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Nucleophile-Assisted Alkene Activation: Olefins Alone Are Often Incompetent

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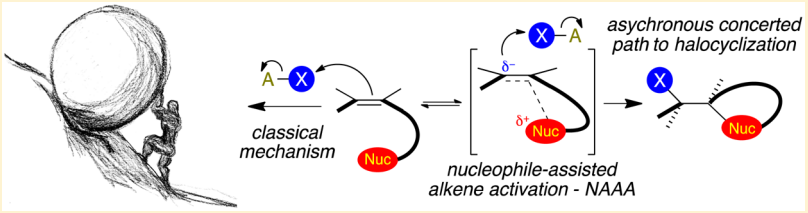
Supporting Information



ABSTRACT: Emerging work on organocatalytic enantioselective halocyclizations naturally draws on conditions where both new bonds must be formed under delicate control, the reaction regime where the concerted nature of the Ad_E3 mechanism is of greatest importance. Without assistance, many simple alkene substrates react slowly or not at all with conventional halenium donors under synthetically relevant reaction conditions. As demonstrated earlier by Shilov, Cambie, Williams, Fahey, and others, alkenes can undergo a concerted Ad_E3-type reaction via nucleophile participation, which sets the configuration of the newly created stereocenters at both ends in one step. Herein, we explore the modulation of alkene reactivity and halocyclization rates by nucleophile proximity and basicity, through detailed analyses of starting material spectroscopy, addition stereopreferences, isotope effects, and nucleophile−alkene interactions, all obtained in a context directly relevant to synthesis reaction conditions. The findings build on the prior work by highlighting the reactivity spectrum of halocyclizations from stepwise to concerted, and suggest strategies for design of new reactions. Alkene reactivity is seen to span the range from the often overgeneralized "sophomore textbook" image of stepwise electrophilic attack on the alkene and subsequent nucleophilic bond formation, to the nucleophile-assisted alkene activation (NAAA) cases where electron donation from the nucleophilic addition partner activates the alkene for electrophilic attack. By highlighting the factors that control reactivity across this range, this study suggests opportunities to explain and control stereo-, regio-, and organocatalytic chemistry in this important class of alkene additions.

INTRODUCTION

Electrophilic alkene additions such as halogenations, selenation, sulfenylation, oxymercuration, and hydrometalation are essential tools of organic synthesis. In introductory organic chemistry texts,[1] these are typically introduced with Br_2 addition and halohydrin formation, and mechanistically presented as two steps: (i) electrophilic attack on the alkene functionality to form a cationic adduct, and (ii) interception of this adduct by a nucleophile (Figure 1, paths A and B) to yield the addition product. This simple sequence implies that, for a given electrophile, it is the nucleophilicity of the olefin alone that dictates the rate of intermediate formation, ultimately determining the overall rate and stereoselectivity of the addition. Although widely useful and commonly invoked as seen, for instance, in recent landmark papers and reviews,[2] this notion is oversimplified; over 50 years ago it was noted by Shilov that the nucleophilic component can strongly affect the rate and regioselectivity of halogen addition reactions.[3] These early insights and extensive further work by Shilov and Staninets,[4] Williams,[5] Cambie,[6] and others[7] (with a key early review by Fahey[8]) clearly implied concerted additions. The relative absence of concert being cited in recent halofunctionalization papers can be attributed to three factors: (a) Most focus on asymmetric synthesis over mechanism; (b) seminal mechanistic and structural studies on cyclic halonium ions have bolstered their image as ubiquitous intermediates (see Supporting Information, section B-ii);[9] and (c) the elegant reports that substantiated the crucial role of nucleophiles in addition reactions remain undercited and, we believe, underappreciated.[3−7] Herein, high-resolution spectroscopies, isotope-labeling, and quantum chemical simulations offer some detailed illustrations and analyses of these classic mechanistic insights.

Our recent mechanistic work,[10] stemming from our ongoing interest in developing asymmetric halofunctionalization reactions,[11] reaffirms the incompleteness of the elementary textbook picture, calling for inclusion of a concerted Ad_E3-type path (formally Ad_E2 for these halocyclizations, where the nucleophile is intramolecular; see Figure 1, path C)[12] in which electrophilic attack on the olefin is activated by the nucleophilic partner's simultaneous electron donation. The present study explores how two species, alkenes and nucleophiles, which otherwise might be expected to electronically repel each other, interact to enable the attack of an approaching electrophile. Quantum chemical modeling finds that this nucleophile−alkene association raises the alkene's HOMO energy, activating

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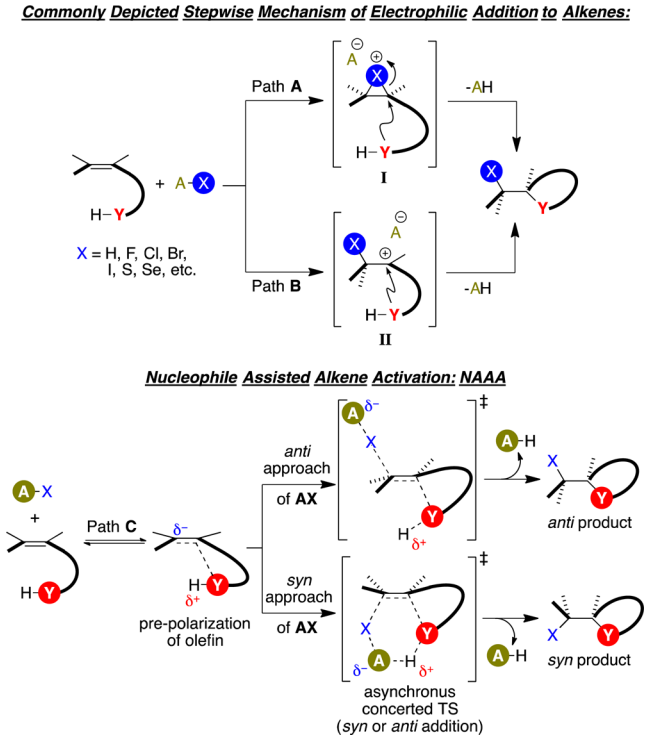

Figure 1. Path A and path B represent the rate-determining classically perceived intermediates (**I** and **II**) involved in electrophilic addition to alkenes. Path C represents the nucleophile-assisted alkene activation pathway (NAAA).

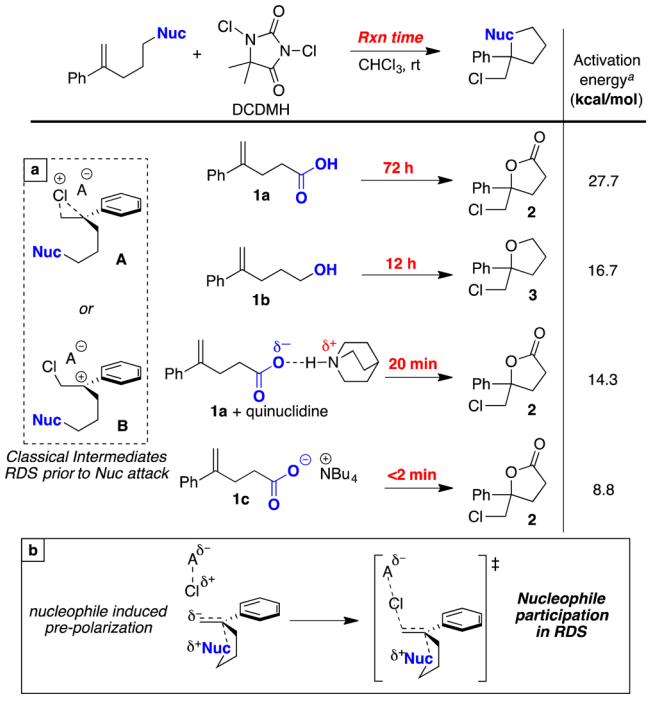

Figure 2. Rate-determining formation of intermediates (**I** or **II**) fails to explain the observed rate ordering, whereas the concerted NAAA pathway predicts the halofunctionalization barriers [a](B3LYP/6-31G*/SM8-$CHCl_3$) in accordance with the observed rates (as determined via ^{1}H NMR and GC−MS analysis).

reaction by narrowing its gap relative to the electrophile (LUMO) (see the Supporting Information). We present here a number of observations that show evidence for concerted Ad_E3-type reactions enabled by this nucleophile-assisted alkene activation (NAAA).

RESULTS AND DISCUSSION

Below, a series of alkene chlorocyclizations is analyzed, demonstrating the range from concerted to stepwise pathways. Because of the irreversibility of chlorenium transfer as found by Denmark et al. and our own group,[10b,13] the first step in paths A and B (Figure 1) is committed (see Supporting Information, section C for further discussion). These two possible paths begin with electrophilic halenium delivery to form a bridged halonium (**I**) or an open β-halo-carbenium ion (**II**),[14] depending on the donor/acceptor nature of substituents attached to the olefin. No buildup of such intermediate ions is seen. This picture has three implications: (i) The reaction rate should be governed by the first step, forming intermediates **I** or **II**; (ii) the regio- and stereopreferences of the nucleophilic attack should be dictated by the stereoelectronic identity of **I** and **II**; and (iii) the nature of the nucleophile should have no significant bearing on the overall addition rate. However, rate and stereochemical findings from multiple prior studies require the alternative concerted scenario.[5a,7b,9a,b,14]

Figure 2 displays chlorocyclizations of 1,1-disubstituted olefins **1a−c**, exhibiting their nucleophile-dependent rates. Intermediates **A** and **B** (Figure 2a), which would be formed from the stepwise mechanistic paths, cannot adequately explain these observations. The nucleophile-dependent variations observed among the reactions' rates imply an intramolecular Ad_E3-type path. Key factors are the nucleophilicity of the olefin's π-electrons, and the electrophilicity of the chlorenium donor. To address these issues, we have recently described the halenium affinity scale (HalA), a quantitative ranking of the strengths of interactions of alkenic and heteroatomic Lewis bases with halenium ions.[10a] Comparing the HalA(Cl) value for an activated olefin (~165 kcal/mol) with that of a common Cl^+ donor such as the monochloro dimethyl hydantoin anion (173.6 kcal/mol), one would predict that simple chlorenium transfer to the alkene would be untenably endothermic (see Supporting Information, section B for further discussion on HalA). Minimization of substrate **1a** with a free chlorenium cation results in a simple chloromethyl-substituted benzylic carbenium ion (Figure 3a); the Cl−C−C bond angle and calculated rotation barrier indicate no chlorine bridging in this intermediate, as expected from prior studies.[10a,b,12,13,15] With the mild Cl^+ donor reagent 1,3-dichloro-5,5-dimethylhydantoin, transfer of Cl^+ to the unassisted olefin (in simulated $CHCl_3$) appears to be monotonically endothermic; computations find the resulting minimum to be a weak van der Waals complex (Figure 3b, resting state). This is simply the result of the higher HalA value of the donor anion versus the olefin. In computational studies of potential reaction paths, the only conformation that effects elongation of the N−Cl bond, leading to a transition state for chlorolactonization, results from the interaction of the carboxylic acid with the olefin at the benzylic carbon (Figure 3c). In this Ad_E3 process, reaction progress depends not only on the nature of the isolated olefin (the nucleophilicity as measured by HalA), but also on the participation of the internal nucleophile. As illustrated in Figure 3b and c, the effective HalA of the alkenoic acid is a composite that includes conformations capable of the nucleophilic activation relative to the isolated, unperturbed olefin. Interestingly, transition state calculations for the

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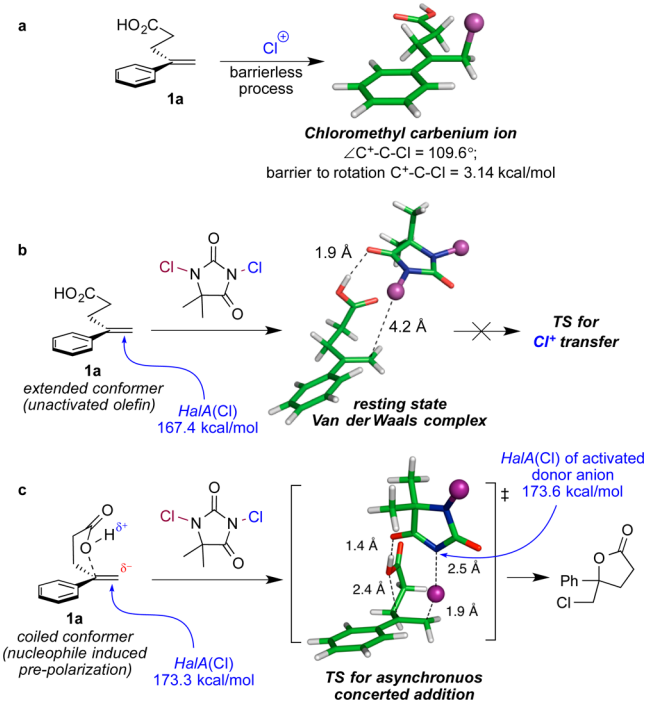

Figure 3. Computational predictions for possible chlorenium atom transfer (B3LYP/6-31G*/SM8-$CHCl_3$). (a) A barrierless transition to the chlorocarbenium intermediate proceeds if a naked chlorenium is used. (b) With the chlorenium donor included in the calculations, a transition state for halogen transferred cannot be reached, even with intramolecular hydrogen-bond activation of the donor carbonyl functionality; instead, a resting state complex is achieved. (c) Prepolarization of the olefin raises the HalA(Cl) of the olefin such that it can now compete with the donor for the chlorenium, resulting in a transition state that initiates halogen transfer.

reactions depicted in Figure 2, with the conformation that predisposes the nucleophile to interact with the alkene, yield activation energies that show the same order as the observed reaction rates. In other words, the short reaction time for **1c** (carboxylate anion, the most nucleophilic substrate in the list, Figure 2) is consistent with the lowest barrier for activation, while the less nucleophilic alcohol, with its higher predicted activation barrier, also has a longer reaction time. The carboxylic acid (least nucleophilic) in **1a** has the highest calculated barrier and the longest reaction time. Significantly, the major product observed at dilute reagent concentrations showed the *syn* stereochemistry expected from the calculated transition state structure (see Supporting Information, section F for details and studies on concentration dependence of stereochemical outcomes).

Studies of kinetic isotope effects (KIE) are powerful in differentiating the mechanistic possibilities outlined in Figure 1. Chlorolactonizations of **1a** and **1d**, traditionally predicted to proceed via the tertiary benzylic carbenium ion, were used as test reactions (Figure 4). Because the cation from **1d** is highly stabilized by the 4-methoxy substituent, its formation as a stable intermediate upon chlorenium attack is expected, and thus **1d** was used to benchmark the KIE values expected for the stepwise ionic pathway (depicted as "control" in Figure 4). We began by measuring natural abundance ^{13}C KIE values,[16] in conjunction with quantum chemical transition state predictions that can report on the changes in hybridization state of the olefinic carbons in the rate-determining step (RDS). To

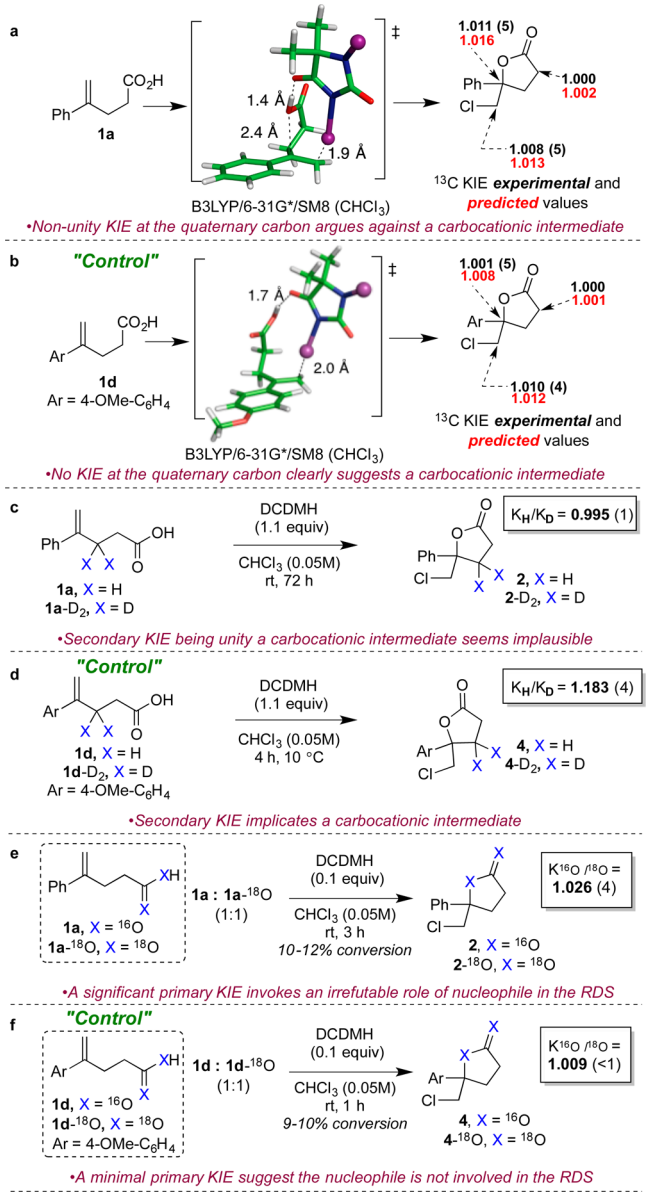

Figure 4. (a,b) ^{13}C KIE results predicted at the B3LYP/6-31G*level of theory and its validation by experimental results. For simplicity, the TS only for *syn*-addition to **1a** is shown; see Supporting Information, section F for details. (c,d) Secondary KIE (^{2}H) for halolactonization of **1a** and **1d.** (e,f) Primary ^{18}O KIE experimental results for **1a** and **1d.** Numbers in parentheses represent the standard deviation in the third decimal place; see Supporting Information, section D.

interpret ^{13}C KIE values along with other KIE measurements highlighted in Figure 4, we considered the three possible pathways depicted in Figure 1. (i) Included for completeness, path A involves the textbook stepwise path wherein both olefinic carbons undergo modest rehybridization during formation of bridged haliranium intermediate **I**. However, the corresponding intermediate formed from **1a** would include benzylic stabilization, rendering the putative haliranium ion asymmetric. If formation of this unsymmetrical haliranium intermediate (Figure 2a, intermediate **A**) is the RDS, the benzylic carbon should be least affected by isotope substitution, and hence the magnitude of the ^{13}C KIE at the benzylic carbon should be lower than that at the chloromethylene carbon. (ii) Path B leads directly to the benzylic carbocation, the carbon of

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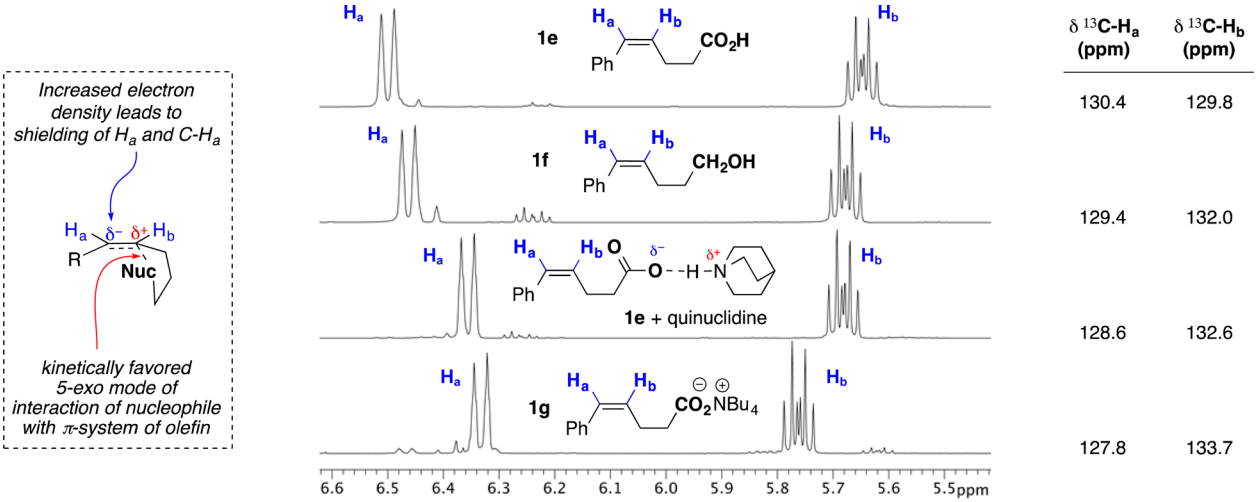

Figure 5. NMR resonances of olefinic C and H (at room temperature in $CDCl_3$) displaying the interaction of a remotely tethered nucleophile with the π-system upon modulation of the nucleophilic strength. The minor impurities appearing in the NMRs are the corresponding *E*-isomers.

which would experience no hybridization change (sp^2 to sp^2), thus yielding an isotope effect near unity, whereas the fully rehybridized carbon that bears the Cl atom β to phenyl should show a substantial KIE. (iii) Finally, the proposed Ad_E3-type process (path C) entails NAAA in the RDS, with the magnitude of the isotope effect reflecting the electronic nature of the nucleophile as well as the substitution pattern of the olefin. If the nucleophile participates in concerted bond formation at the benzylic carbon, substantial ^{13}C KIE should be observable there, as well as at the chloromethyl carbon.

Reports from our lab[10b] as well as earlier studies by others[13a,17] have argued against the role of bridged halonium ions (path A) in reactions of aryl-substituted olefins (see Supporting Information, section C for discussions regarding the bridged halonium ion). The relative magnitude of ^{13}C KIE on the benzylic versus the homobenzylic carbon with **1a** (Figure 4a) supports the elimination of path A (Figure 1) from consideration. Surprisingly, substrate **1a** (certainly capable of forming a tertiary benzylic carbenium ion) shows a nonunity ^{13}C isotope effect of 1.011 (Figure 4a), pointing to rehybridization in the transition state for addition. The control substrate **1d**, on the other hand, which almost certainly proceeds stepwise via the cation, exhibits a near-unity KIE for the benzylic carbon (Figure 4b). The quantum chemically derived TS structures for chlorolactonization of **1a** and **1d** in Figure 4a and b illustrate the path of the reaction that best matches with the measured KIEs. Specifically, for **1a** the Cl^+ capture proceeds via an intramolecular concerted Ad_E3-type process, enabled by NAAA, while **1d** undergoes classical two-step addition via the benzylic carbocation.

Further evidence for the absence of a carbenium intermediate in the reaction of **1a** is obtained from secondary ^2H KIE measurements. The C−H bonds neighboring the carbenium center are expected to contribute to the cation's stabilization via hyperconjugation, and hence the secondary ^2H KIE at that site should be a sensitive probe for the cation's intermediacy. Because it would be less stabilized by neighboring D than H atoms, halocarbenium ion formation should be slower in the labeled substrate **1a**-D_2 than in the parent. The near-unity ^2H KIE for **1a**-D_2 (Figure 4c) argues against carbenium ion development at that site. The TS structure depicted in Figure 4a accounts for this, along with the concomitant proton transfer from the carboxylic acid to the hydantoin, as it avoids charge buildup on any of the reactants.[18] In contrast, the ^2H KIE measurement with the control substrate **1d** verifies the sensitivity to development of charge neighboring the deuterated site, showing a significant β-secondary isotope effect (K_H/K_D = 1.183, Figure 4d). ^{13}C and ^2H KIE results from the alkenol **1b** display the same trend as observed for **1a**, lending further support for the absence of the carbenium intermediate in its reaction (see Supporting Information, section D for details).[19]

Thus far, the KIE studies have focused on charge distributions and hybridization changes at the alkene carbons, confirming that chlorolactonization of **1a** does not involve the cationic intermediate expected in the stepwise scheme. To directly probe the role of the nucleophile in the NAAA process, the KIE of the carboxylic acid oxygen atoms was also investigated. An ^{18}O KIE would be expected from a RDS where the carboxylic acid was involved in bond making/breaking. In fact, chlorocyclization of a mixture of **1a**-$^{16}O_2$ and **1a**-$^{18}O_2$ shows a substantial ^{18}O KIE (K^{16}_O/K^{18}_O = 1.026) indicating direct involvement of the nucleophile, which prefers ^{16}O over ^{18}O for oxygen's switch from a multiple- to a single-bonded setting. In contrast, reaction of "control" substrate **1d**, which proceeds via the benzylic carbocation, shows the substantially lower value of K^{16}_O/K^{18}_O = 1.009 (Figure 4f). These results agree with the transition state calculations described above (Figure 4a), highlighting the nucleophile's role in activating the olefin in **1a** (see Supporting Information for movies of transition states calculated for chlorination of **1a**, **1b**, and **1d**).

If the nucleophile−olefin interaction is independent of the presence of an external electrophile (here, the halogenating agent), it should be manifested in the ground-state ensemble of conformations of the alkene substrate. To probe such potential conformational contributions to the overall reactivity of the olefin, ^1H and ^{13}C chemical shifts of compounds **1e−g** with increasing nucleophilicity of the remotely tethered nucleophile were investigated.[20] As shown in Figure 5, the NMR studies demonstrate the "through-space" interaction of tethered nucleophiles with the π-system of the olefins. The olefinic components (H and C) in free acid **1e** display proton resonances at 6.50 ppm for H_a and 5.62 ppm for H_b, while the corresponding ^{13}C resonances appear at 130.4 and 129.8 ppm.

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Changing the tethered nucleophile to a primary alcohol (more nucleophilic than the carboxylic acid) in **1f** leads to an upfield shift of the distal olefinic H_a's and corresponding carbon ($C-H_a$), whereas the more proximal H_b and $C(-H_b)$ experience deshielding relative to their parent acid. It is important to note that inductive effects are not expected to result in a shielding effect of an atom ($C-H_a$) located five bonds away and a deshielding effect on an atom ($C-H_a$) that is four bonds away. The differential effect can instead be attributed to the interaction between the nonbonding electrons of the nucleophile and the π-orbitals of the olefin at C_b polarizing the π-cloud electron density toward $C-H_a$ and thus resulting in a shielding effect (Figure 5, dashed box).

Consistent with the reactivity patterns presented earlier (Figure 2),[2b] increasing the nucleophilicity extends and magnifies this polarization; free acid **1e** treated with 1.0 equiv of an organic base (quinuclidine) and the tetra-*n*-butyl ammonium salt **1g** display the same trend with enhanced effect. Furthermore, treatment of **1f** with substituted pyridines shows increasing polarization of the olefin with increasing pK_a of the corresponding pyridinium ion. Similar effects in chemical shifts are observed for alkyl-substituted olefins (for more examples, control experiments, and concentration studies, see Supporting Information, section G).[19] The ^1H and ^{13}C resonances observed are concentration independent, and therefore suggest that the observed phenomenon is intramolecular. These observations are consistent with Boltzmann-weighted quantum chemical NMR calculations on the conformers of **1e**, **1f**, and **1g** (see Supporting Information, section G).

The above NMR studies imply that the interaction between the nucleophile and the olefin may be a key mechanistic feature of electrophilic addition reactions in general. Several examples in the literature point in this direction. For instance, the thiourea-catalyzed hydroamination reported by Jacobsen's lab involves activation of an alkene by a tethered hydroxylamine where the intrinsic α-effect leads to enhanced nucleophilicity of the amine nitrogen that allows polarization of the alkene without assistance of any metal ion.[21] Similarly, the exquisite regioselectivity reported by Sigman et al. in the Pd(II)-catalyzed functionalization of alkenes suggests a key role for the tethered alcohol nucleophile.[22] Finally, the inverse electron demand Diels–Alder reaction-mediated tetrazine ligation with *trans* cyclo-octene reported by Fox et al. displays several fold rate enhancement upon placement of a remote nucleophilic alcohol moiety on the cyclo-octene, which appears capable of polarizing the alkene by raising its HOMO energy.[23] Although similarly substituted olefins have similar HOMO energies, the nucleophile assistance may be the key that attenuates the HOMO (olefin)–LUMO (electrophile) gap, allowing them to react with a variety of electrophiles with a wide range of LUMO energies.

CONCLUSION

Although studies as long ago as the 1960s revealed it as one extreme of a larger mechanistic spectrum, the stepwise mechanistic picture of halofunctionalization of olefins, as it appears in nearly every sophomore organic textbook, has served as a useful guide for stereo- and regiochemical studies. Proposed in 1937 by Kimball,[24] and further developed by Fahey,[9a,b] Olah,[9c–e] and Brown,[9f] it has remained the usual scheme due to its conceptual simplicity, structural appeal, and, importantly, its reinforcement by the extensive and elegant work probing stabilized halonium ions. The conditions, however, under which those bridged onium ions are generated and probed are quite different from those used in synthetically relevant additions, so the derived mechanistic insights cannot be generalized with confidence.[25] The theoretical and experimental studies described above return attention to the more nuanced reactivity spectrum mapped out by Shilov and others. The above findings, obtained under conditions like those of our synthesis studies, corroborate these initial reports, highlighting the following key mechanistic ideas: (a) nucleophile participation in the RDS may play a role in many electrophilic addition reactions of olefins; (b) the collision complex of an otherwise unactivated olefin and a neutral imide-based halenium ion donor (the most common type) is often unable to react unaided; rate can then be dictated by the reach and basicity of the nucleophile; and (c) enhancing the electron richness of the olefin via π-donor substituent(s) and increasing the leaving group ability of the halenium ion donor may shift the mechanism from the NAAA enabled Ad_E3-type process to a classical stepwise halomethyl carbenium ion route as depicted in path B (Figure 1). It is important to note, however, that NAAA describes the interaction of the nucleophile with the olefin, irrespective of the presence or absence of an electrophile. Ad_E3 denotes the transition state requiring the presence of the electrophile and that of the nucleophile. In a manner of speaking, NAAA relates to the ability of the olefin to undergo an Ad_E3-type reaction, with higher rates being the result of more effective NAAA. The present exploration offers both mechanistic insight and the promise of new handles on stereocontrol in the classic process of electrophilic addition to alkenes.[26] Ongoing work to be reported in a future publication will further explore the effects of NAAA on rates, stereo-, and regiochemical reaction outcomes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02877.

Experimental details, HalA calculations, KIE experimental details, characterization data, and DFT computational data (PDF)

Movie of transition states calculated for chlorination of **1a** (MPG)

Movie of transition states calculated for chlorination of **1b** (MPG)

Movie of transition states calculated for chlorination of **1d** (MPG)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press, Inc.: New York, NY, 2001. (b) McMurry, J. E. *Organic Chemistry*, 8th ed.; Brooks/Cole Cengage Learning: Belmont, CA, 2012.

(2) (a) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273. (b) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20655. (c) Chen, J.; Zhou, L. *Synthesis* **2014**, *46*, 586. (d) Jiang, X.; Liu, H. *Comprehensive Organic Synthesis II*; Elsevier: Waltham, MA, 2014; Vol. *4*, p 412. (e) Nolsoe, J. M. J.; Hansen, T. V. *Eur. J. Org. Chem.* **2014**, *2014*, 3051.

(3) Rengevich, E. N.; Shilov, E. A.; Staninet, V. I. *Dokl. Akad. Nauk SSSR* **1962**, *146*, 111.

(4) Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev.* **1971**, *40*, 272.

(5) (a) Williams, D. L. H.; Bienvenüe-Goetz, E.; Dubois, J. E. *J. Chem. Soc. B* **1969**, 517. (b) Bienvenüe-Goetz, E.; Dubois, J. E.; Pearson, D. W.; Williams, D. L. H. *J. Chem. Soc. B* **1970**, 1275.

(6) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1864.

(7) (a) Doi, J. T.; Luehr, G. W.; Delcarmen, D.; Lippsmeyer, B. C. *J. Org. Chem.* **1989**, *54*, 2764. (b) Snider, B. B.; Johnston, M. I. *Tetrahedron Lett.* **1985**, *26*, 5497.

(8) Fahey, R. C. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; John Wiley & Sons, Inc.: New York, NY, 1968; Vol. *3*, p 237.

(9) (a) Fahey, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 4681. (b) Fahey, R. C.; Schubert, C. *J. Am. Chem. Soc.* **1965**, *87*, 5172. (c) Olah, G. A.; Bollinger, J. *J. Am. Chem. Soc.* **1967**, *89*, 4744. (d) Olah, G. A.; Bollinge, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 947. (e) Olah, G. A.; Westerma.Pw; Melby, E. G.; Mo, Y. K. *J. Am. Chem. Soc.* **1974**, *96*, 3565. (f) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1996**, *61*, 962. (g) Braddock, D. C.; Hermitage, S. A.; Kwok, L.; Pouwer, R.; Redmond, J. M.; White, A. J. P. *Chem. Commun.* **2009**, 1082.

(10) (a) Ashtekar, K. D.; Marzijarani, N. S.; Jaganathan, A.; Holmes, D.; Jackson, J. E.; Borhan, B. *J. Am. Chem. Soc.* **2014**, *136*, 13355. (b) Yousefi, R.; Ashtekar, K. D.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. *J. Am. Chem. Soc.* **2013**, *135*, 14524. (c) Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 608.

(11) (a) Garzan, A.; Jaganathan, A.; Marzijarani, N. S.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. *Chem. - Eur. J.* **2013**, *19*, 9015. (b) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (c) Jaganathan, A.; Staples, R. J.; Borhan, B. *J. Am. Chem. Soc.* **2013**, *135*, 14806. (d) Soltanzadeh, B.; Jaganathan, A.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 9517. (e) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298.

(12) de la Mare, P. B. D.; Bolton, R. In *Studies in Organic Chemistry*; de la Mare, P. B. D., Ed.; Elsevier Scientific Publishing Co.: Amsterdam, Netherlands, 1982; Vol. *9*, p 1.

(13) (a) Haubenstock, H.; Sauers, R. R. *Tetrahedron* **2005**, *61*, 8358. (b) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232. (c) Halenium exchange via fast pre-equilibrium and rate-limiting attack on the halonium (brominium, iodonium) ion could result in observed rates sensitive to nucleophile character. The irreversibility of chlorenium addition, as demonstrated by Denmark and cowokers (see ref 13b), eliminates this possibility for the chlorocyclization system.

(14) Poutsma, M. L. *J. Am. Chem. Soc.* **1965**, *87*, 4285.

(15) Fahey, R. C.; Monahan, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 2816.

(16) Singleton, D. A.; Szymanski, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9455.

(17) (a) Bogle, X. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 17172. (b) Ohta, B. K.; Hough, R. E.; Schubert, J. W. *Org. Lett.* **2007**, *9*, 2317.

(18) KIE measurements with **1a** versus **1a**-CO_2D yields a substantial K_H/K_D (1.51), supporting the concerted transfer of the proton during the RDS, as predicted by the TS depicted in Figure 4a.

(19) A direct competition in chlorocyclization of **1a** and **1b** in the same pot yields ~5× more product from **1b**, further supporting the nucleophile dependence of the reaction. For details, see section E in the Supporting Information.

(20) ^{13}C chemical shift changes consistent with the proposed theory (NAAA) were observed with **1a** (see Supporting Information, section G for details). Nonetheless, the spectra for the 1,2-disubstituted styryl system (**1e**−**g**) are used in the main text to illustrate the NMR phenomena because the change in the chemical shift of both vinylic protons could be followed.

(21) Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747.

(22) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074.

(23) Darko, A.; Wallace, S.; Dmitrenko, O.; Machovina, M. M.; Mehl, R. A.; Chin, J. W.; Fox, J. M. *Chem. Sci.* **2014**, *5*, 3770.

(24) Roberts, I.; Kimball, G. E. *J. Am. Chem. Soc.* **1937**, *59*, 947.

(25) The seminal mechanistic reports probing the haliranium ion involve the aid of extremely good leaving groups (or weak nucleophiles) such as trifluoromethanesulfonate, *p*-toluenesulfonate as stabilized counterions in a polar protic environment. However, halofunctionalization of alkenes is commonly initiated by imide-based halenium sources (such as NCS, DCDMH, TCCA, *N*-chlorophthalimide, *N*-chlorosaccharin, or close relatives such as chlorine gas) for which the protocols have been widely established in the literature.

(26) Further work in this area with a much larger library of compounds demonstrates the concerted Ad_E mechanism for a variety of halenium sources and olefinic substructures. This work will be reported in due course.

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