Hz). $[\alpha]^{22}_D$ +93.5° (c 0.43, $CHCl_3$). Anal. Calcd for $C_{22}H_{40}O_5Si$: C, 64.04; H, 9.77. Found: C, 63.91; H, 9.62.

1-[(*tert*-Butyldimethylsilyl)oxy]-4(*R*)-[(1*R*)-3(*R*),8(*S*)-dimethyl-4-(*R*)-(methyleneoxy)-2,9-dioxabicyclo[3.3.1]non-5(*Z*)-en-1-yl]-2-methylpent-2(*E*)-ene (20). The above diol **19** (298 mg, 0.723 mmol) was dissolved in 15 mL of THF and cooled to 0 °C. Sodium hydride (150 mg of a 50% oil dispersion, 3.1 mmol) was added, and the mixture was stirred for 10 min. (*p*-Tolylsulfonyl)imidazolide (342 mg, 1.54 mmol) was dissolved in 3.0 mL of the THF, and the solution was added dropwise to the reaction over 5 min.[17] By TLC, the reaction was not quite complete after 2 h, so it was stirred for 30 min at room temperature and then carefully quenched with methanol. The mixture was diluted with 250 mL of ether and extracted with 100-mL portions of brine, then water, and then brine. Brief drying over $MgSO_4$ was followed by filtration and solvent removal (rotary evaporator). The crude material was flash chromatographed with 9% ethyl acetate/petroleum ether to provide 273 mg (96% yield) of the epoxide **20**, which was pure by TLC and NMR. Analysis and spectral data: R_f 0.78 (4:1 petroleum ether/ethyl acetate); IR ($CHCl_3$) 995, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, 0.65 (d, 3 H, J = 7 Hz), 0.92 (s, 9 H), 0.96 (d, 3 H, J = 7 Hz), 1.19 (s, 3 H), 1.60 (s, 3 H), 2.0 (m, 1 H), 2.5 (m, 1 H), 3.53 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 3.75 (d, 1 H, J = 5 Hz), 3.92 (d, 1 H, J = 5 Hz), 4.00 (s, 2 H), 4.29 (t, 1 H, J = 4 Hz), 5.49 (br d, 1 H, J = 9 Hz), 5.57 (d, 1 H, J = 10 Hz), 6.30 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz); $[\alpha]^{22}_D$ +154° (c 0.75, $CHCl_3$). Anal. see following compound (desilyated).

4(*R*)-[(1*R*)-4(*R*)-(Methyleneoxy)-3(*R*),8(*S*)-dimethyl-2,9-dioxabicyclo[3.3.1]non-5(*Z*)-en-1-yl]-2-methylpent-2(*E*)-en-1-ol. The epoxide **20** (91 mg, 0.23 mmol) was dissolved in 2.0 mL of the THF and cooled to 0 °C. A 1 M THF solution of tetra-*n*-butylammonium fluoride (1 mL) was added, and the reaction was stirred for 1 h, at which time it was judged complete by TLC. The solution was diluted with 100 mL of ether and extracted with 25 mL of brine. The organic layer was then dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. Flash chromatography of the residue gave 63 mg (97%) of white crystalline alcohol. Analysis and spectral data: R_f 0.30 (7:3 petroleum ether/ethyl acetate); IR ($CHCl_3$) 3540, 3460 (br), 992 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.21 (s, 3 H), 1.68 (s, 3 H), 1.7 (br s, 1 H), 2.0 (m, 1 H), 2.5 (m, 1 H), 2.76 (d, 1 H, J = 5 Hz), 2.97 (d, 1 H, J = 5 Hz), 3.58 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 4.01 (s, 2 H), 4.32 (t, 1 H, J = 4 Hz), 5.52 (br d, 1 H, J = 9 Hz), 5.59 (d, 1 H, J = 10 Hz), 6.37 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz); $[\alpha]^{23}_D$ +193° (c 0.859, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.63; H, 8.60.

Streptolic Acid Ethyl Ester (21). Dichloromethane (2.0 mL) was cooled to −78 °C and 30 mL (0.34 mmol) of oxalyl chloride was added followed by 30 mL (0.42 mmol) of DMSO. After the resultant mixture was stirred for 15 min, the above alcohol was added in 1.0 mL of dichloromethane and rinsed in with 1 mL more of dichloromethane. This was stirred for 30 min, and 0.15 mL (0.84 mmol) of Hunig's base was added. It was then allowed to warm to room temperature, and 318 mg (0.91 mmol) of (carbethoxymethylene)triphenylphosphorane was added. This reaction mixture was stirred overnight at room temperature. It was then diluted with 100 mL of dichloromethane and extracted with brine followed by sodium bicarbonate. The solution was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. Chromatography on 8 g of silica, eluting with 7% ethyl acetate/petroleum ether, gave 49 mg of the ethyl ester **21** (74%). Analysis and spectral data: R_f 0.43 (4:1 petroleum ether/ethyl acetate). IR ($CHCl_3$) 1690, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (d, 3 H, J = 7 Hz), 1.03 (d, 3 H, J = 7 Hz), 1.23 (s, 3 H), 1.31 (t, 3 H, J = 7 Hz), 1.80 (s, 3 H), 1.9 (s, 1 H), 2.7 (m, 1 H), 2.78 (d, 1 H, J = 5 Hz), 2.98 (d, 1 H, J = 5 Hz), 3.62 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 4.20 (q, 2 H, J = 7 Hz), 4.33 (t, 1 H, J = 4 Hz), 5.69 (d, 1 H, 10 Hz), 5.88 (d, 1 H, J = 16 Hz), 6.06 (br d, 1 H, J = 9 Hz), 6.33 (dd, 1 H, $J_{5,6}$ = 4 Hz, $J_{6,7}$ = 10 Hz), 7.34 (d, 1 H, J = 16 Hz), 7.34 (d, 1 H, J = 16 Hz); $[\alpha]^{23}_D$ +140° (c 0.75, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.87; H, 8.07.

Streptolic Acid (2). A 19-mg sample of the ester **21** (0.055 mmol) in 5 mL of methanol was treated with 3 mL of 10% aqueous sodium hydroxide. After being stirred for 2 h, the mixture was diluted with sodium bicarbonate solution, extracted with 15 mL of petroleum ether, acidified to about pH 2 with 10% HCl, and extracted with three 25-mL portions of chloroform. The chloroform solution was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Drying under vacuum resulted in crystallization of the residue (17.6 mg, 100% crude yield). After three recrystallizations (benzene/petroleum ether) the pure material (15 mg, 86%) was judged identical with streptolic acid (**2**) (from degradation of streptolydigin) by comparisons of melting point, ^1H NMR, IR, and specific rotation.[3] Analysis and spectral data: R_f 0.30 (ethyl acetate); IR ($CHCl_3$) 3000 (br), 1672, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (d, 3 H, J = 7 Hz), 1.02 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.79 (s, 3 H), 1.8 (m, 1 H), 2.7 (m, 1 H), 2.76 (d, 1 H, J = 5 Hz), 2.95 (d, 1 H, J = 5 Hz), 3.6 (dd, 1 H, $J_{3,4}$ = 10 Hz, $J_{3,4'}$ = 2 Hz), 4.30 (t, 1 H, J = 5 Hz), 5.59 (d, 1 H, J = 10 Hz), 5.78 (d, 1 H, J = 16 Hz), 6.09 (br d, 1 H, J = 10 Hz), 6.31 (dd, 1 H, $J_{5,6}$ = 5 Hz, $J_{6,7}$ = 10 Hz), 7.40 (d, 1 H, J = 16 Hz); mp 168-169 °C (lit.[2] 168-170 °C); $[\alpha]^{22}_D$ +138° (c 0.55, 95% EtOH) [lit.[2] $[\alpha]^{25}_D$ +147° (c 1.21, 95% EtOH). Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.35; H, 7.71.

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Kinetic Investigation of the Type 2 Intramolecular Diels-Alder Cycloaddition

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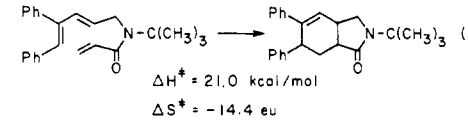
Abstract: Rate constants and activation energy parameters for the type 2 intramolecular Diels-Alder cycloaddition of a series of dienyne esters have been determined. It is noted that the point of substitution of an oxygen atom in the tether joining diene and dienophile results in substantial rate differences. An analysis of these rate differences has provided a transition-state model for the type 2 intramolecular cycloaddition. Variation of the tether length from five to seven atoms produces changes in both the enthalpy and entropy of activation, but no systematic trend in rate is observed. The EM (effective molarity) for the type 2 intramolecular Diels-Alder cycloaddition of dienyne ester **4** was determined to be 0.4-0.5 M.

The intramolecular Diels-Alder reaction has played an important role in the recent advances of synthetic organic chemistry.[1] Despite this fact there has been relatively little effort directed toward developing a quantitative understanding of the rates of intramolecular Diels-Alder reactions. In an important early investigation, Gschwend and co-workers reported the activation energy for intramolecular Diels-Alder cycloaddition of several triene amides. A kinetic analysis of the cycloaddition (eq 1)



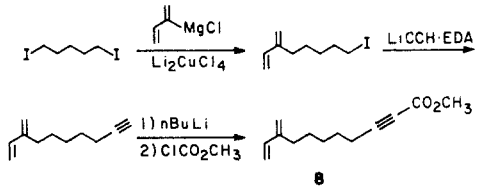
(1)

afforded a reaction enthalpy of $\Delta H^{\ddagger}$ = 21.0 ± 0.1 kcal/mol and an entropy of activation of $\Delta S^{\ddagger}$ = −14.4 ± 0.3 eu ($\Delta G^{\ddagger}_{298}$ = 25.3

(1) (a) Ciganik, E. *Org. React.* **1984**, *32*, 1. (b) Fallis, A. *Can. J. Chem.* **1984**, *62*, 183. (c) Taber, D. F. *Intramolecular Diels-Alder and Ene Reactions*; Springer-Verlag: Berlin, 1984.

0002-7863/88/1510-0860$01.50/0

Scheme I



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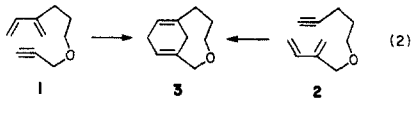
± 0.2 kcal/mol).[2] Comparison with experimentally determined activation energies of related systems was not pursued due to the uncertainty regarding the rate-limiting step; it was noted that the experimental activation free energy was similar to the energy barrier expected for rotation about the amide N–CO bond.

Selected kinetic studies of the intramolecular Diels–Alder cycloaddition involving three-atom tethers yield entropies of activation that range from −13 to −21 eu and activation energies that range from 15 to 25 kcal/mol.[3-9] We are not aware of systematic kinetic investigations of the intramolecular Diels–Alder cycloaddition.[10] In the present report we will examine the kinetic effect of locating heteroatom substituents at various positions in the tether joining diene and dienophile. The results enable us to develop a transition-state model for the type 2 intramolecular Diels–Alder cycloaddition. In a related study, the tether joining diene and dienophile is systematically homologated over three methylene units. Analysis of the activation energies of this series permits one to partition the rate changes between enthalpic and entropic contributions. In addition, the rates of appropriate bimolecular Diels–Alder reactions have been determined to permit calculation of the effective molarity (EM) for the type 2 intramolecular Diels–Alder cycloaddition.

Results and Discussion

Kinetic Effect of Heteroatom Positioning. A preliminary investigation of the type 2 intramolecular Diels–Alder cycloaddition of dienynes **1** and **2** (eq 2) revealed a considerable difference in

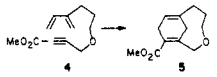
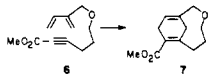
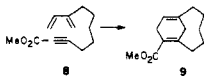


1 **3** **2**

the rate of cycloaddition to bridgehead diene cycloadduct **3**. Although electronic effects could account for some difference in rate, we believed the magnitude of the observed rate difference (ca. 10^2) was too large to be accommodated by this factor alone. We reasoned that closer scrutiny might provide insight regarding the transition-state structure of the cycloaddition.

The cycloaddition of dienyne ethers **1** and **2** proceeds only at temperatures aboye 350 °C (flow pyrolysis, 10-s residence time).[11] At these temperatures, competing side reactions consume portions of both starting material and product. The dienophile-activated members of this series, on the other hand, dienyne esters **4** and **6**, undergo intramolecular Diels–Alder cycloaddition under considerably milder conditions. The cycloadditions follow clean

Table I

reaction	k_{rel}(210 °C)	E_a^*, kcal/mol	ΔS^*, eu
 **4** **5**	62	23.6	−28
 **6** **7**	1	27.0	−29
 **8** **9**	1	27.1	−29

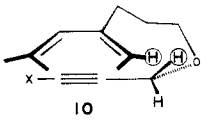
first-order kinetics for over 1 half-life. In addition to ethers **4** and **6**, the hydrocarbon analogue **8** was also prepared for inclusion in the kinetic study.

Since dienyne ester **8** has not been described previously, its synthesis is outlined in Scheme I. An excess of 1,5-diiodopentane is treated with the Grignard reagent of chloroprene in the presence of a catalytic amount of Li_2CuCl_4.[12] Reaction of the resulting diene iodide with lithium acetylide, followed by carboxymethylation (*n*-BuLi, $ClCO_2Me$), affords dienyne ester **8**. The type 2 intramolecular Diels–Alder cycloaddition of dienyne esters **4**, **6**, and **8** proceeds smoothly to yield the corresponding bridgehead diene cycloadducts **5**, **7**, and **9**. The rate constants, summarized in the Experimental Section, were determined over a 40 °C temperature range at a minimum of four temperatures.

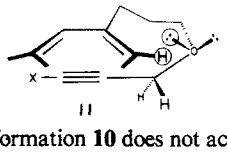
The relative rate constants at 210 °C and the derived activation energy parameters are summarized in Table I. A number of points deserve comment. At 210 °C, dienyne ether **4** is approximately 60 times more reactive than the "oxygen scrambled" ether **6** and the hydrocarbon analogue **8**. The entropies of activation for the three reactions are the same within experimental error. Thus, the reactivity difference between **4** and **6** or **8** is enthalpic in origin.

We considered a number of factors that could influence the rate of cycloaddition of the three similar substrate molecules. One involves the electronic influence of the oxygen atom on the dienophilicity of methyl ester **4**. This factor is indeed important, and its contribution is evaluated in the section on effective molar concentrations. A second factor can arise from differences in the steric demands of the tethers in substrates **4**, **6**, and **8**. This analysis provides an important glimpse of the preferred transition-state geometries for the type 2 intramolecular cycloaddition involving acetylene dienophiles.

Inspection of molecular models of the Diels–Alder precursors reveals two plausible transition states for the cycloaddition. Consideration of conformation **10** reveals a severe nonbonding interaction between the diene methylene and the propargylic methylene group. Since all substrate molecules possess this



10

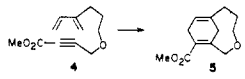
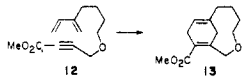
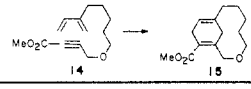


11

structural feature, conformation **10** does not account for the kinetic difference between the two sets of reactants. In conformation **11**, however, the model reveals nonbonding interactions between the vinyl hydrogen on the diene and the homopropargylic position on the tether. In dienyne ether **4** the homopropargylic position is occupied by an oxygen; in both **6** and **8**, this position is occupied by a CH_2 group. The difference in steric demands between an

(2) Gschwend, H. W.; Lee, A. O.; Meier, H. P. *J. Org. Chem.* **1973**, *38*, 2169.
(3) Gschwend, H. W.; Meier, H. P. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 294.
(4) Ciganek, E. *J. Org. Chem.* **1980**, *45*, 1497.
(5) Isaacs, N. S.; Van der Beeke, P. *Tetrahedron Lett.* **1982**, 2147.
(6) Melikyan, T. R.; Torosyan, G. O.; Mkrtchyan, R. S.; Tagmazyan, K. T.; Babayan, A. T. *Arm. Khim. Zh.* **1978**, *31*, 328.
(7) Babayan, A. T.; Tagmazyan, K. T.; Ioffe, A. I.; Mkrtchyan, R. S.; Torosyan, G. O. *Dokl. Akad. Nauk. Arm. SSR* **1974**, *58*, 275.
(8) Torosyan, G. O.; Tagmazyan, K. T.; Babayan, A. T. *Arm. Khim. Zh.* **1974**, *27*, 752.
(9) (a) Melikyan, T. R.; Torosyan, G. O.; Mkrtchyan, R. S.; Tagmazyan, K. T.; Babayan, A. T. *Arm. Khim. Zh.* **1977**, *30*, 138. (b) Tagmazyan, K. T.; Mkrtchyan, R. S.; Babayan, A. T. *Arm. Khim. Zh.* **1974**, *27*, 957.
(10) (a) For a review of the mechanism of the Diels–Alder reaction, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (b) For a discussion of the intramolecular Diels–Alder, see: Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2517.
(11) Shea, K. J.; Burke, L. D. *J. Org. Chem.*, in press.
(12) (a) Tamaura, M.; Kochi, J. *Synthesis* **1971**, 303. (b) Shea, K. J.; Phan, P. Q. *Tetrahedron Lett.* **1983**, *24*, 1003.

Table II

reaction	k_{rel}(210 °C)	E_a^*, kcal/mol	ΔS^*, eu
	5.4	23.6	−28
	5.5	20.6	−35
	1	22.6	−34

oxygen lone pair and a C–H bond is well documented.[13] Neglecting ground-state effects, this repulsive interaction could raise the transition-state energy for the cycloaddition of **6** and **8** by as much as 3.3 kcal/mol, assuming it were the sole origin of the rate differences. The critical response to changes at the homopropargylic position suggests that a transition state approximated by conformation **10** is considerably less important (and of higher energy) in this Diels–Alder reaction.

It is interesting to point out that replacement of methylene groups in the tether by oxygen atoms is not a sufficient cause for an increase in the ease of cyclization; as is demonstrated in the present examples, the location of the oxygen atom is also important.[14]

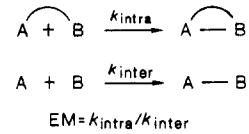
Kinetic Effect of Tether Length. Chemical intuition suggests that as the tether joining diene and dienophile is *increased* in length, the reaction will increasingly resemble a bimolecular process. An important origin of the kinetic consequences of this variation is suggested to reside in the *entropy* of activation term.[15] The type 2 intramolecular Diels–Alder cycloaddition is an ideal candidate for a systematic study of this effect since the homologous series of dienyne esters **4**, **12**, and **14** all undergo first-order cycloaddition to bridgehead dienes **5**, **13**, and **15** (Table II). The relative rates of cycloaddition are summarized in the table as well as the derived activation energy parameters.

At 210 °C, the rates of cycloaddition of dienyne esters **4** and **12** are approximately the same, while the rate of the seven atom homologue falls off to one-fifth of the reference compound **4**. The absence of a clear rate progression for the homologous series can be understood from an analysis of the activation energies. The activation enthalpy decreases then increases in the series **4** → **12** → **14**. While it is true that the entropy of activation becomes more negative as the tether is increased from five to six atoms, the jump from six to seven atoms produces no further change. This trend may be explained by the fact that in a progression of tether lengths, perhaps only three or four bonds (in addition to the diene) need to be "frozen" in the transition state. The residual bonds can remain "floppy" and not extract a price in terms of the transition-state entropy. A similar "dimunition" of entropic demands in macrocyclization reactions has been observed and summarized in other studies.[14,16] The absence of a monotonic increase in the ΔS^* for macrocyclizations, particularly for medium-sized rings, has been attributed to changes in the vibrational partition function along the series.[17] From the present study, it would appear that the entropic advantage of the type 2 intramolecular Diels–Alder cycloaddition levels off at a tether size of six atoms or more.

Accounting for enthalpy changes in this series is by no means straightforward. It is worthwhile, however, to point out that product strain may contribute to the absence of a pattern. For each cycloaddition, the same bonds are made (and broken). The net enthalpy contribution for this process, therefore, remains constant. What does change, however, is the steric energy (strain energy) of the cycloadduct. To evaluate this change, we have calculated the heats of formation and steric energy for cycloadducts **5**, **13**, and **15** by use of the Allinger force field.[18] The *steric energy* in the bridgehead diene series *decreases* from 32.6 to 27.2 to 24.7 kcal/mol. The enthalpy of reaction (ΔH^0_{reactn}) in the homologous series therefore becomes increasingly exothermic (**4** → **12** → **14**) by almost 10 kcal/mol. This progression can lead from a late to early transition state with an expected dimunition in importance of *product strain* in the transition state. It should be pointed out, however, that because of considerable steric energy associated with some cycloadducts in type 2 intramolecular Diels–Alder reactions, the product development arguments discussed above may be unique to this genra.

The absence of monotonic trends in both enthalpy and entropy of activation emphasizes the diversity of contributions to these terms that can complicate the ability to predict kinetic trends even within a closely related series of reactants.

Effective Molarity of the Type 2 Intramolecular Diels–Alder Cycloaddition. Many intramolecular reactions proceed at rates *faster* than their bimolecular counterparts. An understanding of the origins of these differences is important for identifying factors that contribute to the efficiency of catalytic processes. Both the sign and magnitude of the activation entropy of bimolecular reactions is dependent upon the choice of standard state. A direct comparison of these values for unimolecular and bimolecular reactions therefore is not always prudent. Quantification of intramolecularity is best evaluated by determining the effective molarity (EM).[19,20] Effective molarity is defined as the ratio of the intramolecular to the intermolecular rate constants. The ratio has the dimensions of concentration (molarity) and corresponds to the concentration of one reactant in a bimolecular reaction that is necessary to achieve identical rates for both bimolecular and unimolecular reactions:



We have employed two methods for evaluation of EM in the Diels–Alder cycloaddition of dienyne esters **4** and **12**.

For this study, an independent measurement of the unimolecular rate constant for cycloaddition of dienyne ester **4** at 210 °C was determined ($k_5 = 2.91 \times 10^{-4}$ s^{-1}). (Compare with the preceding study where $k_5 = 2.83 \times 10^{-4}$ s^{-1}.)

A bimolecular rate constant for the Diels–Alder cycloaddition of methyl 4-methoxybutynoate (**16**) and 3-methyleneundecene (**17**) (210 °C) was determined (Scheme II). In addition, the rate of cycloaddition between **17** and methyl butynoate (**18**) was also evaluated. The latter reaction was included to permit evaluation of the kinetic effect of an oxygen substituent at the homopropargylic position of the dienophile. The bimolecular cycloadditions give rise to a regioisomeric mixture of products. The ratio of para to meta isomers, determined by a combination of capillary GC and NMR spectroscopy, was found to be k_{19}(210

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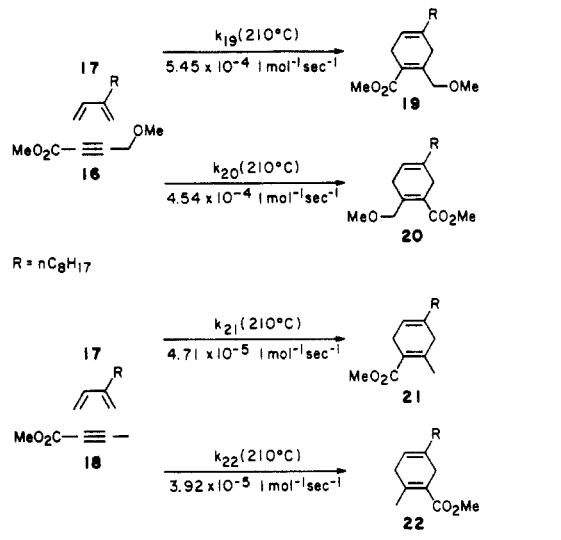
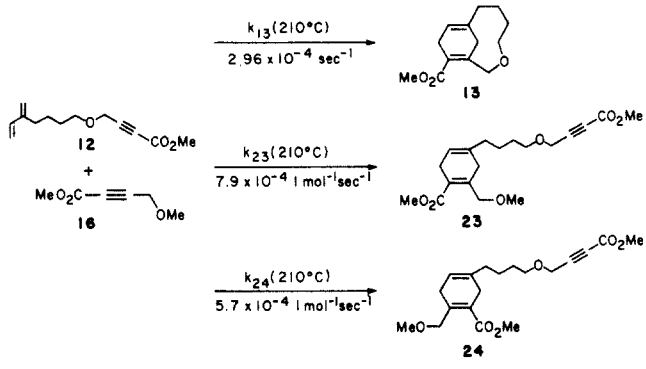
Scheme II



Scheme III



°C)/k_{20}(210 °C) = 1.2. The rate constants for these bimolecular reactions were extracted by computer fitting of time–concentration profiles for each cycloaddition. Compensation was made for a competing polymerization reaction of the diene that consumed approximately 20% of **17** after 3 half-lives. Since the para regioisomer is produced 1.2 times faster than the meta isomer, the combined bimolecular rate was factored to obtain the individual rates. Thus, k_{19}(210 °C) = 5.45 × 10^{-4} L mol^{-1} s^{-1} and k_{20}(210 °C) = 4.54 × 10^{-4} L mol^{-1} s^{-1}. The rate constants are given in Scheme II. For calculation of EM, the bimolecular rate constant for formation of the para regioisomer was used, since a single regioisomer is produced in the intramolecular reaction.

The calculated EM value for the type 2 intramolecular Diels–Alder cycloaddition is

$$EM = k_5/k_{19} = 0.5 \text{ M } (210 \text{ °C})$$

In an independent experiment, a direct competition between the intramolecular Diels–Alder cycloaddition of dienyne **12** and the bimolecular cycloaddition with dienophile **16** was studied (Scheme III).

As before, a computer simulation of the product distribution as a function of time was employed, allowing for a polymerization component of dienyne ester. The analysis permitted evaluation of the rate constants for the competing reactions. These rate constants are summarized in Scheme II. As in the previous example, the bimolecular reaction gave rise to regioisomeric products (para:meta = 1.2), so the combined bimolecular rate constant was factored to yield the rate of para regioisomer formation k_{23}(210 °C). Calculation of EM follows as in the previous example:

$$EM = k_{13}/k_{23} = 0.4 \text{ M} \quad (210 \text{ °C})$$

Since $k_5 \approx k_{13}$, the agreement between the two calculated EM values is gratifying.

EM values have been shown to exhibit an enormous range (10^{-3}–10^{13} M).[20] Within this range the calculated EM value for the type 2 intramolecular Diels–Alder cycloaddition represents only a very modest kinetic advantage.[21] Indeed, although quantitative data are not available, certain type 1 intramolecular Diels–Alder cycloadditions may be estimated to have EMs in excess of 10^4.[22]

In general, type 2 cycloadditions are less reactive than type 1 reactions, an observation that results in part from the reduced exothermicity of the former reactions.

Finally, mention should be made of the fact that the methoxy substituent produces a surprising 11-fold kinetic acceleration in dienophile **16** when compared with ester **18**. This observation requires that the 60-fold kinetic acceleration of dienyne ester **4** over that of the "oxygen scrambled" derivative **6** or the hydrocarbon **8** be attributed to a combination of factors including an inductive effect (factor of 11) and a steric effect (factor of 6).

Experimental Section

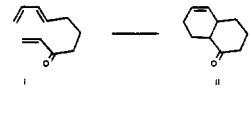
The synthesis and characterization of compounds **1–7** and **12–15** have been described elsewhere.[11] Methyl methoxyalkyne ester **16**[25] was prepared from propargyl bromide and NaOMe in DME (room temperature, 2 h) followed by carboxymethylation as described for the preparation of **8**.

Synthesis of 9-Methylene-10-undecen-2-ynoic Acid, Methyl Ester (8). 8-Iodo-3-methylene-1-octene. A THF solution of Li_2CuCl_4[12] (1.5 mL, 0.45 mmol) was added to a THF solution (200 mL) of 1,5-diiodopentane (15.0 g, 46 mmol) at 25 °C. Chloroprene Grignard (1.1 M THF, 22.0 mmol)[26] was added dropwise and the resultant mixture was stirred an additional 0.5 h. The crude reaction product was isolated by addition to H_2O (100 mL)/pentanes (100 mL) and further extraction with pentanes (75 mL), followed by washing with brine (75 mL) and drying ($MgSO_4$). Purification by flash column chromatography gives 3.0 g (53%) of the diene iodide: IR (CCl_4) 3105, 2950, 2870, 1595, 1465, 1430, 1195, 1165, 900, 895 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.38 (dd, J = 17.5, 10.8 Hz, 1 H, C*H*=CH_2), 5.23 (d, J = 17.5 Hz, 1 H, CH=CH_2), 5.07 (d, J = 10.8 Hz, 1 H, CH=CH_2), 5.02 (s, 1 H, C=CH_2), 4.99 (s, 1 H, C=CH_2), 3.21 (t, J = 7.0 H, 2 H, CH_2CH_2I), 2.23 (t, J = 6.9 Hz, 2 H, =CCH_2CH_2), 1.86 (m, 2 H, CH_2CH_2), 1.50 (m, 4 H, CH_2CH_2); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 146.2, 139.0, 115.9, 113.3, 33.6, 31.3, 30.6, 27.2, 7.1; mass spectrum, m/e (100 eV, CI, isobutane, rel intens) 251 (MH^+, 22), 123 (100), 109 (22), 83 (19), 81 (76); high-resolution mass spectrum, m/e (70 eV, EI) calcd ($C_9H_{15}I$) 250.0220, obsd 250.0211.

3-Methylene-1-decen-9-yne. A DMSO solution (15 mL) of 8-iodo-3-methylene-1-octene (4.2 g, 16.7 mmol) was added dropwise to a DMSO mixture (125 mL) of lithium acetylide–ethylenediamine complex (2.0 g, 21 mmol) and then stirred 1 h. The crude product was isolated by pouring onto ice, adding H_2O (200 mL), and extracting with petroleum ether (3 × 100 mL). The combined organic fractions were washed with brine and dried ($MgSO_4$). Purification by flash column chromatography gives 2.0 g (81%) of dienyne hydrocarbon: IR (CCl_4) 3335, 3105, 2940, 2870, 2120, 1595, 1470, 1435, 900, 890, 625 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.38 (dd, J = 17.6, 10.7 Hz, 1 H, C*H*=CH_2), 5.23 (d, J = 17.6 Hz, 1 H, CH=CH_2), 5.06 (d, J = 10.7 Hz, 1 H, CH=CH_2), 5.01 (s, 1 H, C=CH_2), 4.99 (s, 1 H, C=CH_2), 2.22 (m, 4 H, =CCH_2, C≡CCH_2), 1.95 (t, J = 2.6 Hz, 1 H, CH_2C≡C*H*), 1.50 (m, 6 H,

(21) Operationally the EM for an intramolecular Diels–Alder reaction establishes a concentration that must not be approached if competing bimolecular reactons are to be avoided.

(22) This value was estimated as follows. Oppolzer et al.[23] reported the cyclization of i to ii at 0 °C ($t_{1/2}$ = 4 h), from which a rough estimate of $k_{i\text{–}ii}$(0 °C) = 4.8 × 10^{-5} s^{-1} can be made. From the reported activation energy data for the bimolecular Diels–Alder reaction of isoprene and acrolein (log A = 6.01, E_a = 18.7 kcal/mol),[24] the bimolecular rate constant at 0 °C may be calculated (k_{bi}(0 °C) = 1.0 × 10^{-9}) from which the EM = 4.8 × 10^{-5} s^{-1}/1.0 × 10^{-9} L mol^{-1} s^{-1} = 3.8 × 10^4 M may be calculated.



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$CH_2CH_2CH_2$); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 146.5, 139.1, 115.7, 113.2, 84.7, 68.3, 31.4, 28.9, 28.5, 27.8, 18.6; mass spectrum, *m/e* (100 eV, CI, isobutane, rel intens) 149 (MH^+, 47), 119 (53), 107 (82), 105 (45), 95 (65).

9-Methylene-10-undecen-2-ynoic Acid, Methyl Ester (8). To a THF solution (75 mL) of 3-methylene-1-decen-9-yne (1.90 g, 12.8 mmol) at -78 °C was added dropwise *n*-BuLi (13.0 mmol). The reaction was stirred for 5 min at -78 °C before addition of methyl chloroformate (1.0 mL, 13 mmol). After being stirred for 1 h at -78 °C, the reaction was permitted to warm to 0 °C and then quenched by pouring into H_2O (100 mL) and extracting the aqueous layer with petroleum ether (3 × 100 mL). Purification by flash column chromatography on silica gel gives 2.35 g (89%) of dienyne ester (**8**): IR (CCl_4) 3095, 2945, 2865, 2240, 1725, 1595, 1435, 1210, 1075, 900, 890 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.37 (dd, J = 17.6, 10.8 Hz, 1 H, CH=CH_2), 5.23 (d, J = 17.6 Hz, 1 H, CH=CH_2), 5.06 (d, J = 10.8 Hz, 1 H, CH=CH_2), 4.99 (s, 1 H, C=CH_2), 3.77 (s, 3 H, CO_2CH_3), 2.35 (t, J = 7.0 Hz, 2 H, -CH_2C≡C), 2.22 (br t, J = 7 Hz, 2 H, =CCH_2CH_2); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 154.4, 146.4, 139.1, 115.8, 113.3, 89.9, 73.1, 52.7, 31.3, 28.9, 27.7, 27.6, 18.8; mass spectrum, *m/e* (100 eV, CI, isobutane, rel intens) 207 (MH^+, 52), 175 (13), 147 (100); high-resolution mass spectrum, *m/e* (70 eV, EI) calcd $C_{13}H_{18}O_2$ 206.1307, obsd 206.1324.

3-Methylene-1-undecene (17). Octyl iodide (2.84 g, 11.8 mmol) and a THF solution (1.4 mL) of Li_2CuCl_4 (0.3 M) were treated dropwise over 20 min with a chloroprene Grignard solution (14.2 mL, 14.2 mmol) (exotherm). After the addition, the solution was treated with saturated NH_4Cl (100 mL) and extracted with pentane. Purification was accomplished by flash chromatography; the product was isolated in 75-80% yield. For kinetic runs, small amounts of material were purified by preparative GC. Diene **17**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.37 (dd, J = 17.5, 10.8 Hz, 1 H), 5.25 (dd, J = 17.5, 0.71 Hz, 1 H), 5.05 (dd, J = 10.8, 0.79 Hz, 1 H), 4.9 (m, 2 H), 2.22 (t, J = 7.14 Hz, 2 H), 1.5 (m, 2 H), 1.3 (m, 10 H), 0.9 (t, J = 6.38 Hz, 3 H); ^{13}C NMR (62.86 MHz, $CDCl_3$) δ 146.93, 139.30, 115.66, 113.26, 32.15, 31.63, 29.89, 29.75, 29.55, 28.44, 22.90, 14.36; IR (NaCl, neat) 3450, 3110, 2920, 2870, 1600, 1470, 990, 900 cm^{-1}; mass spectrum, *m/e* (100 eV, isobutane, rel intens) 167 (66), 153 (14), 139 (17); mass spectrum, *m/e* (EI, direct inlet) 166 (1), 155 (7).

Cycloadducts **19** and **20**: ^1H NMR (250 MHz, $CDCl_3$) δ 5.4 (s, 1 H), 4.35 (s, 2 H), 3.7-3.8 (3 H), 3.3 (3 H), 2.8-3.0 (3 H), 2.0 (t, 2 H), 1.2-1.4 (13 H), 0.8-0.9 (t, 3 H); ^{13}C NMR (62.86 MHz, $CDCl_3$) δ 168.4, 144.1 (144.0), 134.6 (134.1), 117.0 (116.7), 72.8 (72.6), 59.5 (58.8), 58.4 (58.2), 52.9 (51.9), 51.5 (51.3), 36.9 (36.2), 32.0 (31.9), 31.1 (29.8), 29.6 (29.6), 29.4 (29.4), 29.3 (28.9), 27.5 (27.4), 22.8, 14.2; IR (neat) 2942, 2875, 1730, 1440, 1260, 1220, 1125, 737 cm^{-1}; mass spectrum, *m/e* (70 eV, CI, isobutane, rel intens) 295 (100), 293 (86), 263 (43), 261 (48); high-resolution mass spectrum, *m/e* (70 eV, EI) calcd (M^+) 294.2194, obsd 294.2151.

Cycloadduct **21**: ^1H NMR (250 MHz, $CDCl_3$) δ 5.4-5.5 (s, 1 H), 3.74 (s, 3 H), 2.9-3.0 (2 H), 2.6-2.75 (2 H), 2.05 (s, 3 H), 1.9-2.0 (2 H), 1.2-1.4 (12 H), 0.8-0.9 (3 H); ^{13}C NMR (62.86 MHz, $CDCl_4$) δ 168.9, 144.2, 133.6, 121.7, 118.0, 51.3, 38.1, 36.7, 32.1, 29.7, 29.6, 29.5, 28.9, 27.4, 22.9, 21.5, 14.3; IR (neat) 2950, 2879, 1720, 1650, 1440, 1250, 1070, 910, 735 cm^{-1}; mass spectrum, *m/e* (70 eV, rel intens) 265 (100), 263 (18), 151 (3); high-resolution mass spectrum, *m/e* (70 eV, EI) calcd 264.2088, obsd 264.2068.

Cycloadduct **23** and **24**: ^1H NMR ($CDCl_3$, 250 Mz) δ 5.65 (s, 1 H), 4.58 (s, 2 H), 4.5 (s, 2 H), 3.9-4.05 (6 H), 3.76 (t, 2 H), 3.55 (3 H), 3.0-3.3 (3 H), 2.25 (t, 2 H), 1.8 (4 H), 1.1 (1 H); ^{13}C NMR ($CDCl_3$, 62.86 MHz) δ 168.4, 153.7, 144.11 (143.81), 134.22 (133.72), 124.25 (124.14), 117.66 (117.32), 84.25, 72.82 (72.74), 70.96 (70.77), 58.48 (58.03), 52.86 (51.54), 36.56, 31.98 (31.18), 29.89, 29.30, 28.99; IR ($CDCl_4$, solution cell) 2960, 2884, 2250, 1735, 1725, 1647, 1440, 1260 (B), 1220, 1120, 1063 cm^{-1}; mass spectrum, *m/e* (CI, direct inlet) 351 (5.91), 350 (0.23), 319 (100); mass spectrum, *m/e* (EI, direct inlet) 350 (4.09); high-resolution mass spectra, calcd 350.1718, obsd 350.1735.

Kinetic Studies. Rate constants for the intramolecular Diels-Alder cycloaddition of dienyne esters **4**, **6**, and **8** were obtained as follows. Microthermolysis solutions (125 μL) were prepared from a benzene solution (10.0 mL) of dienyne ester (10 mg) and cyclododecane (internal standard). The solutions were thermolyzed at the specified temperatures in a molten salt bath with temperature control to within ±0.2 °C. The individual tubes were removed, rapidly quenched by cooling, and then analyzed by capillary GC. First-order kinetics were observed from which the calculated rate constants are as follows: temperature (°C), $k \times 10^6$ (s^{-1}).

Dienyne **8**: 210, 4.6; 220, 7.2; 246, 29; 258, 59.

Dienyne **6**: 226.8, 2.14; 234.4, 2.90; 245.0, 5.71; 249.9, 7.06; 258.0, 9.90.

Dienyne **4**: 170.4, 0.33; 185.2, 0.745; 195.1, 1.27; 200.2, 1.81; 208.5, 2.75; 210.0, 2.83.

Dienyne **12**: 193.3, 2.36; 209.5, 5.00; 223.5, 10.6; 236.8, 17.7.

Rate constants for the bimolecular reactions and competitions between **12** and **16** were extracted by fitting the observed time-concentration profiles with simulated profiles using adjustable rate constants. Rate constants were adjusted to minimize the root-mean-square deviation between the observed and calculated time-concentration values.

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Registry No. 4, 86532-33-4; **5**, 86532-36-7; **6**, 111772-51-1; **7**, 111772-52-2; **8**, 112069-36-0; **9**, 112069-38-2; **12**, 106111-48-2; **13**, 97752-01-7; **14**, 106111-49-3; **15**, 97751-97-8; **16**, 69511-47-3; **17**, 5732-02-5; **18**, 23326-27-4; **19**, 112069-41-7; **20**, 112069-42-8; **21**, 112069-43-9; **22**, 112069-44-0; **23**, 112069-40-6; **24**, 112087-34-0; (*E*)-I, 112069-37-1; II, 109871-41-2; (*E*,*Z*)-PhCH=C(Ph)CH=$CHCH_2$N(Bu-*t*)COCH=CH_2, 39550-09-9; HC≡CCH_2Br, 106-96-7; $I(CH_2)_5I$, 628-77-3; H_2C=CHC(=CH_2)MgCl, 32657-89-9; H_2C=CHC(=CH_2)$(CH_2)_5I$, 112069-45-1; HC≡CLi, 1111-64-4; H_2C=CHC(=CH_2)$(CH_2)_5$C≡CH, 112069-46-2; *n*-$C_8H_{17}I$, 629-27-6; 2-*tert*-butyl-5,6-diphenyl-3a,6,7,7a-tetrahydrophthalimidine, 112069-39-3.

Superacid-Catalyzed Electrophilic Formylation of Adamantane with Carbon Monoxide Competing with Koch-Haaf Carboxylation[1]

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Abstract: The superacid-catalyzed reaction of adamantane with carbon monoxide was investigated. 1-Adamantanecarboxaldehyde together with 1-adamantanecarboxylic acid and 1-adamantanol (the products of the reaction of intermediate 1-adamantyl cation) was obtained. The mechanism of the formation of 1-adamantanecarboxaldehyde by electrophilic formylation involving σ-insertion of the formyl cation is indicated. This is contrasted by the competing protolytic ionization of adamantane to 1-adamantyl cation which gives with CO 1-adamantanoyl cation and subsequently 1-adamantanecarboxylic acid (Koch-Haaf reaction) or by hydrolysis 1-adamantanol.

The reaction of alkyl or cycloalkyl cation with carbon monoxide giving acyl cations constitutes the key steps in the well-known Koch-Haaf reaction[2] used for the preparation of carboxylic acids from alkenes, CO, and water. Synthetic aspects of this reaction

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