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Experimental Investigation into the Mechanism of the Epoxidation of Aldehydes with Sulfur Ylides

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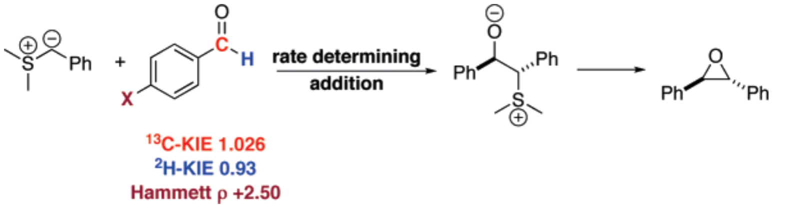
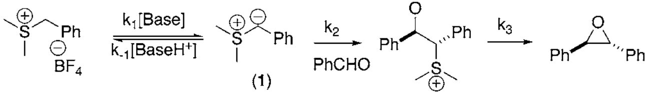
ABSTRACT



A mechanistic study of the epoxidation of aldehydes with sulfur ylides has been carried out. The $\Delta G^{\ddagger}$ of the reaction was determined to be 22.2 kcal/mol at 298 K. A ^{13}C kinetic isotope effect was determined to be 1.026 for the carbonyl carbon of benzaldehyde. A secondary deuterium isotope effect was determined to be 0.93 for the aldehydic hydrogen atom of benzaldehyde. Substituent effects on reaction rate were studied, and a Hammett ρ of +2.50 was found.

The reaction between an aldehyde and an ylide yielding an epoxide has proven to be a versatile and valuable method for the production of epoxides.[1] Since the initial discovery of this reaction,[2] catalytic enantioselective variants have been developed that permit the synthesis of a broad range of products including epoxides, cyclopropanes, aziridines, glycidic amides, and acids.[1] From a variety of mechanistic probes, in addition to theoretical calculations,[3] a general consensus on the mechanism of the reaction has been reached, which is illustrated in Scheme 1.

Scheme 1. Mechanism of Epoxidation



Cross-over experiments indicate that the addition of dimethylsulfonium benzylide to benzaldehyde (k_2) is both nonreversible and rate-limiting.[4] The activation energy (E_a) for this step was predicted to be 4.5 kcal/mol by DFT calculations.[3a] No experimentally determined activation parameters have been reported for the epoxidation of benzaldehyde with dimethylsulfonium benzylide. In fact, to the best of our knowledge, no kinetic parameters have ever been reported for this reaction or the Corey–Chaykovsky[2c]

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(1) (a) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433. (c) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R. I.; Smith, C.; Vasse, J.-L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105. (d) Aggarwal, V. K; Hebach, C. *Org. Biomol. Chem.* **2005**, *3*, 1419. (e) Aggarwal, V. K.; Richardson, J. *Chem. Commun.* **2003**, 2644.

(2) (a) Johnson, A. W.; LaCount, R. B. *Chem. Ind.* **1958**, 1440. (b) Johnson, A. W.; LaCount, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 417. (c) The Corey–Chaykovsky version of this reaction employs Me$_3$S$^+$ species as the ylide precursor rather than the substituted ylides employed herein: Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782.

(3) (a) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747. (b) Volatron, F.; Eisenstein, O. *J. Am. Chem. Soc.* **1987**, *109*, 1. (c) Lindvall, M. K.; Koskinen, A. M. P. *J. Org. Chem.* **1999**, *64*, 4595. (d) Lindvall, M. K.; Koskinen, A. M. P. *Tetrahedron* **2001**, *57*, 4629.

(4) (a) Aggarwal, V. K.; Calamai, S.; Ford, J. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 593. (b) Aggarwal, V. K Charmant, J. P. H; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, *R. J. Chem. Soc., Perkin Trans. 1* **2001**, 3159. (c) Yoshimine, M.; Hatch, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5831.

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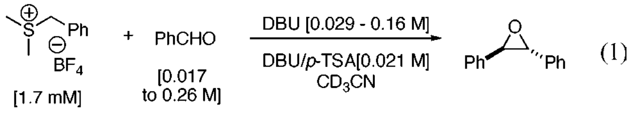
epoxidation of any substrate. Owing to this fact, and the overall importance of this reaction in organic synthesis, we undertook to experimentally determine the rate expression and activation parameters for the sulfur ylide epoxidation of benzaldehyde. Last, it was deemed that the transition state characteristics of the reaction could be obtained by a series of mechanistic probes such as isotope and substituent effects. Doing so, the sulfur ylide epoxidation of benzaldehyde could be placed into context with other similar reactions involving additions to arylaldehydes such as the related Wittig olefination, which have been studied in considerable detail.

Using our standard conditions, epoxidations were carried out in CD_3CN under pseudo-first-order conditions of excess benzaldehyde and limiting sulfonium salt (eq 1). The progress of the reaction could be effectively monitored by high-field ^1H NMR (600 MHz) for loss of sulfonium salt. Under these conditions, nearly complete selectivity for the *trans*-epoxide isomer is observed (ca. 98:2).



(1)

Monitoring the reaction with increasing concentrations of DBU (0.029−0.16 M) and plotting k_{obs} versus [DBU] yields a straight line (Figure 1), indicating that the reaction is first-order with respect to base. The reaction was also monitored under increasing concentrations of benzaldehyde (0.017−0.26 M), and in this instance, plotting k_{obs} versus [benzaldehyde] revealed saturation behavior (Figure 2).

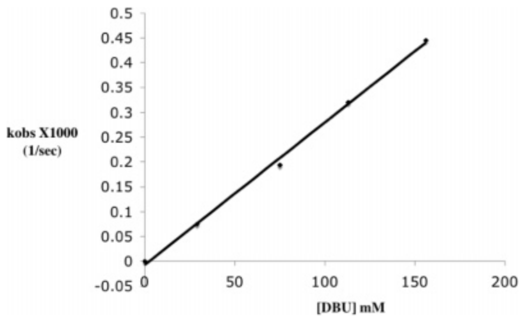


Figure 1. Rate versus [DBU].

The reaction was monitored over a 30 °C temperature range using a concentration of benzaldehyde in which the plot of rate versus [PhCHO] is linear (0.017 M). This permitted us to determine k_{obs} in the usual manner. Working under the assumption that, under these conditions, the addition of **1** to benzaldehyde (k_2) is rate-limiting and is preceded by a pre-equilibrium proton transfer (K_{eq}) to generate the ylide from sulfonium salt, eq 2 can then be derived.[5] From eq 4, then, the apparent second-order rate constant k_{app} was derived. The apparent second-order rate constant determined in this manner is a composite of the individual rate constants of eq 2 and may simply be expressed as $k_{app} = k_2K_{eq}$.

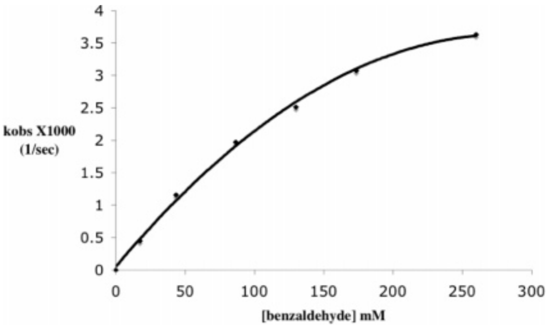


Figure 2. Rate versus [PhCHO].

An Eyring plot was generated by plotting $\log(k_{app}/T)$ versus $1/T$ from which the enthalpy of activation ($\Delta H^{\ddagger} = 11.8$ kcal/mol) and the entropy of activation ($\Delta S^{\ddagger} = -35$ cal/mol/K) were determined. This corresponds to an overall free energy of activation ($\Delta G^{\ddagger}$) for the reaction of 22.2 kcal/mol at 298 K. The large negative $\Delta S^{\ddagger}$ is consistent with a bimolecular addition resulting in the conversion of two molecules into a single activated complex. The analogous Arrhenius treatment of the temperature-dependent rate data results in an E_a of 12.3 kcal.

$$\frac{-d[SM]}{dt} = K_{eq}k_2\frac{[DBU]}{[DBUH]}[PhCHO][sulfonium\ salt] \tag{2}$$

$$\text{where } k_{obs} = K_{eq}k_2\frac{[DBU]}{[DBUH]}[\ PhCHO] \tag{3}$$

$$\text{and } k_{app} = \frac{k_{obs}[DBUH]}{[PhCHO][DBU]} \tag{4}$$

The irreversibility of sulfur ylide addition to benzaldehyde (k_2) has previously been demonstrated in the solvents DMSO and CH_2Cl_2 by cross-over experiments.[4a] The results of these previous studies have been confirmed under the current reaction conditions, by treating betaine precursor *anti*-**2** with base in the presence of a more reactive aldehyde (eq 5). Under these conditions, clean conversion to *trans*-stilbene oxide was observed. No cross-over products were observed, as would be expected if the betaine reverted to benzaldehyde and ylide. Accordingly, the addition of sulfur ylide to benzaldehyde is interpreted as being an nonreversible process.

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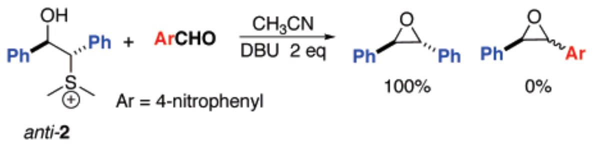
[5] Treating the proton transfer (K_{eq}) as a pre-equilibrium is justified since the ratio of k_{-1}[DBUH]/k_2[PhCHO] is 22.7 under the conditions employed ([DBUH] = 0.021 M, [PhCHO] = 0.017 M). The ratio of k_{-1}/k_2 was determined from the slope of the double reciprocal plot $1/k_{obs}$ vs 1/[benzaldehyde]; see Supporting Information. Treating k_2 as rate-limiting is justified by the combined results of cross-over experiments, isotope effects, as well as substituent effects determined for the reaction.



(5)

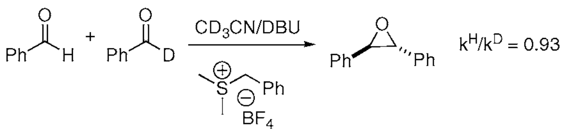
In order to gain further insight into the nature of the rate-limiting step in the sulfur ylide addition to benzaldehyde, a ^{13}C kinetic isotope effect study was carried out using the Singleton protocol.[6] Using this technique, unlabeled, natural abundance ^{13}C-containing benzaldehyde is subjected to a large-scale epoxidation and taken to high conversion. Following reaction, the unreacted starting material is recovered and the enrichment of the slower reacting isotope is determined via quantitative ^{13}C NMR. The *para*-carbon of benzaldehyde is assumed to undergo a negligible KIE during the reaction and, as such, serves as a reference for the enrichment of ^{13}C at the carbonyl center. From these data, a ^{13}C KIE can be calculated in accordance with standard theory utilizing eq 6[7]

$$\mathrm{KIE} = \frac{\ln(1 - F)}{\ln[(1 - F)(R/R_o)]} \tag{6}$$

where F = fractional conversion and R/R_o = ratio of ^{13}C in benzaldehyde prior to and after reaction as determined by quantitative ^{13}C NMR. The ^{13}C KIE of the carbonyl carbon of benzaldehyde was determined to be 1.026 ± 0.003 (average of three experiments, standard deviations calculated by propagation of errors). Full details are provided in the Supporting Information. This relatively large ^{13}C KIE is consistent with a rate-determining addition to the carbonyl.

Secondary deuterium kinetic isotope effects (SDKIEs) are also useful probes for the analysis of rehybridization at the attached carbon undergoing direct bond change during the reaction. Rate-limiting addition of a nucleophilic species to an aldehyde is generally associated with an inverse SDKIE at the aldehydic proton. The inverse nature of the KIE, where $k^H/k^D < 1$, is interpreted as arising from an increase in the aldehydic C−H(D) force constant for out-of-plane bending on going from the ground state (sp^2) to the transition state (sp^3-like).[8]

The SDKIE has been determined for the epoxidation of benzaldehyde with dimethylbenzylsulfonium tetrafluoroborate. A 55:45 mixture of benzaldehyde and d_1-benzaldehyde was subjected to epoxidation under typical reaction conditions in CD_3CN. The relative conversion of each isotopomer was determined by ^{1}H NMR following reaction. From this, a $k_{rel} = k^H/k^D$ was calculated using eq 6. An inverse SDKIE of 0.93 was determined for the addition of dimethylsulfonium benzylide to benzaldehyde. The inverse nature of the SDKIE is typical of processes involving sp^2 to sp^3 rehybridization in the transition state and is consistent with rate-limiting addition of the sulfur ylide to benzaldehyde.[9]



(7)

A Hammett study was then conducted in order to assess the nature of charge development in the transition state of the reaction. The relative reactivity of substituted benzaldehydes was determined by a series of competition experiments in which at least a 10-fold excess of benzaldehyde and *p*-X-benzaldehyde was allowed to compete for a limiting amount of sulfonium salt.[10] Under these conditions, k_{rel} can be calculated from eq 8.[11] The resulting Hammett plot is shown in Figure 3.

$$k^X/k^H = \frac{[\mathrm{Product}^X]/[\mathrm{Product}^H]}{[\mathrm{Aldehyde}^X]/[\mathrm{Aldehyde}^H]} \tag{8}$$

The Hammett slope, ρ, is determined to be +2.50 for the reaction of dimethylsulfonium benzylide with substituted benzaldehydes in CH_3CN. The positive sign of ρ reflects the fact that electron-withdrawing substituents on the aromatic ring accelerate the reaction, which is consistent with a nucleophilic attack of the sulfur ylide on the aldehyde. The large absolute value of ρ indicates that there is a substantial buildup of negative charge in the activated complex as it proceeds through to the transition state.

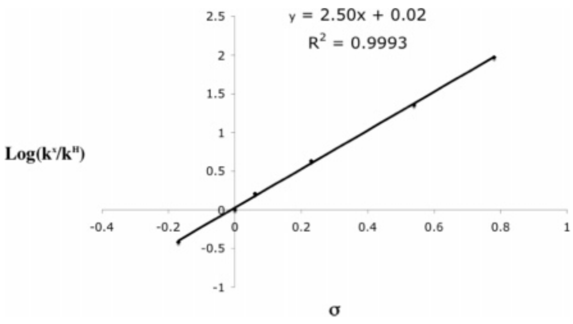


Figure 3. Hammett plot for reaction of ArCHO.

The results of the current kinetic study reveal that the epoxidation reaction is first-order with respect to [DBU] and [sulfonium salt], while saturation behavior is observed in [benzaldehyde]. These results are consistent with the mechanistic proposal depicted in Scheme 1 in which addition of

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[6] Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.

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[8] Buncel, E.; Lee, C. C. *Secondary and Solvent Isotope Effects (Isotopes in Organic Chemistry)*; Elsevier Science Ltd.: Amsterdam, 1997

[9] (a) Gajewski, J. J.; Wojciech, B.; Harris, N. J.; Olson, L. P.; Gajewski, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 326. (b) Gajewski, J. J.; Wojciech, B.; Brichford, N.; Henderson, J. L. *J. Org. Chem.* **2002**, *67*, 4236.

[10] An excess of the slower reacting aldehyde was used in order to obtain a significant proportion of the product derived from this species and allow for accurate integrations to be made in the proton NMR spectrum.

[11] Lansbury, P. T.; MacLeay, R. E. *J. Am. Chem. Soc.* **1965**, *87*, 831.

sulfur ylide to benzaldehyde is rate-limiting. This result is expected based on previously reported results of cross-over experiments,[4] which were verified under the current set of reaction conditions. The reaction is shown to proceed with a $\Delta G^{\ddagger}$ of 22.2 kcal/mol at 298 K. The analogous Arrhenius treatment of the temperature-dependent rate data results in the calculation of $E_a = 12.3$ kcal/mol.

This value is larger than the E_a of 4.5 kcal calculated by Aggarwal using DFT calculations for the title reaction in CH_3CN.[3a] The discrepancy between the two values is likely a result of the means by which each was determined. In the DFT method, the energies of the various intermediates and transition states for the reaction between preformed dimethylsulfonium benzylide and benzaldehyde were calculated. On the other hand, the results presented here were obtained from a kinetic analysis of the reaction and necessarily include the acid−base reaction between DBU and the sulfonium salt to generate the ylide species.

The observed carbonyl ^{13}C KIE of 1.026 is most consistent with a reaction step in which this atom is heavily involved in reaction coordinate motion as in addition (k_2) of sulfur ylide to benzaldehyde. The large Hammett ρ of +2.50 indicates that a buildup of negative charge is occurring at the carbonyl carbon during the course of the reaction. A nucleophilic addition such as that depicted by k_2 might be expected to involve this magnitude of charge development. For example, the Hammett ρ for hydrocyanation of benzaldehyde is reported to be +2.33.[12] Similarly, reduction of acetophenone with sodium borohydride is +3.06,[13] and addition of the phosphonium ylide $Ph_3P^+C^-HPh$ to benzaldehyde is +2.77.[14] The inverse SDKIE of 0.93 for the aldehydic proton of benzaldehyde is indicative of an sp^2 to sp^3 rehybridization occurring during the multistep epoxidation. This interpretation is in line with standard theory, which predicts this outcome based on changes in out-of-plane bending frequencies for sp^2 and sp^3 hybridized CH bonds. It would therefore appear that treating k_2 of Scheme 1 as rate-determining is fully consistent with the results of heavy atom and secondary deuterium isotope effects as well as substituent effects on the reaction.

A useful technique to experimentally probe transition state structure is to compare observed SDKIEs with the predicted equilibrium isotope effect for complete bond formation by means of eq 9.[9] The parameter i is generally believed to be indicative of progress along the reaction coordinate assuming that the observed SDKIE varies monotonically from reactant to product.

$$\mathrm{KIE} = \mathrm{EIE}^{i} \qquad (9)$$

The experimentally determined EIE for the hydrocyanation of *p*-methoxybenzaldehyde is reported to be 0.78.[15] Hill has used a similar value to estimate the EIE for borohydride reductions of benzaldehyde.[16] An EIE of 0.78 has also been used in a study of organolithium and Grignard additions to benzaldehyde.[9a] Employing an EIE of 0.78 along with eq 8 leads to the calculation of $i = 0.29$ for the sulfur ylide epoxidation of benzaldehyde. This would indicate moderate product character in the activated complex. However, it is not completely clear whether or not the EIE of 0.78 is an appropriate model for the current reaction. In fact, Gajewski has demonstrated that the identity of the countercation in the reaction strongly affects the magnitude of the predicted EIEs.[9a] Considering the large Hammett ρ (+2.50) and relatively large ^{13}C KIE (1.026), it appears as though i may be underestimating the position of the transition state for the addition of the sulfur ylide to benzaldehyde.

In conclusion, the reaction between dimethylbenzyl sulfonium tetrafluoroborate and benzaldehyde has been studied using a variety of kinetic tools. All of these methods point to the addition of the ylide to benzaldehyde as rate-determining.[3a,4a] Despite the importance of the epoxidation of aldehydes with sulfur ylides, this represents the first experimental determination of the activation parameters for this reaction. In addition, transition state characteristics have been probed by a combination of isotopic and substituent effects. The results of these studies lend support to the conclusions drawn from the kinetic analyses we have performed. Although the results of the current study fall short of positioning the transition state along the reaction coordinate with confidence, they provide considerable experimental verification for literature and computational postulates of the mechanism of this important reaction. Most importantly, these results shed light on charge development in the activated complex and provide a basis for future study of transition state characteristics.

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Supporting Information Available: Experimental procedures, details of determination of order in benzaldehyde and DBU, justification for eq 2, details of temperature studies, ^{13}C isotope effects, and ^{2}H isotope effect determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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