compound showed no peaks with magnitude greater than 0.3 e/Å^3.

Supplementary Material Available: Positional parameters, anisotropic thermal parameters, hydrogen atom parameters, bond angles, and conformational angles (13 pages). Ordering information is given on any current masthead page.

Mechanism of the Dimethyl Mesoxalate–Alkene Ene Reaction. Deuterium Kinetic Isotope Effects[1]

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Our previous kinetic studies[2] of the addition of dimethyl mesoxalate (1) to alkenes furnished thermodynamic parameters ($\Delta H^{\ddagger}$ = 75 to 96 kJ mol^{-1} and $\Delta S^{\ddagger}$ = -120 to -170 J mol^{-1} K^{-1}) which strongly suggest that this ene reaction (see Scheme I) has a concerted mechanism with a late (product-like) transition state. In the present report we describe an extension of this work aimed at a more detailed elucidation of the structure of the transition state by the study of kinetic isotope effects.

Kinetic isotope effects are a powerful diagnostic tool for the investigation of reaction mechanisms.[3] However, this approach has been used to study relatively few ene reactions.[4] The conclusions that can be drawn from the data can be summarized by two generalizations; viz., (i) a primary isotope effect $k_H'/k_D' \neq 1$ supports a concerted reaction mechanism and (ii) values that are clearly short[3] of the theoretical maximum (k_H'/k_D' = 7) are indicative of a nonsymmetrical transition state. On the other hand an example of such a primary isotope effect (k_H'/k_D' = 2.41) was observed recently[4d] for the reaction of allene with perfluorocyclobutanone and was ascribed to the nonlinear transfer of the hydrogen atom (C··H··O angle of ca. 100 °C). We conclude that isotope effects of this intermediate magnitude could also be due to a deviation from a symmetrical migration of the hydrogen atom or a combination of these effects, and in the absence of independent information on the degree of the C–H bond rupture in the transition state, the inference of its geometry from the value of the isotope effect appears inconclusive.
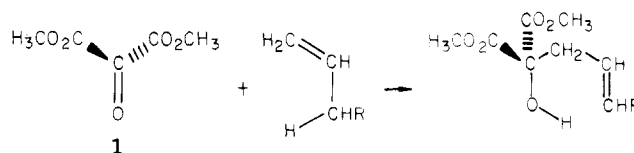
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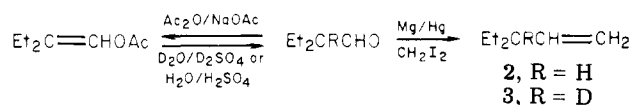
Scheme I

Scheme II

2, R = H
3, R = D

Table I. Primary Isotope Effects for the Reaction of 3-Ethyl-1-pentene with Dimethyl Mesoxalate

temp, °C	120	130	140	150
k_H'/k_D'	2.36 ± 0.16	2.37 ± 0.16	2.29 ± 0.15	2.09 ± 0.13

Results and Discussion

An alkene containing a tertiary allylic hydrogen atom is required to obtain a primary effect directly, free from secondary effects. For our experiments we chose 3-ethyl-1-pentene (2) and its deuterated derivative 3. The alkenes were obtained by the route shown in Scheme II.

The kinetic isotope effect for the reaction of 3-ethyl-1-pentene with dimethyl mesoxalate (1) was determined at various temperatures (Table I) by an independent measurement of the ene reaction rate for deuterated 3 (k_D) and undeuterated (k_H) alkene 2. However, the measured isotope effect for the ene reaction of the 1-heptenes, i.e., with hydrogen atoms at the secondary allylic carbon atom, is actually the resultant of primary (k_H'/k_D') and secondary k_H''/k_D'') effects. To separate these effects, it was necessary to examine the reactions of 1-heptene (4), 1-heptene-3-d$_1$ (5), and 1-heptene-3,3-d$_2$ (6).

The experimental values of the kinetic isotope effects were found from the ratios of the deuterated and protic adducts determined by mass spectrometry, i.e., by the competitive method which ensured an adequately high accuracy.

The reactions with monodeuterated heptene (5) were carried out for the intramolecular comparison and with dideuterated heptene (6) for the intermolecular comparison with 4. The separate primary and secondary isotope effects were calculated by using eq 1 and 2 (see Experimental Section). The solution of these equations gave k_H'/k_D' = 2.16 ± 0.08 and k_H''/k_D'' = 1.05 ± 0.04 values, respectively. Very similar values for the primary isotope effect (Table I) were obtained from the reactions of 3-ethyl-1-pentene. The results also show that isotope differentiation takes place in the rate-determining step.[4e]

In a concerted ene reaction the magnitude of the secondary isotope effect depends on the extent of the sp^3 → sp^2 rehybridization of the alkene C-3 carbon atom in the transition state. The value k_H''/k_D'' = 1.05 is consistent with our previous findings[2] which indicated a late transition state of the ene reaction of dimethyl mesoxalate with alkenes. On the one hand it is lower than the value (1.15) of the secondary isotope effect in a S$_N$1 solvolysis reaction in which the transition state has a structure resembling that of an sp^2 hybridized carbonium ion;[5] on the other hand it is close to the isotope effect for the retrodiene reaction of the tetracyanoethylene-9,10-dideuterio-

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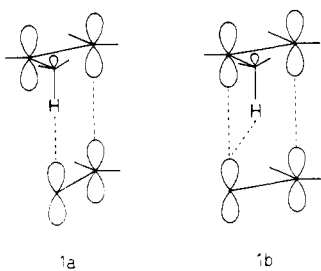
Figure 1.

anthracene adduct (1.09),[6] for which the late transition state has been claimed on the basis of the thermodynamic data expressed in terms of Hammond's postulate.[7]

The primary isotope effect for the ene reaction of 3-ethyl-1-pentene or 1-heptene, amounting to about 2.16, is considerably smaller than the theoretical maximum of $k_H'/k_D' = 7$.[3] Such a small value in a concerted process might be due to hydrogen atom transfer through a non-symmetrical and/or a nonlinear transition state.

A number of attempts were made to correlate the primary isotope effect with the degree of C–H bond breaking in the transition state, designated by the bond order $\mathcal{H}$. For the purpose of our analysis the most suitable method appeared to be the one reported by More O'Ferrall and Kouba[8] concerning a proton migration from the carbon atom to the methoxyl ion. The process considered is a linear hydrogen transfer which is essential for our analysis. Moreover the isotope effect for this reaction depends, as for an ene reaction, on the stretching vibrations of the bonds whose polarization is of the same type in both cases: the proton-type hydrogen migration. The extent of C–H bond rupture in the examined ene reaction was needed in order to apply the relationship of k_H'/k_D' to the bond order $\mathcal{H}$ given by More O'Ferrall and Kouba.[8] It was estimated as follows. The energies were calculated for two loose models of the transition state[2] of the ene reaction, one neglecting O–H bond formation and the other neglecting C–H bond formation. They differed from the experimental values by 125 kJ mol^{-1} and 46 kJ mol^{-1}, respectively. Treating these values as a measure of extent of C–H and O–H bond formation in the actual transition state gave $\mathcal{H}$ = 0.28.

From a plot of the primary isotope effect, k_H'/k_D', vs. bond order $(\mathcal{H})$,[8] the estimated value of $\mathcal{H}$ for the present ene reaction corresponds to a primary isotope effect, $k_H'/k_D' = 4.5$. The much smaller experimental value (2.16) indicates that, apart from nonsymmetrical breaking and formation of the C–H and O–H bonds, the hydrogen transfer takes place through a nonlinear transition state. By use of the calculations of More O'Ferrall,[9] the present value corresponds to an angle of the hydrogen atom transfer (C··H··O) of about 120°.

The dependence of k_H'/k_D' on the angle of hydrogen atom transfer has been calculated for $\mathcal{H}$ = 0.5. Our estimation is based on the assumption that k_H'/k_D' changes analogously for other values of $\mathcal{H}$.[10] Thus the hypothesis that the transition state of an ene reaction involves the linear transfer of a hydrogen atom[11] (see Figure 1a for the

dimethyl mesoxalate–alkene reaction) cannot be reconciled with the present data.

The foregoing hypothesis stemmed from the assumption that the geometry of the transition state of an ene reaction depends on the allylic overlap of the ruptured C–H and arising O–H bonds (Figure 1a). We advance the other factor as more important. An attractive geometry for the transition state includes a stabilizing effect due to a charge-transfer-type interaction between the substrates. This suggestion is supported by the detection of a charge-transfer complex in the ene reaction of another carbonyl enophile (carbonyl cyanide) with alkenes.[12] In this model the juxtaposition of the olefinic bond and the carbonyl group should be favorable and would lead to a geometry (see Figure 1b) that is compatible with the deduced angle for hydrogen atom transfer.

Experimental Section

^{1}H NMR spectra were obtained with a JEOL-JNM-4H-100 spectrometer. IR spectra were recorded on a Unicam SP-200 spectrophotometer. VPC analyses were carried out on a Chromatron G CHF 18.3 instrument. Mass spectra were obtained with a LKB 2091 spectrometer.

Materials. Dimethyl mesoxalate (1), bp 79 °C (14 torr), was prepared according to the procedure described for diethyl mesoxalate.[13] 1-Heptene (4) was obtained commercially. 1-Heptene-3-d_1 (5) and 1-heptene-3,3-d_2 (6) were prepared by a literature method[14] and their isotopic purities, as determined by mass spectroscopy, were 97.1% (2.9% 4) and 84.6% (15.4% 5), respectively. Solvents and other chemicals were purified according to standard methods.

2-Ethyl-1-butenyl acetate was prepared from 2-ethylbutanol by the literature method[15] in 49% yield.

2-Ethylbutanal-2-d_1. A mixture of 2-ethyl-1-butenyl acetate (58.5 g, 0.41 mol), deuterium oxide (15.1 g, 0.75 mol), and dideuterated sulfuric acid (0.5 g) was heated under reflux with stirring for 180 h. The mixture was neutralized with solid NaHCO$_3$, diluted with ether (150 mL), washed with water, and dried over anhydrous MgSO$_4$. Evaporation of the solvent and distillation gave the product (31 g, 75%), bp 55–56 °C (30 torr), 98% isotopic purity (^{1}H NMR).

3-Ethyl-1-pentene-3-d_1 (3). A solution of diiodomethane (30 g, 0.11 mol) and 2-ethylbutanal-2-d_1 (10 g, 0.10 mol) in anhydrous ether (200 mL) was added in a dropwise manner to stirred magnesium amalgam (prepared by shaking mercury (2 g) with magnesium turnings (6 g) under nitrogen for 0.5 h) at a rate assuring gentle reflux. The mixture was stirred for 1 h at room temperature and poured into ice–water (100 g). The aqueous layer was separated and washed with ether, and the combined extracts were dried over anhydrous MgSO$_4$. The residue after evaporation of ether was twice fractionated to give 3 (4.8 g, 49%), bp 84–85 °C, ≥98% (mass spectrum) isotopic purity.

Kinetic Procedure. Kinetic Isotope Effect in the Ene Reaction of 1 with 3-Ethyl-1-pentene. The primary isotope effect was determined by measuring separately, but under the same conditions, k_H and k_D rate constants. The reactions were followed kinetically in the temperature range 110–150 °C by the ampule technique. The pseudo-first-order experiments were run with 12–14 M excess of alkene to at least 70–80% completion. Three measurements were made for each of k_H' and k_D' and the alkene concentration was identical in the compared H and D runs. Product analysis and rate constant evaluation were carried out as described before.[2] The kinetic isotope effect (k_H'/k_D') was calculated as $k_H'/k_D' = k_H/k_D$, where k_H and k_D are pseudo-first-order constants. Results are given in Table I.

Primary and Secondary Isotope Effects in the Ene Reaction of 1 with 1-Heptene. The Intramolecular Variant.

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(10) As already mentioned above, the very similar value (2.41) of the primary isotope effect for the ene reaction of perfluorocyclobutanone with allene led other workers to suggest a transfer angle of 100°.[4d] However, this estimate involved the tacit assumption that $\mathcal{H}$ was 0.5 for this reaction.

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Table II. Ratios of Undeuterated to Deuterated Ene
Adducts for Reaction of 1-Hexenes with Dimethyl
Mesoxalate at 130 °C

intermolecular expt		intramolecular expt	
reaction time, h	content of the deuterated ene adduct, %^{a}	reaction time, h	content of the deuterated ene adduct, %^{a}
5	36.72	6	68.72
8	36.59	7	68.43
10	37.12	9	68.72
12	36.29	16	68.20
	average 36.68		average 68.52

^{a} Arithmetical mean from three samples.

Reaction of 1-heptene-*3*-d_1 (5) with 1 was carried out under pseudo-first-order conditions (18 M excess of 5) at 130 °C as described above. Samples were withdrawn at 1–3-h intervals, quenched by cooling to –20 °C, diluted with benzene, passed through a layer of silica gel, washed with water, dried (anhydrous MgSO$_4$), and evaporated. The deuterium content in the ene adduct was determined with 0.5% accuracy from the relative abundance of M – H$_2$O ions in its mass spectrum.

The Intermolecular Variant. Reaction of 35 M excess of a mixture (about 1:1) of 1-heptene (4) and 1-heptene-*3,3*-d_2 (6) with 1 was followed kinetically, using the experimental procedure and product analysis as in the intramolecular experiment. The results are given in Table II.

Treatment of the Data. The ratios of the undeuterated and deuterated ene adducts of dimethyl mesoxalate with selectively deuterated alkenes 5 and 6 carried out in the intramolecular and intermolecular experiments are related to the primary and secondary isotope effects by eq 1 and 2, respectively, where ([H]/

$$\left(\frac{[H]}{[D]}\right)_{intra} = \frac{k_{D(H)}}{k_{H(D)}} = \frac{k_{H(H)}/k_{H(D)}}{k_{H(H)}/k_{D(H)}} = \frac{k_H''/k_D''}{k_H'/k_D'} \quad (1)$$

$$\left(\frac{[H]}{[D]}\right)_{inter} = \frac{k_{H(H)}}{k_{D(D)}} = \left(\frac{k_{H(D)}}{k_{D(D)}}\right)\left(\frac{k_{H(H)}}{k_{H(D)}}\right) = \left(\frac{k_H'}{k_D'}\right)\left(\frac{k_H''}{k_D''}\right) \quad (2)$$

[D])$_{intra}$ = the ratio of undeuterated and deuterated ene adduct in the intramolecular comparison, ([H]/[D])$_{inter}$ = the same ratio for intermolecular comparison, and $k_{H(H)}$, $k_{D(H)}$, $k_{H(D)}$, and $k_{D(D)}$ are rate constants of the respective ene reactions; subscripts denote the atom transferred to the oxygen atom and atom (in parentheses) which remains bonded to the carbon atom.

Since the alkenes 5 and 6 used were not isotopically pure (5 contained 2.9% 4 and 6 contained 15.4% 5) the ratios of undeuterated and deuterated ene adducts were related to the primary and secondary isotope effects by appropriately modified eq 3 and 4, where ([H]/[D])^{exp} = the ratios of undeuterated and deuterated

$$\left(\frac{[H]}{[D]}\right)_{intra}^{exp} = \left[1 + \left(\frac{k_H'}{k_D'}\right)\left(\frac{c}{100-c}\right)\right]\left[\left(\frac{k_H''}{k_D''}\right)\middle/\left(\frac{k_H'}{k_D'}\right)\right] \quad (3)$$

$$\left(\frac{[H]}{[D]}\right)_{inter}^{exp} = \frac{1 + \left(\frac{k_D'}{k_H'}\right)\left(\frac{100-(a+b)}{a}\right)}{1 + \left(\frac{k_H'}{k_D'}\right)\left(\frac{100-(a+b)}{b}\right)}\left(\frac{k_H'}{k_D'}\right)\left(\frac{k_H''}{k_D''}\right) \quad (4)$$

adducts (Table II), a = 41.2%, b = 49.7%, 100 – (a + b) = 9.1% – the percentage of 1-heptene (4), 1-heptene-*3,3*-d_2 (6), and 1-heptene-*3*-d_1 (5) in the mixture, and c = 2.9% the content of 1-heptene (4) in 5.

Solution of eq 3 and 4 gave kinetic isotope effects values:

$$\frac{k_H'}{k_D'} = 2.16 \pm 0.08$$

$$\frac{k_H''}{k_D''} = 1.05 \pm 0.04$$

Analysis of error from eq 3 and 4, with estimated accuracy of peak measurement in the mass spectra of 0.75%, gave relative error of k_H'/k_D' and k_H''/k_D'' of 3.6%.

A New, Elegant Route to a Key Intermediate for the Synthesis of 9(*O*)-Methanoprostacyclin

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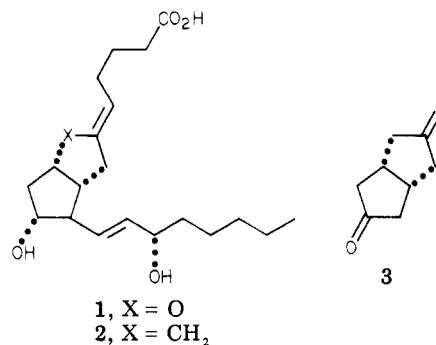
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A significant advance in prostaglandin biochemistry has been made with the discovery of PGI$_2$, 1 (X = O), the most

1, X = O
2, X = CH$_2$

potent of the prostaglandins in inhibiting aggregation of blood platelets.[1] Its very short biological half-life due to hydrolytic lability severely limits its usefulness as potential drug for treatment of thrombosis. In attempts to overcome this problem a sizeable number of papers dealing with the synthesis of stable analogues has already appeared.[2] Interest in the carbocyclic analogue 2 (X = CH$_2$) has developed rapidly and has generated a good deal of effort on its synthesis, which was first announced by one of us,[3] and later by others,[4,5] starting from *cis*-bicyclo[3.3.0]octa-3,7-dione (3) or through different routes.[6–8] Since it became clear that there would be a widespread demand for 2, we have sought a more straightforward approach, which avoids

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