reaction mixture was warmed to room temperature and stirred for 20 min. Most of the TFA was removed in vacuo, and last traces of acid were removed by chasing with CH_3OH on the rotary evaporator. The oily residue was taken up in water, washed with CH_2Cl_2 (10 mL), and lyophilized. Chromatography of the crude product (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) gave the desired **2** (0.11 g, 75%) as an oil: ^1H NMR (CD_3OD) δ 3.27, 3.36 (2 t, 4 H), 2.62, 2.69, 2.73, 2.84 (4 t, 8 H), 1.71, 1.78 (2 t, 4 H), 1.35–1.60 (m, 4 H); IR (film) 2950, 2100, 1680, 1640, 1120 cm^{-1}; CIMS (isobutane) 339 (M + 1, 42%), 311 (67%), 203 (32%), 75 (100%).

Attempted purification of **2** using CH_2Cl_2–CH_3OH–NH_4OH in 6:3:1 proportion instead of 2:2:1 proportion resulted in extensive decomposition during concentration of the chromatography fractions.

Acknowledgment. We thank Dr. A. E. Pegg (Hershey Medical Center, Hershey, PA) for assaying **1** against spermidine/spermine synthase and N^1-acetyltransferase. We also thank Dr. G. E. Kuehn (Department of Chemistry, New Mexico State University) for the transglutaminase studies on **1** and **2**. We are grateful to the National Institutes of Health (Grant AM 26754) for generous financial assistance. The Cornell Nuclear Magnetic Resonance Facility is supported by NSF (Grants CHE 7904825 and PCM 8018643) and NIH (Grant RR02002).

Conformational Analysis of 1,4-Cyclohexadienes. A Shallow Boat-Shaped 1,4-Dihydronaphthalene

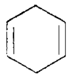
Peter W. Rabideau,* Jennifer L. Mooney, and Julie N. Hardin

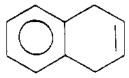
Department of Chemistry, Purdue School of Science at Indianapolis, Indiana University-Purdue University at Indianapolis, Indianapolis, Indiana 46223

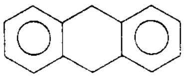
Received June 24, 1985

The metal/ammonia reduction of 7,12-dihydropleiadene affords 3,7,12a,12-tetrahydropleiadene which models indicate can exist in one of three different conformations (or in a dynamic equilibrium). Two of these conformers possess "fully-puckered", boat-shaped 1,4-dihydronaphthalene units (**5a** and **5b**) whereas the third (**5c**) incorporates a "flattened" six-membered ring. This latter conformation is the favored one as deduced by a variety of NMR techniques and is also predicted by MM2 force field calculations. The NMR parameters from **5c** are then applied to stereochemical problems associated with a number of previously investigated 1-R-1,4-dihydronaphthalenes (R = CO_2H, Ph, CH_2OH, or $C(CH_3)_2OH$). MM2 results are also presented for the entire sequence. It is concluded that "flattened" boat conformations are expected to be common for many 1-R-1,4-dihydronaphthalenes.

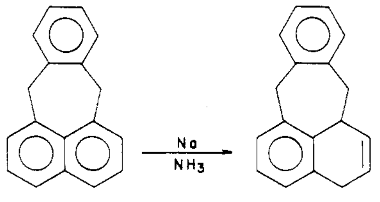
The stereochemistry of cyclohexadienes, which includes 1,4-dihydrobenzenes **1**, 1,4-dihydronaphthalenes **2**, and 9,10-dihydroanthracenes **3**, has attracted considerable attention.[1-8] Various geometries have been suggested for the 1,4-cyclohexadiene ring in these systems including planar, "normal" boat-shaped and "shallow" boat-shaped. Moreover, boat-shaped conformations also allow for the possibility of boat-to-boat, ring inversion processes. The stereochemistry of these compounds is further complicated by substitution, since substituents can, in principle, prefer either pseudoaxial (pa) or pseudoequatorial (pe) positions.[1]


1


2


3

An especially useful approach to the NMR conformational analysis of these systems has involved studies with compounds of fixed geometries.[1,8] This allows application of NMR data so obtained to structures with unknown (and often flexible) geometry. For this reason we became interested in the metal/ammonia reduction of 7,12-dihydropleiadene (**4**) when we realized that the likely product would provide a 1,4-dihydronaphthalene ring which could exist in one or more of three different conformations. However, treatment of **4** with sodium in ammonia according to methods which we had previously developed for naphthalenes,[9] afforded only one product, and variable-temperature NMR suggested a single conformation.



4 5

Results and Discussion

Mechanical Dreiding models suggest three different possible conformations for **5**. Two of these structures involve boat-shaped, central rings similar to the parent

---

[1] Rabideau, P. W. *Acc. Chem. Res.* **1978**, *11*, 141.

[2] Grossel, M. C.; Perkins, J. *Nouv. J. Chim.* **1979**, *3*, 285.

[3] Grossel, M. C. *Tetrahedron Lett.* **1980**, *21*, 1075.

[4] Holy, N. L.; Vail, H. P.; Nejad, A. H.; Huang, S. J.; Marshall, J. L.; Saracoglu, O.; McDaniel, C. R. *J. Org. Chem.* **1980**, *45*, 4271.

[5] Cheetham, A. K.; Grossel, M. C.; James, D. *J. Org. Chem.* **1982**, *47*, 566.

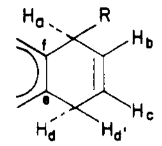
[6] Lamberts, J. J. M.; Haasnoot, C. A. G.; Laarhoven, W. H. *J. Org. Chem.* **1984**, *49*, 2490.

[7] (a) Lipkowitz, K. B.; Rabideau, P. W.; Raber, D. J.; Schleyer, P. v. R.; Kos, A. J.; Kahn, R. A. *J. Org. Chem.* **1982**, *47*, 1002. (b) Raber, D. J.; Hardee, L. E.; Rabideau, P. W.; Lipkowitz, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 2843. (c) Rabideau, P. W.; Lipkowitz, K. B.; Nachbar, R. B., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 3119.

[8] Rabideau, P. W.; Burkholder, E. G.; Yates, M. J.; Paschal, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 3596.

[9] Rabideau, P. W.; Huser, D. L. *J. Org. Chem.* **1983**, *48*, 4266.

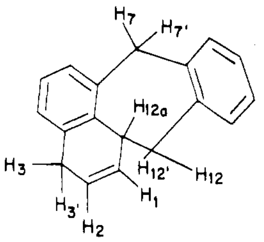
Table I. MM2 Calculated Results



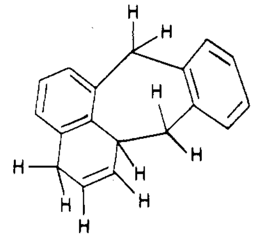
R =[a]	structure	dihedral angles (deg)					ring folding, α,[f] (deg)	total steric energy (kcal/mol)
		$C_fC_eC_dC_c$	$C_cC_bC_aC_f$	$H_bC_bC_aH_a$	$H_cC_cC_dH_d'$	$H_cC_cC_dH_d$		
	5a[b]	36	42	105	25	92		10.9
	5b[b]	35	41	104	26	91		9.1
	5c[c]	12	14	48	68	48	170	6.5
CO_2H	**6a**[c,d]	22	28	34	77	39	<160	-3.3
CO_2H	**6e**[b,e]	17	20	80	44	72		-2.9
CH_2OH	**7**[c,d]	17	20	45	73	44	>160	2.6
$C(CH_3)_2OH$	**8a**[c,d]	20	22	45	76	41	160	6.46
$C(CH_3)_2OH$	**8b**[b,d]	26	30	37	82	35	145–150	6.53
$C(CH_3)_2OH$	**8c**[b,d]	24	25	43	78	43	150	7.0
Ph	**9**	10	11	52	66	50	170	-0.4
	10	24	28	84	37	80	145–150	10.3

[a] Lettering system is unique to this table since the structures do not share a common numbering system. [b] Represents a local minimum. [c] Represents the global minimum. [d] Substituent is in pseudoaxial position. [e] Substituent is in pseudoequatorial position. [f] Approximate, see text.

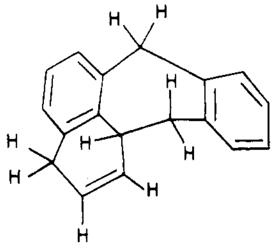
compound, **4**, which undergoes rapid "boat-to-boat" ring inversion,[10] and, in fact, **5a** and **5b** can also be interconverted by inversion of the seven-membered ring. It is also important to note that both **5a** and **5b** incorporate what appears from the models to be a "normal", fully puckered 1,4-dihydronaphthalene ring. On the other hand, the seven-membered ring in **5c** is folded along a different axis (C_7–C_{12a} instead of C_7–C_{12}), and whereas **5a** and **5b** are interconverted by a "complete" ring flip, **5c** is converted to **5a** by a "half" ring inversion on one side (i.e., rotation at C_{12}) and to **5b** by a similar process on the other side (rotation at C_7). It is also important to note that unlike **5a** and **5b**, **5c** incorporates a somewhat "flattened" dihydronaphthalene ring. This is especially interesting since all previous models with fixed geometry have been fully puckered even though flattened geometries have been proposed for several dihydronaphthalenes.[8,11]



5c



5b



5a

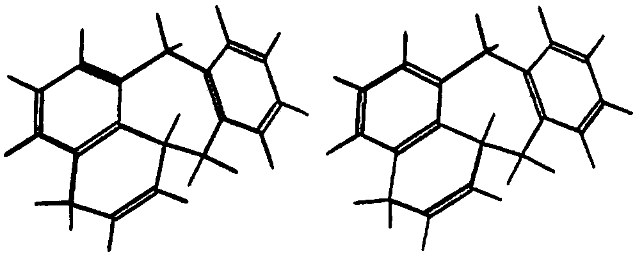


Figure 1. Stereoview of 3,12a,7,12-tetrahydropleiadene (**5c**).

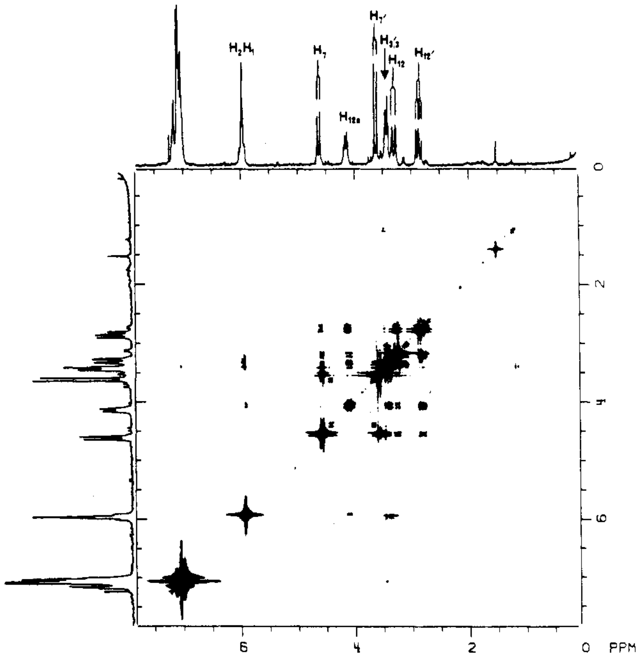


Figure 2. Two-dimensional correlation spectrum (COSY) of 3,12a,7,12-tetrahydropleiadene.

We were able to evaluate potential structures using the Allinger force field,[7,12] MM2. By starting with conformations that were close to each of the three structures under consideration, we were able to determine minimum energies in each case. The results (see Table I) indicate **5a** and **5b** to be local minima with **5c** representing the global minimum (see Figure 1 for a stereoview of **5c**). In fact, the energy differences are such that neither **5a** nor **5b** is

---

(10) Lansbury, P. T.; Bieron, J. F.; Klein, M. *J. Am. Chem. Soc.* **1966**, *88*, 1477.

(11) (a) Marshall, J. L.; Folson, T. K. *J. Org. Chem.* **1971**, *36*, 2011. (b) Marshall, J. L.; Ihrig, A. M.; Jenkins, P. N. *J. Org. Chem.* **1972**, *37*, 1863. (c) Marshall, J. L.; Faehl, L. G.; McDaniel, C. R.; Ledford, N. D. *J. Am. Chem. Soc.* **1977**, *99*, 321.

(12) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734.

Table II. Coupling Constants of 1,4-Dihydronaphthalenes

structure	$^5J_{cis}$	$^5J_{trans}$	ratio (cis/trans)	$J_{3,4}$	$J_{3,4'}$	$J_{2,4}$	$J_{2,4'}$	ref
5c	4.1	4.4	0.93	$3.2^{a,b}$	$2.2^{a,c}$		$3.0^{a,d}$	*e*
6	3.8	4.4	0.86	4.6	2.4	1.2	3.0	*f*
7	3.5	3.7	0.95	3.7	2.1			*f*
8	1.8	3.0	0.60	5.0	2.0	1	2.0	*f*
9	4.6	4.9	0.94	3.8	3.0	1.6	3.0	*g*

[a] These systems do not share a common numbering system. [b] $J_{2,3}$ in **5c**. [c] $J_{2,3'}$ in **5c**. [d] $J_{1,3'}$ in **5c**. [e] This study. Additional coupling constants in **5c** are $J_{1,2}$ = 10.1 Hz, $J_{3,3'}$ = 21.6, $J_{7,7'}$ = 15.0, $J_{7,12'}$ = 1.4, $J_{7,12}$ = 1.6, $J_{12a,1}$ = 3.5, $J_{12a,2}$ = 0.5, $J_{12a,12}$ = 3.6, $J_{12a,12}$ = 12.9, $J_{12,12'}$ = 17.2. [f] See ref 8. [g] See ref 6.

expected to make a significant contribution.

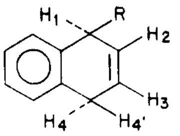
The 300-MHz proton NMR spectrum as well as the 2-D spectrum (COSY) are shown in Figure 2.[13] Single frequency double irradiation of the vinyl signal (~6 ppm) resulted in the appearance of an AB quartet at 3.4 ppm with each of the four lines further split into a doublet. This absorption was assigned as H_3, $H_{3'}$, and the additional splitting represented the five-bond, homoallylic coupling constants $J_{12a,3}$ (4.1 Hz) and $J_{12a,3'}$ (4.4 Hz). Next, irradiation of H_3, $H_{3'}$ (just assigned) allowed observation of the vinyl protons (H_1, H_2) as an AB quartet with additional coupling from H_{12a}. Hence $J_{12a,1}$ (3.1 Hz) and $J_{12a,2}$ (0.5 Hz) were measured. This interrelationship between vinyl and allylic protons received further confirmation (i.e., assignments) from the COSY spectrum. For example, the signal assigned as H_{12a} at 4.1 ppm is clearly coupled to the vinyls and the signal assigned to H_3, $H_{3'}$. The COSY spectrum also shows that H_{12a} is coupled to the signals at 2.84 and 3.27 ppm, and this allowed assignment of these signals as $H_{12'}$ and H_{12} in view of the expected vicinal coupling. Hence, only H_7 and $H_{7'}$ remained unassigned. Double irradiation of the aromatics revealed a small coupling between H_{12}, $H_{12'}$ and one of the two doublets (4.6 ppm) yet to be assigned; this also represents a long-range homoallylic coupling which is maximized at a 90° relationship with the intervening π system. Thus the signal at 4.6 ppm could be assigned to the most axial proton at C_7.

The NMR data allow unambiguous structural assignment since the large value observed for $J_{H_{12a}/H_{12'}}$ (12.9 Hz) is only consistent with a ca. 180° (or 0°) dihedral angle. This immediately rules out **5a** since the calculated dihedral angles (see Table I) of $H_{12a/H12'}$ = 68° and H_{12a}/H_{12} = 44° would lead to a much smaller J value. The most straightforward way to distinguish between **5b** and **5c** was by observation of a nuclear Overhauser enhancement (NOE). Inspection of the structures shows that H_7 and H_{12a} are in close proximity for **5c**, but **5b**, with its "inverted boat" six-membered ring, results in H_7 and H_{12a} on opposite faces of the molecule. Moreover, H_7 could be unambiguously assigned since its geometric relationship with the adjacent aromatic rings (approaching a right angle) maximizes allylic type coupling, and, hence, weak coupling from the aromatic protons leads to broadening. It has been well-extablished by us and others that pseudoaxial protons in 7,12-dihydropleiadenes[10] as well as 9,10-dihydroanthracenes[14] appear broadened and downfield relative to their pseudoequatorial counterparts. Irradiation of H_7 did produce a ca. 10% increase in the integrated intensity of H_{12a} and this completed the assignment of **5c**.

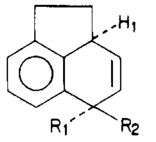
One approach to the conformational analysis of dihydrobenzenes has involved the use of rigid models of known geometry.[1,8] NMR parameters so obtained have then been employed to determine conformational preferences in flexible systems. In this context, **5c** provides an excellent opportunity since the cyclohexadiene ring must exist as a very shallow boat. "Shallow" or "flattened" boats have been suggested for a number of 1,4-dihydronaphthalenes[5,8,11] although a rigid model of this type has not heretofore been investigated.

The extent of ring folding has often been described as α, the angle between the two planes folded across an axis through C_1 and C_4. However, both experimental[4] and theoretical results[7] suggest that these planes may not fold evenly (i.e., twisting), and so consideration of specified dihedral angles may be more useful.[15] Molecular mechanics (MM2) calculations (see Table I) confirm the expectation from Dreiding models that **5c** should exist as a shallow boat. The values of $C_fC_eC_dC_c$ = 12° and $C_cC_bC_aC_f$ = 14° are slightly less than half way between the planar (0°) and fully puckered (35°) state.

The NMR coupling-constant data for 5c (Table II) allow comparison with the previously investigated derivatives **6–10**.[1,6,8] The coupling constants of greatest interest are, of course, those with strong geometric dependence. The vicinal couplings $J_{3,4}$ and $J_{3,4'}$ should be almost equal for a planar form since the angle between H_4 and $H_{4'}$ would be bisected by H_3.[15] Similarly the allylic couplings (e.g., $J_{2,4}$ and $J_{2,4'}$) are also dependent on geometry except, in contrast to the vicinal case, allylic coupling is maximized by a 90° relationship. Unfortunately they are sometimes small and difficult to measure in the presence of stronger and complex coupling. Interestingly, 1,4-cyclohexadienes show unusually large, five-bond couplings, known as homoallylic coupling, between H_1 and $H_{4,4'}$. A considerable



6, R = CO_2H
7, R = CD_2OH
8, R = $C(CH_3)_2OH$



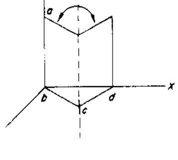
10, $R_1 = R_2 = H$
10a, $R_1 = C(CH_3)_2OH$; $R_2 = H_{4'}$
10b, $R_1 = H_4$; $R_2 = CO_2CH_3$

---

[13] (a) COSY is correlated spectroscopy where the diagonal peaks represent a top view of the normal spectrum, and the cross peaks represent correlation of two peaks linked by J-coupling. (b) Signals above 2 ppm as well as a small doublet at 3.1 ppm represent an impurity which persisted after several recrystallizations. The sample also tends to degrade upon standing in solution.

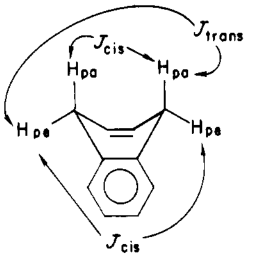
[14] Brinkman, A. W.; Gordon, M.; Harvey, R. G.; Rabideau, P. W.; Stothers, J. W.; Ternay, A. L. *J. Am. Chem. Soc.* **1970**, *22*, 5912.

[15] α was calculated at the unsubstituted end of the molecule to avoid effects from "twisting" or distoration at the substituent site (see text). Calculations were done by analyzing the triangle formed by b, c, and d, with b at the origin, a along the y axis and d along the x axis. In this way, with the z coordinate of c (ignoring its y coordinate), the triangle (folding angle) involving the dotted line could be calculated.



[16] However, see ref 6.

amount of effort (and some controversy) has gone into using the ratio of these coupling constants to determine ring geometry.[1-3] Calculations suggest that $^5J_{cis}/^5J_{trans}$ should be ca. 1.2 for a planar ring.

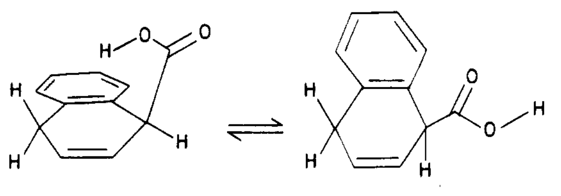


$J_{cis(pa,pa)} > J_{trans(pa,pe)} > J_{cis(pe,pe)}$
(8-9 Hz) (3-4.5 Hz) (1.5-3.5 Hz)

Variations in J_{cis} may be quite large, and values of J_{cis} = 8.5 Hz for a dipseudoaxial relationship and J_{cis} = 1.8 for a dipseudoequatorial arrangement have been observed. In contrast J_{trans}, which always represents a pseudoaxial/pseudoequatorial relatioship, does not vary as much, and extremes of 3.0 and 4.4 were reported in the same study.[8]

Based on the aforementioned NMR data and using rigid dihydroacenaphthenes (i.e., **10**) as models for normally puckered systems, we concluded that structures **6** and **7** were shallow boats, whereas **8** was thought to be fully puckered (i.e., the 35° angle mentioned above).[8] More recently,[6] Laarhoven and co-workers studied the 500-MHz proton NMR spectrum of 1-phenyl-1,4-dihydronaphthalene (**9**), reporting **9** to be more flattened than either **6** or **7**, and, in fact, nearly planar. This is consistent with an earlier report suggesting small space requirements for the phenyl group in 9-phenyl-9,10-dihydroanthracene.[14]

We were quite interested to learn if molecular mechanics would support these conclusions for **6**–**9**. Interestingly, we were able to locate two minima for **6**, both as shallow boats, but more puckered than the rigid model **5c** (see Table I). The pseudoaxial conformation is actually more stable than the pseudoequatorial by 0.4 kcal/mol, although the former is predicted to be more puckered probably due to the orientation of the OH group out over the ring (as illustrated, groups were "rotated" in the calculations to determine rotational local minima for each ring conformation). With **6e**, the carboxyl group can be "flagged out", away from the ring. We have also approximated a folding angle (see α above) based on the MM2 coordinates, but as we have mentioned, twisting of the central ring as well as distortion at the carbon bearing a substituent causes problems with this concept.



6a **6e**

We were only able to determine a single minimum for **7**; a pseudoaxial CH_2OH substituent with the two hydrogens bisected by H_1 and the hydroxyl turned out over the six-membered ring. An earlier suggestion that **6** is more flattened than **7** on the basis of homoallylic coupling constants[8] has been recently challenged.[6] In fact, molecular mechanics does suggest that **7** is slightly flatter (Table I) than the most stable conformer of **6** (i.e., **6a**).

Our calculations also support a very flat structure for **9**. As expected from the Dreiding model, MM2 predicts a pa phenyl substituent which lies in a plane approximately perpendicular to the dihydronaphthalene system. Expected rotation of the phenyl substituent no doubt causes increased puckering of the six-membered ring, but nonetheless **9** is calculated to be the most planar of the systems studied herein and quite comparable to the rigid model **5c**.

As expected, a dimethylcarbinol group (**8**) is predicted to be pseudoaxial. However, three minima were obtained relative to rotation of this large substituent. Interestingly, the most stable conformation (H_1 bisecting Me/OH of dimethylcarbinol with OH toward the aromatic ring) is no more puckered than the carboxylic acid derivative **6**. However, the two additional conformations having different rotational arrangements are noticeably more puckered and do indeed approach the "highly puckered" rigid model **10**. We should also note that calculations predict a slightly different geometry for **10** as compared to the Dreiding model. MM2 indicates more twisting of the ethane bridge, presumably to relieve torsional interactions. However, this results in a slight flattening of the six-membered ring, and so this model may not actually be "fully puckered" as suggested earlier.[8]

We may conclude that the calculations agree quite well with the experiment. Moreover, the model **5c** appears to provide NMR parameters for the study of "flattened" 1,4-dihydronaphthalenes. When taken with the data from previously studied "highly puckered" models, this should facilitate the conformational analysis of these systems. A value of 0.9 to 0.95 for the ratio of homoallylic coupling constants ($^5J_{cis}/^5J_{trans}$) appears to be a reliable indicator for shallow (α = 160–170°) boat conformations (assuming pseudoaxial substituent preference) in 1,4-dihydronaphthalenes. The value for **6** is a bit lower and this may indicate slightly more folding as suggested by the calculations. However, the NMR data reflect an average structure, and **6** may be further complicated by a shallow potential well which includes pe substituent conformers.

In any event, it appears that changes in ring puckering require relatively little energy and we may expect these systems to "breathe" in and out. Presumably this is the case with **8** where different rotational positions of the substituent correspond to significant changes in ring folding (10–15°), but with little difference in overall energy.

Experimental Section

Calculations were performed with the Allinger MM2 molecular mechanics program.[12] Aromatic carbon atoms were defined in terms of the optimum C=C bond length (1.397 Å) and the C=C force constant (8.067 mdyn Å).[4] In determining minima, bond rotation of substituents was carried out after the first geometry optimization to ensure the correct local or global minimum. NMR spectra were recorded on a Nicolet NT-300.

3,7,12a,12-Tetrahydropleiadene. 7,12-Dihydropleiadene[10] (0.5 g, 2.2 mmol) in 50 mL of THF (freshly distilled from benzophenone ketyl) was added to 100 mL of anhydrous ammonia at −78 °C. Sodium metal (11 mmol) was then added in small pieces, and stirring was continued for 20 min. The reaction mixture was then inverse quenched[9] into cooled aqueous NH_4Cl solution. Customary ether extraction and solvent removal furnished an off-white solid. Recrystallization from absolute ethanol furnished 0.4 g (80% yield), mp 109–111 °C. See Table II and Figure 2 for NMR spectrum.

Anal. Calcd for $C_{18}H_{16}$: C, 93.05; H, 6.95. Found: C, 92.88; H, 7.26.

Acknowledgment. We gratefully acknowledge support from the U.S. Department of Energy, Office of Basic Energy Science, and the Indiana University Computer Network. We also thank Professor K. B. Lipkowitz for his assistance with the molecular mechanics calculations, and Dr. Bruce Ray for assistance with the NMR spectra.