Hydrocarbon Chemistry

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Practical Synthesis of the Dendralene Family Reveals Alternation in Behavior**

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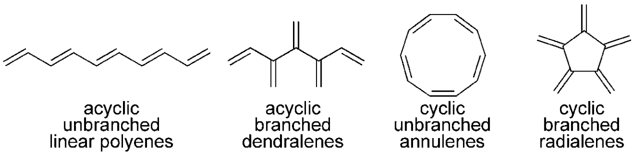
Hydrocarbons are the most diverse and important binary compounds in chemistry, and form the basis of our understanding of organic structure and reactivity. For these reasons, investigations into the chemical synthesis and properties of fundamental hydrocarbons represents an enduring theme of organic chemistry.[1] Four fundamental hydrocarbon families of oligoalkene structures can be defined (Scheme 1); each family differs in the type of atom connectivity (unbranched or branched, cyclic or acyclic).

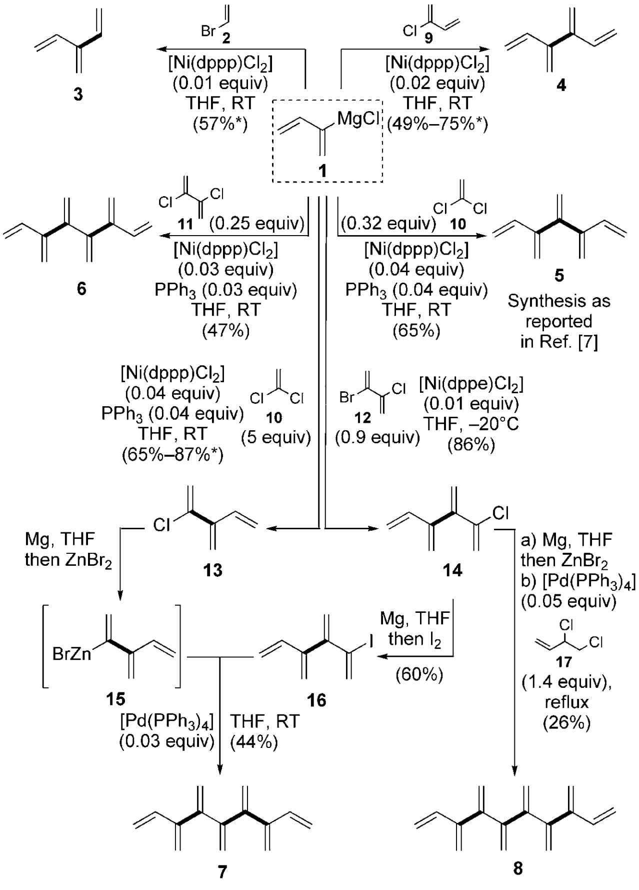


Scheme 1. Fundamental classes of alkenic hydrocarbons.

The unbranched acyclic and cyclic systems, namely linear polyenes and annulenes, respectively, have been thoroughly studied. The alternation in the behavior of the annulenes (that is, aromaticity and antiaromaticity for odd and even numbers of conjugated double bonds, respectively) has played an important role in the development of modern theories of structure and reactivity.[2] However, the acyclic (dendralenes[3]) and cyclic (radialenes[4]) branched systems have not been investigated so thoroughly. In 2000 we reported a multistep synthetic approach to the parent dendralenes, which allowed the preparation of 1–5 mg amounts of the hydrocarbons, including access to [5]-, [6]-, and [8]dendralenes for the first time.[5] More recently, we reported practical single-step approaches to [4]dendralene[6] and [5]dendralene[7] in multigram quantities, along with exploratory investigations into their chemical reactivity. Herein, we report short preparative syntheses of the first six members of the dendralene family, and we demonstrate that these fundamental hydrocarbons exhibit alternation in their physical and chemical properties. We provide evidence that this alternating behavior stems from the different conformational preferences of dendralenes that comprise even and odd numbers of alkene units.

The first synthesis of [7]dendralene and the first practical syntheses of [6]- and [8]dendralenes, along with significantly improved protocols for the preparation of [3]-, [4]-, and [5]dendralenes are shown in Scheme 2. The successful approaches employ Kumada–Tamao–Corriu (KTC)[8] and Negishi[9] couplings and allow rapid access to the hydrocarbons in synthetically useful amounts (200 mg–5 g).

The lower members of the dendralene family, namely [3]-, [4]-, [5]-, and [6]dendralenes (**3**–**6**), were made in one step through KTC coupling reactions of the chloroprene Grignard



Scheme 2. Practical syntheses of [3]–[8]dendralenes using KTC and Negishi couplings. Yields with asterisks refer to THF solutions.

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reagent **1**. In the first two cases, vinyl bromide (**2**) and chloroprene (**9**) were employed as electrophiles; in the latter two cases, twofold couplings were carried out with the dielectrophiles 1,1-dichloroethylene (**10**) and 2,3-dichloro-1,3-butadiene (**11**) respectively. Whilst [Ni(dppp)Cl_2] promoted the cleanest coupling reactions, a wide range of dichloronickel(II)diphosphine precatalysts were also effective.[10] [3]Dendralene was prepared as a THF solution because of the low boiling point of the hydrocarbon (44–45 °C).[11] This one-step approach to triene **3** is more convenient and significantly higher-yielding than the shortest existing route.[12] [4]Dendralene (**4**; boiling point 120 °C)[13] was isolated solvent-free through KTC coupling in significantly higher yield (49 %) than the previous best synthesis (oxidative homocoupling, 26 % yield[6]). Yields are even higher (75 %) if a THF solution of the tetraene is tolerable. The higher boiling [5]- and [6]dendralenes could be distilled to solvent-free purity on the multigram scale in 65 % and 47 % yields.

The synthesis of [7]- and [8]dendralenes required chlorotriene **13**[12] and chlorotetraene **14**, the higher "1,1-ethenologues" of chloroprene (**9**), which are readily accessible through monocoupling of **1** with dihalides **10** and **12**, respectively. Unexpectedly, **13** and **14** were unreactive electrophiles in KTC and Negishi cross-coupling reactions of higher ethenologues of **1**.[14] After considerable experimentation, the first synthesis of [7]dendralene was finally realized through a Negishi cross-coupling reaction between iodotetraene **16** and trienylzinc **15**. The first practical approach to [8]dendralene involved a palladium-mediated oxidative homocoupling[15] of the organozinc derived from chlorotetraene **14**.

As the family of all-*E* linear polyenes (Scheme 1) is traversed from the triene to the decaene, the UV/Vis spectra exhibit progressively red-shifted absorption maxima (λ_{max} ca. +25 nm for each additional alkene) along with steadily increasing molar extinction coefficients for these absorptions.[16] These observations are consistent with increasing conjugation as the number of alkene units increases. In contrast, in all but one case, the first six members of the dendralene family show a single UV/Vis absorption maximum at λ_{max} = 215–217 nm (hexane solution), which is comparable to that of 1,3-butadiene (217 nm, hexane solution; Figure 1, top).[17] The exception is the smallest member of the family, [3]dendralene, which exhibits two maxima (206 and 231 nm, hexane solution). When the observed molar extinction coefficients are plotted against the number of alkene units present in the structure, a clear pattern emerges (Figure 1, bottom).

These data clearly show that dendralenes with an even number of alkene units contain multiples of 1,3-butadiene moieties and the incorporation of additional pairs of alkene units has the effect of increasing the molar extinction coefficient of the absorption maximum by approximately 10000 units. Dendralenes with odd numbers of alkene units behave differently and exhibit significantly lower extinction coefficients than might be expected. It is clear that the spectroscopic properties of "odd" and "even" dendralenes are markedly different.

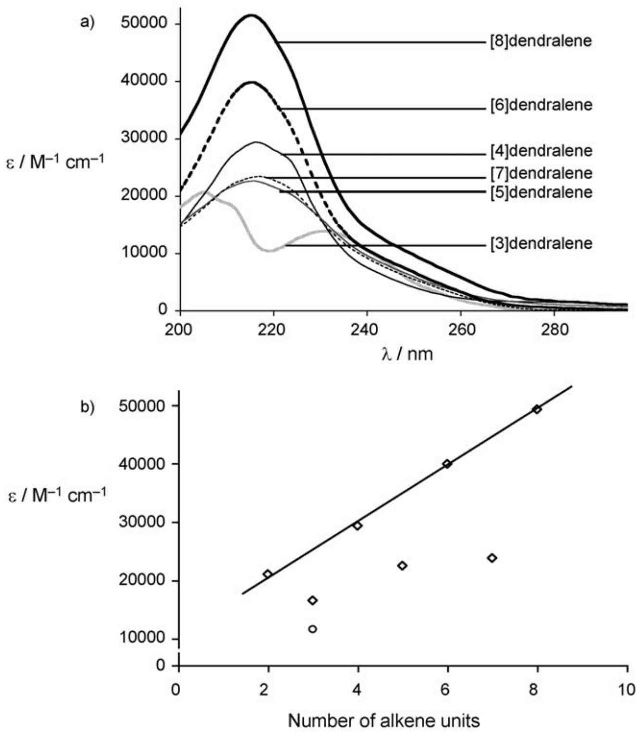
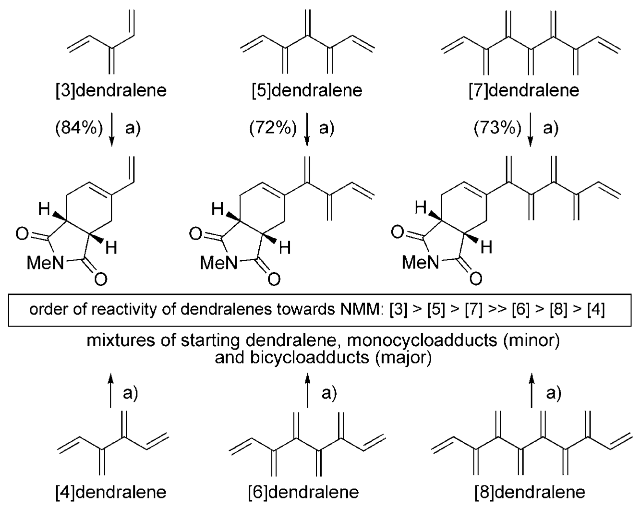


Figure 1. a) UV/Vis spectra of the dendralene family and b) extinction coefficients plotted as a function of alkene composition. Data for 1,3-butadiene[17] is plotted on the lower graph.

The dendralenes have been thought of as unstable compounds for some time. Blomquist and Verdol were the first to report the synthesis of the triene and described it as "a colorless volatile liquid extremely prone to undergo dimerization and polymerization."[11] In 1984, Hopf said of [5]dendralene:[18] "Even if [the hydrocarbon] could be obtained by a preparatively simple route, it would presumably be difficult to study its chemical properties since it is probably a very reactive substance." To the best of our knowledge, no data has been reported on the stability of the parent dendralenes as pure compounds.[19]

To remedy this situation, neat samples of [3]–[8]dendralenes were placed in sealed glass vials at 25 °C and their decomposition was monitored by ^{1}H NMR spectroscopy. To our surprise, [4]-, [6]-, and [8]dendralenes underwent negligible (< 10 %) decomposition over a four week period. In contrast, [3]-, [5]-, and [7]dendralenes exhibited half-lives of 10, 25, and 63 hours, respectively. The main decomposition pathway for the dendralenes is a Diels–Alder dimerization.[20] These results clearly demonstrate that the stabilities of "odd" and "even" dendralenes are significantly different.

Finally, the Diels–Alder reactivity of the dendralenes toward the electron-deficient dienophile *N*-methylmaleimide (NMM) was examined. [3]-, [5]-, and [7]dendralenes underwent a rapid and clean conversion to (predominantly) the corresponding terminal monoadduct at ambient temperature, even in the presence of a small excess of the dienophile (Scheme 3). In contrast, [4]-, [6]-, and [8]dendralenes exhibit significantly lower reactivity toward NMM, these dendralenes required longer reaction times and produced mixtures of



Scheme 3. Divergent reactivities of "even" and "odd" dendralenes towards dienophiles. Reagents and conditions: a) NMM (1 mol equiv), $CDCl_3$ (0.05 M), RT, ≤45 h.[21]

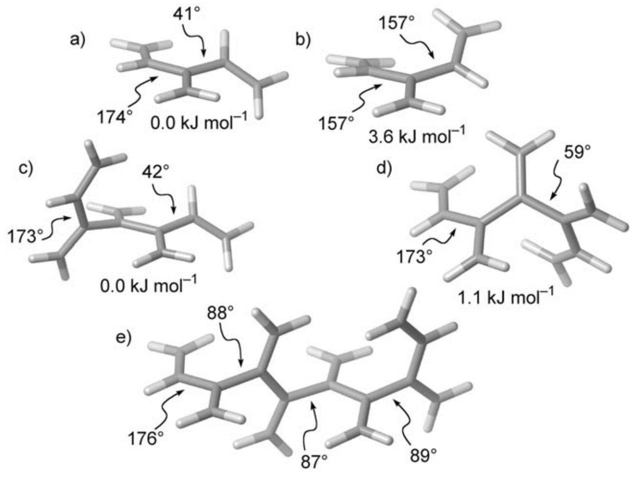


Figure 2. B3LYP/6-31G(d) optimized geometries of a, b) [3]dendralene, c, d) [5]dendralene, and e) [8]dendralene. Pertinent dihedral angles and relative free energies (298 K) are identified.

starting dendralenes, mono-, and bicycloadducts.[21] Multiple cycloaddition could not be arrested, even with a substoichiometric amount of the dienophile. The observation of bicycloadducts can be ascribed to the formation of a more reactive odd-dendralene intermediate from the initial cycloaddition. Thus, there is a clear difference in chemical reactivity between the "odd" and "even" dendralenes.

What is the origin of the dichotomy of the physical and chemical properties of the even and odd series of dendralenes? While a full understanding requires detailed quantum chemical calculations and further experimental studies, we propose, at this stage, a simple explanation based on conformational analyses of the ground states of the dendralenes. Inspection of the B3LYP/6-31G(d) optimized geometries of [3]–[8]dendralenes[22] revealed that there are three distinct conformational relationships between adjacent alkene units: 1) the *s-trans* conformation, in which the alkene units are nearly coplanar, as in the more stable conformational isomer of 1,3-butadiene; 2) the two alkene units are almost orthogonal to each other; and 3) the two alkene units are quasi *s-cis*, making a dihedral angle of about 40° with each other. We find that the lowest energy conformation of [4]-, [6]-, and [8]dendralene consists of *s-trans* butadiene units with each diene unit nearly orthogonal to adjacent diene units.[23] This is illustrated in Figure 2 for [8]dendralene.

The near-orthogonal disposition of the diene units means that even-numbered members of the dendralenes may be regarded as weakly coupled chains of oligo-*s-trans* butadienes. This interpretation is consistent with the finding that the λ_{max} value for these members is the same as that for butadiene. The fact that the magnitudes of ε_{max} for these members are not simple multiples of that for butadiene is no doubt due to the increasing proportion of conformers having quasi *s-cis* diene units (see below) with increasing chain length, thus giving rise to slightly longer wavelength transitions with smaller ε_{max} values. This is reflected in the broad absorbances of [6]- and [8]dendralenes (Figure 1) in their long-wavelength tails. In contrast to the even dendralenes, the lowest-energy conformations of the odd series have at least one quasi *s-cis* unit, as shown in Figure 2 for the two most stable conformations for [3]- and [5]dendralenes (conformation a is more stable than conformation b; conformation c is more stable than conformation d).[24] The two absorbances at 206 and 231 nm for [3]dendralene may be loosely interpreted as arising from the *s-trans* (Figure 2b) and *s-cis* (Figure 2a) conformations, respectively.[25] For longer members of the odd series, the conformation population rapidly increases, each conformation exhibits slightly different excitation energies that result in a broad absorbance envelope. This is evident in the UV/Vis spectra of [5]- and [7]dendralene, which both display a broad absorbance envelope that encompasses both absorbance bands of [3]dendralene.

The enhanced Diels–Alder reactivity observed for the odd-membered dendralenes compared to the even-membered series may be explained by the fact that the odd-dendralenes possess a quasi *s-cis* diene component which is predisposed to react as the diene component in a Diels–Alder reaction (Figure 2). In contrast, the lowest-energy conformations of the even series do not possess such a favorable conformation and should, therefore, have diminished Diels–Alder reactivity compared to their odd counterparts. For [5]dendralene and higher homologues, the quasi *s-cis* diene unit may be either at the terminus (e.g., Figure 2c) or within the chain's interior (e.g., Figure 2d). The Diels–Alder reaction is expected to involve the terminal quasi *s-cis* diene because this diene is 2-substituted, whereas internal quasi *s-cis* dienes are 2,3-disubstituted and therefore are less reactive; this phenomenon is indeed observed experimentally. However, as the chain length increases, the proportion of conformers that possess terminal quasi *s-cis* diene units decreases, which might explain the observed decrease in Diels–Alder dimerization reactivity with increasing chain length of the odd dendralenes ([3] > [5] > [7]). This theory also explains why [4]dendralene is the least reactive dendralene.

In summary, short syntheses of the first six members of the dendralene family of fundamental hydrocarbons have been achieved. The new routes allow short syntheses of the family by using standard laboratory techniques. The syntheses avoid the use of protecting groups, require no specialized equipment or pyrolytic methods, employ little or no chromatography, and allow access to the hydrocarbons on multigram scale. Access to synthetically useful amounts of the dendralene family has allowed the first investigations into their properties. As is the case with the annulenes, the dendralenes exhibit alternating behavior, with the physical and chemical properties of even members of the family being distinctly different from odd members. This alternating behavior has been traced to conformational preferences in the dendralenes. The results described herein should allow the dendralenes and their derivatives[26] to finally break free from their neglected[3] status.

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