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^{13}C and ^{2}H Kinetic Isotope Effects and the Mechanism of Lewis Acid-Catalyzed Ene Reactions of Formaldehyde

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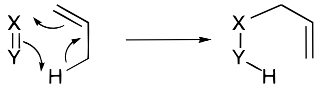
^{13}C and ^{2}H kinetic isotope effects were determined for the ene reaction of formaldehyde with 2-methyl-2-butene at natural abundance catalyzed by diethylaluminum chloride. The reactive methyl group exhibits a $k_{^{12}C}/k_{^{13}C}$ of 1.006−1.009 and a k_H/k_D of ≈1.22−1.23. The latter represents a combination of primary and secondary effects and is consistent with a significant primary deuterium isotope effect. A very close correspondence of the other isotope effects with the equilibrium isotope effects predicted for formation of a model intermediate cation is observed. An intermolecular deuterium isotope effect of 2.0−2.5 was observed under several reaction conditions in the Lewis acid-catalyzed reaction of formaldehyde with d_0/d_{12}-tetramethylethylene. The results are interpreted as supporting the reversible formation of an essentially classical open cation followed by rate-limiting proton transfer.

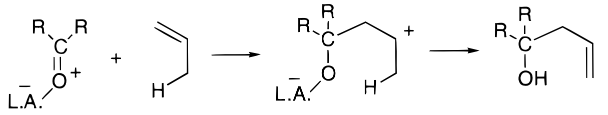
Introduction

Ene reactions are additions of electrophilic double or triple bonds (enophiles) to alkenes (enes) with concomitant transfer of an allylic hydrogen (eq 1). A synthetically important subset of this large class of reactions employs carbonyl or olefinic enophiles to form carbon−carbon bonds. However, the lassitude of these reactions is a significant limitation. Among formally allowed pericyclic processes, ene reactions are relatively slow, and relatively few neutral carbonyl or olefinic enophiles are generally useful in the absence of catalysis. The advent of Lewis acid catalysis of ene reactions has therefore been a tremendous advance;[1] greatly increasing the scope of reactive enophiles while providing opportunities for enantioselective catalysis using chiral Lewis acids.



(1)

Despite the synthetic value of Lewis acid-catalyzed ene reactions, a clear mechanistic understanding of these reactions has been elusive. Many ene reactions have been shown to involve complex mechanisms, including ene reactions of singlet oxygen,[2] nitroso compounds,[3] selenium dioxide,[4] and triazolinediones.[5] Lewis acid-catalyzed ene reactions have presented some of the most interesting mechanistic observations. Salomon found a ρ of −3.9 for the $SnCl_4$-catalyzed ene reaction of diethyl oxomalonate with 1-arylcyclopentenes,[6] indicative of a charge build-up near positive unity in the central carbon of the ene in these reactions.[7] The suggested intermediacy of a carbocation as in eq 2 is consistent with a number of other observations in these reactions, including the formation of oxetanes,[8] the formation of chloride-trapped[9] and intramolecularly trapped[10] products, the influence of pressure on product mixtures,[11] solvent effects,[12] and the high regioselectivity of these reactions.



(2)

On the other hand, kinetic isotope effect (KIE) studies have generally weighed in against simple carbocation intermediates. Stephenson and Orfanopolous found that both intermolecular and intramolecular KIEs for the $SnCl_4$-catalyzed reaction of diethyl oxomalonate with **1** (L, L′ = H or D) were very small (k_H/k_D < 1.2).[13] Arguing that any stepwise mechanism should have exhibited an intramolecular KIE, the authors interpreted this surprising result in terms of an intrinsically small isotope effect in a concerted mechanism. In a key study Snider applied the “Stephenson isotope effect test”[14] to R_2AlCl-catalyzed reactions of formaldehyde or methyl propiolate with isomerically labeled tetramethylethylene.[15] The observation of a substantially smaller intermolecular KIE (with d_0/d_{12}-**2**) than intramolecular KIE (with **3**−**5**) was indicative of multistep mechanism with a product-determining step that follows the rate-determining step. Further, the significant intramolecular KIE observed in each of the

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[1] Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

[2] Frimer, A. A.; Stephenson, L. M. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 68−87.

[3] Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5227.

[4] Stephenson, L. M.; Speth, D. R. *J. Org. Chem.* **1979**, *44*, 4683−9.

[5] Cheng, C.-C.; Seymour, C. A.; Petti, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910.

[6] Salomon, M. F.; Pardo, S. N. Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2473.

[7] For comparison, ρ^+ for solvolysis of 1-arylcyclpentyl *p*-nitrobenzoates is −3.82. See: Brown, H. C.; Ravindranathan, M.; Peters, E. N.; Rao, C. G.; Rho, M. M. *J. Am. Chem. Soc.* **1977**, *99*, 5373.

[8] Kwart, H.; Brechbiel, M. *J. Org. Chem.* **1982**, *47*, 5409.

[9] Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555.

[10] Mehführer, M.; Thirring, K.; Berner, H. *J. Org. Chem.* **1997**, *62*, 4078.

[11] Jenner, G.; Papadopoulos, M. *Tetrahedron Lett.* **1996**, *37*, 1417. Jenner, G. *New J. Chem.* **1997**, *21*, 1085.

[12] Laszlo, P.; Testonhenry, M. *J. Phys. Org. Chem.* **1991**, *4*, 605.

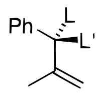
[13] Stephenson, L. M.; Orfanopoulos, M. *J. Org. Chem.* **1981**, *46*, 2200.

[14] Grdina, B.; Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979** *101*, 3111−2.

[15] Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160.

10.1021/jo9917590 CCC: $19.00

labeled stereoisomers **3**−**5** required an intermediate or equilibrating set of intermediates that is still free to abstract H/D from any of the methyl groups. Snider proposed as possibilities the geometrically nonrigid π-complex **6** or three-membered ring nonclassical cation **7**, or the rapidly equilibrating open ions **8** and **9**.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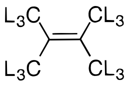
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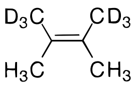
intermolecular k_{d0}/k_{d12} = 1.4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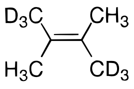
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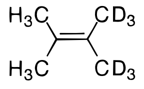
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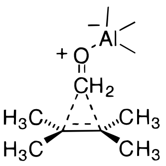
intramolecular k_H/k_D

2.7 2.9 3.3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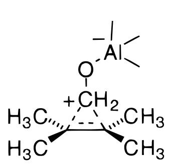
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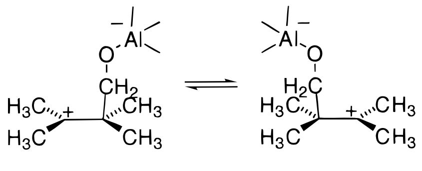
8 **9**

We describe here a study of the ^{13}C and ^{2}H KIEs for the dialkylaluminum chloride-catalyzed ene reaction of formaldehyde with 2-methyl-2-butene. Our initial aim in investigating the ^{13}C isotope effects for these reactions was to distinguish among these interesting possibilities. However, the deuterium KIEs obtained concurrently from the natural-abundance methodology employed suggested a reinvestigation of the intermolecular isotope effects with tetramethylethylene. We report here a combination of studies which support a stepwise mechanism through a reversibly formed open classical cation with a rate-limiting proton-transfer step.

Results and Discussion

The ^{13}C and ^{2}H KIEs for the ene reaction of formaldehyde with 2-methyl-2-butene catalyzed by diethylaluminum chloride were determined combinatorially at natural abundance by NMR.[16] Ene reactions of 2-methyl-2-butene on an ≈1 mole scale employing a 1.5-fold excess of paraformaldehyde were taken to 72 ± 3% and 77 ± 2% conversion at 10 °C in toluene by the slow addition of conversion-limiting diethylaluminum chloride. Under these conditions the reaction is >90% selective for formation of the ene product. The unreacted 2-methyl-2-butene, recovered by an aqueous workup and fractional distillation, was analyzed by ^{13}C and ^{2}H NMR along with a standard sample of the alkene not subjected to the reaction conditions. The changes in ^{13}C and ^{2}H composition were then calculated using the C4 methyl group as an internal standard with the assumption that its isotopic composition does not change during the reaction.[17] From the changes in isotopic composition the isotope effects were calculated as previously described.[16] The results are summarized in Figure 1.

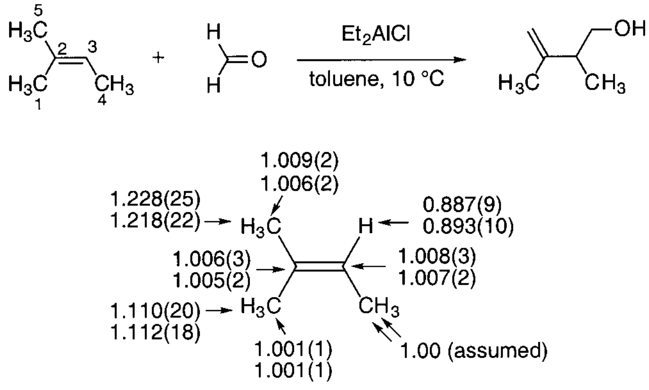

Figure 1. KIEs (k_H/k_D or $k_{^{12}C}/k_{^{13}C}$) for the Et$_2$AlCl-catalyzed ene reaction of 2-methyl-2-butene with paraformaldehyde.

In interpreting these KIEs, it should be noted to start with that the overall deuterium isotope effects obtained in this way may represent a combination of primary and secondary effects. This complicates their interpretation and may make them appear deceptively small compared to the effects usually obtained with fully labeled substrates. Another problem is that the moderate C3 and C5 ^{13}C KIEs are in a range that is consistent with either a primary or a secondary carbon isotope effect. However, we are unable to draw a reasonable mechanism for which a significant secondary ^{13}C KIE at C5 would be expected, so we interpret the KIE of 1.006−1.009 at C5 as suggesting that proton transfer is occurring from this carbon in the rate-limiting step. Snider previously observed a partial preference for reaction of the trans alkyl group in trisubstituted alkenes,[18] and some reaction at the C1 (cis) methyl group may contribute to the observed KIEs. If it is mainly the C5 (trans) methyl group reacting, and proton transfer is happening in the rate-limiting step, the relative rate of reaction of the monodeuterio isotopomer **10** will be $2/\mathrm{KIE}_{2^\circ} + 1/\mathrm{KIE}_{1^\circ}$ compared to a symmetry number-adjusted rate of 3 for the perprotio isotopomer **11**. (KIE_{2° is k_H/k_D when a proton is abstracted from **10** while KIE_{1° is k_H/k_D when a deuterium is abstracted from **10**.) The observed isotope effect would then be $3/(2/\mathrm{KIE}_{2^\circ} + 1/\mathrm{KIE}_{1^\circ})$. Both KIE_{2° and KIE_{1° are unknowns, but the observed KIE at C1 is likely to reflect KIE_{2° (perhaps augmented somewhat by contribution from a primary effect). If KIE_{2° is in the range of 1.04−1.12 and we consider the C5 deuterium KIE in the range

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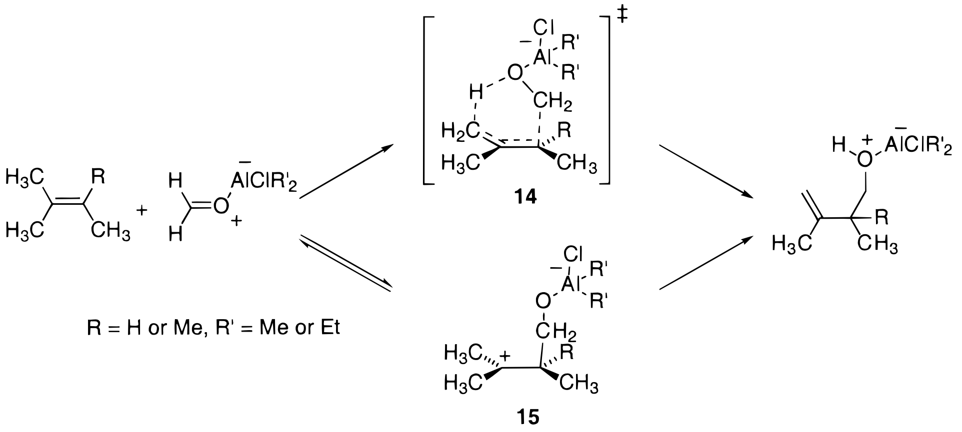
(16) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357.

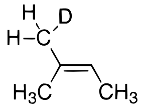
(17) The experimental isotope effects here are *relative* to those in the C4 methyl group, though it is dubious whether the deuterium KIE for the C4 methyl group is negligible. To aid in comparison with experiment, the theoretical isotope effects in Figure 2 are also made relative to the C4 methyl group. The predicted absolute deuterium isotope effect at C4 is 0.957.

(18) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555.

Scheme 1



of 1.20−1.25, then $KIE_{1°}$ is in the range of 1.4−2.1. Allowance for some contribution from reaction at the cis methyl group C1 would tend to increase the calculated $KIE_{1°}$. The observed KIE at C5 is thus consistent with a small but significant primary deuterium isotope effect, and rate-limiting proton transfer.



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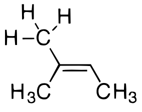
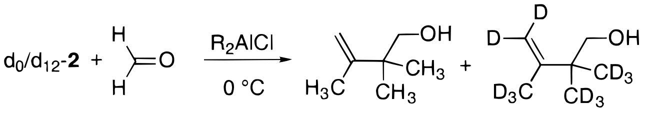


11

This was surprising in light of the results observed previously with **2**. We therefore reinvestigated the intermolecular isotope effect in the Lewis acid-catalyzed ene reaction of formaldehyde with d_0/d_{12}-**2**. Carefully quantitated mixtures of d_{12}-**2**[19] and d_0-**2** at ≈1 M in toluene or CH_2Cl_2 were taken to 10−12% conversion at 0 °C using limiting formaldehyde and either 1 or 2 equiv of Et_2AlCl (in toluene or hexanes, from different sources) or Me_2AlCl (in hexanes) per formaldehyde, with the Lewis acid added last, either all at once or slowly. In each case the k_H/k_D determined from the mixture of products **12** and **13** was in the range of 2.0 to 2.5. The isotope effect observed using Me_3Al as catalyst was 2.5−2.6.



k_H/k_D = 2.0-2.5 **12** **13**

Under no conditions could we reproduce the previously observed small intermolecular KIE[15] for this reaction.[20] The origin of this discrepancy is uncertain—it is perhaps impossible to rule out that small differences in the catalyst solution or reaction conditions could account for the divergent results. However, the requirement for stoichiometric amounts of Lewis acid in these reactions suggests that it is the major form of the aluminum in solution which serves as the active catalyst. NMR observation of these reactions was unfortunately not illuminating; Me_2AlCl-catalyzed reactions of d_0-**2** with paraformaldehyde in CD_2Cl_2 showed the rapid disappearance of the Me_2AlCl peak at δ −0.31 with the rise of a methane peak and two other product peaks at δ −0.51 and −0.53. The latter peaks, similar to peaks observed at δ −0.46 and −0.48 from the reaction of Me_2AlCl with isobutanol, were assigned to the dimethylaluminum and chloromethylaluminum alkoxides of **12**.

The observation here of a large intermolecular KIE under a variety of conditions has a substantial mechanistic implication. The similarity of the intermolecular KIE to the intramolecular KIEs previously observed[21] indicates that under our conditions there is not a product-determining step following the rate-limiting step, as previously proposed. Rather, these results indicate that a product-determining proton-transfer step is rate limiting.

This leaves two mechanisms possible—a concerted ene reaction through a transition state resembling **14** or a stepwise process through a reversibly formed adduct, depicted as **15 (Scheme 1)**. Qualitatively, the vinylic deuterium KIE of ≈0.89 is large, consistent with the C3 carbon being fully sp^3-hybridized in the rate-limiting transition state, and the C3 KIE of 1.007−1008 is smaller than 1° carbon isotope effects in similar reactions.[22] This is consistent with rate-limiting proton transfer in **15**, but it is not possible to exclude on a qualitative basis a concerted ene transition state with nearly complete bond formation between the attacking electrophile and C3.

To aid in the distinction between these two possibilities, theoretical calculations were carried out on the model reaction of 2-methyl-2-butene with a protonated formaldehyde. We were unable to locate a concerted ene transition structure for this reaction. However, the intermediate cation **16** was found in Becke3LYP calculations using a 6-31G* basis set, and predicted equilibrium isotope effects for the formation of **16** were calculated[17,23] (Figure 2). If the rate-limiting step is proton transfer in

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[19] Mazzocchi, H. P.; Klinger, L. *J. Am. Chem. Soc.* **1984**, *106*, 7567.

[20] We have also briefly reinvestigated the intermolecular isotope effect for the $EtAlCl_2$-catalyzed reaction of methyl propiolate with d_0/d_{12}-**2**, finding k_H/k_D = 1.44−1.55. This is only slightly larger than the KIE previously observed (1.1 ± 0.15, see ref 15), but is only moderately smaller than the intramolecular isotope effects observed in this reaction. This hinders any clear interpretation of the isotope effects in this reaction.

[21] The intermolecular and intramolecular isotope effects need not be identical due to differing contributions from secondary effects.

[22] For comparison with reactions involving rate-limiting unsymmetrical electrophilic attack on an alkene, the addition of dichlorocarbene to 1-pentene and the reaction of PTAD with isobutene exhibit terminal olefinic ^{13}C KIEs of ≈1.026 and 1.036, respectively. (Keating, A. E.; Merrigan, S. R.; Singleton, D. A.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3933, and Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885.) Unfortunately, better models are currently lacking.

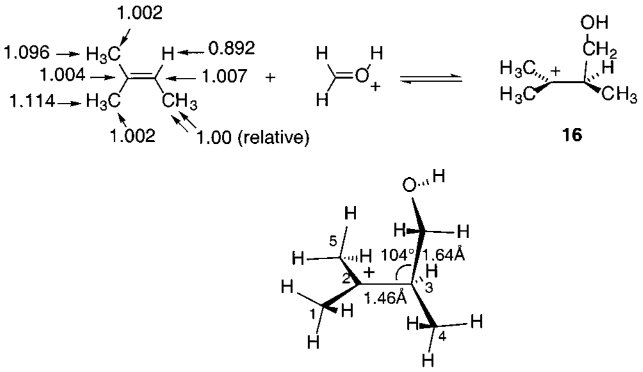

Figure 2. Predicted equilibrium isotope effects[23,17] (K_H/K_D or $K_{^{12}C}/K_{^{13}C}$, 25 °C) for the model reaction forming **16**, and calculated structure of **16**.

15, the KIEs for the overall reaction at centers not undergoing bonding changes in the proton transfer would be expected to resemble the equilibrium isotope effects for formation of **15**. In line with this idea, there is a close correlation between the predicted isotope effects for **16** and the experimental isotope effects at all atoms except the reacting C5 methyl group. This striking correspondence of calculated and experimental isotope effects provides substantial support for the stepwise ene mechanism.

Consideration of the structure of the intermediate **15** is illuminating. The substantially inverse C3 vinylic isotope effect does not support the involvement of a loose π-complex, and the significant secondary deuterium KIE in the cis (C1) methyl group, relative to the C4 methyl group, does not support a symmetrical three-membered ring intermediate. Thus the isotope effects, ignoring the theoretical results, favor an open, classical cation intermediate as depicted in **15.** In line with this idea, the theoretical model structure **16** is essentially classical. However, it does show a lengthening of the C3-hydroxymethylene carbon bond (1.64 Å), some closure of the C2−C3-formyl carbon angle (104°), and some delocalization of positive charge into the hydroxymethylene group ($+0.23\ e^-$ in a Mullikin analysis). This slight "nonclassical character" might be expected to inhibit both carbonium-ion rearrangements[24] and free rotation about the C2−C3 bond. This possibility compromises the expectation of an intramolecular isotope effect for a stepwise mechanism in the previous studies of **1**.[13] A mechanism involving rate-limiting electrophilic attack followed by a predetermined proton abstraction provides the simplest explanation for absence of significant inter- and intramolecular isotope effects in **1**.[25]

Conclusion

The general observations associated with Lewis acid-catalyzed ene reaction, including byproducts,[8−10] regioselectivity, and reactivity observations,[6] have long been associated with carbocation intermediates but provide indecisive mechanistic evidence. For example, regioselectivity and reactivity observations in general do not distinguish stepwise and highly asynchronous concerted mechanisms, and it is always unclear whether byproducts represent the main mechanistic pathway. Isotope effects provide a more powerful mechanistic probe; however, the primary deuterium isotope effects normally obtained address only one of the bonding changes occurring in the ene mechanism. The results here show the increased information available when ^{13}C and secondary ^{2}H KIEs are also obtained. Another complicating factor in Lewis acid-catalyzed ene reactions is the possibility for either the first or second step of a stepwise process to be rate limiting. The combination of isotope effects observed in the reactions here provide substantial support for a stepwise mechanism involving a carbocation intermediate with the second, proton-transfer step being rate limiting.[26]

It would not be surprising for changes in the Lewis acid-complexed enophile or reaction conditions led to a change from the second step to the first step being rate limiting. Such a change can adequately explain the prior results with **1**, and may possibly be responsible for the differing results with **2** here versus previously. Overall, a simple stepwise mechanism through a carbocation intermediate, with either the first or second step being rate limiting, is likely the most common mechanism in Lewis acid-catalyzed ene reactions.

Experimental Section

2,3-Dimethyl-2-butene-d_{12} was prepared as previously described[19] and fractionally distilled, and ^{13}C NMR and GC analysis did not exhibit any detectable impurities. Mixtures of d_{12}-**2** and d_0-**2** were quantitated by weight and by GC analysis of 2,3-dibromo-2,3-dimethylbutane obtained by bromination of the mixtures. The quantitations agreed within 2%. A less precise quantitation in one case by ^{13}C NMR also agreed within experimental error.

Ene Reactions of d_0/d_{12}-2. To an ice-cooled mixture of d_0/d_{12}-**2** (196.5 mg, $d_0/d_{12} = 1.09$, 2.19 mmol total) and 8.1 mg (0.27 mmol) of paraformaldehyde in 2.64 mL of CH_2Cl_2 was added dropwise over the course of 10 min 0.28 mL (0.28 mmol) of 1.0 M Me_2AlCl in hexanes. The ice bath was then removed, and the mixture was stirred for 30 min at 25 °C. The reaction was then quenched by the addition of 2 mL of 10% aqueous NaH_2PO_4. An additional 2 mL of CH_2Cl_2 was added, and 10% HCl was added dropwise until two layers separated (≈2 mL). The organic layer was washed with 5 mL of water and dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. GC analysis of the residue (SE-54, 30 M × 0.32 mm) exhibited a 2.45:1 ratio of **12**:**13** ($k_H/k_D = 2.25$). A ^{1}H NMR spectrum of

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(23) (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261. (b) Wolfsberg, M. *Acc. Chem. Res.* **1972**, *5*, 225. (c) The calculations used the program QUIVER (Saunders, M.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1989**, *111*, 8989) with Becke3LYP frequencies scaled by 0.9614. (Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.).

(24) Lewis acid-catalyzed ene reactions that could involve rearrangeable carbocations sometime show rearrangement and sometimes not. See: Benner, J. P.; Gill, G. B.; Parrott, S. J.; Wallace, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 291.

(25) This is exactly the idea in the explanation of the results with **1** proposed by Snider and Ron (See ref 15). However, an inconsistency arises upon consideration of the three-membered ring intermediate that was proposed. With tetramethylethylene, such an intermediate was concluded to be configurationally fluxional to explain the significant isotope effects with **3**−**5**. Such fluxional character in the intermediate with **1** would allow the intermediate to freely choose between a labeled methylene group and an equally reactive unlabeled methyl group, and the observation of an isotope effect would be expected. The absence of an isotope effect on the product distribution with **1** requires that the product regiochemistry be predecided in the first step of a stepwise process.

(26) In a related reaction, the Lewis acid-promoted cyclization of 5-hexenyl acetals, identical intermolecular and intramolecular isotope effects of 1.65 were observed. (See: Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399.) These results were interpreted in terms of a concerted reaction, but are also consistent with a stepwise process with the second step being rate limiting, as in the mechanism here.

the crude product using a 30 s delay between pulses exhibited a product ratio of 2.59:1 **12**:**13** ($k_H/k_D = 2.37$) based on the relative integrations at δ 4.96 (100.0), 4.86 (101.6), and 3.42 (279.5).

In a repetition of this experiment, k_H/k_D as measured by GC and NMR were 2.28 and 2.36, respectively. After purification of the **12** + **13** by flash chromatography on silica gel using 3:1 pentane:ethyl acetate as eluent, the k_H/k_D determined from the NMR of the peaks at δ 4.96, 4.86, and 3.42 was 2.43. The ratio of **12** and **13** could also be determined in this case by deconvolution of the slightly separated methylene peaks at δ 3.42, giving a k_H/k_D of 2.46.

An analogous reaction using 2.31 mmol of d_0/d_{12}-**2**, 0.3 mmol of paraformaldehyde, and 0.6 mmol of Me_2AlCl, the last added in one portion, exhibited a k_H/k_D of 2.2 as determined by GC and 2.20 as determined by NMR. Another reaction using 3.81 mmol of a 1:4.77 mixture of d_0 and d_{12}-**2** (using excess d_{12}-**2** leads to increased precision in the measured k_H/k_D), 0.37 mmol of paraformaldehyde, and 0.6 mmol of Me_2AlCl added dropwise exhibited a k_H/k_D of 2.38 as determined by GC and 2.45 as determined by NMR.

An Et_2AlCl-catalyzed reaction was carried out using d_0/d_{12}-**2** (218.2 mg, $d_0/d_{12} = 1.09$, 2.43 mmol total), 8.1 mg (0.27 mmol) of paraformaldehyde in 2.0 mL of toluene, and 0.16 mL (0.29 mmol) of 1.8 M Et_2AlCl in toluene, the last added dropwise over the course of 10 min at 0 °C. This reaction was stirred at 25 °C for 30 min, and worked up as above. A k_H/k_D of 2.32 as determined by GC and 2.28 as determined by NMR. An analogous reaction using methylene chloride as solvent instead of toluene exhibited a k_H/k_D of 2.37 as determined by GC and 2.18 as determined by NMR. Another reaction in methylene chloride using Et_2AlCl in hexanes (Acros) instead of Et_2AlCl in toluene (Aldrich) exhibited k_H/k_D's of 2.31 and 2.06 by GC and NMR, respectively. A repetition of this last reaction exhibited k_H/k_D's of 2.15 and 1.95 by GC and NMR, respectively.

A Me_3Al-catalyzed reaction was carried out using d_0/d_{12}-**2** (177.9 mg, d_0/d_{12}=1.05, 2.13 mmol total), 11.7 mg (0.39 mmol) of paraformaldehyde in 2.5 mL of CH_2Cl_2, and 0.15 mL (0.30 mmol) of 2.0 M Me_3Al in hexanes, the last added dropwise at 0 °C. The reaction was stirred at 25 °C for 90 min and worked up as described above. The k_H/k_D's as determined by GC and NMR were 2.65 and 2.51, respectively.

Ene Reaction of 2-Methyl-2-butene. Example Procedure. To an ice-cooled mixture of 65.5 g (0.936 mol) of 2-methyl-2-butene, 42.4 g (1.41 mol) of paraformaldehyde, and 23.8 g (0.24 mol) of 1,2-dichloroethane (used as NMR and GC internal standard) in 1000 mL of toluene was added dropwise 350 mL (0.63 mol) of Et_2AlCl (1.8 M in toluene). After stirring for 2 h at ≈10 °C the reaction was found to be 72 ± 3% complete by both NMR and GC analyses of aliquots, and the NMR analysis found 617 mmol of the ene product (66% based on the total starting 2-methyl-2-butene, 92% based on unreacted 2-methyl-2-butene). The reaction was quenched by the slow addition of 300 mL of cooled 10% KH_2PO_4, and the addition of 750 mL of 20% HCl resulted in the separation of two layers. The organic layer was separated, and the aqueous layer was extracted with two 150-mL portions of toluene. The combined organic layers were washed with three 300-mL portions of water, dried over anhydrous $MgSO_4$, and fractionally distillated over a 30 cm Vigreaux column until the head temperature reached 80 °C. The distillate was then redistilled fractionally to afford 10.5 g of the unreacted 2-methyl-2-butene in >99% purity (GC).

An analogous reaction using 64.7 g of 2-methyl-2-butene was taken to 77 ± 2% conversion, and 9.1 g of unreacted 2-methyl-2-butene was recovered.

NMR Measurements. NMR measurements were taken on neat samples of 2-methyl-2-butene in 10 mm NMR tubes filled to a constant height of 5 cm. A T1 determination by the inversion−recovery method was carried out for each NMR sample, and the T1 for each NMR signal remained constant within experimental error from sample to sample.

The ^{13}C spectra were recorded at 100.58 MHz with inverse gated decoupling, using 175 s delays between calibrated 45° pulses, an acquisition time of 5.999 s collecting 228096 points. The ^{2}H spectra were recorded at 61.395 MHz using 10.0 s delays between calibrated 45° pulses and an acquisition time of 7.956 s collecting 10560 points. Integrations were determined numerically using a constant region for each peak that was ≈5 times the peak width at half-height on either side of the peak, and using only a zeroth order baseline correction.

Results for All Reactions. The relative integration of the C4 methyl carbon was set to 1000 for ^{13}C spectra and 3000 for ^{2}H spectra. The average integrations for the other carbons or deuteriums for each reaction are shown in Table 1, along with the standard results for the starting materials. In each case the averages are based on 6 spectra. Table 1 also shows the relative isotopic enhancements (R/R_0), calculated as the ratio of integrations for the recovered versus standard materials. The standard deviations ($\Delta R/R_0$) were calculated from eq 3, where IntSample is the average integration for each sample peak (listed in the table), IntStandard is the average integration for the corresponding peak in the standard (listed in the table), and ΔIntSample and ΔIntStandard are the standard deviations in the sample and standard peaks, respectively. From the R/R_0's, $\Delta R/R_0$'s, and uncertainties in the % conversion, the KIEs and errors were calculated as previously described.[16]

$$\Delta R/R_0 = R/R_0{*}((\mathrm{IntSample}/\mathrm{IntSample})^2 + (\mathrm{IntStandard}/\mathrm{IntStandard})^2)^{1/2} \quad (3)$$

Table 1. Average ^{13}C and ^{2}H Integrations and R/R_0's for Ene Reactions of 2-Methyl-2-butene

^{13}C Results

	C1	C2	C3	C4	C5
exp 1	1020.12	1018.49	1077.93	1000.0	1058.55
standard	1018.19	1011.08	1067.75	1000.0	1046.51
R/R_0	1.002	1.007	1.010		1.012
$\Delta R/R_0$	0.002	0.004	0.004		0.002
exp 2	1019.41	1018.52	1078.62	1000.0	1055.34
standard	1018.19	1011.08	1067.75	1000.0	1046.51
R/R_0	1.001	1.007	1.010		1.008
$\Delta R/R_0$	0.002	0.003	0.003		0.002

^{2}H Results

	H_{vinyl}	$C1H_2D$	$C4H_2D$	$C5H_2D$
exp 1	1028.50	3283.31	3000.0	3655.76
standard	1210.34	2893.18	3000.0	2886.94
R/R_0	0.850	1.135		1.266
$\Delta R/R_0$	0.011	0.024		0.027
exp 2	1014.58	3353.86	3000.0	3756.63
standard	1210.34	2893.18	3000.0	2886.94
R/R_0	0.838	1.159		1.301
$\Delta R/R_0$	0.017	0.022		0.026

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