3802 *J. Am. Chem. Soc.* **1993,** *115,* 3802-3803

Substituent Field Effects on the Regiochemistry of the Ene Reaction

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Received February 12, 1993

It is remarkable that the understanding and appreciation of the mechanistic diversity and synthetic utility of the ene reaction is continuing to evolve nearly 50 years after its first systematic examination.[1] The development of the Lewis acid-catalyzed ene reaction[2,3] and intramolecular variants[4] along with the recognition of both concerted and stepwise pathways[5] has dramatically expanded the synthetic and mechanistic scope of this valuable reaction.

Of particular importance to synthetic applications of the ene reaction is the ability to control reaction regiochemistry. A variety of structural and environmental factors such as hydrogen alignment,[6] rotational barriers,[7,8] secondary orbital interactions,[9] steric effects,[10-14] and solvent effects[15] have been suggested to play important roles in dictating regiochemical outcome.

We report here the magnitude of the electronic field surrounding a substituent as a new structural factor which can influence the regiochemistry of ene reactions. This electrostatic influence is very apparent in the ene reactions of 1-methyl-1,2,4-triazolinedione (MTAD) with allylic sulfides **1** (protio analogues of **1d$_5$**, Scheme I). The abstraction of a hydrogen from the methyl group geminal to the sulfur-bearing carbon to give ene adduct **4** accounts for 78% of the product composition when Ar = *p*-MeOPh- but only 42% when Ar = *p*-NO$_2$Ph- (Table I). The remote location of the para substituent in these allylic substrates relative to the reaction center argues against any changes in the steric or torsional characteristics of the reaction as the substituent is varied and supports the electrostatic origin of this phenomenon.

Extensive experimental studies have demonstrated that these ene reactions proceed via a stepwise pathway as illustrated for the reaction of **1d$_5$** in Scheme I.[16,17] The irreversible formation of aziridinium imide intermediates has been directly observed in two cases by low-temperature NMR.[18,19] Isotope effect studies also verify that these intermediates are formed irreversibly and are configurationally stable when formed in the reactions of *tetrasubstituted*,[16,17] but not necessarily in the reactions of di- or trisubstituted,[20] olefins.

Scheme I

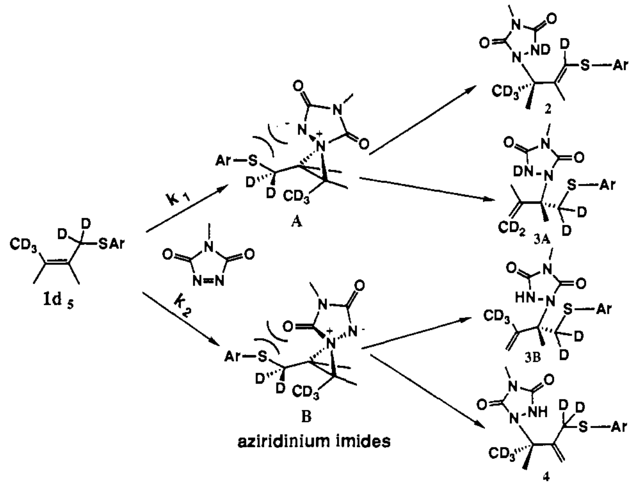

Table I. Product Ratios in the Reactions of **1** and **1d$_5$** with MTAD[a]

		yield, %		
olefin	Ar	**2**	**3**	**4**
1	*p*-NO$_2$Ph-	13	45	42
1	*p*-ClPh-	14	29	57
1	Ph-	7	22	71
1	*p*-MePh-	6	20	74
1	*p*-MeOPh-	9	13	78
1d$_5$	*p*-NO$_2$Ph-	17	13/24[b]	46
1d$_5$	*p*-ClPh-	14	8/17[b]	61
1d$_5$	Ph-	11	6/12[b]	71
1d$_5$	*p*-MePh-	11	5/10[b]	74
1d$_5$	*p*-MeOPh-	9	4/9[b]	78

[a] Product ratios were determined from the cutting and weighing of appropriate expanded peaks in the proton NMR of the crude reaction mixture. The data represent the average of two runs and are good to ±2%. [b] **3A**/**3B**.

The irreversible formations and configurational stabilities of the aziridinium imides provides a unique opportunity to study electrostatic interactions during their formations and decompositions since ([**2**] + [**3A**]) and ([**3B**] + [**4**]) are a direct measure of their concentrations. Consequently, the changes in these values as a function of substituent are a measure of the relative importance of electrostatic effects during the formations of **A** and **B**. In addition, the changes in the magnitudes of the ratios [**2**]/[**3A**] and [**4**]/[**3B**] reflect the relative importance of electrostatic effects during the decompositions of **A** and **B**.

The yields of the products for the reactions of **1d$_5$** are given in Table I, and the mechanistically significant product sums and ratios are in Table II. The decrease in ([**2**] + [**3A**]) and increase in ([**3B**] + [**4**]) as the electron-donating ability of the substituent is increased demonstrates that the sulfur–nitrogen interaction is more destabilizing than the sulfur–carbonyl oxygen interaction during the formations of aziridinium imides **A** and **B**, respectively. On the other hand, the much larger change in [**4**]/[**3B**] in comparison to [**2**]/[**3A**] suggests that during the decompositions of the aziridinium imides the sulfur–carbonyl oxygen interaction is more important than the sulfur–nitrogen anion interaction.

The observation that the sulfur–carbonyl oxygen interaction does not become important until the latter stages of the reaction

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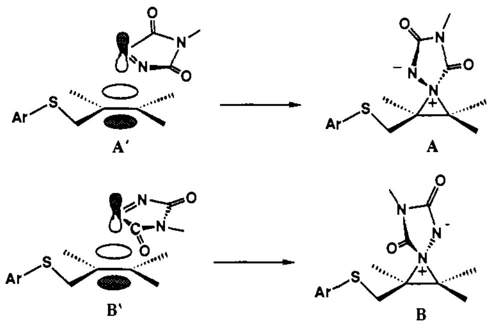
Table II. Product Sums and Ratios in the Reactions of **1d$_5$** and MTAD[a]

Ar	[2 + 3A]	[4 + 3B]	[2]/[3A]	[4]/[3B]
p-NO$_2$Ph	30	70	1.31	1.92
p-ClPh	22	78	1.75	3.59
p-HPh	17	83	1.83	5.92
p-MePh	16	84	2.2	7.4
p-MeOPh	13	87	2.25	8.67

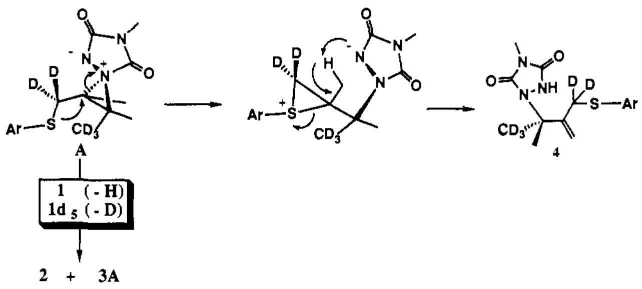
[a] Product ratios were determined from the cutting and weighing of appropriate expanded peaks in the proton NMR of the crude reaction mixture. The data represent the average of two runs and are good to ±2%.

Scheme II



is consistent with the mechanism depicted in Scheme II. In this mechanism a parallel approach of the triazolinedione to the olefin satisfies orbital symmetry considerations and provides maximum frontier orbital stabilization. Examination of molecular models reveals that in the two least sterically congested parallel approaches of the reactants (Scheme II), the incipient nitrogen anion in **A′** and the highlighted carbonyl carbon in **B′** are nearly equidistant from the allylic sulfur. In contrast, the carbonyl oxygen in **B′** actually points away from the sulfur, and to the extent that the transition state for formation of the aziridinium imide approximates this parallel arrangement it is not surprising that the carbonyl oxygen has little electrostatic influence. As the triazolinedione moves from this parallel geometry to the perpendicular geometry in the aziridinium imide, the carbonyl oxygen–sulfur distance substantially decreases while the nitrogen and carbonyl carbon–sulfur distance undergoes little change. Apparently, the transition states for the formations of the ene adducts look very much like the aziridinium imides, and consequently the sulfur–carbonyl oxygen interaction plays the major electrostatic role.

Scheme III



An alternative anchimerically assisted mechanism (Scheme III) which could also account for the substituent-induced growth in the formation of **4** (Table I) is unlikely. Anchimerically assisted formation of **4** should result in an induced isotope effect since it competes with the formations of **2** and **3A** for the common intermediate, aziridinium imide **A**. Formations of **2** and **3A**, in contrast to the formation of **4**, directly involve competitive removal of hydrogen and deuterium from **1** and **1d$_5$**, respectively. (Scheme III) The yield of **4**, however, is identical within experimental error for a given substituent in both the **1** and **1d$_5$** series of compounds despite the large isotope effects usually observed in triazolinedione ene reactions.[17] The absence of an induced isotope effect for the formation of **4** also eliminates from consideration any process which interconverts aziridinium imides **A** and **B**.

The ene reaction[22] now joins an ever increasing number of processes including nucleophilic addition to carbonyls,[23,24] the aldol reaction,[25,26] and the Diels–Alder reaction[27,28] in which electrostatic interactions can play important roles.

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this research.

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