relative yields correspond to the relative reactivity since excess amounts of substrates were added.

The NIH Shift. The NIH shift values were determined for phenols from toluene-4-*d* and anisole-4-*d*. An acetonitrile solution containing 5 mM PhN_3 and 25% toluene-4-*d* or anisole-4-*d* was irradiated for 4 h under oxygen at ca. 20 °C. D contents in *p*-cresol and *p*-methoxyphenol were determined by GC-MS analysis with use of PEG 20M columns. The method and calculation have been described previously.[40]

Hydroxylation of Isopentane. A 3-mL acetonitrile solution containing 5 mM PhN_3 and 5% isopentane was irradiated for 8 h at ≥350 nm under oxygen at ca. 20 °C. The conversion of PhN_3 was 76%, and the yield of nitrobenzene was 42%. The alcohols obtained were 2-methyl-2-butanol (1.9%), 3-methyl-2-butanol (0.5%), and 2- and 3-methyl-1-butanol (0.3%) as determined by GLC with use of Gaskuropack 54. When the yields were divided by the numbers of hydrogens available, the relative reactivity was 1:7.2:62 for primary, secondary, and tertiary CH, respectively.

The hydroxylation of isopentane with hydroxy radical was carried out similarly by irradiating an acetonitrile solution of 0.15 M H_2O_2 and 5‰ isopentane for 8 h at >250 nm under oxygen. Product alcohols were determined similarly and listed in Table III. The relative yields of primary, secondary, and tertiary alcohols were practically the same when the concentration of H_2O_2 was 0.05 or 0.025 M.

Hydroxylation of Decalin. A 3-mL solution of 5 mM PhN_3 and 10% *cis*-decalin in $MeCN-CH_2Cl_2$ (3:1) was irradiated at ≥350 nm for 8 h under oxygen. Dichloromethane was added to solubilize decalin. The resulting alcohols were analyzed by GLC (PEG 20M, 1 m); the yields of *cis*- and *trans*-9-decalol were 7.4 and 3.1%, respectively, in comparison to authentic samples. A similar reaction with *trans*-decalin afforded *trans*-9-decalol (5.6%) and only a trace amount of cis alcohol. The hydroxylation of 10 mM H_2O_2 in place of PhN_3 was carried out similarly, and the results are listed in Table III.

^{18}O-Tracer Study. A 1-mL solution of 5 mM PhN_3 in MeCN was placed in a 20-mL Pyrex test tube with a septum rubber cap. After the solution was purged with argon, oxygen gas $^{18}O_2/O_2$ ($^{32}O_2$:$^{34}O_2$:$^{36}O_2$ = 100:0.6:8.4) was introduced into the test tube through a syringe by exhausting the argon gas with use of another syringe. Irradiations and product analyses were carried out as described above. The ^{18}O contents in $PhNO_2$ were determined by GC-MS. The averaged values after 3-5 determinations are listed in Table V.

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Thermal Cis-Trans Rearrangement of Semirigid Polyenes as a Model for the Anticarcinogen β-Carotene: An *all-trans*-Pentaene and an *all-trans*-Heptaene

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Abstract: To assess the possible role of a 15,15′ 90°-twisted, singlet diradical in the anticarcinogenicity of β-carotene, activation parameters for the thermal, cis-trans interconversion of *all-trans*-β-carotene (**1**) and 15,15′-*cis*-β-carotene (**2**), polyenes of order 11, are needed. Indirect achievement of this goal is initiated here by determining activation parameters for cis-trans rearrangement in a set of semirigid, *all-trans*-polyenes of order 3, 5, and 7 (9 to follow). These data also provide a test of theoretical calculations of stabilization energies of polyenyl radicals. For the coherent series, $\mathbf{3}_{1,1,1}$, $\mathbf{5}_{2,1,2}$, and $\mathbf{7}_{3,1,3}$, these activation parameters ($\Delta H^{\ddagger}$ (kcal/mol), $\Delta S^{\ddagger}$ (cal/mol·K)) are found: 38.9, −6.0; 32.1, −4.4; 27.5, −4.4. The trend is a diminishing return as the order is increased. "Stabilization energies", defined as extra stabilization associated with delocalization of the odd electron and derived with allyl as the reference point (SE_1 = 13.5 kcal/mol), are pentadienyl, SE_2 = 16.9 kcal/mol, and heptatrienyl, SE_3 = 19.2 kcal/mol. Heptaene **7** rearranges in a range, 64-104 °C, that is close enough to 37 °C to forewarn of thermal lability of β-carotene in cell membranes.

Enthalpies of stabilization of polyenyl radicals are fundamental (a) to an experimental, quantitative test of theoretical calculations of their magnitude and (b) to an assessment of thermally induced, configurational interconvertibility in polyenes generally and β-carotenes specifically. In this work, a kinetic study of thermal, cis-trans isomerization about the central double bond in systematically designed *all-trans*-polyenes of order 3, 5, and 7 ("order" specifies the number of double bonds) is undertaken in pursuit of these goals.

β-Carotene as Anticarcinogen

An exciting development in cancer prevention has been the recognition of several anticarcinogenic constituents in the human diet.[1,2] Among these, the common, all-trans stereoisomer of β-carotene (**1**) has gained laboratory and epidemiological support and is currently the subject of long-term, randomized trials.[3] The works of Santamaria and co-workers[4] and of Levenson et al.[5] are particularly noteworthy and provide reference to an extensive literature.

One mechanistic hypothesis parallels that established by Foote, Chang, and Denny[6] for the protection **1** gives to plants against chemically devastating, singlet dioxygen.[7] Its function is reconversion of singlet dioxygen to triplet dioxygen by a quenching process that owes its effectiveness to a perfect match between the energetic splittings of singlet and triplet *all-trans*-β-carotene (**1**) and singlet and triplet dioxygen (both 22 kcal/mol).

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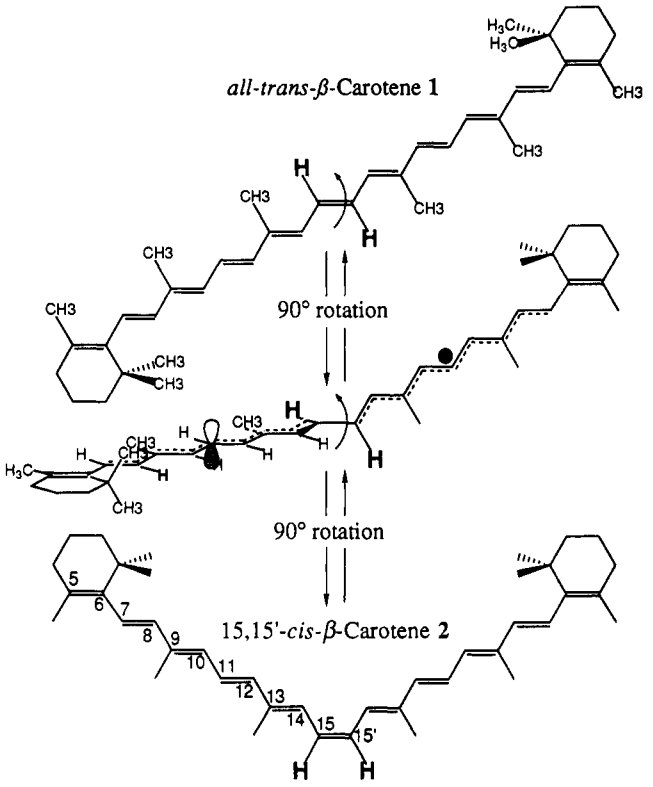
Scheme I



An alternative explanation of the anticarcinogenic action of **1** is based on the widely accepted hypothesis that hydroxyl and other free radicals, arising from radiation damage and peroxides generated inter alia in fried and burned foods,[1] owe their carcinogenicity to irreversible damage to DNA. A consequent mechanism for anticarcinogenesis envisions the trapping of free radicals before such damage to genetic material can be inflicted. This scheme credits **1** with high reactivity toward free radicals and has gained a modicum of credibility from the works of Kasaikina et al.[8] and of Burton and Ingold,[9] in which **1** functions as an inhibitor of free-radical chain reactions.

The original, if provocatively speculative, stimulus for the present undertaking was the suggestion that the radical-trapping potential of β-carotene might derive from a configuration twisted to 90° about its 15,15' double bond, as shown in Scheme I. To such an orthogonal diradical, exceptional reactivity toward free radicals would quite reasonably be ascribed. Being lipid-soluble, it might be expected to wait in the membrane of a cell for intrusive free radicals and trap them with high efficiency. Were the free energy of formation of the 90°-twisted state too high to support such an extreme hypothesis, it might be low enough to confer thermal lability on **1** at 37 °C. In that event, *all-trans*-β-carotene (**1**), the accepted anticarcinogenic agent, would serve as a reservoir for various of its cis isomers, which would then become serious contenders for the role of true agent(s).

Accreditation of Diradical Hypothesis

Plausibility of these speculations depends on the hypothetical, orthogonal diradical having a free energy of formation not much higher than that of conventional, planar **1**. Access to such energies may be had through thermal interconversion of cis and trans olefins (geometric isomerization). Simple examples are ethylene[10] and hexa-1,3,5-triene.[11] Activation parameters for such isomerizations measure the difference in enthalpy and entropy of formation of the planar polyene as educt and that of the orthogonal, singlet diradical as transition state.

Although direct examination of the interconversion of 15,15'-*cis*-β-carotene (**2**) and *all-trans*-β-carotene (**1**) is the obvious approach and is encouraged by numerous references to thermal instability among natural carotenoids,[12] the absence of quantitative thermochemical and kinetic studies is not surprising in light of the report by Tsukida and Saiki[13] that 18 products can be detected from the heating of **1** at 190 °C for 15 min but is perhaps surprising given the key role of **2** in the commercial synthesis of **1**.[14]

An indirect approach to the estimation of the activation parameters for thermal isomerization of **1** involves extrapolation from activation parameters in a series comprised of ethylene, hexatriene, decapentaene, tetradecaheptaene, and octadecanonaene. Although empirical Arrhenius parameters are available for the first two members of the series,[10,11] no higher polyenes have been studied. There are, however, several widely divergent estimates of the "stabilization energy" of the pentadienyl radical[15-20] and one for the heptatrienyl radical.[21] Extrapolation to the system of 11 double bonds in **1** from presently available parameters would overly strain credibility.

Relevance to Quantum Chemical Theory of π-Systems

The classical quantum mechanical model of Hückel theory as applied to coplanar systems of conjugated double bonds[22,23] leads, qualitatively, to the conclusion that stabilization by delocalization in polyenyl radicals increases as the number of double bonds increases, whereas incremental energy of conjugation in polyenes remains constant with increasing number of double bonds. Cis–trans isomerization is thus facilitated by stabilization in the two orthogonal radicals of the transition state, but opposed by stabilization in the starting polyene.[11] The quality of predicted enthalpies of activation is clearly very sensitive to the quantitative accuracy of the calculations.

All theoretical approaches[22-25] agree that enthalpy of conjugation is an essentially linear function of the order of the polyene. Bearing on this point are thermochemical data on butadiene[26] and methyl derivatives[27] and on hexa-1,3,5-triene.[28] Agreement on

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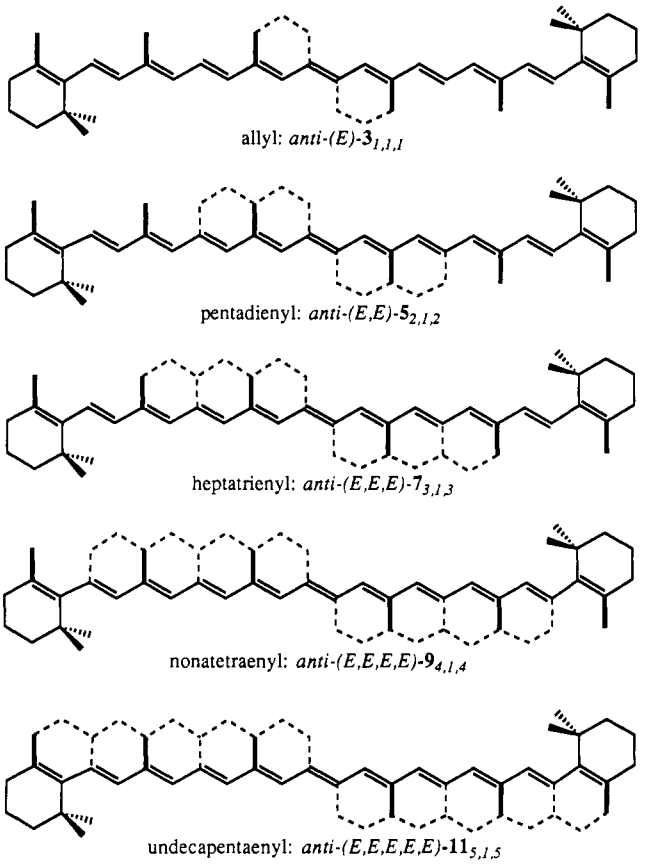
Scheme II



−3.74 kcal/mol as the empirical increment of conjugative interaction in these two systems is good, but the value finds no thermochemical validation in polyenes of order higher than 3.

Several calculations of the enthalpy of delocalization of polyenyl radicals have appeared,[22,23,29-31] but verification depends in every instance but that of Said et al.[31] on comparison with experimental *ratios* of stabilization enthalpies. For that purpose, one ratio alone, that of allyl to the unreliable pentadienyl, is available. Although the theories agree that the increment of stabilization per added double bond decreases as the total number of double bonds increases, they disagree on the rate of decrease and the magnitude of the limit in the polyenyl radical of infinite order.

One theoretical calculation of the enthalpies of activation of thermal cis–trans isomerization of polyenes, owed to Said, Maynau, Malrieu, and Garcia Bach,[31] employs an ab initio calculation that sets a value for ethylene (62.5 kcal/mol) and a nonempirical Heisenberg Hamiltonian for the polyenes and their related polyenyl radicals. Although enthalpies of activation decrease with increasing order of the polyene, they rapidly approach a limiting value predicted to be $\Delta H^{\ddagger} = 18$ kcal/mol. For a useful testing of this and other approaches, data from a more extended series of polyenes are needed.

Experimental Plan and Results

Ideally, the series should consist of unsubstituted polyenes, but their proclivity to react with oxygen, to dimerize and polymerize, to undergo intra and intermolecular Diels–Alder reactions and other thermal reorganizations, such as cyclization of butadienes to cyclobutenes and of *cis*-hexatrienes to cyclohexadienes argues against undertaking their study. Perhaps introduction of relatively minor substitution at the ends of the polyenes and of an occasional methyl group like in the carotenoids would make the problem tractable, but we have decided on a series of polyenes made semirigid by incorporation of all but the central double bond into fused six-membered rings as a means of precluding the extraneous thermal processes noted above (see Scheme II). Precedent for the use of fused-ring systems to rigidify polyenes is found in the work of Lüttke and predecessors in the field of cyanine dyes.[32] The strategy is a compromise between experimental feasibility and the ideal of a series of pristinely unsubstituted, acyclic polyenes.

Of the three polyenes in this initial study, the first two represent allyl and pentadienyl radicals, which are already well documented in the literature, but particularly in the latter case, with widely discordant results. They are included to create a self-consistent series within which comparison can be made with comparative confidence. The three polyenes are synthesized by application of the Mukaiyama–Tyrlik–McMurry (MTM) reaction[33] to their apposite ketones, preparations of which are shown in Scheme III. This fine method of coupling proceeds in good yield undisturbed by the presence of conjugated polyenes in the ketones and thus completely parallels the synthesis of β-carotene and other polyenes.[33b,d]

Scheme III

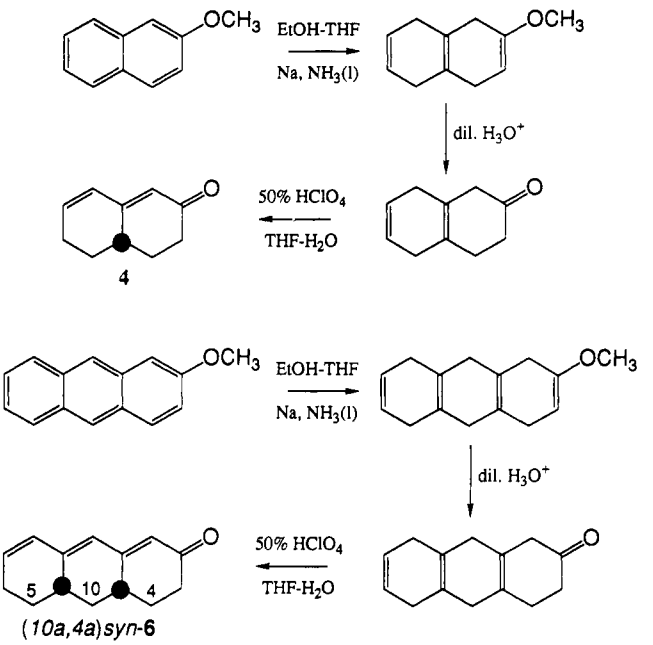


Table I. Proton Chemical Shifts and Values of the Nuclear Overhauser Enhancement in Polyenes **3**, **5**, and **7**

	chem shift, ppm		NOE,[b] %	
polyene[a]	H-α[c]	H-β	H-α[H-β]	H-β[H-α]
anti-**3**[d]	6.59	2.39	27.6	7.0
syn-**3**	6.77	2.26	2.1	1.3
α-*anti*-**5**[d]	6.47	2.83	19.2	13.8
β-*anti*-**5**	6.50	2.88	22.9	16.3
α-*syn*-**5**	6.75	2.54	0.3	0.5
β-*syn*-**5**	6.78	2.69	0.3	0.1
α-*anti*-**7**[e]	6.35	2.86	20.0	9.8
β-*anti*-**7**	6.38	2.90	19.5	8.5
α-*syn*-**7**	6.57	2.59	0.7	2.0
β-*syn*-**7**	6.59	2.77	1.1	0.7

[a] α and β isomers comprise between them meso and racemic isomers (configuration unassigned; refer to Scheme IV). [b] A[B] denotes observation of nucleus A upon saturation of nucleus B. [c] α and β denote H2 and H4 of **3** and H1 and H3 of **5** and **7**, respectively (see Scheme IV). [d] In C_6D_6. [e] In $CDCl_3$.

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Table II. Ultraviolet–Visible Spectra of Polyenes in Spectrograde Hexanes

polyene	λ_{max}, nm (ϵ)		
anti-**3**	267 (28 500)	277 (35 400)	288 (25 800)
β-anti-**5**	337 (48 500)	354 (82 100)	374 (81 600)
β-anti-**7**	389 (54 900)	412 (98 700)	439 (105 000)

Table III. Thermal Cis–Trans Isomerization of *anti*-**3** and *syn*-**3** in Benzene-d_6: Specific Rate and Equilibrium Constants and Activation Parameters

T, °C	k_1 (10^{-6} s^{-1})[a]	K
207.7 ± 0.2	1.01 ± 0.01[b]	0.797
218.1 ± 0.3	2.53 ± 0.03	0.799
235.7 ± 0.2	10.06 ± 0.09	0.809
244.9 ± 0.3	20.50 ± 0.18	0.817
258.7 ± 0.1	60.83 ± 0.63	0.823

Arrhenius Plot ($1/T$ vs log k)
E_a = 39.85 ± 0.60 kcal/mol
log A = 12.14 ± 0.26

Eyring Parameters
$\Delta H^{\ddagger}$ = 38.85 ± 0.60 kcal/mol[c]
$\Delta S^{\ddagger}$ = −6.03 ± 1.18 eu

Thermodynamics ($1/T$ vs log K)
ΔH = 0.34 ± 0.03 kcal/mol
ΔS = 0.25 ± 0.06 eu

[a] Calculated by linear regression using the usual expression for reversible first-order reactions: $k_1 + k_{-1} = (1/t)$ ln $[(x_{eq} - x_0)/(x_{eq} - x)]$; $K = k_{-1}/k_1$. [b] Double all standard errors for 90% confidence limits. [c] Calculated at 233.2 °C.

In all examples, a mixture of syn and anti stereoisomers results without discernibly useful stereoselectivity, even though its composition does not correspond to thermodynamic equilibrium. Assignment of anti stereochemistry is based on observation of a nuclear Overhauser enhancement in H-α when equatorial H-β is saturated (and vice versa); syn configuration is indicated by the absence of such NOE (see Scheme IV and Table I).

A complication arises in the syntheses of $\mathbf{5}_{2,1,2}$ and $\mathbf{7}_{3,1,3}$ where the syn and anti isomers (Scheme IV) are each generated from their respective racemic ketones in achiral and chiral stereochemistries in essentially equal amount. No effort having been made to assign meso and racemic configurations, the pairs are designated α- (H-α signals at higher fields) and β- (H-β at lower fields) (see Table I). Only one of the four isomers produced in the synthesis of **5**, *β-anti*-$\mathbf{5}_{2,1,2}$, could be separated by crystallization, but all four isomers could be identified independently in the ^{1}H NMR spectrum. Because each could be analyzed quantitatively in the presence of the other three, a mixture of α- and *β-anti*-**5** could be employed simultaneously in a single kinetic run and thus provide two rate constants and an internal check on precision.

Stemming from the backbone of the system of fused rings, a further stereochemical complication, which is already encountered in the synthesis of its precursor ketone, 4,4a,5,6,10,10a-hexahydro-2(3*H*)-anthracenone (**6**), is shown by heptaene **7**. From perusal of models of *syn*- and *anti*-**6**, strain can be inferred in the 10a–4a anti configuration, owing to a twisting out of the plane of the system of double bonds by an essentially gauche, *cis*-decalin type of configuration.[34] In the sequence starting from β-methoxyanthracene, the fully conjugated ketone **6** is generated by hydrolysis of the product of Birch reduction under conditions sufficiently acidic to establish equilibrium not only among the various α,β and β,γ isomers but also between anti and the strongly favored syn configurations (Scheme III).

Consistently, this thermodynamic control leads only to the favored 10a–4a syn configuration, as shown by its ^{1}H NMR. Strong coupling (J = 12.4 Hz) between H4a and H10a with H10 at 1.24 ppm and weak coupling (J = 4.3 Hz) with H10 at 1.95 ppm are consistent with the syn configuration, in which dihedral angles H4a–C4a–C10–ax-H10 and ax-H10–C10–C10a–H10a are close to 180°. A small but nonzero NOE (4.5%) between axial H10 and axial H4 provides mild confirmation.

Ultraviolet–visible spectra of the polyenes have been measured in hexanes and are reported in Table II. These values may be compared with those reported for unsubstituted linear polyenes of the structure H(CH=CH)$_n$H, where n = 3–8 and 10.[35]

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Table IV. Thermal Cis–Trans Isomerization of α- and *β-anti*-4,4′,4a,4a′,5,5′,6,6′-Octahydro-2,2′-bi-3*H*-naphthylidenes (**5**) to *α-syn*-**5** and *β-syn*-**5**, Respectively, in Benzene-d_6: Specific Rate and Equilibrium Constants and Activation Parameters

	β-anti-**5**		*α-anti*-**5**	
T,[a] °C	k_1 (10^{-6} s^{-1})1*b*	K	k_1 (10^{-6} s^{-1})[b]	K
121.2	1.52 ± 0.04[c]	0.513	1.35 ± 0.02	0.564
132.0	4.67 ± 0.17	0.533	4.44 ± 0.05	0.575
145.2	16.82 ± 0.14	0.545	15.53 ± 0.08	0.601
155.5	42.54 ± 0.37	0.550	40.65 ± 0.24	0.610
166.8	116.8 ± 2.1	0.569	114.7 ± 1.6	0.614

Arrhenius Plot ($1/T$ vs log k)[e]
E_a = 32.75 ± 0.10 kcal/mol; log A = 12.33 ± 0.05
E_a = 33.37 ± 0.28 kcal/mol; log A = 12.63 ± 0.15

Eyring Parameters
$\Delta H^{\ddagger}$ = 31.93 ± 0.10 kcal/mol; $\Delta S^{\ddagger}$ = −4.75 ± 0.24 eu[d]
$\Delta H^{\ddagger}$ = 32.54 ± 0.28 kcal/mol; $\Delta S^{\ddagger}$ = −3.41 ± 0.68 eu

Thermodynamics ($1/T$ vs log K)
ΔH = 0.71 ± 0.08 kcal/mol; ΔS = 0.49 ± 0.20 eu
ΔH = 0.69 ± 0.09 kcal/mol; ΔS = 0.62 ± 0.21 eu

[a] ±0.2 °C. [b] Calculated by linear regression using the usual expression for reversible first-order reactions: $k_1 + k_{-1} = (1/t)$ ln $[(x_{eq} = x_0)/(x_{eq} - x)]$; $K = k_{-1}/k_1$. [c] Double all standard errors for 90% confidence limits. [d] Calculated at 144.0 °C. [e] The weighted means are E_a = 32.91 kcal/mol and log A = 12.41.

Table V. Thermal Cis–Trans Isomerization of *α-anti*-**7** and *β-anti*-**7** to *α-syn*-**7** and *β-syn*-**7**, Respectively, in Benzene-d_6: Rate and Equilibrium Constants and Activation Parameters

	α-anti-**7**		*β-anti*-**7**	
T, °C	k_1 (10^{-6} s^{-1})[a]	K	k_1 (10^{-6} s^{-1})[a]	K
64.25 ± 0.07	1.10 ± 0.03	0.440	1.18 ± 0.02	0.374
64.25 ± 0.07	1.17 ± 0.02	0.429	1.29 ± 0.03	0.372
80.28 ± 0.04	7.18 ± 0.26	0.455	8.22 ± 0.09	0.389
104.24 ± 0.01	100.5 ± 0.7	0.464	101.7 ± 1.4	0.408
104.30 ± 0.02	104.4 ± 2.0	0.484	105.0 ± 2.9	0.399

Arrhenius Plot ($1/T$ vs log k)
E_a = 28.50 ± 0.32 kcal/mol[b]; log A = 12.51 ± 0.20
E_a = 28.00 ± 0.24 kcal/mol; log A = 12.23 ± 0.15

Eyring Parameters
$\Delta H^{\ddagger}$ = 27.79 ± 0.32 kcal/mol; $\Delta S^{\ddagger}$ = −3.65 ± 0.90 eu[c]
$\Delta H^{\ddagger}$ = 27.29 ± 0.24 kcal/mol; $\Delta S^{\ddagger}$ = −4.94 ± 0.68 eu

Thermodynamics ($1/T$ vs log K)
ΔH = 0.56 ± 0.13 kcal/mol; ΔS = −0.01 ± 0.36 eu
ΔH = 0.50 ± 0.07 kcal/mol; ΔS = −0.47 ± 0.18 eu

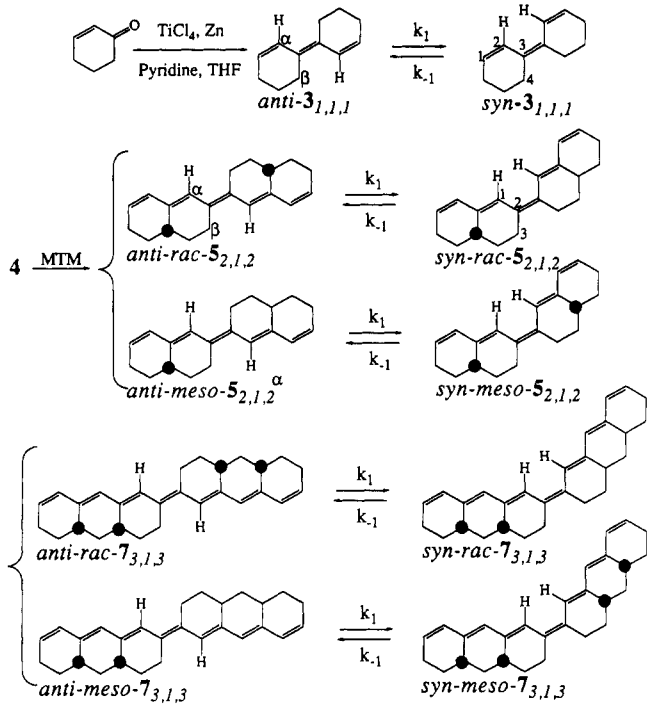
[a] By linear regression of the usual expression for reversible first-order reactions: $k_1 + k_{-1} = (1/t)$ ln $[(x_{eq} = x_0)/(x_{eq} - x)]$; $K = k_{-1}/k_1$. [b] Double standard errors for 90% confidence limits. [c] At 84.3 °C.

Kinetics and Discussion

Kinetics of cis–trans rearrangement of the polyenes are elucidated in benzene-d_6 solutions sealed in NMR tubes. Temperature is controlled by heating in the vapors of suitably chosen, boiling liquids. Quantitative analysis is effected by ^{1}H NMR directly without prior isolation by monitoring the proton, H_α, on C-2; that is, the vinyl proton adjacent to the central double bond

(35) (a) Sondheimer, F.; Ben-Efraim, D. A.; Wolowsky, R. *J. Am. Chem. Soc.* **1961**, *83*, 1675–1681. (b) Mebane, A. D. *J. Am. Chem. Soc.* **1952**, *74*, 5227–5229. (c) Woods, G. F.; Schwatzman, L. H. *J. Am. Chem. Soc.* **1949**, *71*, 1396–1399.

Scheme IV



and most sensitive to the syn/anti configuration of the polyene. Experiments with triene **3** occasionally led to losses by explosion as a result of the high temperatures of reaction required.

Rate constants and activation parameters for **3**, **5**, and **7**, given in Tables III–V, are derived from primary data, which are recorded in Tables VII–IX, respectively, as supplementary material.

Activation parameters for the thermal interconversion of *anti*-**3** and *syn*-**3** have also been determined in the gas phase by Roth et al.[36] in two independent experiments in the temperature range 268.8–319.1 °C: from *anti*-**3**, E_a = 42.0 ± 0.2 kcal/mol, A = (1.4 ± 0.3) × 10^{13}, $\Delta H^{\ddagger}$ = 40.9 kcal/mol, $\Delta S^{\ddagger}$ = −1.7 eu. Their precision is substantially better than ours, although the results overlap at the 95% confidence level. We are also inclined to impute a higher accuracy to their results and would choose their values for the ensuing discussion, were it not for the difference in medium. Unanswered questions raised by the difference between gas and solution phases are being addressed.

As expected, α- and β-*anti*-**5** have indistinguishable activation parameters and rate constants within experimental uncertainties—certainly if 90 or 95% confidence limits are applied. We take the mean based on weights inversely proportional to the errors: $\Delta H^{\ddagger}$ = 32.1 kcal/mol, $\Delta S^{\ddagger}$ = −4.4 eu.

The heptaenes, α- and β-*anti*-**7**, are unexceptional but for a low solubility, which significantly increases the collection time required for good analytical data. Like those for *anti*-**5**, the activation parameters from α- and β-*anti*-**7** in Table V are averaged by weighting inversely to their respective uncertainties: $\Delta H^{\ddagger}$ = 27.5 kcal/mol, $\Delta S^{\ddagger}$ = −4.4 eu.

General Conclusions

The enthalpy of activation for the pentaene **5** lies 6.8 kcal/mol lower than that of the triene **3**. The heptaene **7** reveals a further lowering in enthalpy of activation of 4.6 kcal/mol. The conclusion seems inescapable: each successive conjugated double bond added to the radical contributes only a fraction of the lowering in enthalpy of activation of its predecessor.

Although triene **3** is tetrasubstituted and its congeneric allyl radicals are each trisubstituted, thereafter the series is self-consistent: Pentaene **5** is hexasubstituted and its two related pentadienyl radicals are tetrasubstituted, and so forth along the series. Alternatively, each succeeding member is related to its predecessor by fusion of an additional cyclohexene ring. Comparisons within the series are thought to be valid, although absolute values may only be proportional to those hypothetically associated with the ideal series of unsubstituted polyenes.

The present series properly begins with the triene **3**, not with a monoolefin such as bicyclohexylidene. In **3**, precursor to allyl, *alkyl* is replaced by vinyl, whereas in subsequent members of the series *vinyl* is replaced by butadienyl, which, in turn, is replaced by pentadienyl, in its turn replaced by heptatrienyl, and so forth to the infinite polyene. Each successive member is related to its predecessor by the insertion of a vinylene group; that is, an sp^2–sp^2 bond is replaced by two of the same type. By contrast, in the progression from monoolefin to triene (from a simple radical to allyl), alkyl (sp^3) is replaced by vinyl (sp^2).

With respect to the role of *all-trans*-β-carotene as an anticarcinogenic agent, continuation of the present trend toward lower activation energies admits the possibility of an activation energy low enough to put various cis isomers at the disposal of the cell membrane at 37 °C. More detailed discussion is postponed to a later paper.

Definition of Stabilization Energy: Allyl Radical. Definitions are neither correct nor incorrect but survive by their greater or lesser usefulness. In defining "stabilization energy" in polyenyl radicals, we are at pains to separate enthalpy of conjugative interaction between coplanar adjacent double bonds from enthalpy of delocalization of the odd electron in the radical. The former enthalpy is designated K, after Kistiakowsky who defined the concept and established its magnitude in butadiene;[26] the latter, designated SE_n where n is the number of double bonds interacting with the odd electron, is the stabilization energy. Their sum, $SE_n + (n-1)K$, is the *total* enthalpy of π-electron delocalization of the system of $(2n+1)$ 2p orbitals and electrons in the polyenyl radical.

Stabilization energy is defined here as half the difference in the heat of formation of an appropriate model of the localized diradical and the experimental heat of formation of the diradical believed faithfully to represent the transition state of the isomerization under observation. Scheme V depicts the extraction of SE_1 and SE_2 under this definition. The requisite localized model is taken as a monoolefin of constitution closely related to the polyenes for which it is intended to serve. In Scheme V, we show ethylene and its cis–trans isomerization via an orthogonal, diradical-like transition state for simplicity's sake. A more suitable model might be 3,4-dimethylhexene-3 ($\Delta H^{\ddagger}$ = 59.4 kcal/mol, $\Delta S^{\ddagger}$ = +2.7 cal/mol·deg)[37] or, the model we prefer, the isomerization of bicyclohexylidene, a value for which can be calculated by the method described in that paper ($\Delta H^{\ddagger}$ = 58.1 kcal/mol).

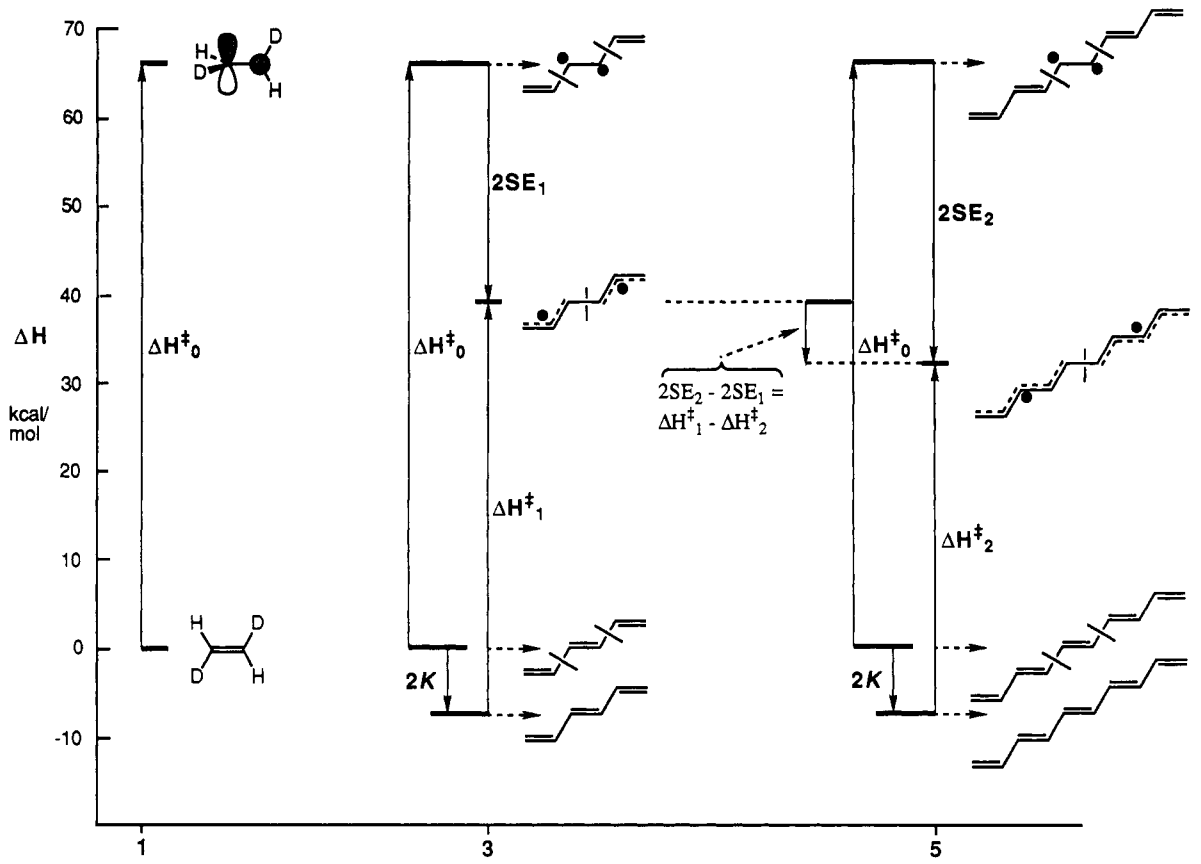
Credible transfer of the activation enthalpy $\Delta H^{\ddagger}_0$ of the model monoolefin to triene requires a model of the triene localized to simulate a monoolefin and a model of its diradical as transition state localized to simulate an unperturbed diradical. In both operations, insertion of two imaginary barriers to π-electron overlap suffices—with the sharp caveat that the change from sp^3–sp^2 to sp^2–sp^2 be ignored. If the change be significant, it becomes a hidden contributor in our stabilization energies, SE_n. Allyl stabilization is then given by the equation, $SE_1 = (\Delta H^{\ddagger}_0 - \Delta H^{\ddagger}_1)/2 + K$. Taking $\Delta H^{\ddagger}_0 - \Delta H^{\ddagger}_1$ = 19.2 kcal/mol leads to SE_1 = 13.3 kcal/mol. Because allyl stabilization is not the focus of this work and an extensive publication is in preparation,[36] we refrain more detailed discussion and accept their value of 13.5 kcal/mol for allyl stabilization in this discussion.

Stabilization Energy of Pentadienyl Radical. The simple way of extracting the stabilization energy of the pentadienyl radical asks how much more effective is it than allyl in facilitating rotation about a central double bond. The difference in enthalpies of activation of **5** and **3** is (38.9 − 32.1) or 6.8 kcal/mol. Half that amount measures the degree of superiority of pentadienyl over allyl. If allyl is taken to have a stabilization energy (SE_1) of 13.5

(36) Doering, W. von E.; Roth, W. R.; Bauer, F.; Boenke, M.; Breuckmann, R.; Ruhkamp, J.; Wortmann, O. *Chem. Ber.*, in press.

(37) Doering, W. von E.; Roth, W. R.; Bauer, F.; Breuckmann, R.; Ebbrecht, T.; Herbold, M.; Schmidt, R.; Lennartz, H.-W.; Lenoir, D.; Boese, R. *Chem. Ber.* **1989**, *122*, 1263–1275.

Scheme V



kcal/mol, then SE_2 of the pentadienyl radical is 16.9 kcal/mol. This procedure obviates any concern that the triene precursor to two allyl radicals has two elements of conjugative interaction ($2K$ or 7.5 kcal/mol), whereas the pentaene precursor to the two pentadienyl radicals has four elements or is stabilized by $4K$. Comparison of illustrations 3 and 5 in Scheme V makes the point. Introduction of the barriers required to make valid the transfer of $\Delta H^{\ddagger}_0$ leaves the butadienyl units in *both* the localized pentaene as educt and the localized model of transition state fully *delocalized*. The argument is clearly stated in the equation given in Scheme V. SE_n is independent of any further correction for conjugative interaction; in SE_1 alone is one correction by K necessary; none is fitting after that. This formulation avoids the counterintuitive prediction that stabilization energy become infinite as n becomes infinite. Stabilization energy may approach a finite limit, whereas it is total enthalpy of π-electron delocalization that becomes infinite.

As an afterthought relating to the sharp eye that needs be kept on the two separate types of delocalization energy operating in the polyenes, each of the butadiene moieties in the heptaene *can* be expressed in localized form by the addition of $1K$, but if that be done, it must be done in both the educt and the transition state, not in one without the other.

Our value for SE_2 = 16.9 kcal/mol may now be compared with others in the literature. In that process, all estimates of SE_2 are readjusted to allyl radical for which SE_1 = 13.5 kcal/mol and consistency with the heats of formation of the simple radicals put forward in the authoritative paper of Seetula, Russell, and Gutman.[38] We reemphasize that SE_1 is defined in terms of replacement of alkyl by vinyl.

Frey and Krantz have compared energies of activation of ring enlargement of cyclopropylbut-1-ene to 3-ethylcyclopentene (ΔE_a = 50.0 kcal/mol)[39] and of *trans*-1-cyclopropylbuta-1,3-diene to 3-vinylcyclopentene (ΔE_a = 44.5 kcal/mol).[16] The difference, 5.5 kcal/mol, may be equated with $SE_2 - SE_1$ if the assumption is accepted that the cost of the obligatory cis configuration of the radicals is the same in both instances. Although Frey and Krantz by the gratuitous addition of $1K$ implicitly reject the definition of "stabilization energy" as that energy released by delocalization specifically of the *radical* in favor of definition of stabilization energy as *total* π-electron delocalization, the value emerging from their work for SE_2, as here defined, is 19.0 kcal/mol; i.e., 13.5 + 5.5 kcal/mol.

In a more convoluted approach, Dolbier and Alonso[17] compare ring expansion of vinylcyclopropane and 1,1-divinylcyclopropane. Contributing to the difference between $\Delta H^{\ddagger}_1$ = 48.4 kcal/mol[40] and $\Delta H^{\ddagger}_2$ = 38.6 kcal/mol are the cis factor (which is presumed to cancel);[41] the change from secondary radical in the localized model of vinylcyclopropane to tertiary in that of 1,1-divinylcyclopropane (this change might amount to 2.6 kcal/mol; that is, the difference in heats of transformation of propane and isobutane to isopropyl and *tert*-butyl radicals, respectively);[38] and the fact that delocalization of the model of the localized transition state from 1,1-divinylcyclopropane liberates the *total* π-electron energy of the pentadienyl radical and therefore requires correction by subtraction of $1K$. These caveats are given expression in the following three equations:

$$SE_2 + 2.6 + K - \text{cis} - (SE_1 - \text{cis}) = \Delta H^{\ddagger}_1 - \Delta H^{\ddagger}_2$$

$$SE_2 - SE_1 = \Delta H^{\ddagger}_1 - \Delta H^{\ddagger}_2 - K - 2.6$$

$$SE_2 = 17.0\ (48.4 + 13.5 - 38.6 - 3.74 - 2.6)\ \text{kcal/mol}$$

A further unresolvable complication in the Dolbier–Alonso example is the availability of either the E,E and/or the E,Z configuration to the developing pentadienyl radical. Although

(38) Seetula, J. A.; Russell, J. J.; Gutman, D. *J. Am. Chem. Soc.* **1990**, *112*, 1347–1353.
(39) Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 4188–4189.
(40) Flowers, M. C.; Frey, H. M. *J. Chem. Soc.* **1961**, 3547–3548.
(41) In the generation of SE_1 by comparing the enthalpy of activation of cis–trans isomerization of cyclopropane (59.8 kcal/mol)[42] with that of the ring enlargement of vinylcyclopropane (48.4 kcal/mol),[40] the cis factor cannot be ignored and may be responsible for the somewhat low value (11.4 kcal/mol).
(42) Waage, E. V.; Rabinovitch, B. S. *J. Phys. Chem.* **1972**, *76*, 1695–1699.

we cannot guess the path of lower free energy actually followed, we note that closure from the *E,Z* configuration would lead to 1-vinylcyclopentene in its enthalpically higher (~2.5 kcal/mol) cisoid conformation as the proximate product.[43]

In the examples of Frey and Krantz, and Dolbier and Alonso, the product cyclopentenes have strain energies of ~6 kcal/mol, an unknown portion of which might already be incorporated at the transition state. This factor also has to be assumed to cancel in the comparisons leading to SE_2.

Trenwith has attempted to establish the heat of formation of pentadienyl radical directly by studying the bond dissociations of 1-ethylbutadiene ($\Delta H^\ddagger$ = 67.1 kcal/mol)[19a] and 3-methylpenta-1,4-diene ($\Delta H^\ddagger$ = 66.0 kcal/mol)[19b] to methyl radical ($\Delta H_f°$ = 34.9 kcal/mol).[38] The heat of formation of 1-ethylbutadiene can be estimated ($\Delta H_f°$ = +13.4 kcal/mol) quite reliably from the known heat of formation of *trans*-piperylene ($\Delta H_f°$ = +18.2 kcal/mol) and the difference (−4.76 kcal/mol) in heat of formation of propene ($\Delta H_f°$ = +4.78 kcal/mol) and butene-1 ($\Delta H_f°$ = +0.02 kcal/mol). As pointed out by Trenwith, the heat of formation of 3-methylpenta-1,4-diene is not known and cannot be calculated precisely by the method of Benson group equivalent values. But a reasonably reliable estimate ($\Delta H_f°$ = +19.05 kcal/mol) can be made by noting that the change in heat of formation associated with the insertion of CH_2 into the 2,3-bond of butane is −4.92 kcal/mol in contrast to insertion into the 2,3-bond of butadiene (−1.05 kcal/mol). Noting further that insertion of CH_3CH into butane involves −11.11 kcal/mol, it is reasonable to project that its similar insertion into butadiene ($\Delta H_f°$ = +26.29 kcal/mol) will cost not far from −7.24 kcal/mol (−11.11 − (−4.92 + 1.05)). Heats of formation of pentadienyl radical from 1-ethylbuta-1,3-diene and 3-methylpenta-1,4-diene are then 45.6 and 50.3 kcal/mol, respectively.

Translation of our value for SE_2 = 16.9 kcal/mol into a heat of formation of pentadienyl is accomplished in two ways that should, in principle, give identical results. One scheme starts with 1,4-pentadiene ($\Delta H_f°$ = +25.24 kcal/mol),[27] adds the change in heat of formation when a methylene group becomes a (localized) secondary radical (46.3 kcal/mol),[38] and subtracts SE_2 and one *K* (3.74 kcal/mol) (*total* π-electron energy is released in this instance on delocalization). The resulting heat of formation is 50.9 kcal/mol. The second starts with *trans*-piperylene, adds the change in heat of formation associated with the conversion of an aliphatic methyl group to a primary radical (48.3 kcal/mol),[38] and subtracts SE_2 but not *K*, conjugative interaction already being present in the starting diene. The resulting heat of formation is 49.6 kcal/mol. A mean value of 50.3 kcal/mol may be taken. One of Trenwith's results is in perfect agreement and the other inexplicably lower by 4.7 kcal/mol (to invoke conjugative interaction as a corrective explanation in 1-ethylpenta-1,3-diene is not acceptable). Corresponding values of SE_2 from Trenwith's experiments with 1-ethylbutadiene and 3-methylpenta-1,4-diene are 20.9 and 17.1 kcal/mol, respectively.

MacInnes and Walton[18e] generate pentadienyl by photolysis of penta-1,4-diene and di-*tert*-butyl peroxide, determine activation parameters for interconversion of the *E,E* and *E,Z* configurations, and find an energy of activation for the thermal conversion of *E,E* to *E,Z* of 11.7 kcal/mol. When compared with the energy of activation of 15.7 kcal/mol found for rotation in allyl radical by Korth, Trill, and Sustman,[44] pentadienyl has a stabilization energy, SE_2 = 17.5 kcal/mol, in good agreement with the present result of 16.9 kcal/mol. This study also reveals that (*E,Z*)-pentadienyl is less stable than *E,E* by 2.4 kcal/mol, a value in good agreement with that of ~2.1 kcal/mol from the comparison of (*E,E*)- and (*E,Z*)-**5**.[45]

Egger and Jola[15c] generate a substituted pentadienyl radical by the addition of NO to 1,*trans*-3,*trans*-5-heptadiene and observe the appearance of 1,*trans*-3,*cis*-5-heptatriene as a measure of the rate of addition of NO. The resulting energy of activation of 16.75 kcal/mol may be compared to the value of 19.2 kcal/mol found in the corresponding allylic example. The resulting value for SE_2 = 16.0 kcal/mol needs no correction by the addition of one *K*.

Of the estimates of pentadienyl stabilization summarized in Table VI, that of Walton et al. based on rotation and that of syn–anti rearrangement are superior in respect to lack of ambiguity about their transition states. We favor a value of 17.0 ± 0.5 kcal/mol for pentadienyl stabilization.

Table VI. Stabilization Energies (SE_n) of Pentadienyl and Heptatrienyl Radicals

SE_n[a-c]	method	ref
	SE_2: Pentadienyl	
16.0 (18.5)	kinetics of NO addition	15c
16.9	syn–anti rearrangement	this work
17.0 (25.0)	1,1-divinylcyclopropane (rearr)	17
17.1 (18.6)	$CH_3CH(CH{=}CH_2)_2$ (pyrolysis)	19b
17.5 (25.0)	rotational barrier (ESR)	18e
19.0 (21.7)	1-cyclopropylbutadiene (rearr)	16
20.9 (18.5)	hexa-1,3-diene (pyrolysis)	19a
	SE_3: Heptatrienyl	
19.2	syn–anti rearrangement	this work
≤20.5 (≤31.8)	rotational barrier (ESR)	21

[a] All results adjusted to allyl = 13.5 kcal/mol (vinyl vice methyl)[36] and expressed in kilocalories per mole. [b] All results adjusted to the alkyl–H bond dissociation energies proposed by Seetula, Russell, and Gutman.[38] [c] Values in parentheses are those reported by the authors.

Stabilization Energy of Heptatrienyl Radical. The enthalpy of activation for syn–anti isomerization of **7**, 27.5 kcal/mol, is 11.4 kcal/mol lower than that of the triene **3**. Stabilization energy of the heptatrienyl radical, SE_3, is thus 19.2 kcal/mol. Like the derivation of SE_2, that of SE_3 warrants no correction by definition for the greater enthalpy of conjugation in **7**.

From the heat of formation of 1,*trans*-3,*trans*-5-heptatriene, estimated to be +31.4 kcal/mol by application of the difference in heats of formation of butadiene ($\Delta H_f°$ = +26.3 kcal/mol)[27] and *trans*-hexatriene ($\Delta H_f°$ = +39.5 kcal/mol)[28] to *trans*-piperylene ($\Delta H_f°$ = +18.2 kcal/mol),[27] a heat of formation of localized heptatrienyl radical can be derived ($\Delta H_f°$ = +79.7 kcal/mol). The heat of formation of delocalized heptatrienyl radical is obtained by subtraction of its stabilization energy: $\Delta H_f°$ = +60.5 kcal/mol.

Examination by Green and Walton[21] of rotation in heptatrienyl radical by electron spin resonance leads to an activation barrier ≤8.5 kcal/mol, which is at least 7.2 kcal/mol lower than that for allyl. The resulting value of 20.7 kcal/mol for SE_2 agrees well with our value of 19.2 kcal/mol.

Experimental Section

General Methods. ^1H NMR spectra are measured in $CDCl_3$ or C_6D_6 solution on Bruker AM-300 (300-MHz) or AM-500 (500-MHz) instruments. Spin–lattice relaxation times (T_1's) are determined by the inversion recovery method on vacuum-sealed solutions in $CDCl_3$ or C_6D_6. ^{13}C NMR spectra are measured on a Bruker AM-500 (126-MHz) or AM-300 (75.5-MHz) instrument. All chemical shifts are reported from TMS (ppm).

Nuclear Overhauser enhancements are determined by the gated decoupling method on degassed solutions in $CDCl_3$ (**6** and **7**) and C_6D_6 (**3** and **5**). For **5**, a relaxation delay and a saturation period 5 times the longest T_1's of the concerned protons are taken between pulses; for 4,4a,5,6,10,10a-hexahydro-2(3*H*)-anthracenone (**6**), they are both 15 s.

Infrared spectra are recorded on a Perkin-Elmer Model 337 grating spectrophotometer (cm^{-1}). Liquid samples are observed as thin films on a NaCl plate whereas solid samples are measured as thin layers prepared by evaporating $CHCl_3$ solutions on a NaCl plate.

UV–visible electronic spectra are determined with a Varian Cary 219 or 2390 spectrophotometer in spectrograde hexanes (λ_{max}, nm).

The Mukaiyama–Tyrlik–McMurry reaction[33] is typically carried out in the following manner: "Titanium reagent" is prepared by the addition of THF, freshly distilled from $LiAlH_4$, to an appropriately sized, three-necked flask, cooled to 0 °C and equipped with magnetic stirrer, reflux condenser, rubber septum, and bent tube containing zinc dust activated with 2% HCl;[46] the titanium tetrachloride is then added, followed by the

(43) Squillacote, M. E.; Sheridan, R. S.; Chapman, O. L.; Anet, F. A. L. *J. Am. Chem. Soc.* **1979**, *101*, 3657–3659.
(44) Korth, H.-G.; Trill, H.; Sustman, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483–4489.
(45) Doering, W. v. E.; Birladeanu, L.; Cheng, X.-h.; Kitagawa, T.; Sarma, K. *J. Am. Chem. Soc.* **1991**, *103*, in press.

zinc dust, pyridine, and, lastly, the ketone. The resulting mixture is refluxed for times specified.

Kinetic studies are conducted as described for the "isomerization of 3 and 4".[47] To maintain temperatures, vapors above these additional boiling liquids serve as thermostats: tetrachloroethylene (121 °C), chlorobenzene (132 °C), *o*-xylene (145 °C), anisole (155 °C), mesitylene (167 °C), *p*-cymene (179 °C), and benzonitrile (192 °C).

Solutions of substrate in C_6D_6 containing diglyme as internal standard are introduced into ampules of lead–potash glass (Corning 0120), 4 mm (o.d.) × 10 cm. After three freeze–thaw cycles, the ampules are sealed under vacuum (10^{-3} mmHg) and then heated in the vapor bath for the specified length of time. The tube is withdrawn and placed in an NMR tube, and the contents are subjected to NMR measurement. Heating and analysis by NMR are repeated, generally until equilibrium between geometrical isomers has been reached. The sample is protected from light during this process.

1,1'-Bi-2-cyclohexenylidene (3). 2-Cyclohexen-1-one (10.0 g, 104 mmol) in THF (40 mL) is added to titanium reagent [29.6 g (156 mmol) of $TiCl_4$, 20.1 g (307 mmol) of activated zinc dust, and 10.0 mL of pyridine in 400 mL of THF] and the resultant mixture boiled under reflux for 30 min. The cooled reaction mixture is treated with 10% aqueous HCl (400 mL) and filtered through Celite. Most of the THF in the filtrate is removed under vacuum prior to extraction with five 200-mL portions of ether. The combined ethereal extracts are washed with 5% aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over $MgSO_4$. Distillation of the residue left after removal of the ether affords a mixture (5.40 g) [bp 70–92 °C (0.02 mmHg)] of *anti*-**3** and *syn*-**3** in the ratio 57:43. The mixture is separated by GLC on a $^3/_8$ in. × 4 m column packed with 20% XF1150 on 60/80-mesh Chromosorb P at 150 °C. *anti*-**3**: ^{1}H NMR (C_6D_6, 500 MHz, assignments based on decoupling experiments) 6.59 (dt, 2 H, J = 10.1 and 2.0 Hz, H2), 5.78 (m, 2 H, H3), 2.39 (t, 4 H, J = 6.3 Hz, H6), 1.97 (m, 4 H, H4), 1.58 (quintet, 4 H, J = 6.2 Hz, H5); ^{13}C NMR ($CDCl_3$, 126 MHz) 129.4 (d), 127.9 (s), 125.7 (d), 25.9 (t), 25.6 (t), 22.8 (t); IR 2922, 1432, 1339, 1258, 1112, 1052, 900, 860, 736, 722; UV–vis 272 sh (27 700), 282 (35 200), 292 sh (27 800). *syn*-**3**: ^{1}H NMR (C_6D_6, 500 MHz, assignments based on decoupling experiments) 6.77 (dt, 2 H, J = 10.2 and 1.9 Hz, H2), 5.73 (m, 2 H, H3), 2.26 (t, 4 H, J = 6.3 Hz, H6), 1.97 (m, 4 H, H4), 1.59 (quintet, 4 H, J = 6.2 Hz, H5); ^{13}C NMR ($CDCl_3$, 126 MHz) 128.4 (d), 128.3 (s), 124.6 (d), 26.4 (t), 25.7 (t), 22.8 (t); IR 2922, 1434, 1340, 1252, 1050, 954, 902, 860, 712; UV–vis 267 (28 500), 277 (35 400), 288 (25 800).

All samples of triene **3** are kept frozen at −20 °C in the dark under vacuum or argon to prevent polymerization. Samples for kinetic experiments are purified by GLC immediately before use.

Kinetics of Trans–Cis Isomerization of 3. Ampules of solutions (0.35 mL) of *anti*- or *syn*-**3** (1.0–1.2%, w/v) in C_6D_6 containing diglyme (0.14%, v/v) are prepared as described above but then, because the ampules do not withstand the internal pressure developed above 200 °C, are placed in an NMR tube (5-mm o.d.). The gap between the NMR tube and the ampule is filled with degassed C_6D_6, and the NMR tube is sealed under vacuum to equalize the pressure inside and outside the ampule. Heating is effected by suspending the tube in a vapor bath as described above. Ampules of *anti*-**3** and *syn*-**3** are heated together at each temperature. Ratios of *anti*-**3** and *syn*-**3** are determined on a Bruker AM-500 NMR spectrometer by integrating their H2 signals at 6.59 (T_1 = 3.82 ± 0.07 s) and 6.77 (T_1 = 3.97 ± 0.07). About 50 scans are carried out with a 90° pulse and a pulse interval of 36.0 s, which is longer than the T_1's of H2 protons and methylene protons of diglyme at 3.61 (T_1 = 5.8 ± 0.7 s) and 3.53 (T_1 = 6.5 ± 0.7 s). Because one of the ^{13}C satellite peaks of H2 of *anti*-**3** overlaps that of H2 of *syn*-**3** and that of H2 of *syn*-**3** overlaps H2 of *anti*-**3**, the integrations are corrected as described below. Resulting data, on which the kinetic parameters of Table III are based, are available as Table VII in the supplementary material. The equilibrium constant is taken as the mean of the longest points starting from *anti*-**3** and *syn*-**3**. Rate constants are optimized by linear least-squares regression of the reversible first-order equation.

1,4,5,8-Tetrahydro-2-methoxynaphthalene. Birch reduction of 2-methoxynaphthalene[48] (37.0 g) using sodium (37.2 g) and ethanol (125 mL) in liquid ammonia (1.2 L) affords a crude product, which is distilled to give 33.5 g (88%) of 1,4,5,8-tetrahydro-2-methoxynaphthalene as a colorless liquid: bp 122–125 °C (8 mmHg) [lit.[48] mp 128 °C (10 mmHg)]; ^{1}H NMR ($CDCl_3$, 500 MHz) 5.73 (s, 2 H), 4.64 (t, 1 H, J = 3.5 Hz), 3.56 (s, 3 H), 2.69–2.65 (m, 2 H), 2.59 (t, 2 H, J = 7.2 Hz), 2.57 (s, 4 H); IR 3030, 2820, 1680, 1443, 1396, 1373, 1225, 1183, 1161, 1127, 1108, 1019, 972, 785, 667.

4,4a,5,6-Tetrahydro-2(3*H*)-naphthalenone (4). 1,4,5,8-Tetrahydro-2-methoxynaphthalene (32.0 g, 0.197 mol) is hydrolyzed with a mixture of 40% $HClO_4$ (1 L) and THF (300 mL) for 5 h at room temperature. Saturated NaCl (400 mL) is added, and the mixture is extracted with ether (400 mL and 2 × 100 mL). The combined extracts are neutralized with solid $NaHCO_3$ in the presence of water (600 mL). The two layers are separated, and the aqueous portion is extracted with ether (2 × 300 mL). The combined ether solutions are washed with saturated NaCl (100 mL) and dried ($MgSO_4$). Distillation of the extract gives 22.4 g (77%) of colorless liquid: bp 133–138 °C (10 mmHg) [lit.[48] mp 137–140 °C (12 mmHg)]; ^{1}H NMR ($CDCl_3$, 500 MHz) 6.31 (m, 1 H), 6.23 (d, 1 H, J = 9.6 Hz), 5.77 (s, 1 H), 2.51 (m, 2 H), 2.41 (m, 1 H), 2.35 (m, 2 H), 2.09 (m, 1 H), 1.92 (m, 1 H), 1.72 (m, 1 H), 1.44 (m, 1 H); IR 2924, 1660, 1617, 1585, 1325, 1256, 1203, 1012, 941, 872, 755, 618.

When the hydrolysis is interrupted after 6 min, 1,2,3,4,5,8-hexahydro-2-naphthalenone[48] is obtained almost quantitatively as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) 5.74 (m, 2 H), 2.94 (s, 2 H), 2.85 (t, 2 H, J = 8.2 Hz), 2.77 (t, 2 H, J = 8.0 Hz), 2.71 (t, 2 H, J = 6.9 Hz), 2.54 (t, 2 H, J = 6.6 Hz).

4,4',4a,4a',5,5',6,6'-Octahydro-2,2'-bi-3*H*-naphthylidene (5). 4,4a,5,6-Tetrahydro-2(3*H*)-naphthalenone (**4**) (12.0 g, 81.0 mmol) in dry THF (24 mL) is added to titanium reagent [from THF (240 mL), 11.4 g (174 mmol) of zinc dust, $TiCl_4$ (16.4 g, 87 mmol), and pyridine (5.8 mL)] and the resultant mixture refluxed for 5 min. The crude product, isolated as described above for **3**, is dissolved in 300 mL of methylene chloride–petroleum ether (1:3) and passed through a silica gel column, which is eluted further with the same solvent (300 mL). Removal of solvent in vacuo gives a mixture (3.7 g) of *α-anti*-**5** (31%), *β-anti*-**5** (24%), *α-syn*-**5** (25%), and *β-syn*-**5** (20%) as yellow crystals. *β-anti*-**5** can be isolated as yellow-orange crystals by three recrystallizations from THF at −20 °C: mp 182–183.5 °C (in evacuated sealed tube): ^{1}H NMR (C_6D_6, 500 MHz, assignments based on decoupling experiments) 6.50 (s, 2 H, H1), 6.28 (dd, 2 H, J = 9.6, 2.4 Hz, H8), 5.77 (m, 2 H, H7), 2.88 (d, 2 H, J = 15.2 Hz, eq-H3), 2.19–2.06 (m, 6 H, ax-H3, H4a, and ax-H6), 2.01 (dt, 2 H, J = 18.1, 5.2 Hz, eq-H6), 1.68 (d of quartets, 2 H, J = 12.4, 3.1 Hz, eq-H4), 1.61 (m, 2 H, eq-H5), 1.28 (m, 4 H, ax-H4 and ax-H5); ^{13}C NMR ($CDCl_3$, 126 MHz) 139.2 (s), 130.0 (d), 129.8 (s), 129.5 (d), 122.6 (d), 35.7 (d), 30.7 (t), 30.1 (t), 26.1 (t), 25.9 (t); IR 2826, 1450, 1433, 1056, 964, 886, 768, 719, 611; UV–vis 337 (48 500), 354 (82 100), 374 (81 600).

Recrystallization from THF at −20 °C of the residue from the concentrated mother liquors gives a mixture of *α*- and *β-anti*-**5** (40:60), which is used for kinetic experiments. Samples are stored in the dark at −20 °C under vacuum.

Kinetics of Trans–Cis Isomerization of 5. Ampules of solutions (0.35 mL) of a mixture of *α*- and *β-anti*-**5** (40:60, 1.5–1.6%, w/v) in C_6D_6 containing diglyme (0.29%, v/v) as internal standard are prepared and heated in the manner described above. The resulting mixtures of isomers are analyzed on a Bruker AM-500 (500-MHz) NMR spectrometer by using H1 signals at 6.47 (*α-anti*-**5**, T_1 = 1.23 ± 0.07 s), 6.50 (*β-anti*-**5**, T_1 = 1.23 ± 0.07 s), 6.75 (*α-syn*-**5**, T_1 = 1.30 ± 0.07 s), and 6.78 (*β-syn*-**5**, T_1 = 1.23 ± 0.07 s). At the beginning and the end of the reaction, two multiplets at 3.46 (T_1 = 5.8 ± 0.7 s) and 3.33 (T_1 = 6.5 ± 0.7 s) belonging to the methylene protons of diglyme are also integrated for recovery calculation. Generally, accumulation of 50 FID's with a 90° pulse gives a spectrum with a satisfactory signal to noise ratio. In order to ensure accuracy of the signal intensity, spectra are recorded with a pulse interval of 6.85 s, which is 5 times the longest T_1 of the H1 protons. When the signals of the methylene protons in diglyme are integrated, a longer pulse interval (36.0 s) is employed corresponding to the T_1's of those protons. The ratios of *α-anti*- to *α-syn*-**5** and of *β-anti*- to *β-syn*-**5** are obtained as follows. Two areas, A_{anti} (6.47 and 6.50 ppm) and A_{syn} (6.75 and 6.78 ppm) are measured by integrating the spectra by the computer built into the NMR instrument. Because the two components, α and β, in each of A_{anti} and A_{syn} overlap slightly (overlapping area, ca. 0.3 and 0.4% of A_{anti} and A_{syn}, respectively), they are resolved by the cut-and-weigh method (averages of two cuts are taken, standard deviations are less than 0.5% of the total area). The resulting data, on which the kinetic parameters of Table IV are based, are available as supplementary material in Table VIII.

2-Methoxyanthracene. This compound is prepared by the general Friedel–Crafts method from phthalic anhydride and anisole according to the procedure of Iwata and Emoto.[49] In the first step, phthalic anhydride (98.0 g, 662 mmol) affords 126 g (74%) of pure 2-(4-methoxybenzoyl)benzoic acid: mp 140–143 °C (lit. mp 122–123.5 °C,[49] 148

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°C[50]); ^{1}H NMR ($CDCl_3$, 500 MHz) 11.05 (br s, 1 H), 8.07 (d, 1 H, J = 8.0 Hz), 7.70 (d, 2 H, J = 8.9 Hz), 7.64 (t, 1 H, J = 7.5 Hz), 7.54 (t, 1 H, J = 7.6 Hz), 7.35 (d, 1 H, J = 7.7 Hz), 6.89 (d, 2 H, J = 8.9 Hz), 3.86 (s, 3 H); IR 3300–2500, 1692, 1667, 1600, 1576, 1421, 1308, 1263, 1150, 1020, 933, 760, 611.

In the second step, this material is reduced by zinc dust to give a low yield (14.4 g) of 2-(4-methoxybenzyl)benzoic acid, mp 113.5–115 °C (lit. mp 117–118 °C,[49] 117.5–119 °C[50]), by direct isolation from the supernatant solution. Additional product is obtained from the solid cake of zinc-containing products by dissolution in concentrated HCl (1 L) and extraction with $CHCl_3$ (700 mL): 100.6 g (total yield 96%); mp 110–114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 11.90 (br s, 1 H), 8.06 (d, 1 H, J = 7.7 Hz), 7.48 (t, 1 H, J = 7.5 Hz), 7.31 (t, 1 H, J = 7.6 Hz), 7.22 (d, 1 H, J = 7.7 Hz), 7.10 (d, 2 H, J = 8.5 Hz), 6.82 (d, 2 H, J = 8.6 Hz), 4.39 (s, 2 H), 3.77 (s, 3 H); IR 3200–2500, 1681, 1573, 1514, 1413, 1311, 1275, 1258, 922, 837, 774, 732, 608.

In the third step, 2-(4-methoxybenzyl)benzoic acid (115 g, 475 mmol) is treated with 500 mL of sulfuric acid at 0 °C to afford 72.0 g (71%) of 2-methoxy-9(10*H*)-anthracenone as yellow crystals: mp 94.5–96.5 °C (lit.[49] mp 96–97.5 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 8.37 (d, 1 H, J = 7.9 Hz), 7.83 (d, 1 H, J = 2.9 Hz), 7.60 (t, 1 H, J = 7.4 Hz), 7.47 (m, 2 H), 7.39 (d, 1 H, J = 8.5 Hz), 7.20 (dd, 1 H, J = 8.5, 2.8 Hz), 4.30 (s, 2 H), 3.92 (s, 3 H); IR 1657, 1603, 1497, 1336, 1300, 730.

Finally, following Ferrari, Hunsberger, and Gutowsky,[51] a mixture of 36.1 g (161 mmol) of 2-methoxy-9(10*H*)-anthracenone, 145 g of zinc dust (activated with 2% HCl),[46] 850 mL of toluene, and 2 L of 2 N NaOH is refluxed (90–95 °C) for 24 h with stirring to yield, after recrystallization from benzene, 25.2 g (75%) of 2-methoxyanthracene as faintly yellow crystals: mp 179–181 °C (lit.[51] mp 183–186 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) 8.34 (s, 1 H), 8.27 (s, 1 H), 7.95 (m, 2 H, J = 9.2 Hz), 7.89 (d, 1 H, J = 9.1 Hz), 7.42 (m, 2 H), 7.20 (d, 1 H, J = 2.3 Hz), 7.16 (dd, 1 H, J = 9.1, 2.5 Hz), 3.96 (s, 3 H); IR 1633, 1467, 1272, 1215, 1177, 1028, 883, 740.

When the reaction is conducted in benzene for 5 h instead of toluene for 24 h, an intermediate, 9,10-dihydro-9-hydroxy-2-methoxyanthracene, is isolated almost quantitatively as a yellow liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.58 (d, 1 H, J = 7.5 Hz), 7.37–7.15 (m, 5 H), 6.82 (d, 1 H, J = 9.0 Hz), 5.53 (s, 1 H), 4.02 (d, 1 H, J = 24 Hz), 3.81 (d, 1 H, J = 24 Hz), 3.79 (s, 3 H), 2.21 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 158.7, 139.9, 138.6, 136.0, 128.5, 127.7, 127.6, 127.5, 126.5, 126.3, 113.7, 111.6, 70.3, 55.4, 34.0.

1,4,5,8,9,10-Hexahydro-2-methoxyanthracene. A hot solution of 2-methoxyanthracene (15.5 g, 74.6 mmol) in ethanol (75 mL) and THF (180 mL) is added to 750 mL of liquid ammonia at −78 °C with vigorous stirring. Sodium (21.5 g) is then added in small pieces over 1 h. After 24 h of stirring at −78 °C, the deep blue color has disappeared. The cooling bath is removed, ammonia is allowed to evaporate, and the residue is treated with water (300 mL) and extracted with methylene chloride (4 × 150 mL). The combined extracts, washed with saturated NaCl (4 × 100 mL) and dried ($MgSO_4$), give practically pure 1,4,5,8,9,10-hexahydro-2-methoxyanthracene (15.7 g, 98%) as light yellow crystals: mp 92.0–92.5 °C after recrystallization from methanol; ^{1}H NMR ($CDCl_3$, 500 MHz, assignment based on decoupling experiments) 5.74 (s, 2 H, H6 and H7), 4.65 (t, 1 H, J = 3.5 Hz, H3), 3.65 (s, 3 H, OCH_3), 2.72–2.67 (m, 2 H, H4), 2.62 (t, 2 H, J = 6.8 Hz, H1), 2.57 (s, 4 H, H9 and H10), 2.46 (s, 4 H, H5 and H8); ^{13}C NMR ($CDCl_3$, 126 MHz) 152.8 (s), 124.42 (d), 124.40 (d), 123.6 (s), 123.3 (s), 123.0 (s), 122.5 (s), 90.5 (d), 53.8 (quartet), 35.8 (t), 35.3 (t), 32.8 (t), 30.9 (t), 30.5 (t), 30.4 (t); IR 2814, 1673, 1225, 777, 655.

4,4a,5,6,10,10a-Hexahydro-2(3*H*)-anthracenone (6). 1,4,5,8,9,10-Hexahydro-2-methoxyanthracene (15.7 g, 73.4 mmol) is hydrolyzed with a mixture of 40% $HClO_4$ (500 mL) and THF (500 mL) for 5 h at room temperature. Addition of saturated NaCl (500 mL) is followed by extraction with ether (200 mL and 2 × 100 mL) and washing the extracts with 10% Na_2CO_3 (4 × 300 mL). The combined aqueous layers are neutralized with a small amount of solid Na_2CO_3 and then extracted with ether (3 × 100 mL). All the ether solutions are combined, washed with saturated NaCl (200 mL), and dried ($MgSO_4$) to afford 15.4 g of crude product. Recrystallization from ethanol–methanol (1:1) gives 7.54 g of yellow crystals, mp 121–124 °C. The crude material recovered from the mother liquor is purified by flash chromatography [silica gel, ether–petroleum ether (1:2)] and then recrystallized from methanol to give 3.04 g of pure material: mp 124–125 °C (total yield 72%); ^{1}H NMR ($CDCl_3$, 500 MHz, assignments based on decoupling experiments and ^{1}H COSY measurements) 6.18 (d, 1 H, J = 10.2 Hz, H8), 6.13 (dt, 1 H, J = 9.7, 4.1 Hz, H7), 5.99 (s, 1 H, H9), 5.79 (s, 1 H, H1), 2.57 (m, 1 H, H4a), 2.49 (m, 2 H, eq-H3 and H10a), 2.41 (m, 1 H, ax-H3), 2.29 (m, 2 H, ax-H6 and eq-H6), 2.08 (m, 1 H, eq-H4), 1.95 (dt, 1 H, J = 12.6, 4.3 Hz, eq-H10), 1.88 (m, 1 H, eq-H5), 1.72 (m, 1 H, ax-H4), 1.37 (m, 1 H, ax-H5), 1.24 (quartet, 1 H, J = 12.4 Hz, ax-H10); ^{13}C NMR ($CDCl_3$, 126 MHz) 199.8 (s), 159.6 (s), 148.5 (s), 135.6 (d), 128.4 (d), 124.0 (d), 123.1 (d), 37.8 (t), 37.0 (t), 35.9 (d), 35.8 (t), 30.1 (t), 29.5 (t), 26.0 (t); IR 2920, 1644, 1586, 1322, 1249, 1197, 893, 620; UV–vis 303 (40 200), 311 (42 800).

When the reaction is conducted with 40% $HClO_4$–ether for 15 min rather than 5 h, an intermediate, 1,4,5,8,9,10-hexahydro-2(3*H*)-anthracene, is obtained almost quantitatively: mp 91–93.5 °C after recrystallization from methanol; ^{1}H NMR ($CDCl_3$, 500 MHz, assignment based on decoupling experiment) 5.74 (s, 2 H, H6 and H7), 2.78 (s, 2 H, H1), 2.58 (s, 4 H, H5 and H8), 2.56–2.51 (m, 4 H, H3 and H9), 2.47 (m, 2 H, H10), 2.38 (m, 2 H, H4); ^{13}C NMR ($CDCl_3$, 126 MHz), 210.6 (s), 126.2 (s), 124.25 (d), 124.24 (d), 123.5 (s), 123.2 (s), 122.7 (s), 43.3 (t), 38.9 (t), 35.9 (t), 35.8 (t), 30.34 (t), 30.30 (t), 29.6 (t); IR 2808, 1714, 1410, 1208, 737, 679.

4,4′,4a,4a′5,5′,6,6′,10,10′,10a,10a′-Dodecahydro-2,2′-bi-3*H*-anthracenylidene (7). To titanium reagent (vide supra) [from 2.80 g (42.8 mmol) of zinc dust, $TiCl_4$ (4.07 g, 21.4 mmol), THF (50 mL), and pyridine (1.43 mL)] is added a solution of 4,4a,5,6,10,10a-hexahydro-2(3*H*)-anthracenone (**6**) (4.00 g, 20.0 mmol) in dry THF (20 mL). The mixture is refluxed for 5 min, filtered to remove unreacted zinc dust, and treated with 10% HCl (200 mL). The mixture is extracted with CH_2Cl_2 (400 mL and 3 × 200 mL), and the combined extracts are washed with 10% Na_2CO_3 (200 mL) and dried ($MgSO_4$). The crude product is dissolved in CH_2Cl_2 (400 mL) and passed through a silica gel column, which is further eluted with 1 L of CH_2Cl_2 and then with 1 L of $CHCl_3$. All the eluents are collected in a flask filled with argon and are then freed of solvent to give a mixture (1.02 g) of four isomers, *α-anti*-**7** (15%), *β-anti*-**7** (16%), *α-syn*-**7** (28%), and *β-syn*-**7** (41%), as orange crystals.

A portion (500 mg) of this mixture is thermally equilibrated in benzene (50 mL) by heating at 121 °C for 5 h in a vacuum-sealed tube. When the solution is cooled slowly to room temperature, crystals (145 mg) consisting only of *α-anti*-**7** and *β-anti*-**7** (32:68) precipitate. This mixture is used for kinetic experiments.

A sample of *β-anti*-**7** can be isolated by recrystallizing a mixture of *α-anti*-**7** and *β-anti*-**7** (47:53) four times from chloroform (2 mL/1 mg of material, heating at 120 °C for 2 min in a vacuum-sealed tube and cooling to room temperature): orange crystals, mp >300 °C (in evacuated sealed tube); ^{1}H NMR ($CDCl_3$, 500 MHz, assignments based on decoupling experiments) 6.38 (s, 2 H, H1), 6.12 (dd, 2 H, J = 9.7, 2.1 Hz, H8), 5.94 (s, 2 H, H9), 5.83 (m, 2 H, H7), 2.90 (d, 2 H, J = 15.7 Hz, eq-H3), 2.39 (m, 4 H, H4a and H10a), 2.30–2.14 (m, 6 H, ax-H3, ax-H6, and eq-H6), 1.93 (dq, 2 H, J = 12.5, 2.9 Hz, eq-H4), 1.88 (dt, 2 H, J = 12.4, 4.4 Hz, eq-H10), 1.83 (m, 2 H, eq-H5), 1.29 (m, 4 H, ax-H4 and ax-H5), 1.08 (q, 2 H, J = 11.9 Hz, ax-H10); IR 2930, 2910, 1451, 1432, 1053, 965, 910, 902, 792, 753, 714, 631, 615, 608; UV–vis 389 (54 900), 412 (98 700), 439 (105 000).

Samples of **7** are stored in the dark at −20 °C under vacuum to prevent polymerization.

Kinetics of Trans–Cis Isomerization of *anti*-7 to *syn*-7. A saturated solution of *α-anti*-**7** and *β-anti*-**7** is made by adding 16–18 mg of a mixture (32:68) to 45 mL of benzene (Analytical Reagent, Mallinckrodt) in a flask filled with argon and agitating the mixture by an ultrasonic bath for 1 min. The undissolved crystals (9–10 mg) are removed by filtration through a 0.45-μm nylon-66 filter (13-mm diameter). Aliquots (4.00 mL) of the solution are introduced into 10 ampules of lead–potash glass (Corning 0120, 15 mm (o.d.) × 5 cm with 6 mm (o.d.) × 10 cm neck). The samples are degassed by three freeze–thaw cycles and sealed under vacuum (10^{-3} mmHg). Heating is effected in an oil bath controlled by a Thermotrol Model 1053A, Hallikainen Instruments. Temperatures are monitored with an iron–constantan thermocouple connected to a Leeds and Northrup Model 8686 millivolt potentiometer using an ice–water reference junction. After being heated for the desired length of time, each ampule is opened and the benzene is evaporated at room temperature with a stream of argon over a period of ca. 10 min. The residue is dissolved in 0.90 mL of $CDCl_3$ containing diglyme (0.003%, v/v) as standard. The solution is introduced into an NMR tube, which is degassed and sealed under vacuum. The sample is protected from light throughout this process.

The reaction mixture is analyzed on a Bruker AM-500 (500-MHz) NMR spectrometer by using H1 signals at 6.35 (*α-anti*-**7**, T_1 = 0.72 ± 0.04 s), 6.38 (*β-anti*-**7**, T_1 = 0.72 ± 0.04 s), 6.57 (*α-syn*-**7**, T_1 = 0.76 ± 0.04 s), and 6.59 (*β-syn*-**7**, T_1 = 0.76 ± 0.04 s). Generally, accumulation of about 700 FID's with a 90° pulse, which requires ca. 45 min, gives a spectrum with satisfactory signal to noise ratio. No isomerization is observed during the measurement. In order to ensure accurate signal

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intensity, spectra are taken with a pulse interval of 4.0 s, which is longer than 5 times the longest T_1 of the H1 protons. For calculation of recoveries, reaction mixtures at $t = 0$ and at equilibrium are measured also with a pulse interval of 36.0 s, which is longer than the T_1's of the methylene protons of diglyme. One hundred scans serve this purpose, the total area of the two methylene signals being used as standard. Ratios of *α-anti*-7 to *α-syn*-7 and *β-anti*-7 to *β-syn*-7 are obtained as follows: two areas, A_{anti} (6.35 and 6.38 ppm) and A_{syn} (6.57 and 6.59 ppm), are measured by computer integration of the spectra. Because the α- and β-components in each of A_{anti} and A_{syn} overlap slightly (overlapping area ca. 0.9 and 2.0% of A_{anti} and A_{syn}, respectively), they are resolved by the cut-and-weigh method (generally, two cuts are taken, standard deviations being less than 0.7% of the total area). The resulting data, from which the kinetic parameters of Table V are derived, are available in Table IX as supplementary materials. Rate and equilibrium constants are optimized simultaneously by the nonlinear least-squares method to fit the reversible first-order kinetic equation to the observed data.

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Supplementary Material Available: Unprocessed kinetic data from the thermal rearrangements of **3**, **5**, and **7** (Tables VII–IX, respectively) (4 pages). Ordering information is given on any current masthead page.

Markedly Different Acyl Papain Structures Deacylate at Similar Rates: Resonance Raman Spectroscopic and Kinetic Evidence†

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Abstract: Resonance Raman (RR) spectroscopy has been used to determine the structure of the acyl group in a series of dithioacyl papains in which the side chain of the substrates P_1 amino acid residue has been extended from 2 (CH_3CH_2–) to 3 ($CH_3CH_2CH_2$–), and to 4 ($CH_3CH_2CH_2CH_2$–) carbon atoms in a linear chain. A conformational analysis was carried out on the corresponding ethyl ester model compounds, *N*-(methyloxycarbonyl)-L-phenylalanyl-L-ethylglycine, *N*-(methyloxycarbonyl)-L-phenylalanyl-L-norvaline, and *N*-(methyloxycarbonyl)-L-phenylalanyl-L-norleucine ethyl dithio esters, based on the RR spectra and known conformational states of glycine and alanine-based dithio esters. Comparison of the RR spectra of the model compounds with those of the corresponding *N*-(methyloxycarbonyl)-L-phenylalanyl-L-ethylglycine, -L-norvaline, and -L-norleucine dithioacyl papains shows that the acyl fragments adopt an A-like structure in the active site. An A-like structure is characterized by a large (near ±160°) nitrogen to thiol sulfur torsional angle about the NHCHR′–CS single bond. This conformation is in marked contrast to that found for *N*-acylglycine dithioacyl papains which have a small (near ±15°) $NHCH_2$–CS(thiol) torsional angle in the P_1 residue giving rise to the so-called B conformer. Thus we have evidence that the two classes of substrate give rise to two substantially different acyl group structures in the active site. However, for the ethylglycine, norvaline, and norleucine dithioacyl papains the deacylation rate constants (k_{cat}'s) are only ca. 3 times greater than k_{cat} for the most reactive *N*-acylglycine substrate. Thus deacylation can occur from both A- and B-type dithioacyl papains with only a small kinetic penalty for the latter. The existence of an A-type conformer in the active site and the need to maintain binding in the oxyanion hole raise the possibility that the acyl group is binding backwards, i.e. in the S_1' and S_2' binding sites.

Introduction

Relating enzyme and enzyme–substrate structure to catalytic reactivity remains a central challenge in biochemistry. Among the plethora of techniques brought to bear on this problem, resonance Raman (RR) spectroscopy offers the advantage of providing detailed molecular information on functioning enzyme–substrate complexes. The RR spectrum of the chromophoric center, e.g. the dithio ester in RC(=O)NHCHR′C(=S)S–papain, enables us to monitor the vibrational spectrum of the bonds undergoing catalytic transformation. Structural detail is accessed by interpreting the spectra usually by reference to vibrational and vibrational-crystallographic analyses of model compounds, e.g. $RC(=O)NHCHR'C(=S)SC_2H_5$.

Detailed RR studies, combined with X-ray crystallographic analysis, of *N*-acylglycine[1,2] and *N*-acylalanine[3-5] ethyl dithio esters have shown that these compounds are present in aqueous solution as an equilibrium mixture of two conformational populations which have been termed the A and B conformers (Figure 1). In the A conformation the nitrogen atom of the first dithio ester amino acid residue eclipses the thiono sulfur atom (C=S) of the dithio ester moiety. This structure is characterized by an angle of ca. 160° about the $NHCH_2$–CS bond (ψ'). In contrast the B con-

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