

factor of two of gluconeogenic flux and may require nonspecific aldolase or FDP anomerase activity. It is also possible that this step could limit the amount of cycling occurring in glycolysis if no anomerase activity were functioning. (3) These calculations may be altered by the effect of pH on anomerization rates, the availability of substrates for anomerization (i.e., whether they are protein-bound or free to anomerize), and whether the above values are maximal. These effects would probably serve to decrease spontaneous anomerization in relation to flux rates and make the anomerization steps more critical.

Thus the anomerization rates *in vitro* are not more than an order of magnitude faster than rates of metabolic flux. *In vivo* rates may be considerably slower. The similar rates, the pattern of coupled and uncoupled specificities, and the observed anomerase activities all suggest a role for these specificities in the partitioning and possibly rates of utilization of these anomeric substrate pools. The possibility arises that anomerase activities may be required and that these steps are potential regulatory points in addition to those already known. Whether this latter possibility is true awaits determination of anomerase activity levels and studies

investigating possible regulators of these activities.

Conclusion

The determination of the anomeric specificities of many of the enzymes of sugar metabolism allows the development of an overview of the reasons for and of the effects of these specificities. Enzyme reaction mechanisms must take into account these specificities, which may account for the anomeric preference observed. These mechanistic considerations or, additionally, possible regulatory needs may have given rise to enzymic development of these specificities. The specificities are well coupled after the rate-determining $F6P \rightleftharpoons FDP$ step in both glycolysis and gluconeogenesis but are uncoupled prior to this step. These uncoupled steps may act to inhibit cycling of F6P and FDP by imposition of an anomerization step between the enzymes. At the same time there is evidence from rate comparisons and observations of anomerase activities that anomerase activities acting on these steps may be required for maximal flux rates.

The authors wish to acknowledge support from the National Science Foundation, GB-40642, and the National Institutes of Health, GM-13306, AM16464, GM-20940, and GM-22378.

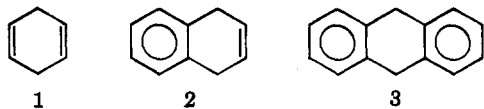
The Conformational Analysis of 1,4-Cyclohexadienes: 1,4-Dihydrobenzenes, 1,4-Dihydronaphthalenes, and 9,10-Dihydroanthracenes

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Received March 22, 1977

As evidenced by coverage in classic tests on stereochemistry,¹ much of our information concerning the conformational analysis of carbocyclic rings has traditionally been based on (and in some cases prejudiced by) the vast amount of data available for the cyclohexane ring system. In recent years, largely due to the continued development of NMR spectroscopic techniques, investigators such as Anet, Roberts, and others have provided reports concerned with a variety of conformational types.² As it turns out, the 1,4-cyclohexadiene ring system must be dealt with in three classes of compounds, 1,4-dihydrobenzenes (1), 1,4-



dihydronaphthalenes (2), and 9,10-dihydroanthracenes

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(3), and each of these systems has caused considerable controversy concerning some aspect of its stereochemistry. It would appear that most of these difficulties have now been resolved, and it is the purpose of this Account to convey an accurate review of our current understanding of these systems, as well as to provide a perspective concerning the emergence of a reasonable pattern of conformational behavior in spite of our efforts to hinder this development through preconceived notions and theoretical predictions.

The basic stereochemical concerns in these systems can be categorized in four general divisions. (1) *The shape of the 1,4-cyclohexadiene ring*: this includes the possibility of a planar ring or a boat-shaped conformation. (2) *The values of the homoallylic coupling constants*: the geometrically dependent long-range, five-bond coupling across the 1,4-cyclohexadiene ring. (3) *The behavior of substituents*: this includes the effect of substituents on the conformational preference of the ring, as well as the effect of the ring on rotational populations of the substituents. (4) *Dynamic processes*:

(1) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965, p 125.

(2) L. M. Jackman and F. A. Cotton, "Dynamic Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1975.

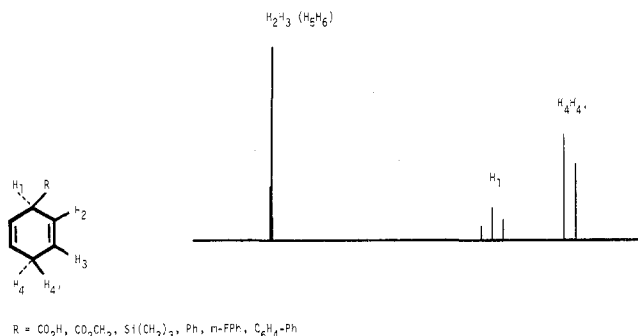
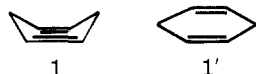


Figure 1. Typical NMR spectrum of various 1,4-dihydrobenzene derivatives (chemical shifts of H_1 and H_4+4' may be reversed in some cases).

these include primarily inversion processes from one boat-shaped ring to another.

1,4-Dihydrobenzenes³ (1,4-Cyclohexadienes)

For a number of years, the 1,4-cyclohexadiene ring system was generally considered to be boat-shaped (1)¹



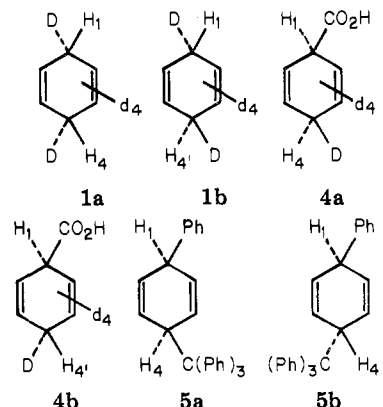
even though a planar structure was suggested in 1949 on the basis of vibrational spectral analysis.⁴ In the mid-sixties appeared a series of reports suggesting a planar structure for the parent compound (1') on the basis of Raman and infrared analysis⁵⁻⁷ as well as electron diffraction⁸ and NMR results.⁹ Subsequently, far-infrared analyses,¹⁰ force-field calculations,¹¹ and ab initio calculations¹² have supported this point of view. However, a conflicting electron-diffraction report suggesting a boat-shaped geometry for the parent diene,¹³ as well as semiempirical calculations¹⁴ and initial NMR results on substituted 1,4-cyclohexadienes¹⁵ that similarly concluded a boat-shaped geometry, have led to a more recent series of NMR studies concerning simple derivatives.

Although one might imagine that relatively simple compounds such as 1-substituted 1,4-dihydrobenzenes should be quite amenable to NMR analysis, this was not to be the case for the following reasons: (1) identical (or nearly identical) chemical shifts for nonequivalent

protons is the usual observation in these derivatives, and (2) unusually large (8–10 Hz) couplings were observed across the ring from one allylic proton to the other (homoallylic, 5-bond coupling).

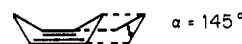
The first problem is illustrated by the typical NMR results for the allylic and vinylic regions of many monosubstituted 1,4-dihydrobenzenes (chemical shifts of H_1 and H_4+4' may be reversed depending on the value of R) depicted in Figure 1. Thus, H_4 and H_4' exhibit identical or nearly identical chemical shifts, and the same phenomenon is observed with $H_{2(4)}$ and $H_{3(5)}$. It appears quite remarkable that such accidental equivalence (or near equivalence) of chemical shifts should be observed in so many derivatives.

Since allylic and vicinal coupling constants can not be measured from these deceptively simple spectra, investigators (by necessity) attempted a solution to the problem by considering the ratio of cis and trans homoallylic coupling constants. Thus, Garbisch and Griffith⁹ reduced perdeuteriobenzene and obtained the two isomers **1a** and **1b** which provided homoallylic



coupling constants of $J_{cis} = 9.63$ and $J_{trans} = 8.04$ Hz. Using the Karplus theory, they calculated that $J_{cis} = J_{trans}$ for a planar ring and concluded that **1** must be nearly planar.^{9b} This prompted Perkins et al.,^{15a} who initially observed these long-range couplings in **5a** and **5b** ($J = 11$ and 7.5 Hz, respectively), to report their own calculations^{15b} which suggested that J_{cis} may be appreciably smaller than J_{trans} for a planar ring, and therefore that **1** must be puckered.¹⁶ Marshall et al.¹⁷ prepared **4a** and **4b** and found homoallylic coupling constants which were nearly identical (8.3 and 8.9 Hz). They reasoned that the J_{cis}/J_{trans} ratio would provide only a rough approximation of the degree of puckering, and since they expected that the substituent in **4** would cause puckering (with the carboxylate in the pseudo-equatorial position), they concluded that **1** and **4** were both puckered to about the same extent. Later, however, after comparing this data with that obtained from 1,4-dihydronaphthoic acid, Marshall and Folsom

(16) (a) They suggest an angle of $\sim 160^\circ$ between planes that result by a folding about the C_{1-4} axis. (b) We will use the terms "boat-shaped" or "highly puckered" to refer to a conformation that approximates the geometry resulting when these ring systems are constructed with Dreiding models. This provides an angle (see below) of $\approx 145^\circ$, which is identical



with the value found for the crystalline state of 9,10-dihydroanthracene.^{9a} For example:

(17) J. L. Marshall, K. C. Erickson, and T. K. Folsom, *J. Org. Chem.*, **35**, 2038 (1970).

(3) For consistency, the numbering system used in this paper will be based on 1,4-dihydrobenzene.

(4) H. Gerding and F. A. Haak, *Recl. Trav. Chim. Pays-Bas*, **68**, 293 (1949).

(5) B. J. Monostori and A. Weber, *J. Mol. Spectrosc.*, **12**, 129 (1964).

(6) H. D. Stidham, *Spectrochim. Acta*, **21** (1965).

(7) R. C. Lord, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1968, PHYS 74.

(8) G. Dallinga and L. H. Toneman, *J. Mol. Struct.*, **1**, 117 (1967).

(9) (a) E. W. Garbisch, Jr., and M. G. Griffith, *J. Am. Chem. Soc.*, **90**, 3590 (1968). (b) It should be noted, however, that a correction in one of the equations (E. W. Garbisch, Jr., and M. G. Griffith, *ibid.*, **92**, 1107 (1970)) subsequently led to a prediction of some degree of ring puckering ($\alpha \approx 165^\circ$; see ref 16b).

(10) J. Laane and R. C. Lord, *J. Mol. Spectrosc.*, **39**, 340 (1971).

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

(12) Recent ab initio calculations indicate a planar geometry for 1,4-cyclohexadiene itself: G. Ahlgren, B. Akerman and J. E. Backvall, *Tetrahedron Lett.*, 3501, (1975).

(13) H. Oberhammer and S. H. Bauer, *J. Am. Chem. Soc.*, **91**, 10 (1969).

(14) F. Herbstein, *J. Chem. Soc.*, 2292 (1959).

(15) (a) L. J. Durham, J. Studebaker, and M. J. Perkins, *Chem. Commun.*, 456 (1965); (b) D. J. Atkinson and M. J. Perkins, *Tetrahedron Lett.*, 2335 (1969).

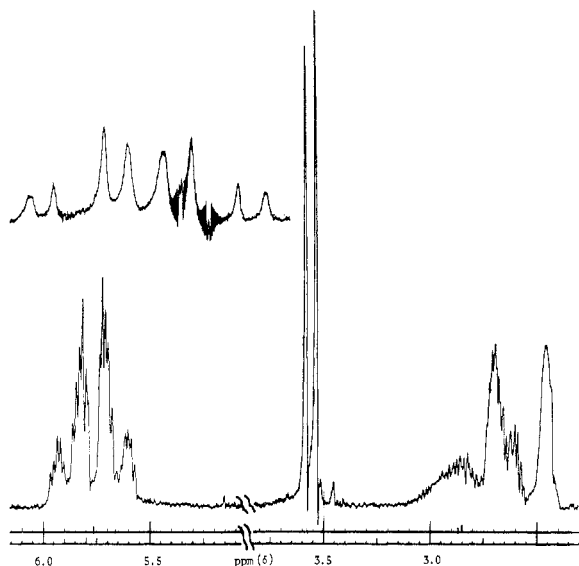


Figure 2. NMR spectrum of 1,4-dihydrobenzyl alcohol (7; ref 27); upper trace, H_4 and $H_{4'}$ in the presence of shift reagent with vinyl protons decoupled.

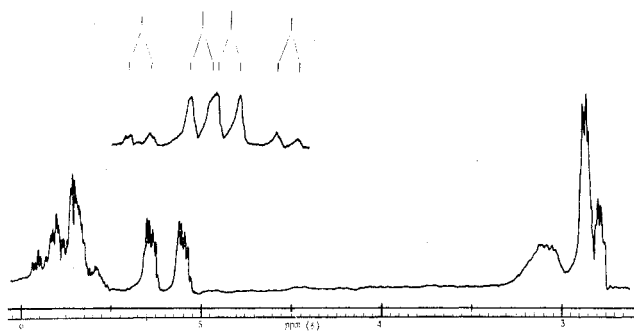
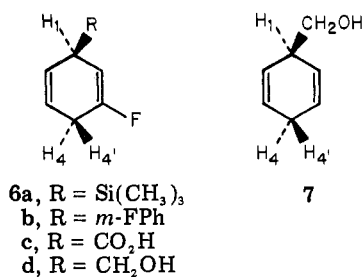


Figure 3. NMR spectrum of 3-fluoro-1,4-dihydrobenzyl- d_2 alcohol (8; ref 27); upper trace, H_4 and $H_{4'}$ in the presence of shift reagent with vinyl protons decoupled.

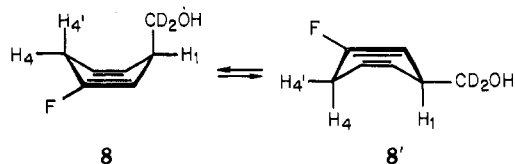
concluded that 4 is nearly planar.¹⁸

Our initial approach to the problem involved the preparation of the 3-fluoro-1,4-dihydrobenzene derivatives 6a, 6b, and 6c,¹⁹ with the expectation that the



geometrically dependent vicinal J_{HF} and J_{H_4F} couplings might be measured and thus might define the stereochemistry of the entire ring. These expectations were based on the fact that proton-fluorine coupling is generally much larger than hydrogen-hydrogen coupling as well as on the consideration that replacing hydrogen with a very electronegative substituent like fluorine would resolve the accidental chemical shift equivalences of H_4 and $H_{4'}$. Surprisingly, none of these compounds afforded useful NMR data due to chemical shift equivalencies of H_4 and $H_{4'}$ and to the apparent

lack of strong coupling to fluorine (except for H_2). We were finally successful in achieving the first complete NMR analysis of 1,4-dihydrobenzene derivatives by the use of shift reagents with the alcohols 6d and 7.²⁰ The NMR spectra of these compounds are shown in Figures 2 and 3, and it is apparent that H_4 and $H_{4'}$ again have identical (or nearly identical) chemical shifts, appearing together as somewhat complex doublets around 2.5 ppm. However, the use of $\text{Eu}(\text{fod})_3$, with simultaneous decoupling of the vinyl protons, led to the desired chemical shift separation of H_4 and $H_{4'}$ (Figures 2 and 3: upper trace), and the homoallylic coupling constants could be directly measured for both 6d ($J_{1,4} = 8.3$, $J_{1,4'} = 7.5$ Hz) and 7 ($J_{1,4} = 8.6$, $J_{1,4'} = 7.4$ Hz). With suitable decoupling techniques, all of the coupling constants could be measured, and it was found that $J_{3,4} = J_{3,4'}$ in both cases. Thus, H_3 must bisect the angle between H_4 and $H_{4'}$, indicating a planar conformation. A rapid boat



to boat ring-inversion process which would also lead to $J_{3,4} = J_{3,4'}$ was ruled out on the assumption that it would average in relatively large H_4F and $H_{4'}F$ coupling constants, since the H_4F and $H_{4'}F$ dihedral angles become small in 8 and 8', respectively (in 2-fluoropropene, for example, $J_{F,CH_3} = 16.0$ Hz).²¹ As it turns out, the coupling between F and $H_4, H_{4'}$ was too small to measure under the conditions of the experiment but was determined to be no greater than 2 Hz. The homoallylic J_{cis}/J_{trans} ratios of 1.11 for 6d and 1.16 for 7 would also seem to support a planar structure.²² As mentioned above, a Karplus treatment suggested near unity for a ratio of these values but was followed by calculations suggesting that in fact $J_{trans} > J_{cis}$ for the planar conformation.^{15b,23} However, the most recent INDO calculations suggest a value of $J_{cis}/J_{trans} = 1.29$ ^{24,25} for the planar arrangement, in excellent agreement with the results for 6d and 7. These results are also consistent with recent ab initio calculations^{26a} as well as with photoelectron spectroscopic results^{26b} which also indicate a planar structure for the parent diene.

Once it had been determined that certain 1,4-cyclohexadienes prefer a planar conformation, it became of interest to determine NMR parameters for a boat conformation so that if such a geometry be encountered (due to substitution, etc.) it might be recognized. To

(20) (a) J. W. Paschal and P. W. Rabideau, *J. Am. Chem. Soc.*, **96**, 272 (1974). (b) In cases involving shift reagents, at least one conformationally dependent coupling constant was determined to be equal both in the presence and absence of shift reagent to rule out the possibility of conformational changes caused by the $\text{Eu}(\text{fod})_3$.

(21) M. Y. DeWolf and J. D. Baldeschwieler, *J. Mol. Spectrosc.*, **13**, 344 (1964).

(22) See ref 20 for additional evidence supporting a planar structure.

(23) M. C. Grossel and M. J. Perkins, *J. Chem. Soc., Perkin Trans. 2*, 1544 (1975).

(24) P. W. Rabideau, J. W. Paschal, and J. L. Marshall, *J. Chem. Soc., Perkin Trans. 2*, 842 (1977).

(25) J. L. Marshall, L. G. Faehl, C. R. McDaniel, Jr., and N. D. Ledford, *J. Am. Chem. Soc.*, **99**, 321 (1977).

(26) (a) G. Ahlgren, B. Akermarck, and J. Backvall, *Tetrahedron Lett.*, 3501 (1975); (b) E. Heilbronner, F. Brogli, and E. Vogel, *J. Electron Spectrosc.*, **9**, 227 (1976).

(18) J. L. Marshall and T. K. Folsom, *J. Org. Chem.*, **37**, 1863 (1972).

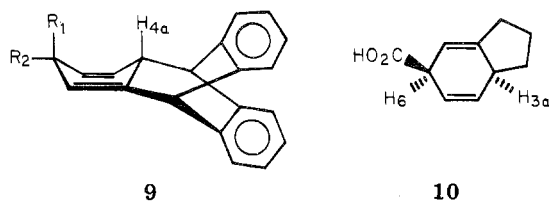
(19) P. W. Rabideau and J. Rosenbaum, unpublished results.

Table I
Average Values of Homoallylic Coupling Constants
in 1,4-Dihydrobenzenes for Planar and
Boat-Shaped Geometries^a

	Planar	Boat	
$J_{1,4}(\text{cis})$	8.3		12.0
$J_{1,4}'(\text{trans})$	7.5	4.7	

^a Values in Hz from 100 MHz data.²⁷

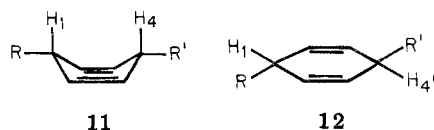
this end, the dihydrotriptycene derivatives *cis*-9 and *trans*-9 were prepared;²⁷ these incorporate a 1,4-cyclohexadiene ring forced into a boat-shaped geometry with a "normal" degree of puckering indicated by Dreiding models. The most striking feature of this



trans: $R_1 = \text{CO}_2\text{CH}_3$; $R_2 = \text{H}_2'$
cis: $R_1 = \text{H}_2$; $R_2 = \text{CO}_2\text{CH}_3$

NMR analysis is the very large homoallylic coupling constant ($J_{2',4a} = 12$ Hz) determined for the *cis* isomer. It is expected, however, that this value be maximized in (or near) a pseudoaxial/pseudoaxial relationship, and the value for *trans*-9 ($J_{2,4a} = 4.7$ Hz) is considerably smaller, as would be expected for the pseudoaxial/pseudoequatorial relationships.²⁸ It is interesting to note that an identical value ($J_{3a,6} = 12$ Hz) was found for the dihydroindan derivative 10, also providing a rigid boat-shaped ring.²³

Thus, NMR parameters have now been provided for planar and boat-shaped 1,4-cyclohexadienes, and it would appear as though the homoallylic coupling constants (summarized in Table I) might be the most useful for general conformational determinations since they have a substantial range and often are the most easily measured. In principle, these data may be used to determine the stereochemistry of additional derivatives. Little is known about the effects of substituents on the conformation of the 1,4-cyclohexadiene ring, but available evidence suggests¹⁷ that *cis*-1,4-disubstituted-1,4-dihydrobenzenes may be boat-shaped with substituents dipseudoequatorial since in 11, where R



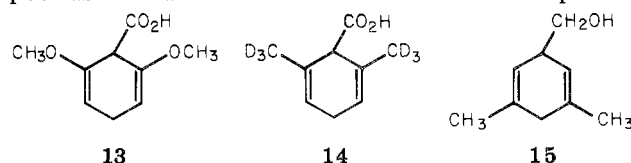
= Ph and $R' = \text{C}(\text{Ph})_3$, $J_{1,4} = 11$ Hz, which compares favorably with the value of 12 Hz found for the rigid dihydrotriptycene system (*cis*-9). In contrast, it would appear that, contrary to earlier beliefs, the planar structure is preferred in the *trans* compounds since 12 with $R = \text{Ph}$ and $R' = \text{C}(\text{Ph})_3$ shows $J_{1,4}' = 7.5$ Hz, which matches the values of 7.4 and 7.5 Hz found for the planar compounds 6d and 7. These results may be

(27) P. W. Rabideau, J. W. Paschal, and L. E. Patterson, *J. Am. Chem. Soc.*, **97**, 5700 (1975).

(28) M. Barfield and S. Sternhell, *J. Am. Chem. Soc.*, **94**, 1905 (1972).

rationalized as follows. In a planar ring, steric interactions may be expected across the ring between substituents in *cis* compounds whereas the boat conformation can accommodate both substituents in a pseudoequatorial environment. On the other hand, the location of one substituent in the pseudoequatorial position of a boat-shaped *trans* derivative forces the other to an unfavorable pseudoaxial position, whereas a planar geometry can accommodate both substituents with no 1,4-interactions whatsoever.

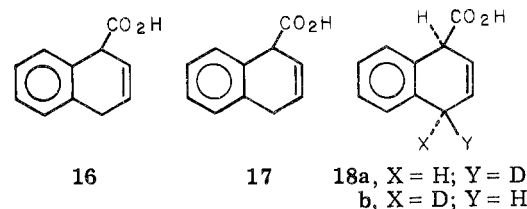
In an attempt to determine the effect of adjacent substituents, Grossel and Perkins²³ investigated compounds 13 and 14 and concluded that these compounds



are planar on the basis of the homoallylic coupling constants. The fact that the *trans* coupling was slightly larger than the *cis* agreed with their calculations for a planar structure, and they attributed the diminished values for both *cis* and *trans* coupling constants to a substituent effect using 2,5-dihydro-*m*-xylene as a model. However, the NMR analysis²⁴ of 15 indicates that the methyl groups have little effect on the homoallylic coupling constants, and it was concluded that 13 and 14 are indeed slightly puckered. In addition, INDO calculations indicated, contrary to the previous study, that $J_{\text{cis}} > J_{\text{trans}}$ and that diminished values of both coupling constants are to be expected for a slight puckering of the ring.

1,4-Dihydronaphthalenes

In the hope of uncovering some information that might help settle the controversy with 1,4-dihydrobenzoic acid and related compounds, Marshall and Folsom¹⁸ investigated the NMR behavior of 1,4-dihydronaphthoic acid (16) and concluded the structure



to be boat-shaped on the basis of vicinal and allylic coupling constants. Later, however, in view of accurately obtained values for the homoallylic coupling constants, a nearly planar conformation was preferred by this research group.²⁹ Although disputed by some,²⁷ at the time this observation appeared consistent with the previous suggestion that J_{trans} should be slightly larger than J_{cis} for a planar 1,4-cyclohexadiene.^{15b,23} More recently, however, measurements of three-bond carbon-carbon couplings in 17,³⁰ and the homoallylic carbon-proton couplings in 18a and 18b,²⁵ together with a recalculation that $J_{\text{cis}} > J_{\text{trans}}$ for a planar ring,^{24,25} have led to the general conclusion that 16 is somewhat puckered, but not truly boat-shaped as defined earlier

(29) J. L. Marshall, A. M. Ihrig, and P. N. Jenkins, *J. Org. Chem.*, **37**, 1863 (1972).

(30) J. L. Marshall, L. G. Faehl, A. M. Ihrig, and M. Barfield, *J. Am. Chem. Soc.*, **98**, 3406 (1976).

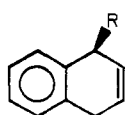
Table II
Homoallylic Coupling Constants for
1,4-Dihydronaphthalene Systems (in Hz)

Compound	Cis	Trans
16 ^a	3.8	4.4
19 ^b	3.5	3.7
20 ^b	1.8	3.0
21 ^b	8.5	
22 ^b		3.2

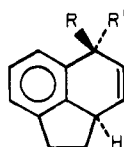
^a Data from ref 29. ^b Data from ref 31.

in this article (referred to as a "flattened boat" by Marshall).²⁵

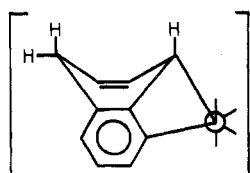
In view of the fact that a considerable amount of effort and controversy had revolved around a single compound (i.e., 16), it seemed reasonable to examine further examples. To this end, 1,4-dihydronaphthalenes were prepared with a relatively small substituent (19) and a large substituent (20), together with cis and trans model compounds (21 and 22) which provided a rigid



19, R = CD₂OH
20, R = C(CH₃)₂OH



21, R = CO₂CH₃;
R' = H
22, R = H; R' =
C(CH₃)₂OH

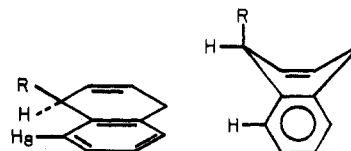


boat-shaped geometry (illustrated in brackets).³¹ Homoallylic coupling constants for the rigid derivatives were determined to be 8.5 Hz for the cis,dipseudoaxial relationship³² (21) and 3.2 for the trans,pseudoaxial/pseudoequatorial relationship (22). For purposes of comparison, the homoallylic coupling constants for these compounds, together with those for 16, are presented in Table II. Although one must be careful in drawing conclusions from small differences in coupling constants, the slight reduction of both values in going from 16 to 19 is consistent with a slight increase in puckering caused by the somewhat larger CD₂OH group as compared to CO₂H.³³ Compound 20, however, shows a substantial difference particularly in the cis homoallylic coupling constant, which has a value of 1.8 Hz. This relatively small value is indicative of a pseudoequatorial/pseudoequatorial relationship which would, of course, place the substituent in a pseudoaxial position. The value of 3.0 Hz for the trans coupling compares favorably with the model compound 22 and suggests that 20 adopts a complete boat-shaped conformation. The major steric factor is presumably the interaction of the large substituent with H₈. As illustrated, this effect is minimized by puckering of the

(31) P. W. Rabideau, E. G. Burkholder, M. J. Yates, and J. W. Paschal, *J. Am. Chem. Soc.*, **99**, 3596 (1977).

(32) The parent carboxylic acid of 21 was previously reported, and has an identical homoallylic coupling constant: M. C. Gossel and R. C. Hayward, *J. Chem. Soc., Perkin Trans. 2*, 851 (1976).

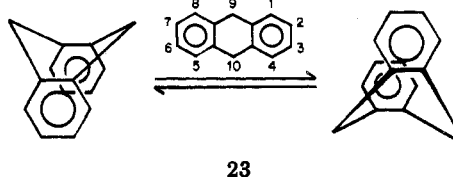
(33) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962.



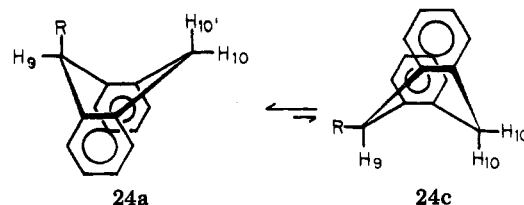
cyclohexadiene ring. Although such effects would not be present in 1,4-cyclohexadiene itself, it should be noted that the effect of a single large substituent in the parent diene has not been investigated.

9,10-Dihydroanthracene

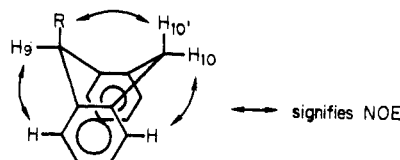
9,10-Dihydroanthracene (23) has been shown by x-ray



diffraction³⁴ to be nonplanar and is presumed to undergo rapid boat to boat ring inversion even at very low temperatures³⁵ (NMR time scale). However, it is clear that a single substituent at the 9-position can bias the equilibrium, and the position of this equilibrium has been a matter of some dispute. Although initial chemical studies suggested pseudoaxial preference (24a),³⁶ the pseudoequatorial conformation was pre-



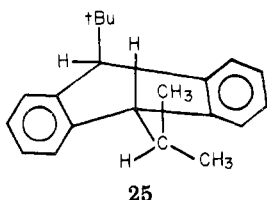
ferred later by NMR analysis,^{36,37} primarily due to a comparison with the NMR behavior of cyclohexane. The rationale was based on the fact that axial protons absorb at higher field than equatorial in cyclohexanes. With the assumption that this would also be the case in 9,10-dihydroanthracenes, H₁₀ was assigned to the higher field signal and H_{10'} to the lower field signal. Since H₉ absorbed at a position very close to that of H₁₀ and since it was assumed that H₁₀ was pseudoaxial, it was therefore concluded that H₉ was also pseudoaxial. This interpretation would, of course, place the substituent in the pseudoequatorial position, which is considered to be favored on steric grounds, again by comparison to the cyclohexane ring system. However, a subsequent NMR study³⁸ investigated nuclear Overhauser effects in 9-alkyl-9,10-dihydroanthracenes, and it was found that irradiation of the aromatic protons caused an increase in the integrated intensities of H₉ (~15%) and H₁₀ (5-10%). Furthermore, in the case of R = *t*-Bu,



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irradiation of the *t*-Bu group resulted in a 14% enhancement of H_{10} . Thus, these results firmly establish the pseudoaxial position of the substituent. In addition, homoallylic coupling constants were measured and estimates of conformational preferences were made using the values found for R = isopropyl (assumed to be 100% pseudoaxial). On this basis, the 9-methyl derivative was estimated to be 75% pseudoaxial, while 9-phenyl appears to be a 1:1 mixture. These results are in sharp contrast with the cyclohexane system which indicates much more steric crowding from phenyl than from methyl (conformational free-energy differences of 3.1 and 1.7, respectively).³³ It was suggested, however, that the phenyl group can lie parallel to the C-9,10 axis in 9-phenyl-**23** as the system inverts from **24a** to **24e**, thereby reducing the steric interactions with the peri positions. A similar theory was postulated to account for the relatively low barrier to ring inversion of 9,10-diphenyl-9,10-dihydrophenanthrene.³⁹

Although it had been reported that methoxy substituents on the aromatic rings slow the inversion process in dihydroanthracenes such that observation of distinct pseudoaxial and pseudoequatorial protons could be made by NMR,⁴⁰ this was later shown to be incorrect.⁴¹ In fact, the "freezing out" of a 9,10-dihydroanthracene has never been accomplished, even with large 9 and 10 substituents trans to one another. A possible reason for failure in detecting such an inversion is that two large substituents cause a flattening of the ring similar to the situation with 1,4-disubstituted 1,4-dihydrobenzenes which appear to be boat-shaped in the *cis* case, but flat with *trans* derivatives.²⁷ However, the NMR results for **25**^{39,42,43} indicate a nu-



clear Overhauser enhancement of 21% at H_{10} when the *t*-Bu group is irradiated, and this relatively large effect does not seem consistent with ring flattening which would move the *t*-Bu group and H_{10} further apart. Furthermore, a coupling constant of 2.6 Hz was observed between H_{10} and the isopropyl methine proton, and the fact that this represents an unusually small vicinal coupling (for a freely rotating group) led to the suggestion of a preferred rotational conformation for the isopropyl group as indicated in the figure. This again suggests that the isopropyl group is in a pseudo-equatorial position, and the observation of a NOE from the aryl protons to H_9 but not to H_{10} rules out a time average through ring inversion.

It appears that *cis*-9,10-dialkyl-9,10-dihydroanthracenes are boat-shaped with both alkyl groups in pseudoaxial positions. However, when a large alkyl

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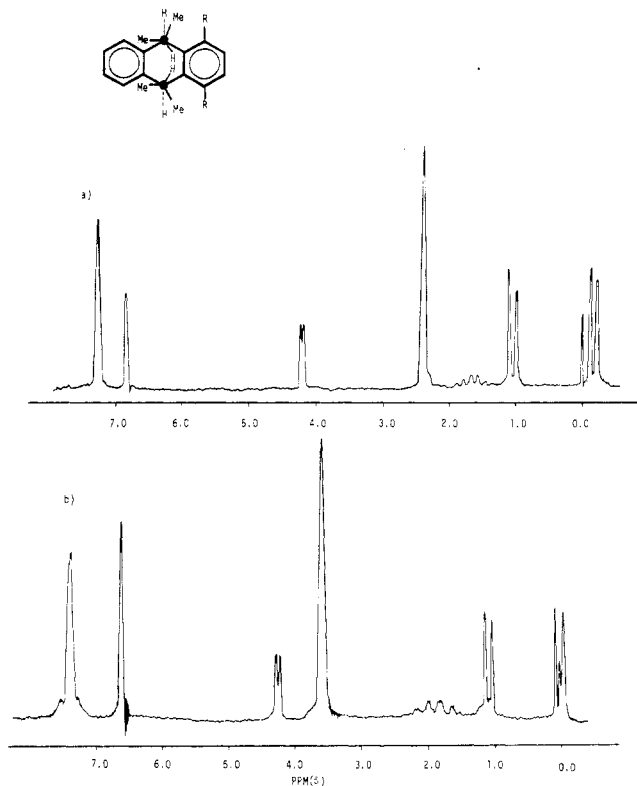
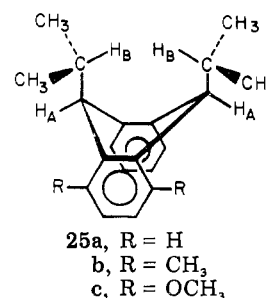


Figure 4. NMR spectra of *cis*-1,4-di-R-9,10-diisopropyl-9,10-dihydroanthracene.⁴⁶ (a) R = CH₃, (b) R = OCH₃. Suggested conformation illustrated.

group is involved, this apparently causes some flattening of the central ring as evidenced by the rather large homoallylic coupling constant of 1.3 Hz found for *cis*-9-*tert*-butyl-10-ethyl-**23** as compared to the more normal value of 0.3 observed with *cis*-9-isopropyl-10-ethyl-**23**.⁴² This crowding of *cis* substituents was first observed by Zieger,⁴⁴ who investigated the NMR spectrum of *cis*-9,10-diisopropyl-9,10-dihydroanthracene (**25a**) and suggested that the relatively large coupling



constant between the isopropyl methines and the 9 and 10 protons ($J_{AB} = 9.5$ Hz) indicated restricted rotation of the isopropyl groups leading to a large ($\sim 180^\circ$) dihedral angle between H_A and H_B . These results stimulated an interest in creating further dissymmetry in the molecule, since any restricted rotation should significantly enhance the chemical shift differences between the methyl groups in each of the isopropyl substituents (i.e., in addition to intrinsic asymmetry contributions).⁴⁵ To this end, **25b** and **25c** were prepared and do, in fact, show substantial chemical shift differences for the diastereotopic methyl groups.⁴⁶ It

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is interesting to note that not only is the chemical shift difference between the methyl pairs large (up to 74 Hz) but one methyl group pair is shifted to such high field so as to be upfield of Me_4Si (see Figure 4). This led to the suggestion that rotation of the isopropyl groups is restricted not only by opposition between 9 and 10 positions but also due to the 1 and 4 substituents, and this results in one pair of the methyl groups being positioned in the shielding region of the unsubstituted outer ring. Similar effects were noted for the analogous 9,10-diethyl and 9,10-dibenzyl derivatives, where the result could be confirmed by the significant differences in coupling constants between H_9 (and H_{10}) and each of the protons in the adjacent CH_2R group.

Conclusions

In retrospect, it is not difficult to understand why the 1,4-cyclohexadiene ring system has provided so many problems with regard to its conformational analysis. Although it now appears that 1,4-dihydrobenzenes, 1,4-dihydronaphthalenes, and 9,10-dihydroanthracenes prefer planar, flattened boat and boat-shaped conformations, respectively, when bearing a single small substituent (or presumably no substituent), it is evident that appropriate substitution can lead to wide variation in geometry. For example, the usually planar 1,4-dihydrobenzene adopts a boat conformation with cis-1,4-disubstitution, the nearly flattened 1,4-dihydro-

naphthalene becomes highly puckered with a single large substituent, and the normally boat-shaped 9,10-dihydroanthracene becomes flattened with two large cis substituents in the 9 and 10 positions. It is obvious that such diversity in structure cannot be approached without the firm establishment of characteristic parameters which, in this case, appear to be the homoallylic coupling constants. In fact, it has been primarily the delay in establishing theoretical predictions and empirical values for these relationships that has withheld the key to understanding the stereochemistry of this system.

Future studies will no doubt provide additional information concerning the effect of substitution (particularly multiple substitution) in these systems, especially in 1,4-cyclohexadienes and 1,4-dihydronaphthalenes where relatively little work has been done. We are also very interested in the possible application of ^{13}C NMR to the dynamic processes such as ring inversion in dialkyl-9,10-dihydroanthracenes which cannot be observed within the range of ^1H NMR. In any event, it is hoped that these studies on the cyclohexadiene ring systems may provide another pillar on which our general information about the conformational analysis of carbocyclic rings will rest.

I thank my co-workers, many of whom have been undergraduates, and also the following for financial support: Lilly Research Laboratories, Indianapolis, Ind., and the Donors of the Petroleum Research Fund, administered by the American Chemical Society.

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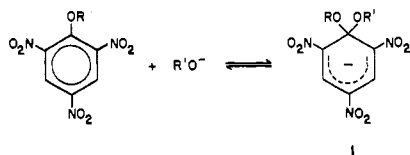
Kinetic Behavior of Short-Lived Anionic σ Complexes

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Received August 22, 1977

The interest in anionic σ complexes goes back to the beginning of the century when Jackson and Gazzolo¹ proposed structure 1 for the strongly colored species



which form when potassium alkoxides interact with picryl ethers. Experiments by Meisenheimer,² in which the same complex was isolated by treating either 2,4,6-trinitroanisole with ethanolic KOH or 2,4,6-trini-

trophenetole with methanolic KOH, lent strong support to structure 1; such complexes are therefore often referred to as "Meisenheimer complexes".

The advent of NMR spectroscopy led to a significant breakthrough in the structural identification of anionic σ complexes; after the publication of the first spectrum (1 with $\text{R} = \text{R}' = \text{CH}_3$) by Crampton and Gold,³ NMR quickly became the main tool in the structure determination of numerous such complexes.⁴

Rate studies were not reported before 1955 when Caldin and Long⁵ investigated the reaction of ethoxide ion with 1,3,5-trinitrobenzene and some other nitroaromatics. The main reason for the absence of earlier reports appears to be the high rates associated with most of these reactions and thus the necessity of using

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