Alcohol Products. Alcohol epi-7-OH was identified by spectral comparison. The other alcohol products show very complex spectra that only allow partial assignment of structure, *viz.*, the two major alcohol products, A and B, both contain two cyclopropane rings and one trans double bond: unknown alcohol A, ir (CS$_2$) 3590, 3300, 960 cm^{-1}; nmr (CS$_2$, τ) 4.4 (m, 2), 6.4 (m, 1), 7.5–9.6 (m, 17), 9.7–10.5 (m, 2); ketone corresponding to A, ir (CS$_2$) 3060, 1717, 970 cm^{-1}; unknown alcohol **B**, ir (CS$_2$) 3600, 3400, 3050, 965 cm^{-1}; nmr (CS$_2$, τ) 4.5 (m, 2), 6.3 (m, 1), 7.5–9.8 (m, 18), 10.15 (m, 1); ketone corresponding to **B**, 3057, 1710, 965 cm^{-1}.

The Vinyl Anion[1]

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Received September 2, 1970

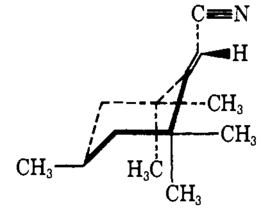
Abstract: The chiral molecule, 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile (**1**), was synthesized in order to study the stereochemistry of the vinyl anion in protonic solvents. At 90° the vinyl anion exhibits a very high degree of retention of configuration (>99%) in methanol using sodium methoxide as the base, $k_e/k_r = 140$. Evidence is provided to show that the proton is abstracted directly from the vinyl carbon rather than being exchanged by an addition–elimination mechanism. A small kinetic isotope effect ($k_H/k_D \approx 2$) is observed. It is suggested that in neither the exchange nor the racemization of **1** is proton abstraction rate determining.

Recently there have been reports from this laboratory on the stereochemical fate of the cyclopropyl anion.[2,3] It was found that the 1-cyano-2,2-diphenylcyclopropyl anion, generated by sodium methoxide in methanol, was capable of maintaining its configuration. On the other hand, the anion derived from the optically active acyclic analog, 2-methyl-3,3-diphenylpropionitrile, was totally racemized under the same conditions. A number of factors influence the energy barrier for the racemization of carbanions including, among others, (1) the initial hybridization of the central carbon atom and (2) constraint in a small ring (I strain).[4] In order for these factors to be evaluated (cyclopropyl *vs.* vinyl) information was needed on a corresponding vinyl system. This article presents the data obtained on the stereochemical fate of the anion derived from 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile.

Results and Discussion

Studies have been made on the configurational stability of vinyl anions by Miller[5] and by Cram.[6] The systems used and the results of those investigations are insufficient for present purposes since a number of complicating factors are involved: (1) *cis–trans* energy differences with its concomitant driving force for isomerization; (2) the competing addition–elimination mechanism or thermal isomerization; (3) delocalization energy differences due to different substituents attached to the carbanion site.

In order to study the vinyl anion a suitable system had to be chosen. There were several necessary qualities for the molecule to possess. Obviously it had to have a double bond with at least one vinyl hydrogen. Second, a suitable molecule would need an acidifying substituent on the double bond to make the olefinic proton more readily removable. Third, there should be no allylic hydrogens in the system so that rearrangements would be avoided. Furthermore, it was desirable to have the β-carbon of the double bond as sterically hindered as possible so that the addition–elimination mechanism (*vide infra*) could be avoided. Lastly, a chiral molecule would be useful since the rate of isomerization could be measured directly by measuring the rate of racemization and, moreover, it would obviate the problem of cis–trans energy differences with its resulting chemical potential difference. A molecule which meets all those requirements is 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile (**1**).



1

It is readily seen that the molecule is chiral, possesses a double bond with no allylic hydrogens, and that it has an acidified vinyl hydrogen. Furthermore, it is certainly sterically hindered since it is analogous to a dineopentyl-substituted olefin. The nitrile group was chosen as the acidifying substituent because nitrile substitution increases the kinetic acidity of the carbon–hydrogen bond and also it permits a comparison with our previous studies on the cyclopropylnitrile.[2]

Syntheses. The synthesis of 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile (**1**) was attempted by several different routes, all of which used 2,2,4,6,6-pentamethylcyclohexanone (**2**) as the starting point. Pentamethyl ketone **2** was obtained by a sodium hydride–methyl iodide alkylation of the commercially available

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(1) The support of this work by grants from the National Science Foundation and the Public Health Service, Grant No. 04065 from the National Cancer Institute, is gratefully acknowledged.

(2) H. M. Walborsky and J. M. Motes, *J. Amer. Chem. Soc.*, **92**, 2445 (1970).

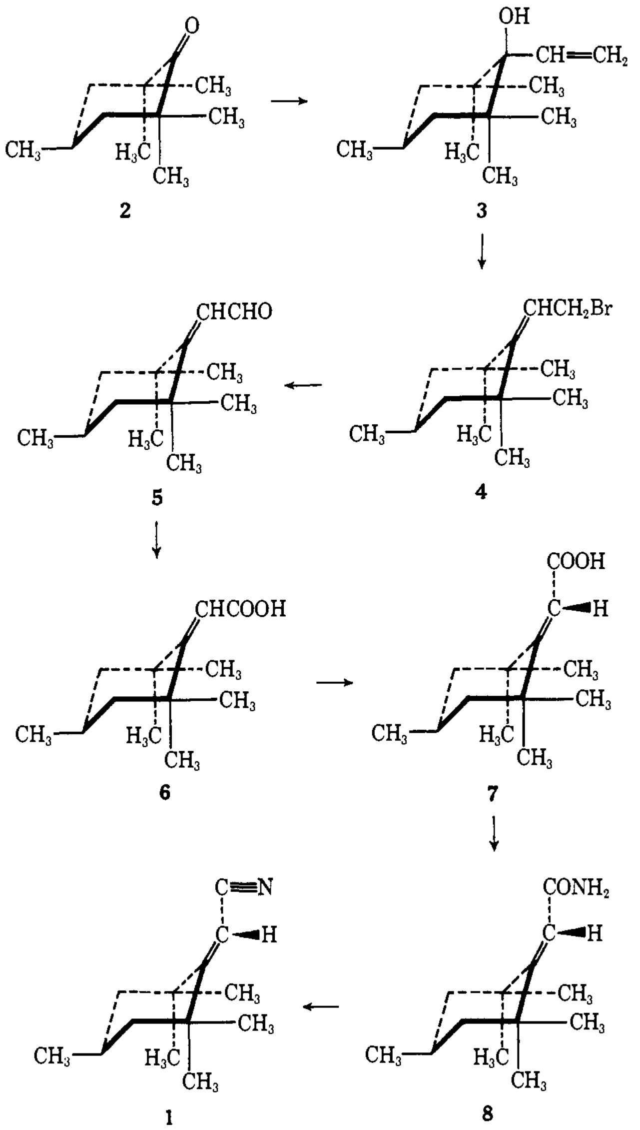
(3) J. M. Motes and H. M. Walborsky, *ibid.*, **92**, 3697 (1970).

(4) H. C. Brown, *et al.*, *ibid.*, **73**, 212 (1951); H. C. Brown and M. Borkowsky, *ibid.*, **74**, 1894 (1952).

(5) S. I. Miller and W. G. Lee, *ibid.*, **81**, 6316 (1959).

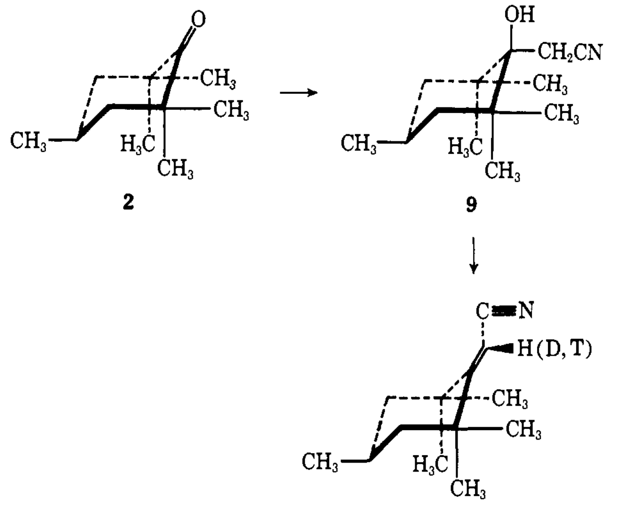
(6) D. H. Hunter and D. J. Cram *ibid.*, **86**, 5478 (1964).

4-methylcyclohexanone. Attempted Wittig-type condensations of **2** with the ylides from triethylphosphonoacetate or diethylphosphonoacetonitrile failed, as did attempts at the Reformatsky reaction of **2** with ethyl bromoacetate. However, the synthesis was accomplished in a manner shown in Scheme I, which started with the condensation of ketone **2** with vinyllithium to give 2,2,4,6,6-pentamethyl-1-vinylcyclohexanol (**3**). Vinyl carbinol **3** was treated with phosphorus tribromide to give 1-(2,2,4,6,6-pentamethylcyclohexylidene)-2-bromoethane (**4**), which in turn was treated with the sodium salt of 2-nitropropane to give 2,2,4,6,6-pentamethylcyclohexylideneacetaldehyde (**5**). Oxidation of the aldehyde was accomplished with silver oxide to give 2,2,4,6,6-pentamethylcyclohexylideneacetic acid (**6**). Resolution of the acid with brucine gave (−)-2,2,4,6,6-pentamethylcyclohexylideneacetic acid (**7**) and the (−) acid could be converted directly to the nitrile using thionyl chloride–DMF followed by reaction with liquid ammonia (*vide infra*), but unfortunately the nitrile obtained from optically active acid was totally racemic. Therefore the acid, **7**, was converted to (−)-2,2,4,6,6-pentamethylcyclohexylideneacetamide (**8**) by treatment with oxalyl chloride followed by reaction with anhydrous ammonia. Finally, (−)-2,2,4,6,6-pentamethylcyclohexylideneacetonitrile ((−)-**1**) was obtained from the amide, (−)-**8**, by dehydration using thionyl chloride–DMF solution.



Scheme I. Synthesis of (−)-2,2,4,6,6-Pentamethyl-2,2,4,6,6-Pentamethylcyclohexylacetonitrile (**1**)

Somewhat later a different synthesis was found for making racemic nitrile **1**. Ketone **2** was condensed with the lithium salt of acetonitrile to give 1-hydroxy-2,2,4,6,6-pentamethylcyclohexylacetonitrile (**9**). Dehydration with thionyl chloride–DMF gave racemic nitrile **1** in good yield. Attempts were made to hydrolyze racemic nitrile **1** to acid **7** for resolution purposes, but both acidic and basic hydrolyses failed.



1(-*d*,-*t*)

The deuterated nitrile, **1**-*d*, was made by successive treatments of the protionitrile with sodium methoxide in methanol-*d*. Similarily the tritiated nitrile, **1**-*t*, was synthesized by reaction of the protionitrile with sodium methoxide in tritiated methanol.

The structure of nitrile **1** was confirmed by elemental analysis and nmr, ir, and mass spectra and the nitrile was shown to be homogeneous by gas chromotographic analysis.

Kinetics. The kinetic study was carried out in the manner of Walborsky and Motes[2] and is described in the Experimental Section. Methanol was chosen as solvent and sodium methoxide as base. The rate of exchange, k_e, of the vinyl hydrogen was measured and compared with the rate of racemization, k_r, of the optically active vinyl compound. The rates gave good first-order plots, and the second-order rate constants were obtained by dividing the pseudo-first-order constants by the base concentration.

The experimentally found ratio of k_e/k_r was 140 at 90°. See Table I. This corresponds to a 99.3% retention of configuration. That is, the vinyl anion is formed at least 140 times as it is racemized. The configurational change probably occurs by racemi-

Table I. Exchange *vs.* Racemization Rates

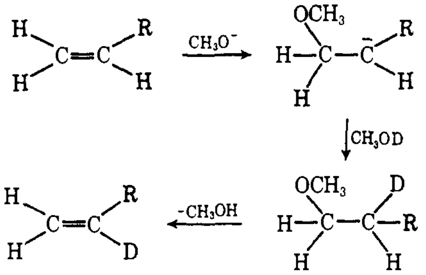
Temp,[a] °C	k_e,[b] l./mol sec	k_r,[b] l. mol sec	k_e/k_r
90.0	2.33×10^{-4}	1.67×10^{-6}	140 ± 7
50.0	8.03×10^{-7}	2.78×10^{-9}	289 ± 14
25.0	1.03×10^{-8}	2.15×10^{-11}	480 ± 24

[a] Temperature ±0.1°. [b] Concentration of **1** = 0.05 *M*; concentration of methoxide = 0.98 *N*.

zation mechanism rather than by the inversion or isoracemization processes (*vide infra*).

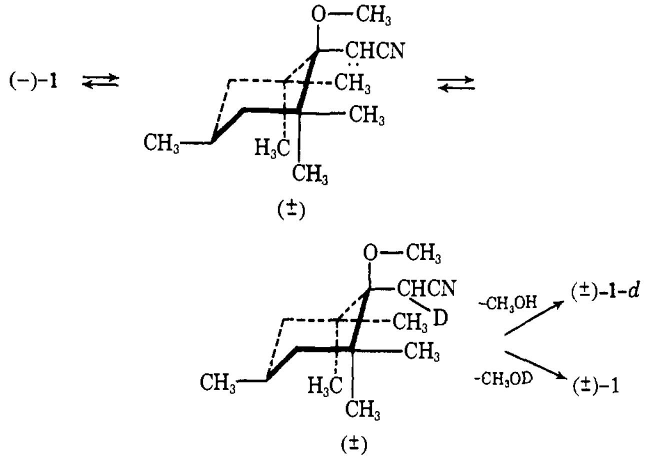
As was mentioned earlier, one of the most important limitations of the work on vinyl anions was the possibility of exchange occurring by the addition–elimination mechanism in which the solvent attacks the β position of the double bond giving a tetrahedrally hybridized carbanion which can remove a deuteron from solvent. Elimination of methanol-*h* would give an exchanged vinyl system without having formed a vinyl anion. The addition–elimination mechanism is illustrated in Scheme II.

Scheme II. The Addition–Elimination Mechanism



It is important to note that for the cyclohexylideneacetonitrile of the present research the exchange does not go by the addition–elimination mechanism. In Scheme III it can be seen that addition of methoxide ion to the double bond would result in total loss of optical activity.[7] Thus the exchange rate at the most would be only half as fast as the racemization, whereas it was found experimentally to be 140 times as fast.

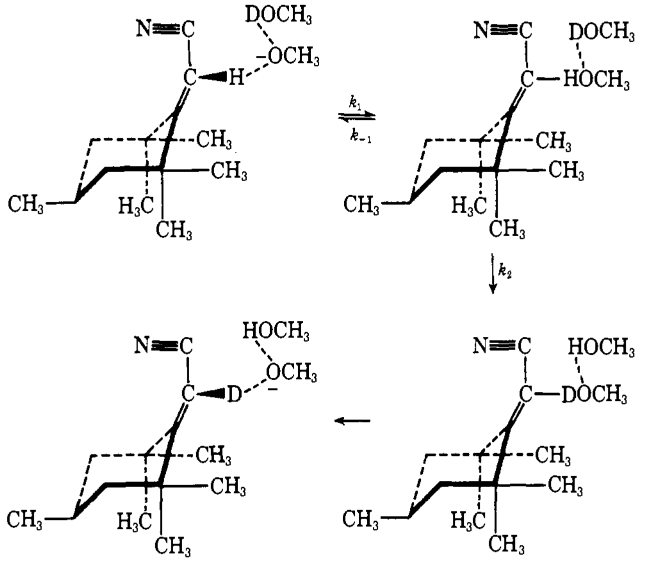
Scheme III. Addition–Elimination Mechanism for 2,2,4,6,6-Pentamethylcyclohexylideneacetonitrile



Exchange Reaction. A mechanism has been proposed by Cram[8] and Walborsky and Motes[2,3] for base-catalyzed hydrogen–deuterium exchange reactions For the present system the mechanism is illustrated in Scheme IV.

Sodium methoxide in methanol is known to be strongly hydrogen bonded to one or more methanol molecules.[9] The first step of the exchange reaction would be the removal of the vinyl proton by the base–solvent complex to give the vinyl anion with a rate constant, k_1. The reverse of the first step would be expected to be very fast, based on the recombination rates for nitriles.[10] That is, k_{-1} would be large since the carbanion would be a much stronger base than the methoxide. On the other hand if a solvent reorganization takes place (with rate constant k_2) then the carbanion becomes primarily associated with methanol-*d*, and capture of the deuteron by the carbanion would result in overall hydrogen–deuterium exchange. The rate constant, k_2, would be large since only hydrogen bonds are broken in the step. The overall rate constant for the exchange reaction would be given by eq 1, which assumes the steady-state concentration approximation

Scheme IV. Mechanism of Exchange Reaction



$$k_e = \frac{k_1 k_2}{k_{-1} + k_2} \qquad (1)$$

Under certain conditions eq 1 can be simplified. Thus if $k_2 \gg k_{-1}$ the rate constant, k_e, is given by

$$k_e = \frac{k_1 k_2}{k_2} = k_1$$

and the proton removal step is rate limiting.

On the other hand, if $k_{-1} \gg k_2$ then the rate constant, k_e, is given by

$$k_e = \frac{k_1 k_2}{k_{-1}} = Kk_2$$

where K is the equilibrium constant for the proton removal-recapture equilibrium. Thus k_2 becomes rate limiting; but the rate is determined by the product of the equilibrium constant, K, and the kinetic rate constant, k_2.

If k_2 and k_{-1} are of the same order of magnitude then eq 1 could not be simplified, and the observed rate constant would not be associated with a simple step of the reaction. That is, there would be approximately equal competition between the second step and the reverse of the first step.

Racemization. The experimentally found ratio k_e/k_r indicates that the vinyl hydrogen of **1** is exchanged 140 times as fast as it is racemized. That is, there is 99.3% retention of configuration.

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[7] The addition of methoxide is assumed to be stepwise and leads to a delocalized carbanion which would, of course, be racemic as with other acyclic nitriles.[2]

[8] D. J. Cram and L. Gosser, *J. Amer. Chem. Soc.*, **86**, 2950 (1964).

[9] D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *ibid.*, **83**, 3678 (1961).

[10] R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1955).

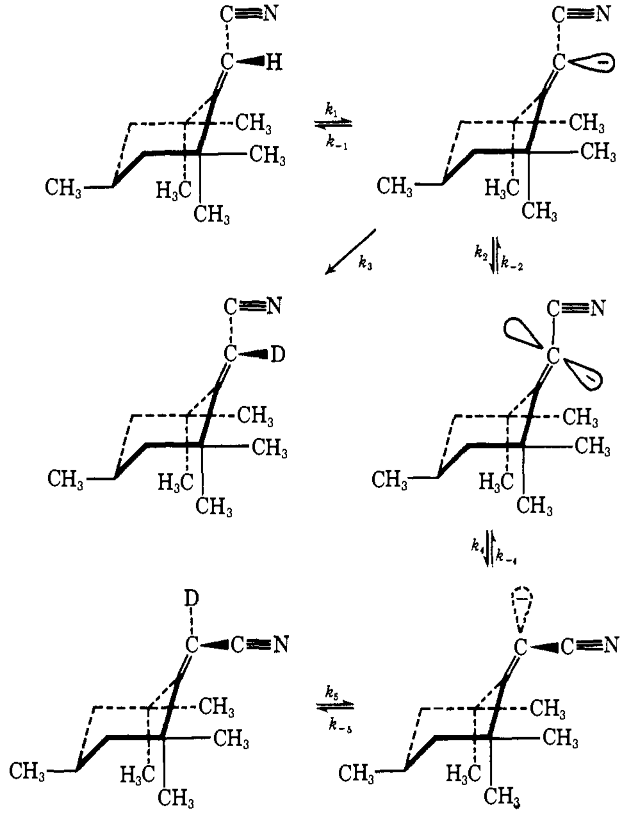
Table II. Kinetic Isotope Effects

Temp,[a] °C	k_H/k_D	k_D/k_T
90.0	2.05 ± 0.06	1.38 ± 0.04
75.0	1.66 ± 0.04	1.24 ± 0.04
60.0	1.20 ± 0.04	1.09 ± 0.03

[a] Temperature ±0.1°.

The retention and racemization mechanisms are illustrated in Scheme V.

Scheme V. Retention and Racemization Mechanisms



Isotope Effects. The kinetic isotope effects for the exchange reaction are listed in Table II. The hydrogen–deuterium exchange reactions were necessarily run in methanol-*d*, and the method of Andreades[11] was used to correct for solvent isotope effects.

The striking feature of the data of Table II is the small isotope effect for the exchange reaction. If the isotope effect were large (*e.g.*, $k_H/k_D \approx 6.0$) then carbon–hydrogen bond breaking in the rate-determining step would be indicated. However, small isotope effects can be accounted for in at least two different manners. One is that the carbon–hydrogen bond is broken in the rate-determining step, but the transition state is asymmetric. The hydrogen atom either is much closer to the carbon atom than to the oxygen atom, or the reverse. The asymmetry of the transition state would result in a cancellation of some of the difference in zero point energy for the carbon–hydrogen and carbon–deuterium bond and would lead to a small isotope effect.

A second explanation for k_H/k_D being small is that the carbon–hydrogen bond is not broken in the rate-limiting step of the reaction. For example, consider the postulated scheme in Scheme VI. If k_2 were much larger than k_{-1} then removal of the proton by base would be rate limiting, and the isotope effect would be large or small depending on the symmetry of the transition state. On the other hand, if k_2 were much smaller than k_{-1} then a preequilibrium would exist with the overall rate constant being the product of an equilibrium constant and a rate constant ($k_H = k_2K$). For such a case the isotope effect would be given by the expression

Scheme VI. Exchange Reaction Scheme

$$\text{R—H} + \text{CH}_3\text{O}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{R}^- + \text{CH}_3\text{OH} \xrightarrow[\text{CH}_3\text{OD}]{k_2} \text{RD} + \text{CH}_3\text{O}^-$$

$$k_H/k_D = (K_H/K_D)(k_{2_H}/k_{2_D})$$

Thus the overall isotope effect would be the product of an equilibrium isotope effect and a kinetic isotope effect. On this basis small and even inverse isotope effects can be obtained.[12]

While the small isotope effect by itself is not indicative of the mechanism of the exchange reactions,[13] it is interesting to note the variation of the isotope effect with temperature. The data of Table II show that the k_H/k_D increases with increasing temperature. If the carbon-hydrogen bond-breaking step alone were rate limiting (*i.e.*, $k_2 \gg k_{-1}$ and $k_2 \ll k_1$) then one would expect the isotope effect to decrease with increasing temperature.[14] The detailed dependence of kinetic isotope effects on temperature is not well understood at this time and it is impossible to predict the temperature dependence of isotope effects for the case where the solvent exchange (k_2) competes about evenly with the reverse of the first step (k_{-1}). Nevertheless, the decrease of the isotope effect with decreasing temperature is evidence against the mechanism with the carbon–hydrogen bond-breaking step as rate limiting.

In the case of 2,2-diphenylcyclopropylnitrile, it was concluded that C–H bond breaking was not involved in the rate-determining step.[2] One of the criteria used was to determine whether the Swain[15] equation, relating deuterium and tritium isotope effects, holds. If bond breaking is the rate-determining step in the reaction, then this equation should apply. Using the data from Table V (Experimental Section), which is uncorrected

$$\frac{k_H}{k_D} = \left(\frac{k_D}{k_T}\right)^{2.26} = 1.66$$

for solvent isotope effects, we find that the experimentally determined $k_H/k_D = 2.52$ and that obtained from the Swain equation is 1.66, which is 34% lower than the experimental value. Thus the same situation obtains in the vinyl as in the cyclopropyl system.

Activation Parameters. The activation parameters for the exchange and racemization reactions are listed in Table III. If the rate-limiting step of the overall reaction were a simple carbon–hydrogen bond-breaking step one would expect the activation enthalpy $\Delta H^{\ddagger}$ to vary only slightly for all three exchange reactions, since

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[11] S. Andreades, *J. Amer. Chem. Soc.*, **86**, 2003 (1964).

[12] For a detailed discussion, see D. J. Cram, D. A. Scott, and W. D. Nielsen, *ibid.*, **83**, 3696 (1961).

[13] For an interesting discussion and conclusion concerning low isotope effect, see W. K. Kwok, W. G. Lee, and S. I. Miller, *ibid.*, **91**, 468 (1969).

[14] L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960.

[15] C. G. Swain, E. C. Stivers, J. I. Reuwer, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.*, 80, 5885 (1958).

Table III. Activation Parameters

Reaction	$\Delta F^{\ddagger}_{100}$, kcal/mol	$\Delta F^{\ddagger}_{50}$, kcal/mol	$\Delta F^{\ddagger}_{25}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
T-H	28.0 ± 0.2	27.6 ± 0.2	27.4 ± 0.2	24.9 ± 0.2	−9 ± 1
D-H	27.8 ± 0.2	27.7 ± 0.2	27.7 ± 0.2	27.1 ± 0.2	−1 ± 1
H-D	27.2 ± 0.2	27.6 ± 0.2	27.9 ± 0.2	30.7 ± 0.2	9 ± 1
Rac	31.0 ± 0.2	31.6 ± 0.2	32.0 ± 0.2	36.6 ± 0.2	15 ± 1

only the difference in zero point energies for the carbon-hydrogen, carbon-deuterium, and carbon-tritium bonds would be involved. Also similar entropies of activation would be observed if the transition state and solvent orientations were the same for all three exchanges.

On the other hand, if the solvent exchange step were rate limiting, then the observed activation parameters would be functions of the overall rate constants, which in turn would be functions of the rate constants for the several steps of the reaction. Therefore if

$$k_{\text{obsd}} = \frac{k_1 k_2}{k_{-1} + k_2}$$

then

$$\exp(-\Delta F^{\ddagger}_{\text{obsd}}/RT) = \frac{\exp(-\Delta F^{\ddagger}_1/RT)\exp(-\Delta F^{\ddagger}_2/RT)}{\exp(-\Delta F^{\ddagger}_{-1}/RT) + \exp(+\Delta F^{\ddagger}_2/RT)}$$

It can be seen from this equation that it would be very difficult to predict quantitatively the changes in activation parameters with isotopic substitution where there is a preequilibrium or where solvent exchange competes with the reverse reaction of step 1.

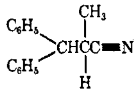
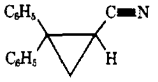
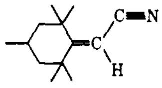
Nevertheless, it is interesting to note qualitatively that the entropy of activation increases as the reaction changes from T-H exchange to D-H exchange to H-D exchange to racemization. Negative entropies of activation are normally associated with highly orienting factors such as a bimolecular transition state or strong solvent participation. Positive activation entropies, on the other hand, are usually associated with unimolecular transition states or the release or breaking of a strong solvent shell. While the overall activation entropies for the exchange and racemization reactions cannot be attributed to any one transition state, their orderly increase is indicative of progress along the overall reaction coordinate, that is increasing importance of the solvent exchange step or, in the case of the racemization reaction, the solvent shell disruption to form a linear molecule.

The methoxide ion in methanol is known to be strongly associated with one or more solvent molecules[9] and it can be inferred that the vinyl carbanion would also be strongly associated with solvent molecules. Also, the carbanion is a much stronger base than methoxide and is known to be very rapidly protonated by methanol (the reverse of step 1). Thus the activation parameter evidence for the solvent exchange (step 2), being rate limiting, is quite reasonable although by itself not conclusive.

For the racemization the large positive entropy of activation is consistent with the picture of a strongly solvated trigonal carbanion breaking its solvent shell and becoming linear in the transition state and then collapsing to racemic product. The activation energy of 31 kcal/mol is a reasonable value for such a process.

Comparison of the Vinyl Anion with the Cyclopropyl Anion. The base-catalyzed removal of protons from the tetrahedrally hybridized carbon acid 2-methyl-3,3-diphenylcyclopropylnitrile resulted in some loss of configuration by the intermediate anion.[2] In contrast to this observation the cyclopropyl anion was shown to maintain its configuration. That is, k_e/k_r for 2,2-diphenylcyclopropylnitrile was found to be 913 at 90°.[2] The vinyl anion also maintains its configuration, though to a somewhat lesser degree than the cyclopropyl anion. The ratio k_e/k_r for the vinyl system 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile was found to be 140 at 90°. The reaction conditions for all three studies were the same: sodium methoxide in methanol. Also all three compounds used the cyano group as an acidifying agent. The data are summarized in Table IV. The common delocalizing group and common reaction medium for the three nitriles allow an assessment of the contribution of hybidization to the stereochemical stability of anions from carbon acids. It has been postulated that the s character of the carbon-hydrogen bond determines the stability of the resulting anion. Thus the vinyl anion, sp^2, would be more configurationally stable than the cyclopropyl (sp$^{2.28}$) anion which in turn would be more stable than the tetrahedrally hybridized (sp^3) system. However, there is the complicating factor in the case of the cyclopropyl system that the geometrical strain of the small ring would oppose the planarity of the transition state for the racemization. Therefore ring strain would contribute to the stability of the cyclopropyl anion. The results in Table IV indicate that the ring strain effect overcomes the rehybridization effect and the cyclopropyl anion is configurationally more stable than the vinyl anion.

Table IV. Comparison of Carbanions

Compd	Hybrid	k_e/k_r	k_H/k_D	% ret of confign
 $(C_6H_5)_2CHC(CH_3)(H)C{\equiv}N$	sp^3	1.87	2.60	47
	sp$^{2.28}$	913	1.50	99.0
	sp^2	140	2.05	99.3

Experimental Section

The infrared spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer, the nmr spectra with a Varian A-60 analytical spectrometer, and optical rotations with a Bendix automatic polarimeter using a 4-cm cell. Tritium counts were obtained with a Packard Tricarb liquid scintillation counter.

Solvents. Methyl alcohol-*d* and methyl alcohol-*t* were prepared by the method of Streitwieser, *et al.*[16] Methanol was dried by distillation from magnesium.

Stock Base Solutions. Stock base solutions of 1.0 *N* sodium methoxide in methanol were prepared by adding a weighed amount of clean sodium metal to the alcohol at −78° under an argon atmosphere. After all of the sodium metal had reacted, the solution was allowed to come to room temperature and was transferred to a volumetric flask. The stock solution was standardized with hydrochloric acid.

2,2,4,6,6-Pentamethylcyclohexanone. To a stirred solution of 22.4 g of 4-methylcyclohexanone in 300 ml of dry dimethoxyethane at 0° under a nitrogen atmosphere was added 42.0 g of sodium hydride dispersion (57% in mineral oil). After 30 min a solution of 142.0 g of methyl iodide in 250 ml of dimethoxyethane was added dropwise over a period of 12 hr. The reaction mixture was allowed to come to room temperature and stirred overnight. Water was added a few drops at a time until the hydrogen gas evolution ceased. The reaction mixture was poured onto ice, diluted with water, and extracted with three 200-ml portions of pentane. The combined pentane extracts were washed with saturated salt solution and dried over anhydrous sodium sulfate. Removal of the solvent followed by distillation using a spinning band column gave 28.6 g of 2,2,4,6,6-pentamethylcyclohexanone, bp 68° (13 mm), 194–195° (760 mm) (lit.[17] bp 194–196°).

1-Vinyl-2,2,4,6,6-pentamethylcyclohexanol. To a cooled solution of 25.2 g of 2,2,4,6,6-pentamethylcyclohexanone in 100 ml of dry tetrahydrofuran (distilled from lithium aluminum hydride), stirred under a nitrogen gas atmosphere, was added 130 ml of vinyllithium (1.2 *M* in tetrahydrofuran). The reaction was stirred at 0° for 1 hr, poured onto a mixture of ice and dilute HCl and extracted with ether and the ether extract dried over anhydrous sodium sulfate. Removal of solvent gave 27.2 g of 1-vinyl-2,2,4,6,6-pentamethylcyclohexanol: bp 64–66° (1 mm); ir (neat) 3610, 3500 (broad), 1638, 1465, 1396, 1388, 1372, 1140, 1075, 915 cm^{-1}; nmr (CCl_4) δ 6.30 (q, 1 H, J_{AX} = 18 Hz, J_{BX} = 11 Hz), 5.25 (q, 1 H, J_{AB} = 2 Hz, J_{AX} = 18 Hz), 5.17 (q, 1 H, J_{BX} = 11 Hz, J_{AB} = 2 Hz), 2.1–0.8 (m, 21 H).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.32; H, 12.25.

2,2,4,6,6-Pentamethylcyclohexylidenemethyl Bromide. To a solution of 19.6 g (0.1 mol) of 1-vinyl-2,2,4,6,6-pentamethylcyclohexanol in 50 ml of dry benzene was added 10.3 g of phosphorus tribromide in 15 ml of dry benzene. The solution was heated slowly to 60° and stirred for 4 hr. Care was taken not to allow the temperature to go above 65°. The solution was poured into a mixture of dilute sodium bicarbonate and ice. The benzene layer was extracted with aqueous bicarbonate, washed with water, and dried with molecular sieves, and the solvent removed to give 16.7 g of crude 2,2,4,6,6-pentamethylcyclohexylidenemethyl bromide. The bromide was unstable and was not further purified: nmr (neat) δ 5.58 (t, 1 H, J = 9.0 Hz), 4.08 (d, 2 H, J = 0.0 Hz), 2.1–0.8 (m, 20 H); ir (neat) 1622, 1465, 1388, 1372, 1205, 918 cm^{-1}.

2,2,4,6,6-Pentamethylcyclohexylideneacetaldehyde. To a solution of 25.9 g of 2,2,4,6,6-pentamethylcyclohexylidenemethyl bromide in 60 ml of dimethylformamide was added a mixture of 7.84 g of potassium hydroxide and 10.68 g of 2-nitropropane dissolved in water (8 ml) and dimethylformamide (30 ml). The resulting solution was stirred at room temperature for 24 hr, diluted with water, and extracted with petroleum ether. The petroleum ether extract was shaken with cold 1 *N* sodium hydroxide, washed with water, and dried with molecular sieves, and the solvent removed to give 2,2,4,6,6-pentamethylcyclohexylideneacetaldehyde (16.7 g) which was not further purified: nmr (CCl_4) δ 10.6 (d, 1 H, J = 8.0 Hz), 6.07 (d, 1 H, J = 8.0 Hz), 2.1–0.8 (m, 20 H); ir (neat) 1670, 1595, 1465, 1385, 1370, 1225, 1138.

2,2,4,6,6-Pentamethylcyclohexylideneacetic Acid. To 17.0 g of silver nitrate in 100 ml of water was added with stirring 6.5 g of potassium hydroxide in 100 ml of water. The brown curdy precipitate was collected, washed with water, and transferred to a round-bottomed flask. A solution of 1.6 g of potassium hydroxide in 150 ml of water was added, followed by 3.9 g of crude 2,2,4,6,6-pentamethylcyclohexylideneacetaldehyde. The reaction mixture was stirred vigorously and heated by a steam bath for 14 hr. The solution was decanted, and the residue was washed several times with hot water (80°). The washings and the decanted liquid were extracted with 20 ml of pentane, and the aqueous layer was poured onto a mixture of ice and dilute hydrochloric acid to give an amorphous solid 2,2,4,6,6-pentamethylcyclohexylideneacetic acid. Crystallization from methanol–water gave 1.24 g of white crystals: mp 91–93°; nmr (CCl_4) δ 12.0 (s, 1 H), 5.77 (s, 1 H), 2.0–0.8 (m, 20 H).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.30; H, 10.54.

Resolution of 2,2,4,6,6-Pentamethylcyclohexylideneacetic Acid. To a solution of 4.67 g of brucine in acetone was added a solution of 2.10 g of 2,2,4,6,6-pentamethylcyclohexylideneacetic acid in acetone; the resulting solution was heated for 30 min, and allowed to cool, and the acetone removed under vacuum to give an amorphous solid. The solid was dissolved in a minimum amount of methanol with heating. The methanol solution was allowed to stand overnight, and crystals of the brucine salt appeared. The crystals were filtered off, recrystallized twice from methanol, and again being dissolved in methanol were added to a mixture of ice and dilute hydrochloric acid. The mixture was diluted with water, and extracted three times with ether, and the ether extract was shaken with saturated sodium chloride solution. After drying the solvent was removed to give 0.80 g of (−)-2,2,4,6,6-pentamethylcyclohexylideneacetic acid: $[\alpha]^{24}_{\mathrm{Hg}}$ −53.2° (1% in $CHCl_3$); mp 66–68°; nmr and ir spectra were identical with the racemic acid.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.15; H, 10.52.

(−)-2,2,4,6,6-Pentamethylcyclohexylideneacetamide. To 1.05 g of (−)-2,2,4,6,6-pentamethylcyclohexylideneacetic acid ($[\alpha]^{24}_{\mathrm{Hg}}$ 51.8° (1% in $CHCl_3$)) in 15 ml of dry benzene at 0° was added 0.40 g of freshly distilled oxalyl chloride. After being stirred at ice bath temperature for 45 min, the reaction mixture was poured with vigorous stirring into an ice cold concentrated ammonium hydroxide solution. The white solid was filtered off, dissolved in chloroform, and combined with the chloroform extract of the filtrate. The chloroform solution was extracted with saturated sodium chloride solution, and dried over molecular sieves and the solvent evaporated to give 0.62 g of (−)-2,2,4,6,6-pentamethylcyclohexylideneacetamide: $[\alpha]^{24}_{\mathrm{Hg}}$ 10.1° (1% in $CHCl_3$); mp 102–104°; ir ($CHCl_3$) 3510, 3390, 1665, 1625, 1578, 1460, 1370, 1320 cm^{-1}; nmr (DCl_3) δ 6.7 (b, 1 H), 5.95 (s, 1 H), 5.7 (b, 1 H), 2.0–0.8 (m, 20 H).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.76; H, 11.27; N, 6.58.

(−)-2,2,4,6,6-Pentamethylcyclohexylideneacetonitrile. A solution of 0.314 g of (−)-2,2,4,6,6-pentamethylcyclohexylideneacetamide ($[\alpha]^{24}_{\mathrm{Hg}}$ −9.8°) in 10 ml of dry dimethylformamide (dried over molecular sieves) was cooled in an ice bath under a nitrogen gas atmosphere. To the stirred solution was added 0.200 g of thionyl chloride (freshly distilled from cottonseed oil). After being stirred for 4 hr at ice bath temperature, the solution was allowed to come to room temperature and was stirred overnight. The reaction mixture was poured onto ice and dilute sodium bicarbonate solution, diluted with water, and extracted with pentane. After the pentane extract was dried over molecular sieves, the solvent was removed to give 0.256 g of (−)-2,2,4,6,6-pentamethylcyclohexylideneacetonitrile: $[\alpha]^{25}_{\mathrm{Hg}}$ 21.4° (1% in $CHCl_3$); nmr and ir solution spectra of the (−)-nitrile were identical with those of the racemic nitrile.

1-Hydroxy-2,2,4,6,6-pentamethylcyclohexylacetonitrile. A solution of 0.41 g of acetonitrile (dried over molecular sieves) in 20 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was cooled under a nitrogen atmosphere in a Dry Ice–acetone bath to −70°. To the cooled solution was added 14.6 ml of 0.68 *M* *sec*-butyllithium in tetrahydrofuran, and the mixture was stirred for 1 hr at −70° and 1.68 g of 2,2,4,6,6-pentamethylcyclohexanone was added. After stirring for 5 min at −70°, the cooling bath was removed. After 10 min, the solution was poured onto a mixture of ice and dilute hydrochloric acid and extracted with ether. The ether extract was washed with a saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed to give an oil consisting of 1-hydroxy-2,2,4,6,6-pentamethylcyclohexylacetonitrile together with a small amount of starting ketone. The ketone was removed by vacuum distillation, and the pot residue which crystallized upon cooling was recrystallized from pentane to give 1.38 g of crystalline 1-hydroxy-2,2,4,6,6-pentamethylcyclohexylacetonitrile: mp 58–60°; ir (CCl_4) 3600, 3510, 2222, 1460, 1390, 1378 cm^{-1}; nmr δ 2.70 (s, 2 H), 2.45 (s, 1 H), 1.8–0.8 (m, 20 H).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.57; H, 10.94; N, 6.60.

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2,2,4,6,6-Pentamethylcyclohexylideneacetonitrile. A solution of 1.05 g of 1-hydroxy-2,2,4,6,6-pentamethylcyclohexylacetonitrile in 10 ml of dimethylformamide (dried over molecular sieves) was cooled under a nitrogen atmosphere in an ice bath, and 1.2 g of freshly distilled (from cottonseed oil) thionyl chloride was added. The solution was stirred at 0° for 4 hr, allowed to rise slowly to room temperature, and stirred overnight. The reaction mixture was poured onto a mixture of ice and sodium bicarbonate solution, diluted with water, and extracted with pentane. The organic layer was washed with saturated sodium chloride solution, and dried, and the solvent evaporated to give 0.90 g of 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile: bp 95° (1 mm); ir (neat) 2215, 1800, 1470, 1390, 1375, 1225, 820, 675 cm^{-1}; nmr (neat) 5.45 (s, 1 H), 2.0–0.8 (m, 20 H).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.32. Found: C, 81.46; H, 11.30; N, 7.38.

2,2,4,6,6-Pentamethylcyclohexylideneacetonitrile. Alternate Method. To 0.55 g of 2,2,4,6,6-pentamethylcyclohexylideneacetic acid dissolved in 5 ml of thionyl chloride (freshly distilled) was added 0.4 g of dimethylformamide, and the mixture was stirred at 0° under a nitrogen atmosphere for 1 hr. The excess thionyl chloride was removed under vacuum, and a Dry Ice condenser was connected to the reaction flask. Anhydrous ammonia (3 ml) was condensed into the flask, and stirring was continued for 3 hr and the ammonia allowed to evaporate. Water was added and the mixture extracted with pentane. The pentane solution was dried and evaporated to give 0.41 g of 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile.

α-Deuterio-2,2,4,6,6-pentamethylcyclohexylideneacetonitrile. A 10-ml sample of a 1 *N* solution of sodium methoxide in methanol-*d* was added *via* syringe to a culture tube fitted with a Teflon-lined cap and flushed with dry nitrogen. To the solution was added 1 g of 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile, and the tube was lightly capped and placed in an oil bath at 90° for 24 hr. The tube was cooled in an ice bath, and 1 ml of D_2O was added. The solution was extracted with three 5-ml portions of pentane, and the pentane solution was evaporated to give deuterated nitrile. The procedure was repeated on the deuterated nitrile using a fresh batch of sodium methoxide in methanol-*d*. The resulting deuterio-2,2,4,6,6-pentamethylcyclohexylideneacetonitrile was analyzed by nmr and mass spectral techniques and found to have 96% deuterium in the α position: ir (neat) 2215, 1590, 1470, 1390, 1375, 1233, 790, 760, 732 cm^{-1}.

α-Tritrio-2,2,4,6,6-pentamethylcyclohexylideneacetonitrile. Tritiated methanol (5 ml) (9800 cpmmg) was placed in a culture tube and cooled under a nitrogen atmosphere in an ice bath, and 0.115 g of freshly cut sodium was added. After the sodium had dissolved 0.200 g of 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile was added, and the culture tube was closed with a screw-top cap with a Teflon liner. The tube was placed in an oil bath at 90° for 48 hr, and then the sample was diluted with water and extracted with pentane. The pentane solution was evaporated and the nitrile residue was distilled to give 0.160 mg of α-tritio-2,2,4,6,6-pentamethylcyclohexylideneacetonitrile (485 cpm/mg).

Kinetic Runs. For a typical kinetic run an appropriate amount of nitrile was weighed into a clean dry volumetric flask. The flask was flushed with argon and then filled to the mark with stock base solution which had been withdrawn by syringe. The flask was stoppered and shaken to ensure complete solution. Individual samples (5 ml) were withdrawn by syringe and placed into thick-walled reaction tubes fitted with Teflon-lined screw caps. The reaction tubes were cooled and under an argon blanket at time of the transfer after which they were sealed. The sample tubes were placed into a well-stirred thermostatically controlled oil bath at the selected temperature and 30 sec was allowed for the tubes to come to thermal equilibrium at which the counter was started. As each point was withdrawn from the oil bath, it was placed in a Dry Ice-acetone slurry to quench the reaction. A dilute hydrochloric acid solution was added and the reaction mixture extracted with pentane. The pentane extract was shaken with dilute sodium bicarbonate solution and then with saturated sodium chloride solution. The pentane solution was dried over molecular sieves and the pentane removed to give the nitrile.

During each run the temperature variation of the bath was less than 0.1°. From five to ten points per run were taken and excellent pseudo-first-order kinetics were observed. For example on a typical run where log % D observed decreased from 1.929 to 1.217 the root mean square of the residuals was 0.009 using the least-squares approximation.

Table V. Exchange and Racemization Rate Constants[a] for 2,2,4,6,6-Pentamethylcyclohexylideneacetonitrile (0.05 *M*) with 1.0 *N* Sodium Methoxide in Methanol[b]

Reaction	Temp,[c] °C	k_2(av),[a] l. mol^{-1} sec^{-1}
H–D	90.0	3.62×10^{-4}
H–D	75.0	5.54×10^{-5}
H–D	60.0	7.42×10^{-6}
D–H	90.0	1.40×10^{-4}
D–H	75.0	2.65×10^{-5}
D–H	60.0	4.88×10^{-6}
T–H	90.0	1.12×10^{-4}
T–H	75.0	2.45×10^{-5}
Rac	100.0	6.68×10^{-6}
Rac	90.0	1.68×10^{-6}

[a] These are average rate constants from two to three runs and in each run five to ten points were taken. [b] These rate constants have not been corrected for solvent isotope effects. [c] ±0.1°.

Quantitative Infrared Analysis. In order to determine mole per cent deuterium in a sample from a kinetic run, the nitrile was dissolved in carbon disulfide and placed in a 1-mm path length infrared cell. The approximate overall concentration of nitrile was adjusted using the *gem*-dimethyl absorption (1380 cm^{-1}) as a standard. The region from 800 to 625 cm^{-1} was run five times and the average relative absorbances for H-nitrile to D-nitrile determined. From the ratio the mole per cent deuterium was obtained using a standard curve. The plot of log *c vs.* time yielded a straight line in all cases. The first-order rate constants were determined using the least-squares approximation on the experimental data with the aid of the CDC 6400 computer.

The standard curve for quantitative infrared analysis was obtained in the following way. A key absorption band was selected for the deuterated and nondeuterated nitrile. Ten samples of varying content were prepared by mixing carefully weighed amounts of pure H-nitrile and D-nitrile. For these samples the relative absorbances at the key frequencies were determined using the method described above. The ratio of absorbances A_D/A_H was plotted *vs.* mole per cent deuterium to yield a smooth curve. The accuracy of the calibration curve was estimated to be ±0.5%.

Radioactive Counting. The relative tritium concentrations of kinetic samples were obtained by scintillation counting. The unknown nitrile was carefully weighed into a counting vial, and 15.0 ml of the scintillation fluid (50 mg of 1,4-2-(5-phenyloxazoyl)-benzene and 4 g of 2,5-diphenyloxazole/l. of toluene) was added. The vial was capped, shaken to ensure solution, and placed in the scintillation counter. Four 10-min counts were taken with the first count always discarded to allow thermal equilibrium of the sample. Adjustments were made for background radiation and the activity of the sample (in counts per minute per milligram) was determined.

Optical Rotation. The rotations of samples from racemization reactions were determined directly on the reaction mixture. The rotations were taken in a 2-cm cell on a Bendix automatic polarimeter.

Acknowledgment. We thank Professor M. A. Schwartz for a number of helpful suggestions during the course of this work.