Stereoselectivity of the Thermally Initiated Free-Radical Chain Addition of Cyclohexane to 1-Alkenes

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Alkanes can be added to alkenes in a thermally initiated free-radical chain reaction (one reaction). The addition of cyclohexane to 1-alkenes 1a–1 yields a mixture of (Z)- and (E)-2-cyclohexyl-1-alkenyl radicals 2a–1 which absorb hydrogen from cyclohexane to yield the products 3a–1. The stereoselectivity of the addition has been measured in the temperature range of 160–260°C. It strongly depends on the substituent X of the radical center and varies over a range of almost four orders of magnitude from |(Z)-3a|:|(E)-3a| = 33 (X = OMe) at 160°C to |(Z)-3I|:|(E)-3I| = 0.012 (X = 8Bu) at 260°C. The stereoselectivity is further influenced by the temperature and in most cases by the concentration of the hydrogen donor cyclohexane. The reaction is discussed in terms of the stereoselectivity of the addition of cyclohexyl radicals to the alkene, of the structure of the 1-alkenyl radical (α and π radical, respectively), the rate of inversion in the case of α-alkenyl radicals, and the relative rates of syn and anti hydrogen transfer.

Alkanes can be added to alkenes in a thermally initiated free-radical chain reaction (one reaction). The radical chain is initiated by a molecule-induced homolysis of alkane and alkene to give two alkyl radicals. The alkane can also be applied to alkenes. Thus, cyclohexane has been added to acetylene at 400°C and a pressure of 40 bar to give vinylcyclohexane.

Free-radical additions to alkenes have been reviewed. There are only relatively few examples of the intermolecular addition of carbon-centered radicals to alkenes. The stereochemistry of free-radical additions to alkenes has been discussed and reviewed. In the first step, free radicals attack the triply bonded carbon perpendicularly to the acetylenic bond to form an electron-paired π linkage and an alkyl radical at the adjacent carbon. It has been shown by ESR spectroscopy that 1-alkenyl radicals can be characterized as either "bent" σ radicals (X = H, alkyl, Hal, OMe) or as "linear" π radicals (X = Ph, CO₂R, CN). However, the conclusion that the latter 1-alkenyl radicals are π radicals has been questioned. Mason spin rotation spectroscopy confirmed the conclusion that 1-alkenyl radicals with X = Ph, SiMe₃ are linear π radicals.

In the case of linear π radicals, for example 2, the ratio of the stereospecific product is determined exclusively by the stereochemistry of the hydrogen transfer to the 1-alkenyl radicals. Because the approach of the hydrogen donor from the α-stereoisomer (away from the β-stereosubstituent) requires less activation enthalpy than the attack from the syn side, a hydrogen atom is transferred normally preferentially anti with respect to the β-stereosubstituent to give the thermodynamically more stable cis-alkene.

In the case of σ-alkenyl radicals the stereoselectivity is more complicated. It has been shown experimentally and by ab initio calculations that the free-radical addition to an alkene affords a (Z)-alkenyl radical, for example (Z)-2. Synchronously with the formation of the new bond, the remaining odd-electron orbital, which is situated at the adjacent carbon, is forced to occupy a position opposite to the direction of the attacking free radical due to stereoelectronic requirements. If the hydrogen transfer step is much faster than inversion to the (E)-alkenyl radical (É), then kinetically controlled anti addition products (Z)-3 are formed. But if the rate of the hydrogen transfer step is comparable to the rate of inversion, the syn and anti addition products are formed, depending on the relative rates of inversion and syn and anti hydrogen transfer. Finally, if the hydrogen transfer is much slower than inversion, equilibriums of (Z)- and (E)-alkenyl radicals can be reached, and the difference of stability of the two stereoisomeric radicals and the relative rates of syn and anti hydrogen transfer are now important for the stereochemical outcome of the addition reaction. Steric effects play a dominant role making the radical (É)-2 more stable than the corresponding radical (Z)-2. The relative rates of syn and anti hydrogen transfer are also influenced by steric effects.

We have shown that the one reaction is suitable to study the stereoselectivity of free-radical additions of cyclohexane to phenylacetylene. We have now investigated the stereoselectivity of the thermally initiated free-radical addition of cyclohexane to 1-alkenes 1 via alkyl radicals 2 to give 1,2-disubstituted alkenes. Some preliminary results have been reported.

Results

Cyclohexane was allowed to react in the absence of air with the alkenes 1 (ratio 500:100:1) in the temperature range from 160 to 260°C. The addition products 3 were...
formed with high regioselectivity. The cyclohexyl group is added preferentially to the unsubstituted terminus of the C,C triple bond. For example, in the case of methyl propionate (1d) the ratio of the regiospecific addition products 3d to methyl 2-cyclohexylethylate was 21:1 [29]. The reaction time was chosen such that the conversion (<10%) sufficed for the determination of the stereoisomeric ratio of the products by capillary gas chromatography. No (Z) to (E) isomerization of the products could be detected by variation of the reaction time and conversions of up to 50%. However, a [1,5]-sigmatropic rearrangement of product (Z)-3ε was observed [30].

All the products 3 were unambiguously identified by a comparison with authentic compounds or isolation of the products and characterization by 1H-NMR spectroscopy. The reaction could also be performed on a preparative scale.

In that case the alkynes and cyclohexane were allowed to react in an autoclave for several hours. In most cases, only some minor products had to be removed by chromatography or distillation, and the stereoisomeric product mixture 3 could easily be obtained.

To prove the dependence of the stereoselectivity on the concentration of cyclohexane, the alkynes were allowed to react with mixtures of cyclohexane and benzene, the latter solvent being inert in the ane reaction [31]. The concentration of cyclohexane varied from 2 to 6 M. The results are compiled in Figures 1 and 2. It is remarkable that the stereoselectivity varies over a range of almost four orders of magnitude. There are cases with almost exclusive formation of (Z)-3a (X = OMe) and others with almost exclusive formation of (E)-3f (X = tBu).

In most cases, the ratio of the stereoisomeric products [(Z)-3]/[(E)-3] decreases linearly with decreasing concentra-

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Figure 1. Temperature dependence of the addition of cyclohexane to 1-alkynes 1

Figure 2. Dependence of the ratio of the addition products [(Z)-3]/[(E)-3] on the concentration of the hydrogen donor cyclohexane at 240°C (The ratio of the addition products to the alkynes 1d, 1f, and 1h was measured at 260°C)
tion of the hydrogen donor cyclohexane with the exception of X = COMe, SiMe₃, Bu. Figure 2). The ratio of ([Z]-3) to (E)-3 decreases with increasing temperature in all cases (Figure 1). (E)-3 is formed preferentially in most cases, and the stereoselectivity increases with rising temperature. However, (Z)-3 is formed preferentially if X = CN, OMe, and the stereoselectivity decreases with increasing temperature.

**Discussion**

The kinetics expected to be involved in the reaction sequence is illustrated by Scheme 1. The addition products (Z)-3 and (E)-3 are formed in a competition reaction by hydrogen transfer from cyclohexane to the alkenyl radicals 2. Radicals 2 are formed by the addition of cyclohexyl radicals to alkenes 1. The free-radical chain reaction is initiated by molecule-induced homolysis of cyclohexane and alkylene 1. Depending on the structure of the formed alkenyl radical 2 — either a bent σ or a linear π radical — different competition kinetic schemes are to be expected.

**Scheme 1**

![Scheme 1](image)

Arrenius relationship of the ratio ([Z]-3):([E]-3) should be observed:

$$\frac{[Z]-3}{[E]-3} = \frac{k_2 k_{11}}{k_2 k_{12}} \frac{k_2 [c-C_6H_{11}]}{k_2 [c-C_6H_{12}]}$$  \hspace{1cm} (1)

Two borderline cases should be discussed: If inversion is fast relative to radical scavenging, the second term of equation (1) approaches zero, and the product ratio is determined by equation (2) and the Curtin-Hammett principle has to be applied. A linear Arrenius relationship with a positive or negative slope is expected because $\Delta H^\circ_{E3} - \Delta H^\circ_{Z3} < 0$, whereas $\Delta H^\circ_{E3} - \Delta H^\circ_{Z3} > 0$.

$$\frac{[Z]-3}{[E]-3} = \frac{k_2}{k_2} \frac{k_{12}}{k_{11}}$$  \hspace{1cm} (2)

However, if the inversion is slow relative to radical scavenging, the product ratio is determined by the second term of equation (1) and equation (3) should apply. In this case, a linear relative Arrenius relationship is to be expected, and the ratio of [Z]-3:([E]-3) greatly depends on the concentration of cyclohexane.

$$\frac{[Z]-3}{[E]-3} = \frac{k_2}{k_2} \frac{k_{11}}{k_{12}}$$  \hspace{1cm} (3)

**Linear π Alkenyl Radicals 2**

In the case of linear π radicals the ratio of the stereoisomeric products should be determined exclusively by the ratio of the hydrogen transfer rate constants given in equation (4).

$$\frac{[Z]-3}{[E]-3} = \frac{k_2}{k_2}$$  \hspace{1cm} (4)

A linear relative Arrenius relationship with a positive slope is assumed. The slope should be more positive than in the case of equation (2). The ratio of the products should be independent of the concentration of the hydrogen donor.

Applying equations (1)–(4) to the experimental results given in Figures 1 and 2, we can observe and differentiate in most cases all the possibilities discussed above.

**Addition of Cyclohexane to Methoxyacetylene (1a)**

A configurationally very stable 1-methoxalkenyl radical (Z)-2a is formed by the addition of cyclohexyl radical to alkylene 1a. Equation (3) can be applied (Figure 3), and the relative Arrenius parameters of hydrogen transfer and inversion of radical (Z)-2a are obtained. The differences of the activation enthalpies and activation entropies are $\Delta H^\circ_{Z3} - \Delta H^\circ_{E3} = 32$ kJ mol⁻¹ and $\Delta S^\circ_{Z3} - \Delta S^\circ_{E3} = 61$ J mol⁻¹ K⁻¹, respectively.

Unfortunately, there are no reliable values of rate constants and activation parameters for hydrogen transfer reactions to alkyl radicals available. However, it can be assumed that alkyl radicals are more reactive than the...
respective alkyl radicals. Assuming an activation enthalpy \( \Delta H^* \approx 40 \text{ kJ mol}^{-1} \), we can estimate an inversion barrier of radical (Z)-2a of approximately 70 kJ mol\(^{-1}\). The difference of the activation entropies of inversion and hydrogen transfer leads to a reasonable ratio of the A factors of \( \log(\lambda_{a} / \lambda_{b}) = 3.2^{(9)} \).

Figure 3. Temperature dependence of the stereoselectivity of the addition of cyclohexane to methoxycarbonyl (1a) applying equation (3)

Addition of Cyclohexane to Alkynes (1e), 1,3-Butadiene (1g), 1-Hexyne (1h), Cyclohexylethylene (1k), and 3,3-Dimethyl-1-butene (11)

The addition of cyclohexyl radical to these alkynes gives the \( \sigma \) alkynyl radicals (Z)-2. It can clearly be seen from Figure 2 and Table 1 that the ratio of \( k_{Z} / k_{E} \) given by the slope of the respective straight lines decreases with increasing steric effect of the alkyl substituent X (Me < Et < Bu < c-C\(_3\)H\(_7\) < i-Bu) (Table 1). We assume that this effect is essentially due to the increasing rate of inversion of alkynyl radical (Z)-2. In the case of radical 21 (X = Bu) the ratio of the products [(Z)-3] / [(E)-3] seems to be independent of the concentration of cyclohexane, and equation (2) holds. With increasing steric demand of substituent X the rate constant of reverse inversion \( k_{inv} \) decreases. Thus, the first term of equation (1) decreases, and more (E)-3 is formed, and the stereoselectivity is nicely correlated with the steric substituent constant \( E_{s}^{(9)} \) of substituent X (Figure 4). The ratio of the rate constants of hydrogen transfer \( k_{Z} / k_{E} \) may also be influenced by the steric effect of substituent X. This effect, however, seems to be relatively small compared to the effect on the inversion rates as can be deduced from the ratio \( k_{Z} / k_{inv} \) which increases with increasing steric effect of substituent X (Table 1).

Table 1. Ratio of the stereoisomers and relative kinetic data of the addition of cyclohexane (0.02 M) to alkyl-substituted acrylonitriles at 250°C

<table>
<thead>
<tr>
<th>Limiting</th>
<th>( k_{Z}/k_{E} )</th>
<th>( k_{Z}/k_{inv} )</th>
<th>( k_{E}/k_{inv} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.596</td>
<td>0.247</td>
<td>0.057</td>
</tr>
<tr>
<td>4</td>
<td>0.124</td>
<td>0.088</td>
<td>0.039</td>
</tr>
<tr>
<td>5</td>
<td>0.223</td>
<td>0.082</td>
<td>0.030</td>
</tr>
<tr>
<td>6</td>
<td>0.106</td>
<td>0.019</td>
<td>0.014</td>
</tr>
<tr>
<td>7</td>
<td>0.013</td>
<td>0.013</td>
<td>-</td>
</tr>
</tbody>
</table>

Additions of Cyclohexane to Alkynes Cyanoethylcyclohexane (1b), 3-Butyn-2-one (1c), Methyl Propionate (1d), Phenylethene (1f), and (Trimethylsilyl)ethykyne (11)

The alkynyl radicals 2 formed by the addition of cyclohexyl radicals to these alkynes may be \( \pi \) radicals, because the odd electron can be delocalized. As already discussed, ESR andMuon spin rotation studies gave clear evidence that 1-phenylalkynyl radicals such as 2f and 1-(trimethylsilyl)alkynyl radicals such as 2i are \( \pi \) radicals. Kinetic measurements revealed that radical 1d is a \( \sigma \) radical. The ESR results seem to be ambiguous, and the problem is open to discussion. ESR spectroscopy gave evidence that 1-cyanoalkynyl radical could be trapped and measured by ESR at 4 K. Radicals 2e have obviously not been investigated previously by spectroscopic methods.

In the case of \( \pi \) radicals equation (4) should be fulfilled, and the product ratio should be independent of the concentration of the hydrogen donor. However, only in the case of the addition of cyclohexane to alkynes 1e and 1i was the stereoselectivity independent of the hydrogen donor concentration indicating that the respective radicals could be linear \( \pi \) radicals, whereas in the case of alkynes 1b, 1d, and 1f a dependence of stereoselectivity on the hydrogen donor concentration was observed. This is a surprising and remarkable result. To explain these effects we assume that the enthalpy differences between the respective \( \sigma \) and \( \pi \) radicals are rather low in the cases of the 1-alkynyl radicals 2b, 2d, and 2f as indicated by AM1 calculations, which show a very
Free-Radical Chain Addition of Cyclohexane to 1-Alkynes

Carlo Erba GC 6000 Vega Series II with FID detector, fused silica capillary column DBI 30 m. — Liquid chromatography: Merck silica gel 60, 0.04–0.063 mm. — Autoclave High-grade steel tube with a volume of 140 ml. — Solvents were purified and dried in the usual way.

Starting Materials 1: Alkynes 1a–4 were commercially available and were purified by distillation. Cyanoethene (1b) was obtained from B. Witschi and H. Hopf, Institut für Organische Chemie, TU Braunschweig, Germany. Methoxyacetylene (1a) was best prepared from 2-chloroacetylene dimethyl acetal by a method described by Brandsma13.

Competitive Kinetic Measurements: The reactions of the alkynes 1a–4 with cyclohexane were carried out in vacuum-sealed Duran glass ampoules (outer diameter 7 mm, inner diameter 4 mm, length 170 mm, volume 2.1 ml). The solutions (0.01 M) were deoxygenated by 3–4 freeze-thaw cycles. For each measurement three ampoules were used to carry out the reaction at constant temperature in an oil bath (Haake N 4–B, ±0.01 °C). The solutions were analyzed directly by GC. The products were identified by a comparison of the retention times of independently synthesized reference compounds.

n-Dodecane was used as internal standard.

Addition Products 3 are described in the literature with the exception of 3l. They were independently synthesized by thermal addition of cyclohexane to the respective alkynes on a preparative scale or by adapted laboratory procedures.

1-Cyclohexyl-2-methoxyethylene (3a): 5.0 g (11.5 mmol) of (methoxymethyl)triphenylphosphonium bromide/sodium azide in 30 ml of THF was stirred under N2 for 15 min. To this suspension 2 ml (15 mmol) of cyclohexanecarboxaldehyde was added. After stirring for 60 min at room temp, 60 ml of water was added, and the solution was extracted with diethyl ether. The organic layer was separated, dried with MgSO4, and concentrated. Bulb-to-bulb distillation of the residue gave 1.5 g of a product (yield 93% based on the ylide) containing 70% of (E)-3a and about 30% of (Z)-3a. The 1H-NMR data corresponded in all respects with the compound described in ref.10.

1-Cyano-2-cyclohexylethene (3b): A solution of 11.69 g (66 mmol) of diethyl cyanomethylyphosphonate in 50 ml of THF was added under N2 to a solution of 2.73 g (70 mmol) of sodium azide in 75 ml of THF. After stirring for 8 h at room temp., 40 g (36 mmol) of cyclohexanecarboxaldehyde dissolved in 150 ml of THF was added. After 18 h the solution was hydrolyzed with 120 ml of water, concentrated, and the separated aqueous layer was extracted with diethyl ether. The combined organic layers were dried (MgSO4) and concentrated. The resulting crude product was purified by bulb-to-bulb distillation. Yield: 4.76 g (85%) containing 60% of (E)-3b and 40% of (Z)-3b, b.p. 191–193 °C. The 1H-NMR data corresponded in all respects with the compound described in ref.10.

4-Cyclohexyl-3-buten-2-one (3c): 0.68 g (10 mmol) of 3-butyne-2-one and 2.8 g (10 mmol) of cyclohexane/methylene chloride were dissolved in 200 ml of dichloromethane. Then a solution of 3.0 g (80 mmol) of NaN3 in 4 ml of water was added. After 15 min, the solution was dried with MgSO4, and the filtrate was subjected to bulb-to-bulb distillation to give 180 mg (12%) of 3c (E/Z-$\alpha$-2,3): E : Z = 2.5:1. — 1H NMR (CDCl3) δ = 0.5–2.00, 2H, δC(3H)1, 1.8 (3H, Z-CH3), 1.9 (3H, E-CH3), 5.51 (dd, 1H, Z-CH=CH2), 5.65 (1H, Z-CH=CH2), 5.85 (dd, 1H, E-CH=CH2), 6.46 (dd, 1H, E-CH=CH2), 16.1 (Z-CH3), 9.6 (E-CH3), 16.1 (E-CH3), 12.7 Hz. — MS (3e) (EL 70 ev, m/z %): 152 (22[ M+ ]). — The compound is described in ref.10.


Experimental

1H and 13C NMR: Bruker AM 300; solvents CDC13 and C6D6 internal standard tetramethylsilane (TMS). — MS: Finnigan MAT 212 (for GC/MS coupled with a Varian 3700). — Analytical GC.

Figure 5. Dependence of the ratio of the addition products [(Z)-3d]; [Z]-3d] on the concentration of the hydrogen donor cyclohexane from 200 to 260 °C. **(Z)-3d**: 220 °C, δC = 240 ° C, δC = 250 °C, δC = 260 °C.

Thus, our results give additional evidence12,13 that 1-alkenyl radicals 2b, 2d, and 2l could be bent at least at elevated temperatures up to 260 °C, whereas 1-alkenyl radicals 2e and 2l are linear.

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B
Methyl 3-Cyclohexylacrylate (34) was prepared as described in refs. 23, 38.

1-Cyclohexyl-1-propene (34): 80 ml of cyclohexane was saturated with propylene and the mixture was heated under N₂ for 8 h in an autoclave at 250°C. Bulk-to-bulk distillation gave 70 mg of 3e[[E]-3e][z-[Z]-3] = 16.1]. The [H-NMR data correspond with the compound described in ref. 31.

1-Cyclohexyl-2-phenylethene (35): A mixture of 80 ml of cyclohexane and 80 mg (0.78 mmol) of phenylethene was heated for 8 h in an autoclave at 240°C under N₂. Cyclohexane was removed, and the residue was subjected to column chromatography yielding 88 mg (61%) of 3f[[E]-3f][z-[Z]-3f] = 16.1]. The compound is described in ref. 31.

1-Cyclohexyl-1-butene (3g): 80 ml of cyclohexane was saturated with butylene and the mixture heated under N₂ in an autoclave for 8 h. The [H-NMR data correspond with the compound described in ref. 31.

1-Cyclohexyl-1-phenylethene (3h): A mixture of 80 ml of cyclohexane and 82 mg (1 mmol) of 1-phenylethene was heated for 8 h in an autoclave at 250°C under N₂. Cyclohexane was removed, and bulk-to-bulk distillation of the residue yielded 90 mg (54%) of 3h[[E]-3h][z-[Z]-3h] = 5.1]. The [H-NMR data corresponded with the compound described in ref. 31.

1,2-Dicyclohexylethane (3k): A mixture of 80 ml of cyclohexane and 549 mg (5 mmol) of cyclohexylethene was heated for 8 h in an autoclave at 250°C under N₂. Cyclohexane was removed, and column chromatography of the residue yielded 120 mg (18%) of 3k[[E]-3k][z-[Z]-3k] = 8.1]. 3k is described in ref. 31. However, the [H-NMR data of (3k) given in ref. 31 correspond with the compound (Z)-3k. = [H-NMR (CDCl₃): δ = 1.0 (t, 3H, CH₃CH₂CH₂CH₃), 1.42 (s, 2H, CH₂CH₂CH₂CH₃), 3.35 (s, 4H, CH₂CH₂CH₂CH₃)].

(E)-1-Cyclohexylethyl-3-dimethyl-1-buten (3d): A mixture of 70 ml of cyclohexane and 250 mg (3 mmol) of 3-dimethyl-1-butene was heated for 9 h in an autoclave at 250°C under N₂. Cyclohexane was removed, and column chromatography of the residue furnished 50 mg (10%) of 3d = [H-NMR (CDCl₃): δ = 0.9 (s, 2H, 2H, CH₂CH₂CH₂CH₂CH₂), 5.25 (dd, 1H, =CHCH₂), 5.41 (dd, 1H, =CHCH₂), 15.8 (s, 1H, =CHCH₂)].

(E)-1-Cyclohexylethyl-3-dimethyl-1-buten (3d): A mixture of 13.1 g (0.05 mol) of trimethylphosphine and 9.0 g (0.051 mol) of (bromomethyl)cyclohexane was heated for 2 h at 150°C under N₂. The product was washed with diethyl ether to afford 15.3 g (0.015 mol, 70%) of phosphonite salt with a melting point of 208°C.
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[174/93]