter case, the rate constants in Table 1 indicate that the β-methyl-substituted radical cation is over 100 times less reactive than the β-H analogue. In fact, it is likely that the lower yield of product from the more reactive radical cation reflects the much higher rate constant for addition of this radical cation to its neutral precursor (1.4×10^9 vs $\leq 10^6$ M^{-1} s^{-1} for 4-methoxy-β-methylstyrene);[8,14] partitioning of the initial radical cation adduct between cycloadduct formation and other reactions may also play a role. These results demonstrate the importance of considering the rate constants for all the potential reaction pathways for the radical cation of interest in the design of rational synthetic strategies that maximize the yields of the desired product. Experiments aimed at providing the necessary kinetic data for a range of alkene radical cations are currently in progress.

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