

58°. Although the calorimetric measurements were made on ortho esters at concentrations of 0.02–0.05 *M*, when no side reactions could be detected in such reaction solutions, concentrations around 0.1 *M* were used for glpc analysis. A 6- μ l sample of a reaction mixture from trimethyl orthoformate gave no observable peak for dimethyl ether; although if such a peak had had 0.3% of the area of the methyl formate peak, it would have been 1 mm high and 2 mm wide and would have been clearly visible. (The retention time was well separated from that of other peaks and the noise level was on the order of 0.2 mm.) Analogous results were obtained with tetramethyl orthocarbonate. With trimethyl orthoacetate there appeared to be a peak about 0.2 mm high at the retention time for dimethyl ether. The reaction mixture from the hydrolysis of

triethyl orthoformate showed no peak at the retention time for diethyl ether although addition of enough diethyl ether to correspond to a 1% yield gave a peak 4.5 mm high and 3 mm wide. On the basis of this evidence the hydrolysis of all the ortho esters was assumed to proceed without side reactions.

The extent of the hydrolysis to formic acid that took place during the hydrolysis of trimethyl orthoformate was determined by potentiometric hydrolysis.

Acknowledgment. We are indebted to Professors E. M. Arnett and F. E. Rogers for advice and to Dr. F. C. Kokesh for building and testing the calorimeter system.

A Comparative Study of the Rates and Mechanisms of Conformational Interconversion in Derivatives of Cyclohexanone and Methylenecyclohexane¹

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Abstract: The cyclohexanone derivatives **2a**, **3a**, **4a**, and **5a** were studied by variable temperature pmr and their behavior was compared to that of the analogous methylenecyclohexane derivatives **2b**, **3b**, **4b**, and **5b**. All compounds except **4a** gave temperature-dependent spectra which by means of computer spectral simulations allowed the determination of the activation parameters characteristic of chair inversion. An interconversion map which allows a simple description of all inversion mechanisms possible is devised and the different trends observed for the two series of compounds are explained in terms of a mechanism in which the most energetical conformation of the inversion profile is different for each series.

The investigation of the conformational properties of cyclic and acyclic molecules has been considered a very important area of fundamental chemical experimentation^{2–7} and, among the systems studied, six-membered rings, by virtue of their abundance and importance as structural units of many natural products, have received greatest attention. Furthermore, nuclear magnetic resonance has revealed itself to be among the best suited experimental techniques for the study of both static and dynamic properties of molecular conformations.

Although only a few classes of molecules have been studied, it has been observed that carbocyclic derivatives of cyclohexane containing sp² hybridized ring carbon atoms are appreciably more flexible than the parent cyclohexane molecule. For example, the dnmr method^{3–6} has been applied to cyclohexene^{8,9} and its

derivatives^{10–12} and to derivatives of cyclohexane-1,4-dione¹³ and 2,2,5,5-tetramethylcyclohexane-1,3-dione,¹⁴ all of which contain two sp² ring carbon atoms.

Even fewer reports have been concerned with cyclohexane derivatives containing only one sp² ring carbon atom. Authors of previous works state unanimously that the barrier to ring inversion for cyclohexanone (**1a**) is much smaller than that of methylenecyclohexane¹⁵ (**1b**) whose barrier to chair–chair interconversion is 8.4 kcal/mol. Estimates of ΔG^\ddagger were published for cyclohexanone-2,2,6,6-*d*₄ (~ 4.9 kcal/mol)¹⁵ and for 4,4-difluorocyclohexanone (~ 2.3 kcal/mol),¹⁶ even though no characteristic spectral change was observed for both cases. In fact, until the recent publication by Anet,¹⁷ the only accurate inversion barrier for a cyclo-

(1) A preliminary account of this work was presented at the Second International Symposium on Nuclear Magnetic Resonance Spectroscopy, July 1972, University of Surrey, England.

(2) (a) E. L. Eliel, N. L. Allinger, S. L. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965; (b) M. Hanack, "Conformational Theory," Academic Press, New York, N. Y., 1965.

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(4) H. Booth in "Progress in NMR Spectroscopy," Vol. 5, J. W. Emsley, J. Feeney and L. H. Sutcliffe, Ed., Pergamon Press, Toronto, Canada, 1969, p 149.

(5) F. A. L. Anet and R. Anet in "Determination of Organic Structures by Physical Methods," Vol. 3, F. C. Nachod and J. J. Zuckerman, Ed., Academic Press, New York, N. Y., 1971, p 344.

(6) I. O. Sutherland, *Annu. Rep. NMR (Nucl. Magn. Resonance) Spectrosc.*, **4**, 71 (1971).

(7) E. Wyn-Jones and R. A. Pethrick, *Top. Stereochem.*, **5**, 275 (1970).

(8) F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.*, **87**, 3147 (1965).

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(12) M. Bernard and M. St-Jacques, *Tetrahedron*, in press.

(13) (a) M. St-Jacques and M. Bernard, *Can. J. Chem.*, **47**, 2911 (1969); (b) J. B. Lambert, J. L. Gasnell, and D. S. Bayley, *J. Org. Chem.*, **37**, 2814 (1972).

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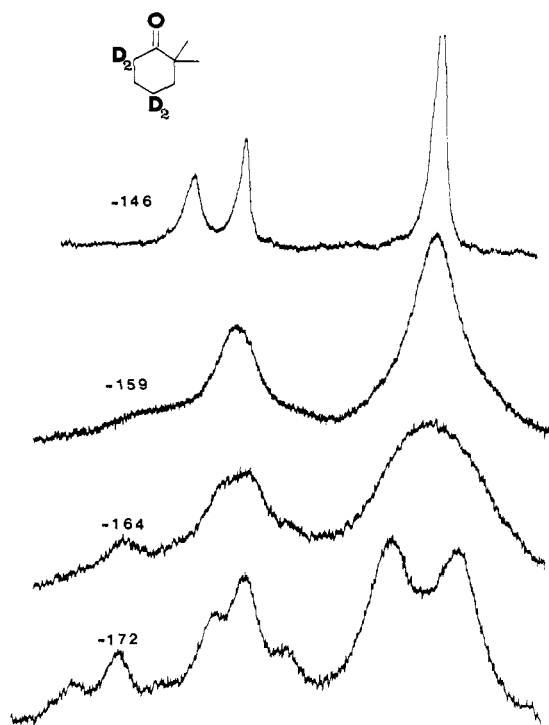
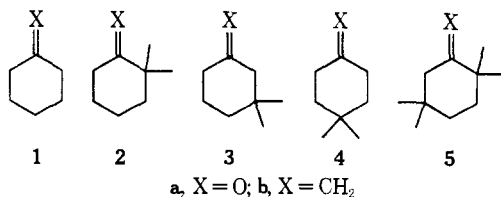


Figure 1. The 100-MHz pmr deuterium decoupled spectra of **2a-d₄** at several temperatures.

hexanone derivative was that of 8.1 kcal/mol determined for 2,2,5,5-tetramethylcyclohexanone (**5a**).¹⁸ Recently (after our work was completed), Anet and co-workers,¹⁷ through a brilliant pmr tour de force at 251 MHz, succeeded in observing a pmr spectral change near -183° for cyclohexanone-3,3,4,4,5,5-*d*₆ and determined a ΔG^\ddagger_{cc} value of 4.2 kcal/mol.

Our interest in the cyclohexanone system derived from our previous observation for **5a**¹⁸ and had as the objective the determination of experimental activation parameters characteristic of selected derivatives which could unravel the conformational properties of this fundamental class of molecules. The work reported herein is concerned particularly with the investigation of the pmr spectral behavior of several methyl derivatives with structures **2** to **5**, most of which



(except compound **4a** only) showed spectral modifications characteristic of the slowing down of ring inversion of the nmr time scale.

Results

(a) **Preparation of Compounds.** The cyclohexanone derivatives **2a**, **3a**, and **4a** were prepared by published procedures,¹⁹⁻²¹ whereas **5a** was obtained pure as a

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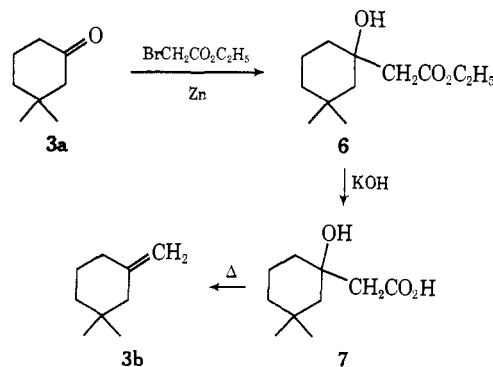
(19) (a) F. E. King, T. J. King, and J. G. Topliss, *J. Chem. Soc.*, 919 (1957); (b) W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.*, **69**, 1361 (1947).

(20) J. P. Wibaut and H. P. L. Gitsels, *Recl. Trav. Chim. Pays-Bas*, **60**, 577 (1941).

(21) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

gift.²² Compounds **2b** and **4b** were obtained by a standard Wittig reaction²³ on the ketone precursor. Since this reaction did not work with **3a** and **5a**, the derivatives **3b** and **5b** were prepared by a sequence of reactions as illustrated for **3b** in Scheme I. A Reformatsky reaction²⁴ with ethyl α -bromoacetate on **3a** gave **6** which was hydrolyzed to **7**. Pyrolysis²⁵ then gave the required compound **3b**. It was later found that compound **5b** could also be obtained directly through a reaction with methylene iodide and magnesium amalgam.²⁶

Scheme I



(b) **Pmr Spectra of Dimethyl Derivatives.** Of the six dimethyl derivatives investigated, all but **4a** exhibited pmr spectral changes at low temperatures which are described below. Table I contains a summary of the pertinent experimental results.

A study of the 100-MHz pmr spectrum of **2a** revealed a well defined spectral modification in the methyl region only. Since a deuterated derivative 2,2-dimethylcyclohexanone-4,4,6,6-*d*₄ (**2a-d₄**) was available as an intermediate from another investigation,¹² a description of the temperature behavior of its spectrum is more instructive. At room temperature, the 100-MHz deuterium decoupled spectrum consists of three singlets: δ 1.10 (two methyl groups), 1.66 (two methylene protons), and 1.81 (two methylene protons). Below -150° , the peaks broaden and ultimately the methyl signal splits into a doublet below -164° , the coalescence temperature (T_c), while the signal near δ 1.81 changes into an AB quartet below -159° as revealed from the spectrum taken at -172° shown in Figure 1. It is seen that the upfield part of the AB quartet overlaps with the signal from the other methylene protons.

Similarly, the methyl singlet of compounds **3a**, **2b**, **3b**, and **4b** changes into a doublet below coalescence temperatures listed in Table I, whereas that of **4a** does not split up at least down to -170° .

The free energies of activation characteristic of the chair to chair interconversion (ΔG^\ddagger_{cc}) calculated at the coalescence temperatures are listed in Table I. The small chemical shift differences observed below T_c and the very low temperatures involved (especially for the

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(24) (a) O. Wallach, *Justus Liebigs Ann. Chem.*, **347**, 328 (1905); (b) E. H. Charlesworth, H. J. Campbell, and D. L. Stachiw, *Can. J. Chem.*, **37**, 877 (1959).

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Table I. Experimental Data, Rate Constants, and Activation Parameters for the Dimethyl Compounds

Compd	Signal observed (chemical shift, ppm)	Chemical shift difference, ^a Hz	T_c , ^b °C	k at T_c , sec ⁻¹	ΔG^\ddagger_{oo} at T_c , kcal/mol ^c
2a-d ₄	CH ₃ (1.10)	19 ± 1	-164	47	5.3
2a-d ₄	CH ₂ (1.81)	48 ± 2 (13.5 ± 0.8) ^d	-159	130 ^e	5.3
3a	CH ₃ (0.97)	19.5 ± 0.5	-163	40	5.4
4a	CH ₃ (1.10)	No change observed			<5
2b	CH ₃ (1.09)	3.3 ± 0.1	-123	5.6	8.1
3b	CH ₃ (0.90)	15.4 ± 0.3 ^f	-107	43	8.3
4b	CH ₃ (0.96)	8.9 ± 0.2	-125	15.5	7.6

^a Chemical shift difference ($\Delta\nu$) in Hz at the lowest temperature for which a good spectrum was recorded. ^b The error in temperature measurement is $\pm 0.5^\circ$, but since the determination of T_c involves visual evaluation, the error in T_c is more likely about $\pm 2^\circ$. ^c The error in ΔG^\ddagger_{oo} is estimated at ± 0.2 kcal/mol. ^d The number in parentheses is the coupling constant obtained from the analysis of the AB quartet at -172° . ^e This value was calculated from the equation $k = \pi(6J^2 + \Delta\nu^2)^{1/2}/(2)^{1/2}$; R. J. Karland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, **40**, 2426 (1964). ^f The value of $\Delta\nu$ for this compound is temperature dependent and varies from 14.6 Hz at -100° to 15.8 Hz at -150° . The value listed was measured at -134° .

Table II. Experimental Data, Rate Constants, and Activation Parameters for the Tetramethyl Compounds

Compd	Signal observed (chemical shift, ppm)	Chemical shift difference, Hz	T_c , °C	k at T_c , sec ⁻¹	ΔG^\ddagger_{oo}	E_a	ΔH^\ddagger_{oo}	ΔS^\ddagger_{oo}
5a	5-CH ₃ (0.93)	24.3 ± 0.2	-106	66				
	2-CH ₃ (1.06)	16.5 ± 0.2	-114	22.3	8.1	7.2	6.8	-8
	CH ₂ (2.16)	68.7 ± 0.5 (13.5 ± 0.3) ^a	-98	169 ^b	±0.2	±1.0	±0.9	±5
5b	5-CH ₃ (0.88)	18.9 ± 0.2	-75	37.5				
	2-CH ₃ (1.08)	7.2 ± 0.2	-82	15.2	10.0	9.8	9.4	-3
	CH ₂ (2.03)	45.2 ± 0.5 (13.0 ± 0.3) ^a	-67	128 ^b	±0.2	±0.7	±0.6	±3

^a The number in parentheses is the coupling constant obtained from the analysis of the AB quartet at -140° . ^b This value was calculated from the equation $k = \pi(6J^2 + \Delta\nu^2)^{1/2}/(2)^{1/2}$; R. J. Kurland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, **40**, 2426 (1964).

ketones) did not permit a complete computer line-shape analysis with sufficient accuracy to afford all activation parameters. Nevertheless, free energies of activation were calculated from rates obtained reliably by a procedure whereby the line shape of the methyl signal was simulated at several temperatures near T_c .

The computer program used was based on Saunders' multiple site exchange program²⁷ to which was added a CALCOMP plotting subroutine. The ΔG^\ddagger_{oo} values thus obtained are comparable to those calculated from approximate equations valid only at T_c .²⁸

(c) Pmr Spectra of Tetramethyl Derivatives. Compounds **5a** and **5b** both showed temperature-dependent pmr spectra. That of **5a** has previously been reported in a preliminary communication¹⁸ and a summary of the pertinent features is contained in Table II. The spectrum of **5b** (shown partly in Figure 2) contains five signals at room temperature: δ 0.88 (singlet, methyl groups at C₅), 1.08 (singlet, methyl groups at C₂), 1.41 (broad singlet, methylene protons at C₃ and C₄), 2.03 (methylene protons at C₆), and 4.65 (multiplet, olefinic methylene protons). A spectral change occurs at lower temperature whereby the methyl singlets each split into a doublet while the signal at δ 2.03 becomes an AB quartet with parameters given in Table II.

Complete line-shape simulation of the spectral modification in the methyl region was carried out for both **5a** and **5b** by means of a modified version of the computer program described earlier such that it could handle two different but overlapping equally populated spin systems with input parameters characteristic of each.

The temperature variation of the line width in the

(27) M. Saunders and F. Yamada, *J. Amer. Chem. Soc.*, **85**, 1882 (1963).

(28) D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).

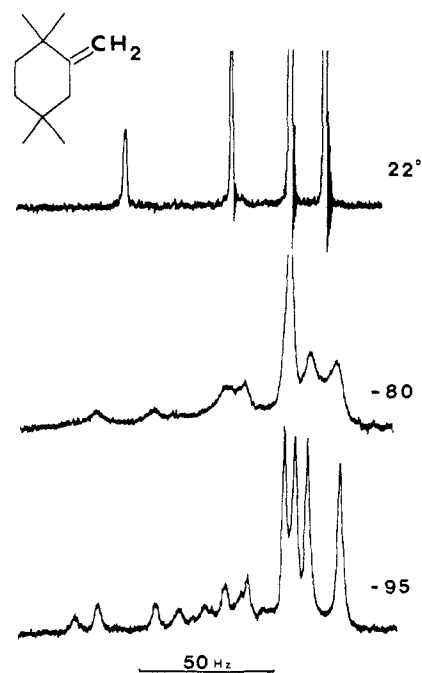


Figure 2. The upfield portion of the 100-MHz pmr spectra of **5b** at several temperatures.

absence of exchange constitutes a persistent source of difficulty which continuously limits the accuracy of the results from such simulations. For example, in our work, the TMS line width did not vary significantly in the experimental temperature range of interest, but its use as a measure of experimental line width in the absence of exchange for the exchanging methyl groups proved to be unsatisfactory. Furthermore, the absence of an unperturbed singlet in the spectrum of either

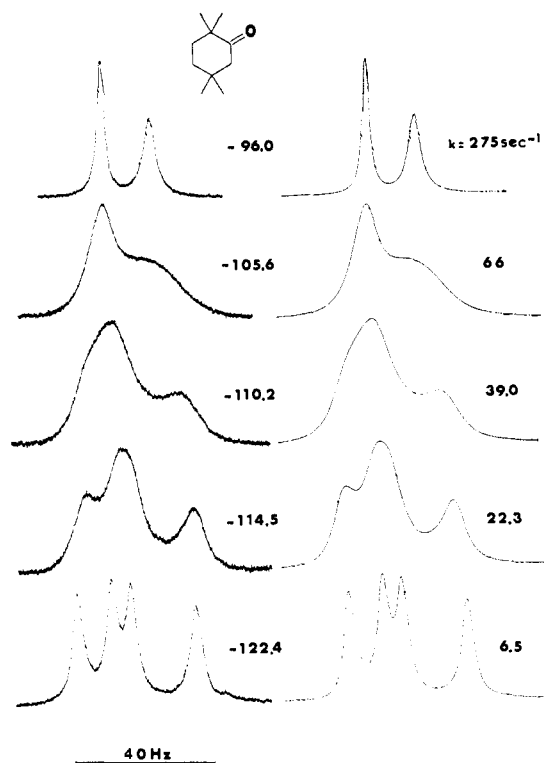


Figure 3. Comparison of the experimental (left) and theoretical (right) 100-MHz pmr spectra of the methyl signals of **5a** at several temperatures.

compound made it imperative to use an approximate method to determine this input parameter. The different contributing factors to the experimental line width at low temperatures have been amply discussed²⁹⁻³² and several mathematical functions have been proposed.^{29,30,33,34} Owing to unequal line widths for the four methyl lines at low temperatures, the application of these equations was not successful. Finally, the line widths utilized were obtained from extrapolation between values measured well below and well above T_c . This procedure is analogous to that used by Becker and coworkers³¹ and Bushweller and coworkers.³⁴

A comparison of experimental and calculated spectra for compound **5a** is illustrated in Figure 3. A least-square regression analysis of the rate constant data using either the Arrhenius or Eyring equation³⁵ gave the activation parameters listed in Table II.

Discussion

The differences observed in Tables I and II no doubt reflect substituent effects on the ground state and/or the transition state conformations, and a complete discussion of these effects requires a knowledge of the

(29) Z. M. Holubec and J. Jonas, *J. Amer. Chem. Soc.*, **90**, 5986 (1968).

(30) H. G. Schmid, H. Friebohn, S. Kabuss, and R. Mecke, *Spectrochim. Acta*, **22**, 623 (1966).

(31) R. R. Shoup, E. D. Becker, and M. L. McNeel, *J. Phys. Chem.*, **76**, 71 (1972).

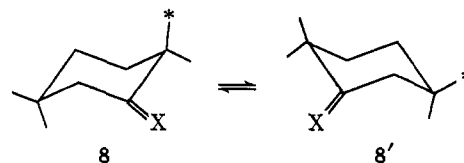
(32) B. Nilsson, R. E. Carter, K. Dahlqvist, and J. Marton, *Org. Magn. Resonance*, **4**, 95 (1972).

(33) P. Stilbs, *Acta Chem. Scand.*, **25**, 2635 (1971).

(34) C. H. Bushweller, J. W. O'Neil, and H. S. Bilofsky, *Tetrahedron*, **28**, 2697 (1972).

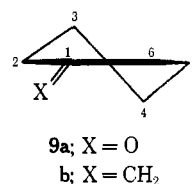
(35) D. F. Detar, "Computer Programs for Chemistry," Vol. 3, W. A. Benjamin, New York, N. Y., 1969, p 6.

appropriate inversion mechanism. The purpose of Figure 4 is therefore to summarize the various pathways for inversion possible for substituted cyclohexanone derivatives existing in the chair conformation.



The interconversion map shown in Figure 4 represents all possible inversion pathways for compounds **5a** or **5b** whose over-all result is given by the transformation of **8** into **8'** (where the prime indicates an inverted chair, mirror image of the original chair). It is noteworthy to point out that, although the conformations involved contain four methyl groups, this map is general for all six-membered rings containing an sp^2 ring carbon atom with or without substituents. In particular, it is well suited to represent all possible inversion pathways for the chair inversion of **2** and **3** for which only the appropriate pair of methyl groups need be retained. Furthermore, it is evident that for **1a** or **1b** some of the various conformations become equivalent. It is important to stress at this point that generality requires drawing perfect chairs for all compounds when in fact many are actually distorted. The exact nature of the particular deformations will be taken up later.

The map contains three basic families of conformations, namely chairs (C), boats, or twist boats (B or TB) and other conformations (Tr_i) with a ring geometry similar to **9**, which in fact is the form of the transition state that was calculated by Allinger and coworkers³⁶ for the inversion of cyclohexanone.



It is useful to classify the possible inversion pathways into two distinct groups, called simple or complex mechanisms. The simple mechanisms, symbolized $M(i, j)$ are defined as inversion itineraries which include two transition states similar to **9**, labeled Tr_i and Tr_j , and a single twist boat form, TB_n , where i, j , and n are numerical labels. The complex mechanisms, on the other hand, involve several boat forms interconverting by pseudorotation. These pathways are represented by $M(i, \psi, j)$.

Thus, there exist three distinct simple mechanisms which are $A = M(1, 6)$, $B = M(2, 5)$, and $C = M(3, 4)$, as well as their equivalent mirror image pathways occurring in the reverse direction. The energy profiles for such pathways are dissymmetrical as illustrated in Figure 5. On the other hand, the energy profiles for the complex mechanisms can be either symmetric ($i = j$) or dissymmetric ($i \neq j$). Detailed itineraries for pathways $M(1, 6)$ and $M(1, \psi, 1)$ are shown as examples in Scheme II, where the primes indicate in-

(36) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972).

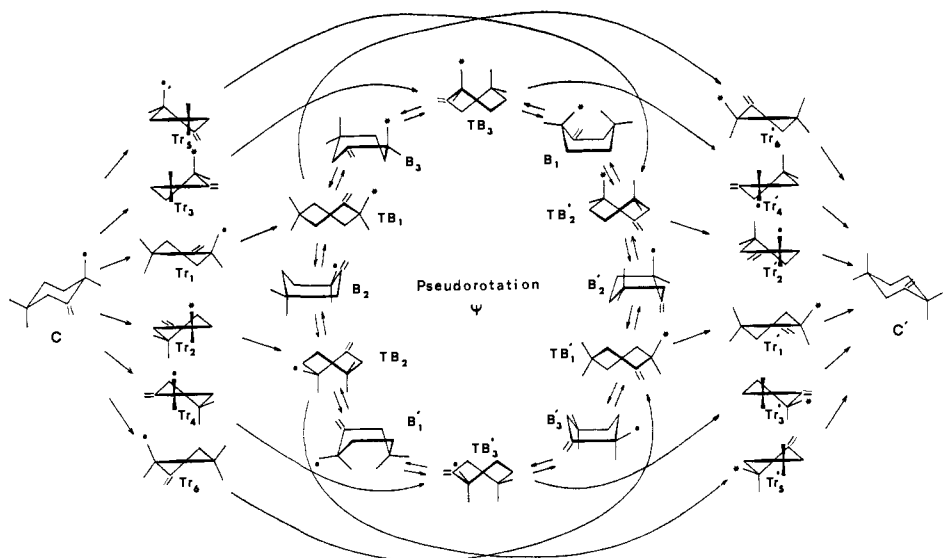
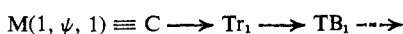
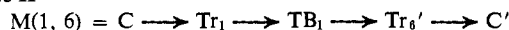


Figure 4. Interconversion map for cyclohexanone and its derivatives.

Scheme II



verted forms (or mirror images). The corresponding energy profiles are illustrated qualitatively in Figure 5.

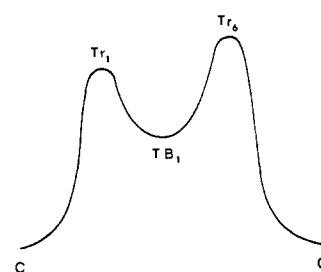
The precise values of the activation parameters depend on details of the data treatment using the Eyring equation. For symmetrical energy profiles involving a metastable intermediate, a transmission coefficient of one-half is normally used whereas a value of one is used in the absence of such a species.³⁷ Cyclohexanone is a typical example for which the chair to boat parameter $\Delta G^{\ddagger}_{cb} = 4.0$ kcal/mol is slightly lower than the corresponding value for the chair to chair interconversion $\Delta G^{\ddagger}_{cc} = 4.2$ kcal/mol.¹⁷ The situation is more complex for cases involving unsymmetrical profiles, and it is more prudent to use the ΔG^{\ddagger}_{cc} parameter which is independent of mechanistic details. Since ΔG^{\ddagger}_{cc} and ΔG^{\ddagger}_{cb} differ by less than 0.3 kcal/mol, discussions in terms of ΔG^{\ddagger}_{cc} alone are therefore quite acceptable.

Results reported in Table II for **5a** and **5b** show negative entropies of activation (ΔS^{\ddagger}) with relatively large uncertainty margins. This lack of precision is most likely attributable to a combination of saturation effects, the proper selection of experimental line widths in the absence of exchange, and the availability of rate constants over rather small temperature intervals.^{5,38} Values of ΔS^{\ddagger} near zero are most often observed,³ but negative values have been reported for several substituted derivatives of cyclohexane.^{3,38b} Under the present circumstances, it seems preferable to assume similar magnitudes for the ΔS^{\ddagger} terms characteristic of the molecules within each series studied. It therefore appears reasonable that, when comparing the behavior of two molecules within a series, $\Delta\Delta G^{\ddagger}$ is an acceptable estimate of $\Delta\Delta H^{\ddagger}$.

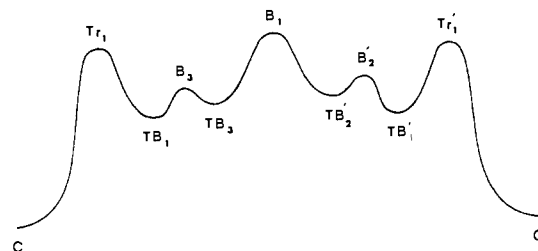
Having introduced the necessary formalism, our aim

(37) R. K. Harris and N. Sheppard, *J. Mol. Spectrosc.*, **23**, 231 (1967).

(38) (a) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966); (b) O. Yamamoto, M. Yanagisamu, K. Kayamizu, and G. Kotowycz, *J. Magn. Resonance*, **9**, 216 (1973).



M(1,6)



M(1,Ψ,1)

Figure 5. Qualitative representations of typical simple (M(1, 6)) and complex (M(1, ψ , 1)) mechanisms of chair interconversion for derivatives of cyclohexanone.

is now to discuss and interpret successively the experimental results for the dimethyl and tetramethyl derivatives.

(a) Dimethyl Derivatives. Any discussion of derivatives of cyclohexanone and methylenecyclohexane inevitably requires a consideration of the properties of the parent compounds. Allinger and coworkers have calculated that conformation **9a** is the transition state for the conversion of the chair conformation of cyclohexanone into a boat form and that the energy barrier for this process is 3.86 kcal/mol.³⁶ The excellent agreement between this value and the free energy barrier of 4.0 kcal/mol (ΔG^{\ddagger}_{cb}) determined experimentally for cyclohexanone-*d*₅¹⁷ supports the contention that **9a** actually represents the maximum on the energy profile of chair inversion.

Table III. Free Energy of Activation (kcal/mol) for the Inversion of Cyclohexanone, Methylenecyclohexane, and Their Methyl Derivatives

Compd	1	2		3		4		5	
	$\Delta G^{\ddagger}_{\text{cc}}$	$\Delta G^{\ddagger}_{\text{cc}}$	$\Delta\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{\text{cc}}$	$\Delta\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{\text{cc}}$	$\Delta\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{\text{cc}}$	$\Delta\Delta G^{\ddagger}$
a	4.2	5.3	1.1	5.4	1.2	<5		8.1	3.9
b	8.4	8.1	-0.3	8.3	-0.1	7.6	-0.8	10.0	1.6

The recent observation that methylenecyclohexane has an inversion barrier appreciably higher than that of cyclohexanone, namely 8.1 kcal/mol³⁹ for the chair to boat process,^{40b} and the evidence that its inversion mechanism involves a transition state of geometry **9b**⁴¹ suggests the interesting comparison of the activation parameters characteristic of the **a** and **b** series of dimethyl compounds.

To the extent that the *R* values⁴² are a measure of flattening of chair conformations, the values of 1.72 for cyclohexanone and 1.87 for methylenecyclohexane suggest a similar deformation although the cyclohexanone chair could be slightly more flattened. The C(sp³)-C(sp²)-C(sp³) angle of acetone⁴³ (117°, identical with that of cyclohexanone⁴⁴) and that of isobutene⁴⁵ (115.9°) being the same within experimental error support this contention.

With similar geometries existing for the ground states (chair forms) and transition states (**9a** and **9b**) of cyclohexanone and methylenecyclohexane, it has been suggested previously^{17,36,41} that their difference in $\Delta G^{\ddagger}_{\text{cb}}$ (4.1 kcal/mol) is due mainly to differences in the torsional barriers about two sp²-sp³ C-C bonds which undoubtedly reflect the observed differences in the rotational barriers of the two model compounds, acetone and isobutene, for which barriers to rotation were reported to be 0.78 and 2.2 kcal/mol, respectively.^{43,45}

Table III contains a list of the pertinent values for $\Delta G^{\ddagger}_{\text{cc}}$ together with $\Delta\Delta G^{\ddagger}$ terms defined as differences in free energy of activation between derivatives and the parent compound for each series. The $\Delta\Delta G^{\ddagger}$ column reveals that different trends exist for each series. In fact, substitution of a gem-dimethyl moiety at either position 2 or 3 of methylenecyclohexane does not change the barrier significantly (*i.e.*, $\Delta\Delta G^{\ddagger} \approx 0$), whereas an increase of more than 1 kcal/mol is observed for the corresponding cyclohexanones **2a** and **3a**. It is therefore evident that the absolute value of the $\Delta\Delta G^{\ddagger}$ parameter is a measure of the methyl substitution effect on the inversion barrier and that differences in trend for each series of compounds reflect differences in behavior whose interpretation necessarily requires a consideration of ground and transition state effects.

Information about transition states is much more difficult to obtain. At present, strain energy calculations are considered the best source of information regarding the geometry of these energetic conformations. In particular, calculations by Allinger and coworkers³⁶ suggest that the geometry of the transition state for the

(39) A value of 7.7 kcal/mol was originally reported,^{40a} but because of the approximate nature of the calculation involved, the value of 8.1 kcal/mol for $\Delta G^{\ddagger}_{\text{cb}}$ calculated from the rates obtained by complete line-shape analysis appears more reliable (the corresponding $\Delta G^{\ddagger}_{\text{cc}}$ is 8.4 kcal/mol).

(40) (a) J. T. Gerig, *J. Amer. Chem. Soc.*, **90**, 1065 (1968); (b) J. T. Gerig and R. A. Rimerman, *ibid.*, **92**, 1219 (1970).

(41) M. Bernard and M. St-Jacques, *Can. J. Chem.*, **48**, 3039 (1970).

(42) J. B. Lambert, *Accounts Chem. Res.*, **4**, 87 (1971).

(43) R. Nelson and L. Pierce, *J. Mol. Spectrosc.*, **18**, 344 (1965).

(44) C. Romers, *Recl. Trav. Chim. Pays-Bas*, **75**, 956 (1956).

(45) V. W. Laurie, *J. Chem. Phys.*, **34**, 1516 (1961).

inversion of cyclohexanone is essentially that of **9a**. The extrapolation from other calculations⁴⁶ for 1,1-dimethylcyclohexane and 1,1,4,4-tetramethylcyclohexane suggests that the order of preference for the location of a gem-dimethyl group on carbons of structure **9a** is 3,4 > 2,5 > 6. This conclusion is especially important for nonsymmetrical dimethyl derivatives because there will be a tendency for the methyl groups to adopt the most favorable of two possible positions. In addition, skeleton conformations other than **9a** must also be considered for derivatives of cyclohexanone which need not necessarily imitate the parent compound.

At first thought, it is tempting to try to explain the trends in $\Delta\Delta G^{\ddagger}$ observed for the series **a** and **b** of dimethyl compounds by means of a unique inversion mechanism and ascribe the differences to interactions created by the presence of olefinic protons in series **b**. This approach is very unsatisfactory especially for the pair of compounds **3a** and **3b** because mutual interactions cannot exist between the widely separated olefinic protons and methyl groups of **3b**. The substitution of C=O by C=CH₂ is not expected to change the ground state conformation appreciably, and to explain the different $\Delta\Delta G^{\ddagger}$ values (-0.1 and 1.2 kcal/mol) one must postulate either serious deformations or differences in the transition states.

In order to find an explanation, it is necessary, at this point, to estimate the relative energy of the various Tr_{*i*} and boat forms shown in Figure 4, firstly for cyclohexanone for which Tr₁ and Tr₂ are equivalent and then for the various derivatives of immediate interest. Although the absolute value of the strain energy calculated for the three different Tr_{*i*} (*i* = 1, 3, and 5) forms is slightly high,⁴⁷ the order of stability predicted is nevertheless correct: Tr₁, Tr₂ > Tr₃, Tr₄ > Tr₅, Tr₆. In fact, this order is predictable intuitively since Tr₁ involves the flip of the unsaturated side of the chair whereas Tr₅ involves the flip of the saturated side of the ring much like cyclohexane. These arguments suggest that only pathways M(1, ψ , 1) and M(1, ψ , 2), which involve the most stable Tr_{*i*} forms, need be considered further as favored inversion mechanism. Furthermore, the most recent calculations on cyclohexanone³⁶ indicate that the skeleton conformation B₂ is approximately 1.5 kcal/mol higher than B₁ or B₃ and higher than Tr₁ by nearly as much. It therefore follows that the most likely inversion pathway is M(1, ψ , 2), which does not involve energetic B₂ boat forms.

Effects responsible for the different $\Delta\Delta G^{\ddagger}$ values characteristic of **3a** and **3b** are expected to manifest themselves in either Tr₁, Tr₂, B₁, or B₃, that is in whichever form is the maximum on the energy profile of the M(1, ψ , 2) inversion mechanism. Let us consider

(46) M. T. Tribble and N. L. Allinger, *Tetrahedron*, **28**, 2147 (1972).

(47) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tymiński, *J. Amer. Chem. Soc.*, **91**, 337 (1969).

firstly that the calculated conformational energies of the Tr_1 (equivalent to **9a**) and B_1 conformations of cyclohexanone are essentially equal (3.86 and 3.77 kcal/mol, respectively⁴⁶) and then determine the probable effect of the exomethylene group in methylenecyclohexane.⁴⁸ The B_1 form of both compounds is characterized by an eclipsing of the double bond with a proton on the "prow" carbon and by a staggered arrangement between the double bond and the ring protons on the other carbon atom. This means that the B_1 conformation of methylenecyclohexane should be more stabilized than that of cyclohexanone by about 1.4 kcal/mol, that is by an amount approximately equal to the difference in rotational barriers of isobutene and acetone (or 2.2–0.78 kcal/mol).^{43,45} Therefore, compared to the transition state (Tr_1) in which both bonds next to the sp^2 carbon are staggered, there will be a greater stabilization of the B_1 form for the hydrocarbon than for the ketone.

Examination of the B_1 form for **3a** and **3b** reveals a significant "prow-prow" methyl-proton interaction. It appears that the 1.2 kcal/mol $\Delta\Delta G^\ddagger$ term for **3a** (Table III) can be explained by this interaction which effectively makes B_1 more energetic than both Tr_1 and Tr_2 and therefore rate determining. On the other hand, the negligible $\Delta\Delta G^\ddagger$ term for **3b** is not a reflection of such a nonbonding interaction but rather suggests that B_1 is not rate determining and that either Tr_1 or Tr_2 is the maximum energy form on the inversion profile. Thus, the "prow-prow" methyl-proton repulsion in the B_1 form of **3b** is not sufficient to raise its energy over that of Tr_1 and Tr_2 as it does for **3a**.

The pair of compounds **2a** and **2b** is further complicated by the additional repulsion between the equatorial methyl and the nearby olefinic proton, similar to the $A^{1,3}$ interaction studied by Johnson.⁴⁹ Nevertheless, the difference in behavior for these compounds is most adequately rationalized in terms of a rate-determining B_1 conformation for **2a** as opposed to a maximum consisting of either the Tr_1 or Tr_2 form for **2b**.

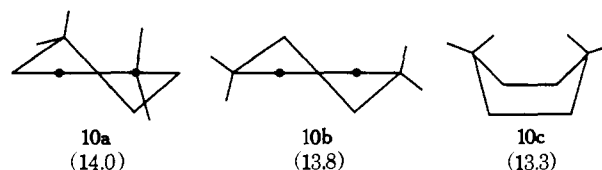
Considering that the rate-determining conformation for the inversion of **2b** and **3b** is the more energetic of either the Tr_1 or Tr_2 form, then the $\Delta\Delta G^\ddagger$ terms characteristic of these compounds measure the methyl substituent effect in the transformation of the chair to the appropriate Tr_i form. Now the conclusion that B_1 conformations are rate determining for the inversion of **2a** and **3a** suggests that the methyl substituent effect on the same Tr_i form as above has a magnitude less than the $\Delta\Delta G^\ddagger$ values reported for these two cyclohexanones. Thus the methyl effect on a common Tr_i conformation appears more comparable for the two series.

Finally, the lower barrier of **4b** relative to **1b** ($\Delta\Delta G^\ddagger = -0.8$ kcal/mol) appears to be a consequence of appreciable ground state destabilization arising from nonbonded 1,3-axial methyl-proton repulsions in the chair.

(b) Tetramethyl Derivatives. The analysis of the low-temperature pmr spectra and the magnitudes of the activation parameters calculated from the spectral changes of **5a** and **5b** are consistent with favored chair

conformations. A general description of the static and dynamic properties of these compounds was given in relation to Figure 4 where possible mechanisms for chair inversion were discussed. Our objective in this section is concerned with the determination of the most probable inversion pathways and the identification of the conformation of maximum energy on the inversion profile.

It is useful to consider at first the available information for 1,1,4,4-tetramethylcyclohexane. Its $\Delta G^\ddagger_{\infty}$ is about 1 kcal/mol higher than that of cyclohexane,⁵⁰ and calculations by Friebolin and coworkers⁵¹ provide estimates for the conformational energy of the three possible transition states **10a**, **10b**, and **10c**. The absolute values for these energies relative to the chair form taken as zero reference (written in brackets under each structure) are a bit high, but the relative order of stability is probably reliable. These results suggest that the "prow-prow" interaction in **10c** is an important contributor to the overall energy of this boat form.



Arguments in the previous section have suggested that the most favored inversion mechanism for **2a** and **3a** is $M(1, \psi, 2)$. Assuming that this pathway is also followed by **5a** as it inverts its chair conformation, then one would expect a large $\Delta\Delta G^\ddagger$ as a consequence of the serious "prow-prow" methyl-methyl repulsion in B_1 . This interaction would undoubtedly make B_1 the most energetic form on the inversion pathway. This expectation is apparently confirmed by the large $\Delta\Delta G^\ddagger$ value (3.9 kcal/mol) determined for **5a** as summarized in Table III.

Other mechanisms such as $M(3, 4)$ or $M(1, \psi, 4)$ are difficult to rule out rigorously since it would be necessary to show that the conformational energy of Tr_4 is significantly higher than that of B_1 . This is not possible experimentally and could only be done in principle through elaborate computer calculations. Therefore, our most prudent statement for the moment is that the energy of Tr_4 appears to be at least comparable to that of B_1 .

In contrast to **5a**, compound **5b** exhibits a much smaller $\Delta\Delta G^\ddagger$ value equal to 1.6 kcal/mol. In fact, this number is comparable to the difference of ΔG^\ddagger values for 1,1,4,4-tetramethylcyclohexane⁵⁰⁻⁵² and cyclohexane and suggests a certain analogy between them. This similarity can be explained by means of a mechanism identical with that of **2b** and **3b**, namely $M(1, \psi, 2)$ for which either Tr_1 or Tr_2 is rate determining.

Such a conclusion for **5b** implies that the larger energy difference⁴⁸ between the skeleton conformations Tr_1 (or **9b**) and B_1 for methylenecyclohexane is not overcome by the "prow-prow" interaction which tends to increase the energy of B_1 more than that of Tr_1 or Tr_2 . Alternatively, one could suggest that in fact the methyl-

(50) H. Friebolin, W. Faisst, H. G. Schmid, and S. Kabuss, *Tetrahedron Lett.*, 1317 (1966).

(51) H. G. Schmid, A. Jaeschke, H. Friebolin, S. Kabuss, and R. Mecke, *Org. Magn. Resonance*, 1, 163 (1969).

(52) R. W. Murray and M. L. Kaplan, *Tetrahedron*, 23, 1575 (1967).

(48) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, 90, 5773 (1968).

(49) F. Johnson, *Chem. Rev.*, 68, 375 (1968).

methyl repulsion is sufficient to make B_1 rate determining for **5b** but that only part of this energy contributes to the $\Delta\Delta G^\ddagger$ term. On the other hand, this cannot be implied for **5a** since calculations³⁶ have shown that both the Tr_1 and B_1 forms of cyclohexanone have comparable energies. In this case, the methyl-methyl repulsion would contribute wholly to $\Delta\Delta G^\ddagger$, which consequently should be much larger as observed. In the absence of further evidence, it seems more reasonable to suggest that **5b** inverts through the $M(1, \psi, 2)$ mechanism with either Tr_1 or Tr_2 being rate determining.

In conclusion, we suggest that all the compounds studied invert through the same $M(1, \psi, 2)$ pathway for which B_1 is the rate-determining conformation for **2a**, **3a**, and **5a**, whereas either Tr_1 or Tr_2 is the most energetic conformation on the energy profile for chair interconversion in **2b**, **3b**, **5b**, and conceivably **4a**.

Experimental Section

The vpc analyses and separations were carried out on a Varian-Aerograph A90-P3 instrument using 0.25-in. columns. Mass spectral analyses were performed on an Associated Electrical Industries Model MS-902 mass spectrometer operating at 12 and 70 eV.

Routine analytical pmr spectra were recorded on a JEOL C-60H spectrometer operating at 60 MHz in the external lock mode. The low-temperature pmr spectra were obtained at 100 MHz using a JEOL JNM-4H-100 spectrometer. The samples studied were solutions in chlorodifluoromethane (3% by volume) with the exception of **5a** which was examined as a 3% solution in vinyl chloride-chlorodifluoromethane (85:15). All solutions containing a small quantity of TMS were degassed and sealed. Deuterium decoupling, when required, was effected by means of the JEOL Hetero Spin Decoupler Model JNM-SD-HC.

Temperatures were monitored by means of a JEOL temperature control unit Model JES-VT-3 and determined accurately with a calibrated thermocouple placed inside a solvent-containing dummy nmr tube. Temperature measurements were taken before and after recording several pmr spectra at each reported temperature. A variation of less than 0.5° was ordinarily observed between the two sets of temperature readings.

Rate constants were obtained from an iterative comparison of experimental and computer calculated spectra. For this purpose, five to eight spectra were recorded at a sweep rate of 0.15 Hz/sec without saturation at each temperature. The region of interest was digitized manually taking from 50 to 120 experimental points which provided the basis for iterative adjustment of the experimental and theoretical spectra calculated, using programs identified in the text, on either a CDC 6600 or CDC CYBER 74 computer and then traced by means of a CALCOMP plotter.

Preparation of Derivatives of Cyclohexanone. The compounds **2a**, **3a**, and **4a** were prepared by published procedures.¹⁹⁻²¹ Compound **5a** was a gift²² while **2a-d₄** was prepared in the course of another study.¹²

2,2-Dimethylmethylenecyclohexane (2b) and 4,4-Dimethylmethylenecyclohexane (4b). These compounds were prepared from quantities of 3 to 5 g of known ketone precursors **2a** and **4a** through a Wittig reaction using the procedure developed by Corey and co-workers.²³ The products isolated and purified by vpc showed analytical data characteristic of structures **2b** and **4b**. Pmr spectrum of **2b** in CHF_2Cl at room temperature: 1.09 ppm (singlet, two CH_3), a complex multiplet between 1.30 and 1.70 ppm (6 protons, methylene at C_3 , C_4 , and C_5), 2.23 ppm (triplet, methylene at C_6), and 4.64 ppm (singlet, $=CH_2$).

Anal. Calcd for C_9H_{16} : C, 87.02; H, 12.98. Found: C, 86.94; H, 13.21.

Pmr spectrum of **4b** in CHF_2Cl at room temperature: 0.96 ppm (singlet, two CH_3), 1.37 ppm (triplet, CH_2 at C_2 and C_6), 2.18 ppm (triplet, CH_2 at C_3 and C_5), and a broad peak at 4.60 ppm ($=CH_2$).

Anal. Calcd for C_9H_{16} : C, 87.02; H, 12.98. Found: C, 87.25; H, 12.86.

3,3-Dimethylmethylenecyclohexane (3b). Compound **3b** was prepared by a sequence of reactions (Scheme 1) patterned along the line of analogous transformations.²⁴

To a solution of 5.0 g of **3a** in 20 ml of benzene was added 3.3 g of activated zinc (treated with 3% NaOH and 5% HCl and dried under vacuum at 100°). Ethyl bromoacetate (13.5 g) was added dropwise to the refluxing solution. After the zinc had disappeared, the solution was maintained at refluxing temperature for 2 hr. Allowed to cool, the solution was then poured on crushed ice; 20 ml of 6 *N* H_2SO_4 was added and the organic phase was separated and washed with a saturated solution of $NaHCO_3$ followed by water and finally dried over $MgSO_4$. Distillation at 15 mm gave 4.83 g (57%) of a colorless liquid whose pmr spectrum in $CDCl_3$ is in accord with structure **6**: 0.88 ppm (singlet, CH_3), 1.11 ppm (singlet, CH_3), 1.25 ppm (triplet with $J \approx 7$ Hz, CH_3), multiplets between 1.3 and 1.8 ppm (8 ring methylene protons), 2.40 ppm (singlet, CH_2), 3.07 ppm (singlet, OH, disappears on addition of D_2O), 4.17 ppm (quartet, CH_2 of ethyl group).

Compound **6** (4.83 g) was dissolved in 15 ml of methanol and refluxed 30 min with a solution of 3.0 g of KOH in 10 ml of water. HCl (3 *N*) was then added to precipitate a compound which was filtered, dried, and recrystallized from a mixture of benzene-petroleum ether to give 3.17 g (76%) of a white solid, mp 108-110°, whose pmr spectrum in $CDCl_3$ is in accord with structure **7**: 0.90 ppm (singlet, CH_3), 1.10 ppm (singlet, CH_3), multiplets between 1.25 and 1.75 ppm (8 ring methylene protons), 2.48 ppm (singlet, CH_2), and a very broad band between 6 and 10 ppm (two OH groups).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.76; H, 9.94.

The acid **7** (1.25 g) dissolved in 5 ml of quinoline and 0.2 g of copper was added.²⁵ Heating gradually to 260° gave a liquid product, isolation by distillation, which was found by vpc analysis (10% SF-96, 10 ft, 120°) to contain two products of which one was identified as **3a**. The compound with shorter retention time possessed analytical data consistent with structure **3b**. Pmr spectrum in CHF_2Cl : 0.90 ppm (singlet, two CH_3), a multiplet between 1.3 and 1.8 ppm (two CH_2 groups on C_4 and C_5), 1.93 ppm (singlet, CH_2 on C_2), 2.10 ppm (broad triplet, CH_2 on C_6) and 4.6 ppm (multiplet, $=CH_2$).

Anal. Calcd for C_9H_{16} : C, 87.02; H, 12.98. Found: C, 87.67; H, 12.69.

2,2,5,5-Tetramethylmethylenecyclohexane (5b). Compound **5a** (4.0 g) was treated similarly with 2.86 g of activated zinc and 7.0 g of ethyl bromoacetate to give 2.28 g (36%) of a compound identified as ethyl 1-hydroxy-2,2,5,5-tetramethylcyclohexylacetate. Pmr spectrum in $CDCl_3$: four singlets at 0.88, 0.89, 0.95, and 1.10 ppm (four CH_3), 1.29 ppm (triplet with $J \approx 7$ Hz, CH_3 of ethyl group), 1.45 ppm (singlet, CH_2 on C_6), multiplets between 1.2 and 1.7 ppm (CH_2 on C_3 and C_4), 2.43 ppm (AB quartet, CH_2), 4.17 ppm (quartet with $J \approx 7$ Hz, CH_2 of ethyl group), 3.5 ppm (broad band due to OH which disappeared on addition of D_2O).

The saponification of the above compound (2.28 g) gave 0.85 g (43%) of a white solid with mp 110-112.5° after recrystallization. The following analytical data are consistent with 1-hydroxy-2,2,5,5-tetramethylcyclohexylacetic acid. Pmr spectrum in $CDCl_3$: 0.91 ppm (singlet, two CH_3), 0.97 and 1.08 ppm (singlets, two CH_3), a multiplet between 1.2 and 1.8 ppm (CH_2 on C_3 and C_4), 1.52 ppm (singlet, CH_2 on C_6), 2.51 ppm (AB quartet with $J = 15.5$ Hz, CH_2), a very broad band between 6 and 10 ppm (two hydroxyl protons).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.46; H, 10.10.

Pyrolysis of the above acid in quinoline in the presence of copper gave a mixture of **5a** and another compound isolated by vpc and shown to be **5b**. Pmr spectrum in CHF_2Cl : 0.88 ppm (singlet, two CH_3), 1.08 ppm (singlet, two CH_3), 1.41 ppm (broad singlet, CH_2 on C_3 and C_4), 2.03 ppm (singlet, CH_2 on C_6), 4.65 ppm (multiplet, $=CH_2$).

Anal. Calcd for $C_{11}H_{20}$: mol wt, 152.1565. Found (mass spectrum at 70 eV): mol wt, 152.1566.

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