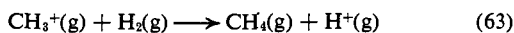


ence base. This can be demonstrated by comparing the methyl carbonium ion with the proton. The heats of formation of H^+ (367 kcal) and of CH_3^+ (262 kcal) at 25° are needed.⁶² We have the following gas phase reactions.



$$\Delta H^\circ = 87 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 104 \text{ kcal/mole at } 25^\circ$$



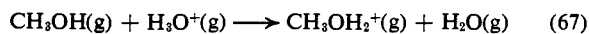
$$\Delta H^\circ = 115 \text{ kcal/mole at } 25^\circ$$



$$\Delta H^\circ = 100 \text{ kcal/mole at } 25^\circ$$

For the last equation we need the result that the proton affinity of methanol exceeds that of water by 15 kcal.⁶³

(62) D. D. Wagman, *et al.*, Technical Notes 270-1 and 270-2, National Bureau of Standards, Washington, D. C., Oct 1965, May 1966.
(63) M. S. B. Munson, *J. Am. Chem. Soc.*, **87**, 2305 (1965).



$$\Delta H^\circ = -15 \text{ kcal/mole at } 25^\circ$$

We have the result that H^+ is a stronger acid than CH_3^+ for all possible combinations of a strong, soft base (H^-), a weak, soft base (I^-), a strong, hard base (OH^-), and a weak, hard base (H_2O). These gas phase reactions are the best measure of intrinsic acid strength.

In passing, it may be noted that the effect of the methyl group, when replacing hydrogen, is to always increase the proton affinity of a base by about 15 kcal.⁶³ This is usually considered to be a base strengthening inductive effect, as in eq 67. It is more consistent to say that eq 67 is exothermic because H^+ , which is strong, prefers OH^- , which is strong. The weaker CH_3^+ is then left with the weaker base H_2O . In the same way CH_3NH_2 is a stronger base than NH_3



because H^+ binds NH_2^- strongly and the CH_3^+ is left with the weaker base NH_3 . As mentioned earlier, the methyl group can be electron donating by hyperconjugation but appears to have an electron-withdrawing inductive effect.

A Direct, Qualitative Determination of Nonchair and Distorted-Chair Conformations of Six-Membered Rings

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Abstract: The ratio (R) of the average $^3J_{trans}$ to the average $^3J_{cis}$ in six-membered rings of the type I has been found to be nearly independent of the electronegativity of X and Y. Hence, R becomes a direct measure of conformational effects. For molecules that exist in the perfect-chair conformation, R is close to 2.0. Deviations from this value are taken to indicate the presence of distortions from the ideal chair. A number of nonchair and distorted-chair conformations have thus been detected and described. For molecules in the flexible family, R is approximately 1.2 ± 0.2 . Certain deformations of the chair associated with the inclusion of sulfur or selenium atoms in the ring are characterized by $R \geq 2.75$. Although unsubstituted cyclohexanone assumes a slightly flattened chair ($R = 1.7$), the 4,4-disubstituted derivatives may be in the flexible conformation.

Seventy-five years after Sachse's postulation¹ of the existence of the chair and boat forms of cyclohexane, the generally less favored boat family of conformations has achieved sufficient status to warrant extensive reviewing.²⁻⁵ Three overlapping classes of "boat" forms may be enumerated: (1) compounds that are constrained to the boat conformation by geometrical considerations, such as bridging in norbornane, ring fusion in *trans,syn,trans*-perhydrophenanthrene, complexation in the piperazine-palladium chloride adduct,⁶ or hydrogen bonding in ψ -tropine;⁷ (2) ring

systems that assume the boat or twist-boat forms to relieve steric interactions of bulky substituents, as in *trans*-1,3-di-*t*-butylcyclohexane⁸ and a number of steroids; and (3) molecules such as 1,4-cyclohexanedione⁹ that appear to have an "inherent" preference for the boat family.¹⁰ We shall be exclusively interested in the third class, which has become populated only recently. Membership in this group has generally been restricted to molecules containing more than one trigonally hybridized atom: 1,4-cyclohexanedione,^{8,9,11-13}

- (1) H. Sachse, *Ber.*, **23**, 1363 (1890).
- (2) J. Levisalles, *Bull. Soc. Chim. France*, 551 (1960).
- (3) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962).
- (4) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965, p 275 ff.
- (5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 469 ff.
- (6) O. Hassel and B. F. Pedersen, *Proc. Chem. Soc.*, 394 (1960).
- (7) G. Fodor and K. Nador, *Nature*, **169**, 462 (1952).




(8) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960).

(9) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *ibid.*, **88**, 2999 (1966).

(10) By the "boat family" we mean the whole spectrum of "pseudo rotamers." A discussion of the various conformational arrangements is given in ref 5, pp 472-473. In the present context, we shall use the term "boat" for $\theta = 0, 60, \text{ or } 120^\circ$, "twist-boat" for $\theta = 30, 90, \text{ or } 150^\circ$, and "flexible form" or "boat family" to indicate the continuous conformational set of interconverting pseudo rotamers.

(11) P. Groth and O. Hassel, *Acta Chem. Scand.*, **18**, 923 (1964).

Table I. Average Vicinal Coupling Constants in Six-Membered Rings (I)

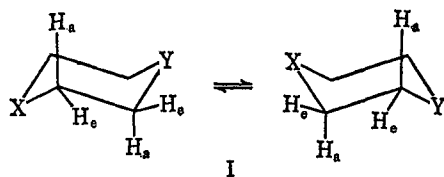
	X	Y	J_{trans} , Hz	J_{cis} , Hz	$R =$ J_{trans}/J_{cis}	Source
1.	O	O	6.11 ± 0.05	2.78 ± 0.05	2.20	a
	NH	O	6.66	3.04	2.19	b
	NCH ₃	O	6.65	3.05	2.18	b
	NH	NH	6.54	3.04	2.15	a
	C(CH ₃) ₂	C(CH ₃) ₂	8.27^c	4.03^c	2.05^c	a
			8.34^d	4.30^d	1.94^d	a
			8.82	4.59	1.92	a
2.	S	O	7.35	2.65	2.77	b
	S	S	8.11	2.40	3.38	a
	Se	Se	8.49	2.43	3.49	a
3.	C=O	C=O	8.05	6.23	1.29	a
	C=NOH	C=NOH	7.3	6.5	1.12	e
	C=CH ₂	C=CH ₂	7.52	5.31	1.42	a
4.	C=O'	CD ₂	8.61	5.01	1.72	a
	C=O'	C(CH ₃) ₂	7.81	5.46	1.43	a
	C=O', ^o	C(C ₆ H ₅) ₂	7.78	5.44	1.43	a
	C=O'		8.08	6.25	1.29	a

^a This work. ^b Adapted from data in ref 22. ^c From the carbon-13 satellites at room temperature. ^d From the low-temperature, slow-inversion spectrum; cf., H. Friebolin, W. Faist, H. G. Schmid, and S. Kabuss, *Tetrahedron Letters*, 1317 (1966). ^e Reference 14. ^f The differences between the geminal coupling constants of the α - and β -methylene groups are 1.4, 0.0, 0.0, and 1.2 Hz, in the order given in the table. The second and third values are approximate. ^o Analysis of both the 60- and 100-MHz spectra was performed for this compound. The author is extremely grateful to Professor M. R. Willcott, University of Houston, for supplying the 100-MHz spectrum.

its dioxime,^{14,15} and possibly 1,4-dimethylenecyclohexane.^{16,17} Previous studies have generally concentrated on single systems, utilizing infrared and Raman spectroscopy,⁹ dipole moments,⁹ or X-ray crystallography.^{11,12,15} The object of the present study is to develop a general method for determining the existence and nature of nonchair and distorted-chair conformations in six-membered rings by means of nuclear magnetic resonance spectroscopy. The goals are twofold: to reach as many systems as possible and to describe the nature of the distortions as accurately as possible.

Results and Discussion

Consideration of the chair conformation of the general molecule I reveals that two couplings between the ring protons may be measured when ring inversion is rapid.^{19,20}



- (12) A. Mossel and C. Romers, *Acta Cryst.*, **17**, 1217 (1964).
 (13) C.-Y. Chen and R. J. W. LeFèvre, *Australian J. Chem.*, **16**, 917 (1963).
 (14) H. Saito and K. Nukada, *J. Mol. Spectry.*, **18**, 355 (1965).
 (15) P. Groth, *Acta Chem. Scand.*, **20**, 579 (1966).
 (16) F. Lautenschlaeger and G. F. Wright, *Can. J. Chem.*, **41**, 1972 (1963).
 (17) "Inherent" boat family preference has also been suggested for *cis*-1,4-dithiane 1,4-dioxide¹⁴ and various piperazines.¹⁸
 (18) M. V. George and G. F. Wright, *J. Am. Chem. Soc.*, **80**, 1200 (1958).
 (19) If X = Y, these couplings are measured from the carbon-13 satellites of the main peak.
 (20) We shall be concerned for the present with molecules of the type I, in which X and Y are symmetrical groups such as O, S, C(CH₃)₂, C=O, and NR (inverting). Since low-temperature nmr methods have failed to "freeze" out ring inversion in most of these systems,²¹ any general criterion should not rely on observation of the spectral properties at slow rates of ring inversion. Our analysis is therefore based on the averaged coupling constants, J_{trans} and J_{cis} .

$$J_{trans} = \frac{1}{2}(J_{aa} + J_{ee}) \quad (1)$$

$$J_{cis} = \frac{1}{2}(J_{ae} + J_{ea}) = J_{ae} \quad (2)$$

Smith and Shoulders^{22,23} have reported quantities akin to J_{cis} and J_{trans} . We display in Table I data from our laboratories, supplemented by some literature values,^{14,22} on which our analysis will be based.

When the chair conformation and all the various conformational extremes in the boat family are considered, there is a wide range of variability in the stereochemical relationships between the ring protons. The work of Karplus^{24,25} has served as a general guideline for organic chemists in search of stereochemical information from nmr spectra. Our discussion will rely *qualitatively* on the Karplus relationship. The dangers of using *quantitative* correlations to obtain precise dihedral angles are well known. The coupling constants, J_{aa} , J_{ee} , and J_{ae} , for the ideal chair correspond to dihedral angles of 180, 60, and 60°, respectively. By examination of the effect that a given distortion has on these dihedral angles, we will predict the direction of the corresponding effect on each coupling constant. These predictions will be compared with the observed values of J_{trans} and J_{cis} , and conclusions will be drawn concerning the nature of the actual distortions.

The first six entries in Table I (group 1) undoubtedly assume a conformation quite close to the ideal chair.^{26,27} The values of J_{trans} and J_{cis} for these compounds will therefore serve as a standard of reference in the discussion of the properties of distorted molecules. Al-

- (21) R. K. Harris and R. A. Spragg, *Chem. Commun.*, 314 (1966).
 (22) W. B. Smith and B. A. Shoulders, *J. Phys. Chem.*, **69**, 579 (1965).
 (23) These authors assume that J_{ee} equals J_{aa} , and thereby report "exact" values of J_{aa} calculated from eq 1. We do not think this assumption is wholly justified, so we prefer to discuss the averaged couplings.
 (24) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
 (25) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
 (26) O. Hassel and H. Viervoll, *Acta Chem. Scand.*, **1**, 149 (1947).
 (27) P. Anderson and O. Hassel, *ibid.*, **3**, 1180 (1949).

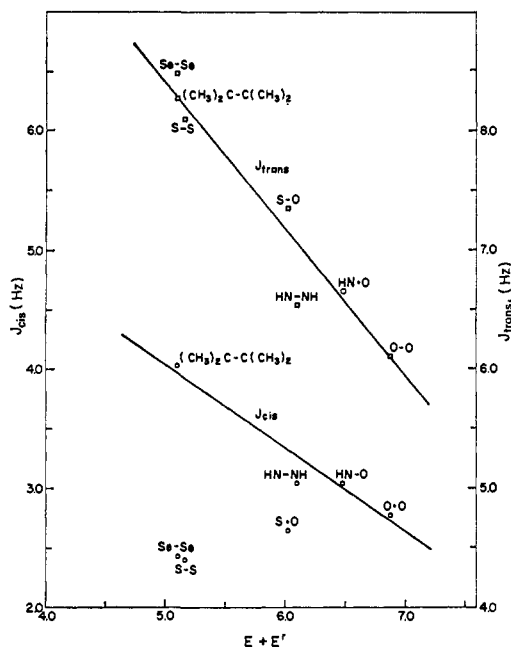


Figure 1. The vicinal coupling constants, J_{trans} and J_{cis} , of compounds of the type I as a function of the sum of the electronegativities of the atoms in the 1 and 4 positions.

though there is a pronounced drift in the values of J_{trans} and J_{cis} in group 1, their ratio (R) is constant to within 10–15%.

$$R = J_{trans}/J_{cis} \cong 2.0$$

Karplus²⁵ discusses four variables that can alter $J_{vicinal}$: (1) the H–C–C–H dihedral angle, (2) the electronegativity of the groups attached to carbon, (3) C–C bond length, and (4) the H–C–C angle. The nature of our system assures the constancy of variables 3 and 4. The effects of 1 and 2 on J_{trans} , J_{cis} , and R will be scrutinized in order to draw conclusions and make predictions concerning conformational distortions. Abraham²⁸ and others^{25,29,30} have established that an increase in the electronegativity of substituents will decrease the coupling constant. Abraham has also stated³¹ that the staggered nature of the lone pairs on X or Y in I precludes the special effects associated with eclipsing.³² Furthermore, since we are treating symmetrical X and Y groups²⁰ on rings that are inverting rapidly, each ring proton spends an equal amount of time in the axial and the equatorial positions. Thus, the consequences of the electronegativity changes of X and Y should be nearly identical for both $1/2(J_{aa} + J_{ee})$ and J_{ae} . These effects should therefore cancel or at least be minimized in the ratio R . Its constancy among the members of group 1 corroborates this prediction. Further substantiation is obtained from Figure 1, which plots the sum of the Pauling–Allred electronegativities³³ of X and Y vs. J_{trans} (upper curve, right ordinate) and J_{cis} (lower curve, left ordinate) for the members of groups 1 and 2. The curves described by the group 1 compounds possess a nearly constant

(28) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1964).

(29) K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963).

(30) J. D. Graham and M. T. Rogers, *ibid.*, **84**, 2249 (1962).

(31) R. J. Abraham and W. A. Thomas, *Chem. Commun.*, 431 (1965).







(32) M. Anteunis, *Bull. Soc. Chim. Belges*, **75**, 413 (1966).

(33) A. L. Allred, *J. Inorg. Nucl. Chem.*, **17**, 215 (1961).

ratio of slopes, and would appear to intersect close to $J_{trans} = J_{cis} = 0$.³⁴ It is our contention that deviations from constancy, as reflected in variations of R , are caused by distortions from the perfect chair. Thus, the ratio of coupling constants, R , in which electronegativity effects (variable 2) are minimized, is a *direct* measure of the conformational effect (variable 1), deviations from $R \cong 2$ being indicative of distortions from the chair conformation. In the following discussion, we shall consider distortions of the members of groups 2, 3, and 4 in terms of the deviations of J_{trans} , J_{cis} , and R from the ideal-chair values.

Table II reviews a number of possible distortions. The boat form with eclipsed interactions ($\theta = 0^\circ$) is omitted, for it is undoubtedly of high energy. A de-

Table II. Changes in Dihedral Angles and Coupling Constants Caused by Distortions from the Ideal Chair

Conformation	φ_{aa} , deg	J_{aa}	φ_{ee} , deg	J_{ee}	φ_{ae} , deg	J_{ae}
A, chair:	180 ^a	<i>a</i>	60 ^a	<i>a</i>	60 ^a	<i>a</i>
						
B, boat, $\theta = 60, 120^\circ$: ^c	0 ^b	0	0	0	0	0
						
C, twist-boat, $\theta = 90^\circ$:	0	0	0	0	0	0
						
D, twist-boat, $\theta = 30, 150^\circ$:	–	–	+	–	–	+
						
E, flattened chair:	–	–	+	–	–	+
						
F, the sulfur distortion:	–	–	–	+	+	–
						

^a These entries are the standards to which the changes in the values for the other conformations are referred. ^b 0 indicates no change from the value of φ or J in the ideal chair A; – indicates a decrease, and + an increase. ^c The pseudo-rotation parameter, θ , is described in ref 5 and 9.

crease in φ_{aa} (the only possibility) will decrease J_{aa} (Figure 2), whereas a decrease in φ_{ee} (φ_{ae}) will increase J_{ee} (J_{ae}). An increase in φ_{ee} or φ_{ae} should in turn cause a decrease in the corresponding coupling constants. The changes in φ caused by these distortions and the corresponding changes in J are listed in Table II. These predictions follow directly from the form of the Karplus curve (Figure 2).

We are now in a position to examine the probable distortions in groups 2, 3, and 4 in terms of R . The second group of compounds in Table I, those containing sulfur and selenium, are considered to exist in the chair conformation.^{28,35} Consideration of Drieding and

(34) Both curves intersect the x axis near $E + E' = 11.3$.

(35) R. E. Marsh and J. D. McCullough, *J. Am. Chem. Soc.*, **73**, 1106 (1951).

framework molecular models discloses the existence of two important distortions from the perfect chair. The lengthening of the C-X bonds³⁶ spreads the molecule apart, whereas the reduced C-X-C angle pushes the atom X further up and out of the plane of the four carbon atoms. The result of the latter distortion (use of models is recommended at this point) is to bring the axial protons slightly closer together, an effect which is made possible by the spreading distortion. Then, since φ_{aa} and φ_{ee} both decrease, J_{aa} decreases and J_{ee} increases (see Table II), resulting in no over-all conformational effect on the average J_{trans} . For this reason, the normal electronegativity change maintains J_{trans} on the line in Figure 1. On the other hand, the decrease in $J_{cis} = J_{ae}$ caused by the increase in φ_{ae} is in no way compensated for, so the group-2 compounds fall well below the J_{cis} line of Figure 1. The over-all effect of this distortion (F) on $R = J_{trans}/J_{cis}$ is, therefore, an increase, since the denominator is reduced, the numerator is unchanged, and both are influenced in an equivalent manner by the electronegativity factor.

The members of group 3 have previously been established to exist in the flexible conformation.^{8,9,11-16} For this group, there is a significant and consistent reduction of R from the value of 2.0 for the perfect chair (group 1). We must therefore inquire into the nature of the distortion that can give rise to an R value of 1.1-1.4. Both the boat (B, $\theta = 60, 120^\circ$) and the twist-boat (C, $\theta = 90^\circ$), favored by Allinger for 1,4-cyclohexanedione,⁴ have ring protons with dihedral angles (Table II) identical with those of the undistorted chair (180, 60, 60°). Furthermore, pseudo rotation from 60 to 120° does not alter this geometrical relationship at any point in the itinerary. Only if the pseudo rotation extends closer to $\theta = 30$ and 150° (twist-boat D) will deviations from chair-like coupling constants be expected. For the twist-boat D, φ_{aa} decreases and φ_{ee} increases, thus decreasing both components of J_{trans} . φ_{ae} , however, decreases substantially, thus giving rise to an increase in J_{cis} (Table II). The R value for a flexible family that includes forms B, C, and D would, therefore, have a somewhat smaller numerator (J_{trans}) and a larger denominator (J_{cis}) than the ideal chair for an over-all decrease, as observed.³⁷ It is particularly interesting to compare 1,4-cyclohexanedione (group 3) with its bisethylene ketal (group 1). The variations in both of the coupling constants, as well as their ratio, follow our predictions precisely.

The cyclohexanones (group 4) pose problems that go beyond the present analysis. Cyclohexanone itself, deuterated in the 4 position, has an R value of 1.72, somewhat below that of the perfect chair. This small perturbation in R probably results from a slight flattening of the carbonyl end of the ring.³⁸ Such a deformation (E in Table II) would decrease J_{aa} and J_{ee} (and hence J_{trans}), while increasing J_{ae} (J_{cis}). Therefore, since R would undergo a slight decrease, the effect is in the same direction but not so large as that of the flexible family (B, C, D).

The values of R for the 4,4-disubstituted derivatives (1.29-1.43) are in the same range as those of group 3. One might, therefore, conclude that these systems exist

(36) Reference 4, p 300.

(37) An alternative explanation for the decrease in R is given below.

(38) W. Moffitt, R. B. Woodward, A. Moscovitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

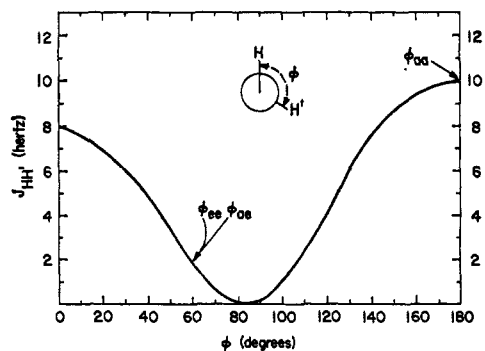


Figure 2. The vicinal coupling constant, $J_{HH'}$, as a function of dihedral angle, ϕ (following Karplus).

in the flexible conformation. This conclusion is not unreasonable, since the flexible form is already of relatively low energy for cyclohexanones,⁹ and, in these cases, interactions of the axial substituent that are necessarily present in the chair form would be relieved. Alternatively, the decrease in R might be due to a more pronounced flattening of the carbonyl portion of the ring than is present in cyclohexanone.³⁹ Since good model systems for conformation E are not available, it is not yet possible to state whether the flattening distortion could cause such a large perturbation in R . This ambiguity cannot be formally denied without crystallographic evidence. In either case, the R method indicates the presence of severe distortions in the 4,4 derivatives, not only from the perfect chair but even with respect to unsubstituted cyclohexanone. It is doubtful that this ambiguity carries over to the molecules with two sp^2 atoms in the ring (group 3). If the decrease in the R value of the members of this group had arisen solely because of flattening of both ends of the ring, an additive effect on R in going from zero to one to two sp^2 atoms should have been observed. Rather, two groupings, exclusive of the sulfur compounds, are observed, those with all sp^3 atoms (group 1) and those with either one or two sp^2 atoms (groups 3 and 4). Absence of an additive effect is particularly evident in the series 1,4-cyclohexanedione:ketal:bisketal (2 sp^2 : sp^2 - sp^3 :2 sp^3).

In summary, we believe that use of the ratio R in systems I removes the major ambiguities associated with electronegativity changes. Therefore, according to its deviations from the perfect-chair value of 2.0, R will be a valid indication of nonchair and distorted-chair conformations. By adding slowly to the complexity of the systems and ascertaining at each step if the use of the R criterion is still valid, it may be possible to determine the presence of nonchair distortions in a vast assembly of structural cases. At each step of complexity, however, it must be kept in mind that re-assessment and alteration of the criterion may be necessary. These extensions are in progress.

Experimental Section

Gas-liquid partition chromatography experiments were performed on an F & M Model 700 vapor fractometer equipped for both analytical and preparative work. Mass spectral analyses were carried out by the Morgan-Schaffer Corp., Montreal, Quebec. Proton magnetic resonance spectra were measured on temperature-

(39) N. L. Allinger and M. A. DeRooge, *ibid.*, **84**, 4561 (1962).

adaptable Varian Associates Model A-60 and A-60A⁴⁰ spectrometers. Spectral analyses were carried out on the CDC-3400 computer equipped with the Calcomp plotting accessory. Analyses followed the method of Swalen and Reilly,⁴¹ with preliminary trial solutions obtained from the Wiberg program.⁴² Carbon-13 satellite spectra were used in the analysis of the symmetrical compounds ($X = Y$ in I).

Materials. 1,4-Dithiane and 1,4-cyclohexanedione were supplied by Aldrich Chemical Co.; 1,4-dioxane was obtained from J. T. Baker Chemical Co.; and piperazine was obtained from Distillation Products Industries. All of these materials were used without further purification.

1,1,4,4-Tetramethylcyclohexane was prepared according to the method of Grant, Gleason, and Bushweller.⁴³

1,4-Diselenane was prepared following the method of Gould and Burlant.⁴⁴

1,4-Dimethylenecyclohexane was prepared by the method of Ball.⁴⁵

Ethylene Ketal and Bisethylene Ketal of 1,4-Cyclohexanedione. In a 100-ml, three-necked, round-bottomed flask equipped with a Barrett water trap and a reflux condenser were placed 55 ml of benzene and 2.2 g of ethylene glycol. Approximately 20 ml of benzene was distilled into the trap in order to dry the solution. 1,4-Cyclohexanedione (4 g) was added, and the mixture was refluxed for 8 hr. Approximately 0.5 ml of water was removed to the trap during this period. Barium oxide was added, the reaction mixture was filtered, and the precipitate was washed with benzene. The solvent was removed by rotary evaporation at reduced pressure. The residue contained approximately 1:2:1 ketone to ketal to bisketal according to nmr spectroscopy. The products were separated by column chromatography over 150 g of silica gel with benzene-ether mixtures as the eluent. Crystalline samples of the ketal and bisketal obtained in this way were quite pure by nmr spectroscopy.

4,4-Dimethylcyclohexanone and 4,4-diphenylcyclohexanone were kindly supplied to the author by Mr. J. G. Strong, Northwestern University.

Dimethyl Malonate-2,2-*d*₂. A mixture of methanol-*d* (33 g), sodium (0.5 g), and dimethyl malonate (70 g) was allowed to reflux for 24 hr. The methanol was removed by distillation, 33 g of methanol-*d* was added, and the mixture was refluxed for an additional 24 hr. This process was carried out a total of six times. Finally, deuterium oxide was added to dissolve the salts. The layers were separated, and the organic portion was washed three times with deuterium oxide and dried over magnesium sulfate. After removal of the drying agent and the solvent, the product was distilled to give 76% of dimethyl malonate fully deuterated in the 2 position.

1,3-Propanediol-2,2-*d*₂. Dimethyl malonate-*d*₂ (105 g, 0.78 mole) in anhydrous ether (170 ml) was added dropwise to 38 g (1 mole) of lithium aluminum hydride in 1250 ml of ether. The mixture was refluxed for 6 hr and then stirred magnetically overnight. Water (144 ml) containing sodium hydroxide (6.8 g) was added over a 4-hr period. The mixture was filtered, and the yellow precipitate was washed liberally with ether and returned to the reaction flask. Tetrahydrofuran (600 ml) was added, and the mixture was brought to reflux for 30 min. The precipitate was again filtered and washed. The entire process of refluxing with tetrahydrofuran was repeated twice more. The organics were concentrated to give 38 g (0.44 mole, 63%) of 1,3-propanediol-2,2-*d*₂.

1,3-Dibromopropane-2,2-*d*₂ was prepared by the action of phosphorus tribromide (150 g) on 1,3-propanediol-*d*₂ (38 g, 0.49 mole). The components were mixed at 0° and permitted to react slowly as the temperature rose. The mixture was refluxed for 8 hr, and

(40) The author is indebted to Professor J. W. Wilt for the use of the A-60A at Loyola University, Chicago, Ill.

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(44) E. S. Gould and W. Burlant, *J. Am. Chem. Soc.*, **78**, 5825 (1956).

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50 ml of water was added. A small amount of orange precipitate was removed by filtration. The filtrate was extracted five times with methylene chloride, and the combined organic portions were dried over magnesium sulfate. 1,3-Dibromopropane-*d*₂ (63.5 g, 0.31 mole, 63%) was isolated by distillation at the pressure of the aspirator.

Glutaric-3,3-*d*₂ acid (29.5 g, 0.22 mole) was prepared by way of glutaronitrile-*d*₂ in an over-all yield of 71% according to the method described by Vogel.⁴⁶

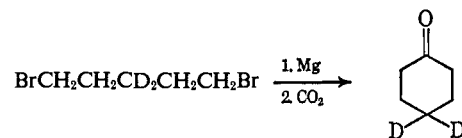
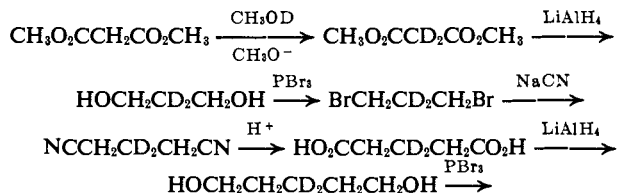
1,5-Dibromopentane-3,3-*d*₂ (27.6 g, 0.12 mole) was obtained from glutaric-3,3-*d*₂ acid by way of the diol with an over-all yield of 55% in a manner described previously.⁴⁷

Cyclohexanone-4,4-*d*₂. To a 100-ml, three-necked, round-bottomed flask equipped with a magnetic stirrer, dropping funnel, and reflux condenser was added 0.55 g of magnesium together with a crystal of iodine. The flask was flamed out, and 2.5 g of 1,5-dibromopentane-3,3-*d*₂ in 25 ml of ether freshly distilled from lithium aluminum hydride was added slowly. When the Grignard reaction had run its course, Dry Ice, in a separate flask, was allowed to evaporate in such a way that the effluent gas bubbled into the reaction mixture. Ice was dropped in to hydrolyze the complexes. The mixture was filtered, and the layers were separated. The aqueous portion was extracted twice with ether. The combined organics were extracted three times with dilute sodium hydroxide in order to remove any adipic acid. The ether was distilled from the organics to leave a residue (0.66 g) of cyclohexanone, which was purified by preparative vapor phase chromatography. According to the mass spectrum, there was >85% cyclohexanone-*d*₂.⁴⁸

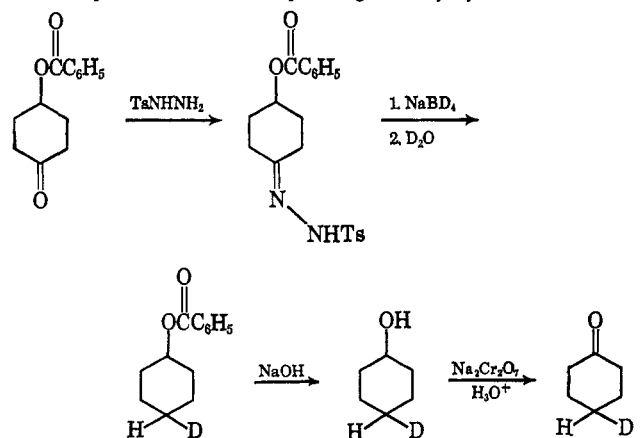
(46) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green, and Co., London, 1955, pp 409-410, 491.

(47) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).

(48) This synthetic pathway may be summarized as follows



Another plausible reaction sequence gave only cyclohexanone-*d*₁.



Since fully deuterated intermediates were used, the 4-proton must come from the proton on nitrogen in the tosyl hydrazone. Such a mechanism has, in fact, been proposed by L. Caglioti, *Tetrahedron*, **22**, 487 (1966).