The Conformational Analysis of Alkylated 7,12-Dihydropleiadenes. Molecular Mechanics Calculations and Proton and Carbon NMR

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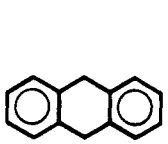
A series of 7-alkyl- and 7,12-dialkyl-7,12-dihydropleiadenes (alkyl = methyl, ethyl, and isopropyl) is investigated by variable-temperature proton and carbon NMR. Cis/trans assignments are made, as well as conformational preferences, and these are rationalized with the aid of MM2 molecular mechanics calculations. The trans dimethyl and diethyl derivatives show inversion barriers about the central seven-membered ring that are lower than the unsubstituted, parent compound. This unusual result is interpreted in terms of a steric acceleration caused in part by a transannular steric repulsion. Carbon chemical shifts are discussed in terms of the dihydropleiadene structure.

A number of studies have appeared dealing with the conformational analysis of 9,10-dihydroanthracenes (1) and related compounds.[1-3] It now appears that derivatives of 1 may assume a wide variety of conformational preferences in solution, including planar states as well as rapidly interconverting boat conformations. The parent hydrocarbon is either planar, as suggested by molecular mechanics calculations, or has an extremely low barrier for the interconversion of boat-shaped conformations.[4] In the solid state, 1 does indeed exist as a boat-shaped molecule[2] with an angle of 145° between the planes containing the benzene rings.[5]



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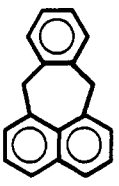

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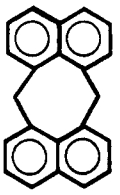

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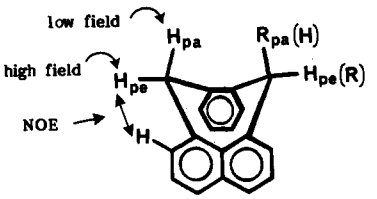
As noted earlier,[6] substitution of a naphthalene ring, as in 7,12-dihydropleiadene (2), greatly increases the tendency toward folded structures, and 2 undergoes inversion about the central seven-membered ring with a barrier of 13.6 kcal/mol. Similarly, incorporation of a second naphthalene unit (i.e., 3) further increases the barrier to 23 kcal/mol.

Our recent alkylation studies have made many derivatives of 2 available for the first time.[7] In view of the substantial amount of work that has been done with alkylated derivatives of 1,[1-3] we were interested in the behavior of 2 so as to learn how the two systems compare. We should also note that hydroaromatics and the NMR spectral characterization of aryl–CH_2–aryl units have become quite important in many areas of fossil fuel research.[8]

Results and Discussion

The proton NMR behavior of 7,12-dihydropleiadenes (DHP's) was investigated in some detail by Lansbury and his co-workers,[9] and this work provides several approaches for structural assignments. As with 1, pseudoaxial (pa) hydrogens (at C_7 and C_{12}) in DHP's absorb at lower field and pseudoequatorial (pe) at higher field. These resonance positions are well separated and are consequently quite characteristic of the respective pa and pe hydrogens. Moreover, pe hydrogens can also be distinguished by the observation of a nuclear Overhauser enhancement (NOE) when the aromatic protons are irradiated.[10]



R = Me; 90% pe, 10% pa
R = Et; 50% pe, 50% pa
R = i-Pr; 100% pa

This type of analysis by the Lansbury group on monoalkyl DHP's revealed some unusual substituent preferences.[11] A single methyl group exhibits strong pseudoequatorial preference with 90% pe and 10% pa. On the other hand, ethyl shows little preference at all (~50:50), and isopropyl is 100% pa. Hence this pattern is quite different from cyclohexane where conformational free energy differences have served as a general guide to substituent "size". However, two substituents cannot both be accommodated in pa positions due to a transannular steric effect, and so cis disubstituted DHP's are pe/pe. The trans compounds exist in dynamic equilibrium (pe/pa ⇌ pa'/pe'), but equal contributions of pe/pa and pa'/pe' can only be expected when the two substituents are identical.

Dimethyl-, diethyl-, and diisopropyldihydropleiadenes were prepared by *n*-butyllithium deprotonation of the appropriate 7-alkyl-7,12-dihydropleiadene, followed by reaction with the analogous alkyl halide.[7] This produced a mixture of isomers in two instances (Me, Et) and a single isomer in the third (*i*-Pr). In the first two cases, the isomers whose NMR spectra underwent change with lowering of the temperature were assigned as trans; the single diisopropyl isomer was also assigned as trans on the same basis except that a temperature increase was required.

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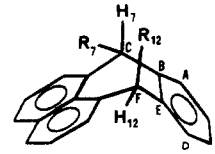
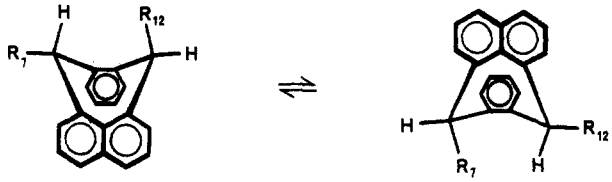
Table I. MM2 Molecular Mechanics Calculations for 7-Methyl- and *trans*-7,12-Dialkyl-7,12-dihydropleiadenes[a]



		dihedral angles, deg				total steric energy,
R_7	R_{12}	A,B,C,R_7	A,B,C,H_7	D,E,F,R_{12}	D,E,F,H_{12}	kcal/mol
H	H	12	125	125	12	-3.0
Me	H	24	136	124	11	2.0
Me	Me	25	136	104	-5[b]	8.5
Et	Et	28	138	104	-5[b]	10.9
i-Pr	*i*-Pr	34	144	105	-4[b]	13.8

[a] Optimized geometries; rotations about substituent bonds were carried out to avoid local minima. [b] A negative angle means that the final atom in the series is below the first atom relative to the orientation provided by the illustration.

Since the monoalkyl DHP's show rather unusual conformational preferences,[11] we were anxious to learn if the corresponding trans dialkyl DHP's would show similar peculiarities. As expected, all three compounds had temperature-dependent spectra which showed average resonances at elevated temperatures and separate axial and equatorial resonances at lowered temperatures. The temperatures at which H_7 and H_{12} underwent coalescence in each case were measured, and $\Delta G^{\ddagger}$ values were determined in the usual manner.[12] The diethyl compound has a



R = Me, $\Delta G^{\dagger}$ = 11.0 kcal/mol (T_c = -44°C)

R = Et, $\Delta G^{\dagger}$ = 12.2 kcal/mol (T_c = -19°C)

R = *i*-Pr, $\Delta G^{\dagger}$ = 15.4 kcal/mol (T_c = 48°C)

somewhat slightly higher barrier to inversion than dimethyl (12.2 vs. 11.0 kcal/mol) whereas diisopropyl is several kcal/mol higher (15.4 kcal/mol). These results do follow the general pattern of conformational free energy values for these substituents (*i*-Pr > Et ≳ Me). However, the barriers for dimethyl and diethyl are *actually less than the unsubstituted parent hydrocarbon* (13.6 kcal/mol, T_c = 8 °C).[9] Hence these observations raise two important questions. (1) What causes peculiarities in the monosubstituted cases (and why not also with disubstitution), and (2) why are inversion barriers lowered by the addition of dimethyl or diethyl substitution? We shall attempt to answer these questions with molecular mechanics calculations.[13]

We have recently demonstrated that the unusual group preferences in monoalkyl DHP's are due to the ability of a methyl group to "just fit" in the pe position.[7] MM2 calculations[13] show a minimized geometry wherein a pe methyl can "lift up" to minimize the steric interaction from the nearby peri protons. This results in an angle distortion around C_7 (labeled C in Table I) which can be evaluated by inspection of the dihedral angles A,B,C,R_7 (where R_7 = methyl) and A,B,C,H_7. These angles, which are 12° and 125°, respectively, in unsubstituted 7,12-dihydropleiadene, are 24° and 136° in the methyl derivative. The upward

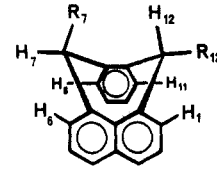
Table II. MM2 Energies for *trans*-R,R′-7,12-dihydropleiadene Conformers[a]

pseudoaxial R	pseudoequatorial R	total steric energy, kcal/mol
Me	Et	9.9
Et	Me	9.0
Me	*i*-Pr	12.5
i-Pr	Me	10.1
Et	*i*-Pr	13.7
i-Pr	Et	11.2

[a] Optimized geometries; rotations around substituent groups were carried out to avoid local minima.

movement of the methyl at C_7 also forces H_7 out over the central seven-membered ring, but this is of no consequence in the monomethyl derivative since the bond angles at C_{12} (across the ring) are unaffected. However, this is not the case with trans dimethyl. In this instance, the pe methyl is in the same position as monomethyl, but the pa methyl (at C_7) shows a ca. 20° distortion of bond angle representing movement away from the central ring. Consequently, the pe hydrogen (at C_7) is "forced down" by 16° (Table I). The trans diethyl and diisopropyl DHP's show a similar distortion except that the outward movement of the pa substituent becomes more serious with increasing group size.

Consideration of these calculated geometries allows rationalization for the observed increase in ring inversion rates with methyl and ethyl substitution. H_7 is already below H_6 and H_8 and so any peri interaction will, in fact, favor further ring flattening (i.e., ring inversion). Simi-



FACTORS INFLUENCING INVERSION BARRIER

Increase	Decrease
R_{12} passes by H_1 and H_{11}	1. repulsion between R_7 and H_{12}
	2. repulsion between H_7 and H_6,H_8

larly, repulsion between R_7 and H_{12} will also favor further ring flattening, and these two repulsions taken together provide a substantial *steric acceleration* to ring inversion. Of course R_{12} must pass by H_1/H_{11}, and this represents the major nonbonded interaction contributing to the overall inversion barrier (which is, no doubt, mainly due to angle distortions in the seven-membered ring, although a planar transition state cannot be assumed). We should add that for R_7 to become pe, it must also move by H_6/H_8. However this process must be well past the transition state and therefore does not contribute to the barrier. Hence

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Table III. Carbon-13 NMR Chemical Shifts for Alkylated 7,12-Dihydropleiadenes[a]

compound	H / —C / R	R / —C / H	CH_3 pe	CH_2CH_3 pe	CH_2CH_3 pa	CH_2CH_3 pe	CH_2CH_3 pa	$CH(CH_3)_2$ pe	$CH(CH_3)_2$ pa	$CH(CH_3)_2$ pe	$CH(CH_3)_2$ pa
EtDHP[b]	45.4	59.0		22.6	29.9	12.9[c]	13.1[c]				
i-PrDHP		65.7							31.7		22.0, 22.2
cis-Et_2DHP	45.6			23.2		13.0					
trans-Et_2DHP[d]	44.3	58.3		22.5	31.6	12.9[c]	13.5[c]				
cis-MeEtDHP	45.5[e]		17.4	23.1		12.9					
	38.0[f]										
trans-MeEtDHP[g]	36.8[f]	58.9[e]	16.8		31.3		13.5				
trans-Me-*i*-PrDHP	37.0[f]	65.8[h]	16.9						33.1		22.5
trans-Et-*i*-PrDHP	44.7[e]	65.7[h]		22.8		12.8			33.5		22.5
trans-*i*-Pr_2DHP[i]	51.0	65.0						25.7	33.9	21.9, 22.1	22.5, 22.8
methylene *i*-PrDHP		65.5							31.4		21.5, 22.2

[a] In $CDCl_3$ as solvent and lock with internal tetramethylsilane as reference. [b] Run at −30 °C. [c] Assignments could be reversed. [d] Run at −50 °C. [e] R = Et. [f] R = Me. [g] Run at −35 °C. [h] R = *i*-Pr. [i] Run at −20 °C.

we conclude that for small substituents like methyl and ethyl, the repulsion terms outweigh the steric barrier at R_{12}, and inversion rates are increased. With the relatively large isopropyl group, however, this steric barrier becomes large enough to become dominating.

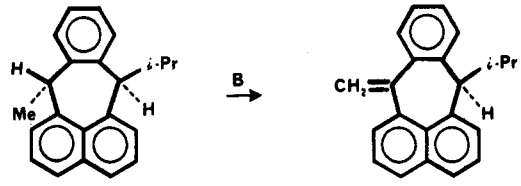
Examination of the isomeric 7-methyl-12-ethyl DHP's showed one isomer with H_7,H_{12} resonances at 5.4 and 5.06 ppm and the other at 5.0 and 4.2 ppm. Hence the latter values would seem to indicate a trans isomer with H_7 in a pa position and H_{12} as pe. Further confirmation of this pe Me/pa Et arrangement was achieved by irradiation of the aromatic hydrogens which produced a ~6% nuclear Overhauser enhancement at H_{12} with no significant increase at H_7.

In view of the monosubstituted equilibrium positions noted above, it might be expected that the other possible conformer (i.e., pa Me/pe Et) would not be much higher in energy. In fact, molecular mechanics calculations (Table II) predict this conformer to be ~0.9 kcal/mol higher in energy, and this corresponds to a contribution of about 10–20%. As predicted, a decrease in temperature did produce NMR coalescence followed by the emergence of a minor isomer. Due to "freezing" problems, the spectrum of the minor conformer was not well resolved, but its contribution could be estimated at around 10%, in agreement with the calculations.

Alkylation of isopropyl DHP monoanion with either methyl iodide or ethyl bromide produced mainly one isomer in each case. Once again, trans assignments were made on the basis of low-field H_7 resonances (pa) and high-field H_{12} signals (pe). There was no evidence for conformers other than pa isopropyl and this is exactly what is predicted by MM2 calculations (Table II). In each case, there is an increase of ~2.5 kcal/mol to exchange substituent positions (i.e., place the isopropyl pe), and this corresponds to a contribution of less than 2%.

The calculations also indicate that a pa isopropyl group will be significantly lower in energy if it is "flagged out" away from the central ring. For example, with pa isopropyl and pe methyl, the isopropyl methine hydrogen/H_{12} dihedral angle is predicted to be 161° (the isopropyl is skewed slightly toward the benzene ring and away from the naphthalene ring). The proton NMR spectrum provides evidence for this preferred rotamer, since the coupling constant between these two protons is quite large (J = 9.6 Hz).[14] A similar observation was made in 7-ethyl-12-isopropyl DHP (J = 9.9 Hz). As expected, the individual methyl groups of the isopropyl unit in all of these derivatives show different resonances due to the diastereotopic relationship. However, the observed differences are not large (0–0.2 ppm) even though there may be contributions from preferred conformations.

Interestingly, attempted base-catalyzed epimerization of trans 7-methyl-12-isopropyl DHP resulted in hydride loss, producing the exo methylene compound 4. Once



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again the isopropyl is pa as evidenced by the highfield H_{12} (3.48 ppm). We expected that "flagging" of the isopropyl might be even more pronounced in this case due to the absence of the interfering pa hydrogen across the ring. MM2 calculations do predict this, and the isopropyl methine/H_{12} bond angle is increased to 173°. In support of the calculations, NMR shows an increase in the coupling constant to 10.8 Hz.

Carbon NMR. The ^{13}C NMR assignments provided in Table III were made in the following way. Conformational preferences were already known from proton NMR due to the characteristic pe and pa chemical shifts of H_7, H_{12} together with nuclear Overhauser experiments. In this way, we were able to determine characteristic carbon chemical shifts. For example, cis diethyl DHP provided data for a pe ethyl group as well as a pe-substituted bridge carbon (i.e., C_7). Subsequent low-temperature carbon NMR of trans diethyl DHP then provided a "match" for the pe ethyl and allowed characterization of the pa ethyl and its bridge carbon. Off-resonance decoupling and in some cases cross correlation decoupling with the proton frequencies were used to confirm assignments. This approach quickly established a pattern of downfield positions for pa substituent carbons as well as pa-substituted bridge carbons and upfield resonances for the pe counterparts.

Bridge Carbons. In several cases where a direct comparison can be made, there appears to be a ca. 14 ppm difference between a pa-substituted bridge carbon (C_7 or C_{12}) and one with a pe substituent. The latter is always at higher field. This effect, which we have observed with both ethyl and isopropyl groups, is much larger in the DHP system when contrasted to pe and pa methyls in the solid-state carbon NMR spectrum of *trans*-9,10-dimethyl-9,10-dihydroanthracene (14 vs. 7.5 ppm).[2] It is, however, in the same direction. As we mentioned above, a pe substituent causes considerable bond angle distortion at the

(14) As noted previously by Lansbury et al.[11] They reported a value of $J \simeq 10$ Hz.
(15) Gorenstein, D. G. *J. Am. Chem. Soc.* **1977**, *99*, 2254.

bridge carbon (i.e., 15–20°; see Table I). Hence these observations are quite consistent with Gorenstein's[15] interpretation of the "gauche" NMR effect in terms of bond angle distortions.

As one would expect, a pe substituent on one bridge carbon has little effect on the chemical shift of the second bridge carbon across the ring. However, a pa group does produce a ca. 1.0 ppm upfield shift, and this appears quite reasonable for the expected δ effect.[16]

Substituent Carbons. The difference in chemical shifts at the α-carbon of pe and pa ethyl substituents is about 8 ppm. A similar value is observed for the isopropyl group. This is best interpreted as an upfield shift of the pe CH_2CH_3 carbon due to two γ effects[16] from the "ortho" positions on the adjacent aromatic rings. The net upfield shift is a little smaller than that observed for a pe methyl in solid-state *trans*-9,10-dimethyl-9,10-dihydroanthracene (13.2 ppm).[2] This may be due to the difference in the relevant dihedral angles for the two systems.

Experimental Section

Proton NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer with tetramethylsilane as reference and $CDCl_3$ as solvent. NOE experiments were conducted on deoxygenated samples. Carbon NMR spectra were recorded at 20 MHz on a Varian CFT-20 spectrometer with $CDCl_3$ as solvent and lock and internal tetramethylsilane as reference. Variable-temperature experiments were carried out on both instruments, but $\Delta G^{\ddagger}$ calculations were performed with the proton data with temperature measurements made with a methanol temperature calibration sample.

Calculations were performed with the Allinger MM2 molecular mechanics program.[13] Aromatic carbons were defined in terms of the optimum C=C bond length (1.397 Å) and the C=C force constant (8.067 mdyn/Å).

We have recently reported the preparation of 7-alkyl- and 7,12-dialkyl-7,12-dihydropleiadenes.[7] This was accomplished by reaction of *n*-butyllithium (2.1 mmol) with the DHP in THF at 0 °C for 30 min followed by the addition of excess alkyl halide.

7-Methylene-12-isopropyl-7,12-dihydropleiadene (4). *n*-Butyllithium (2.09 mmol) in hexane was added to *trans*-7-methyl-12-isopropyl-7,12-dihydropleiadene (150 mg, 0.52 mmol) in dry cyclohexane (7 mol) containing TMEDA (0.32 mL, 2.09 mmol). The mixture was heated at reflux for 23 h, cooled, and poured into water. The product was isolated by ether extraction, and *GLPC* indicated ca. 40% 4 and 60% starting material. Pure 4, mp 108–109 °C, was isolated by chromatography on 230–400 mesh silica gel (Merck) with petroleum ether/carbon tetrachloride/ethyl acetate (98:1:1): NMR ($CDCl_3$) δ 0.72 (6 H, d; expansion reveals 2 d separated by 1.2 Hz), 2.8 (1 H, m), 3.45 (1 H, d), 5.5 (2 H, AB q, vinyl), 7.4 (10 H, m, aryl); mass spectrum, *m/e* 284 (M^+).

Anal. Calcd for $C_{22}H_{23}$:[17] C, 92.96; H, 7.04. Found: C, 92.57; H, 6.96.

Acknowledgment. We express our gratitude to the U.S. Department of Energy, Office of Basic Energy Science, for support of this work and to the Indiana University Computer Network.

Registry No. EtDHP, 15529-85-8; *i*-PrDHP, 14529-25-0; *cis*-Et_2DHP, 100021-40-7; *trans*-Et_2DHP, 100021-41-8; *cis*-MeEtDHP, 100021-36-1; *trans*-MeEtDHP, 100021-37-2; *trans*-Me-*i*-PrDHP, 100021-39-4; *trans*-Et-*i*-PrDHP, 100021-43-0; *trans*-*i*-Pr_2DHP, 100021-44-1; methylene-*i*-PrDHP, 102683-33-0; DHP, 4580-70-5; MeDHP, 7119-78-0; *trans*-Me_2DHP, 17430-42-1.

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(17) This analysis was performed on a rather small sample (ca. 5 mg).

Hydrolysis and Rearrangement of O^6-Substituted Guanosine Products Resulting from Reaction of Guanosine with Styrene Oxide

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The preparation and properties of four diastereomeric O^6-substituted guanosines which result from reaction between guanosine and styrene oxide are described. While the two diastereomers for O^6-(2-hydroxy-2-phenylethyl)guanosine (**1bI** and **1bII**) are reasonably stable under mildly acidic aqueous conditions, the two diastereomers for O^6-(2-hydroxy-1-phenylethyl)guanosine (**1aI** and **1aII**) undergo acid-catalyzed hydrolysis to cleave the O^6-aralkyl ether linkage. In neutral and alkaline aqueous conditions **1aI** and **1bI** or **1aII** and **1bII** interconvert. An equilibrium is established between the isomers such that at equilibrium the ratio of **1bI**/**1aI** or **1bII**/**1aII** is 2.0. The rate of equilibration is first-order in hydroxide ion although the equilibrium constant is independent of pH over the range 7.5–12. The configuration about the α-carbon of the substituted phenylethyl side chain is retained during isomer equilibration.

Styrene oxide is a mammalian metabolite of styrene, a widely produced monomer used in the production of plastics and rubber products. The oxide is mutagenic[1,2] and carcinogenic,[3] and it has been shown to react at the 7-position of DNA guanine residues.[2,4,5] In later investigations of its reactions with guanosine under totally aqueous conditions, products derived from reaction at the exocyclic N^2- and O^6-position were detected in addition

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