Cyclopropane. XXVII. The Cyclopropyl Anion[1]

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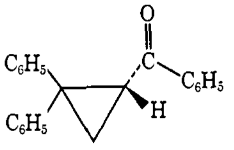
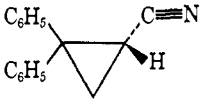
Abstract: The rate of hydrogen–deuterium exchange and rate of racemization of 1-benzoyl-2,2-diphenylcyclopropane (**1**) have been investigated. The ketone **1** exhibited only a moderate degree of retention of configuration (27%) which contrasts with the high degree of retention (99%) observed with the corresponding 1-cyano-2,2-diphenylcyclopropane (**2**). From hydrogen–deuterium and hydrogen–tritium isotope effects, it has been suggested that in both the base-catalyzed exchange and racemization reactions of **1** the rate-determining step is proton abstraction.

We recently reported[2] that the 1-cyano-2,2-diphenylcyclopropyl anion, obtained by the reaction of **2** with sodium methoxide in methanol, was capable of retaining its configuration. Moreover, it was established that proton abstraction was not involved in the rate-determining step. We wish now to present our data on the rates of sodium methoxide catalyzed racemization and exchange reaction of **1**. In contrast to **2** we will demonstrate that proton abstraction by methoxide ion is the rate-determining step in both the exchange and racemization reactions of **1**.


(−)-(*R*)-1


(−)-(*R*)-2

Results and Discussion

The synthesis of **1** has previously been described[3] and its absolute configuration is based on the previously determined absolute configuration of its precursor carboxylic acid.[4] The syntheses of the 1-deuterio and 1-tritio derivatives may be found in the Experimental Section.

The kinetic methods used are described in the previous article.[2] The second-order rate constants were determined by dividing the pseudo-first-order rate constants by the base concentration. The first-order rate plots yielded straight lines in all cases studied.

Racemization of (−)-(*R*)-1-Benzoyl-2,2-diphenylcyclopropane (1). The data in Table I show that the reaction of **1** with sodium methoxide in methanol occurs with a moderate degree of retention of configuration. This contrasts strongly with the cyclopropyl nitrile (**2**) which shows a very high degree of retention (>99%). In order for racemization or loss of configuration to occur the asymmetric carbanion must either become planar (delocalized) or undergo inversion. Since Cram[5] has shown that solvation effects alone cannot preserve the configuration of a carbanion stabilized by an α-carbonyl, the cyclopropyl ring must be exerting its influence by providing an energy barrier to the inversion or delocalization of the carbanion. The energy barrier for the racemization of the cyclopropyl carbanion is a function of a number of factors,[2] but in this case the most important ones are ring strain and the ability of the carbonyl group to delocalize the electron pair. The former provides a barrier toward racemization since the formation of an exocyclic double bond (delocalized form) to a cyclopropyl ring is energetically unfavorable (I strain) whereas the latter provides a mode for racemization.

Table I. Hydrogen–Deuterium Exchange *vs.* Racemization for 1-Benzoyl-2,2-diphenylcyclopropane

Solvent	Temp, °C	$NaOCH_3$ concn, *M*	k_e/k_r[a]	% retention
Methanol	75	0.1	1.37	27

[a] Ratio of second-order rate constants for exchange to racemization and corrected for solvent isotope effect.

Our results indicate that the delocalization energy associated with the carbonyl group is just sufficient to overcome the barrier to planarity of the carbanion.[6] Since the cyclopropyl nitrile (**2**) shows such a high degree of retention in the same solvent–base system, it is apparent that the carbonyl delocalization energy is much larger than that of the nitrile[7] and is the controlling factor in determining the degree of racemization.

The racemization of **1** can best be explained in terms of the following reaction scheme (Scheme I).

The racemization of **1** in methanol probably occurs largely through the planar-delocalized form of the carbanion. The moderate degree of retention of configuration observed in this system must reflect a *small energy difference* between the delocalization energy and the sum of ring constraint and the hydrogen bonding effects of the solvent.

Exchange Reactions and Isotope Effects. A plausible mechanism for the hydrogen–deuterium exchange reaction of **1** is that proposed by Cram[5,8] and coworkers.

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(1) The support of this work by a grant from the National Science Foundation and a Public Service Research Grant No. CA 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) H. M. Walborsky and L. Plonsker, *ibid.*, **83**, 2142 (1961).

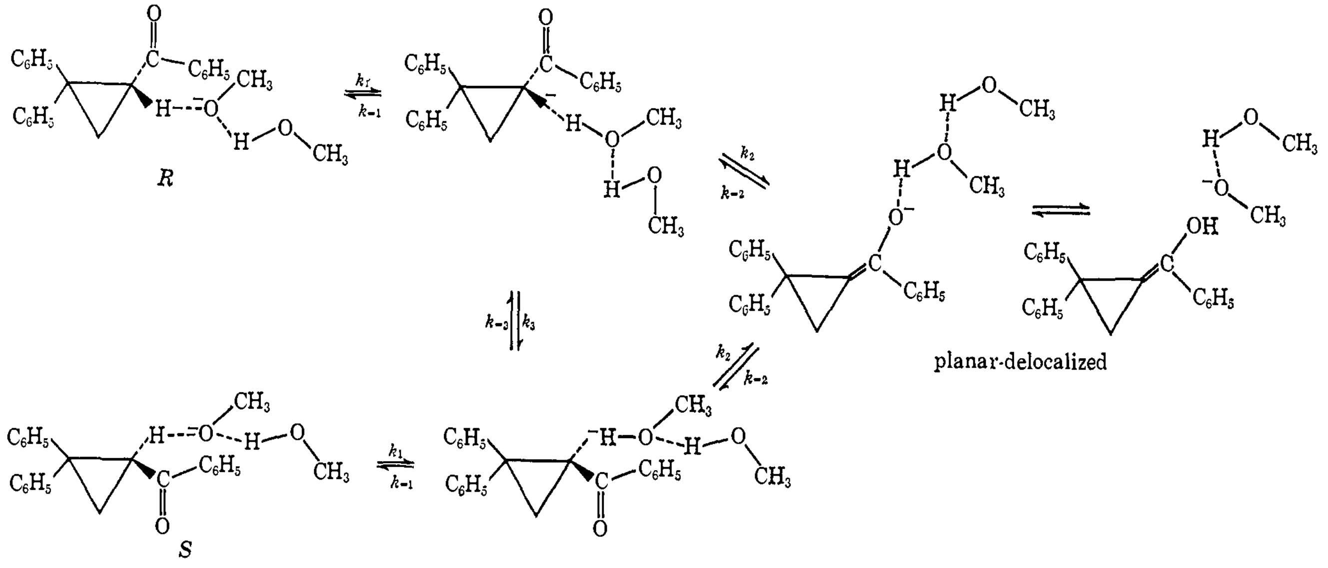
(4) H. M. Walborsky and C. G. Pitt, *ibid.*, **84**, 4831 (1962).

(5) D. J. Cram and L. Gosser, *ibid.*, **86**, 2950 (1964); C. A. Kingsbury and P. Haberfield, *ibid.*, **83**, 3678 (1961).

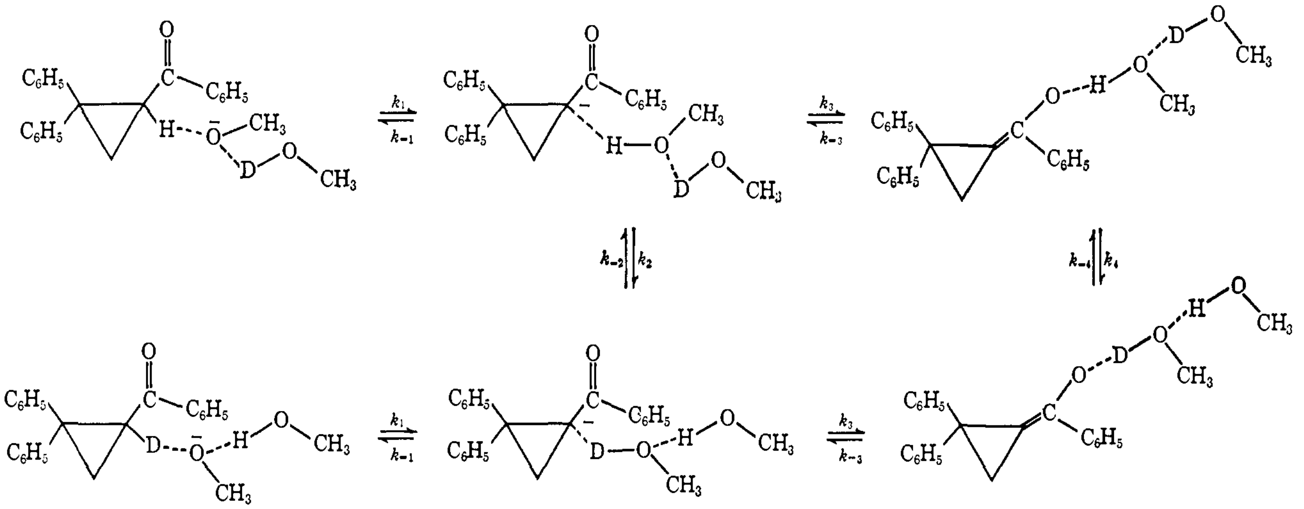
(6) This is shown by the observation that the rate of exchange of methine protons in isopropyl phenyl ketone is *ca.* 150 times faster than in cyclopropyl phenyl ketone; see W. Th. Van Wijnen, H. Steinberg, and Th. S. DeBoer, *Rec. Trav. Chim. Pays-Bas*, **87**, 844 (1968); see also, C. Rappe and W. H. Sachs, *Tetrahedron*, **24**, 6287 (1968), and H. W. Amburn, K. C. Kauffman, and H. Shechter, *J. Amer. Chem. Soc.*, **91**, 530 (1969).

(7) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1955); L. A. Cohn and W. M. Jones, *ibid.*, **85**, 337, 3402 (1963).

Scheme I



The first step involves the removal of the acidic proton by the active base[8] (methoxide ion hydrogen bonded to one or more methanol molecules) to form a hydrogen-bonded carbanion (k_1). Once the hydrogen-bonded carbanion is formed, the solvent exchange reaction (k_2 or k_4) occurs in competition with the back reaction (k_{-1}). Using the steady-state condition, one can easily derive the following rate expression for the observed rate constant for the exchange reaction.



$$\mathrm{RH} + \mathrm{B}^- \underset{k_{-1}^{\mathrm{H}}}{\overset{k_1^{\mathrm{H}}}{\rightleftharpoons}} \mathrm{R}^-\cdots\mathrm{HB} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{R}^-\cdots\mathrm{DB} \underset{k_{-1}^{\mathrm{D}}}{\overset{k_1^{\mathrm{D}}}{\rightleftharpoons}} \mathrm{RD} + \mathrm{B}^- \quad (1)$$

$$k_{\mathrm{obsd}} = k_1k_2/(k_{-1} + k_2) \quad (2)$$

$$k_{\mathrm{obsd}} = k_1 \quad (3)$$

If the rate constant for the solvent exchange (k_2) is significantly larger than the reverse reaction (k_{-1}), the expression, 2, will be reduced to eq 3. In light of the observed kinetic isotope effect (see Table II) ($k_{\mathrm{C-H}}^{\mathrm{O-D}}/k_{\mathrm{C-D}}^{\mathrm{O-H}} = 6.06$ and $k_{\mathrm{C-H}}^{\mathrm{O-H}}/k_{\mathrm{C-D}}^{\mathrm{O-H}} = 5.06$) we believe this to be the case for the ketone **1**.

This raises the question as to why the cylcopropyl ketone (**1**) is so different from the cyclopropyl nitrile (**2**). The best explanation lies in the relative acidities of these compounds.[9] Carbon acids stabilized by the carbonyl group are usually several pK_a units more acidic and have much smaller recombination rate constants (k_{-1}) than those stabilized by cyano groups.[7] This is borne out by our calculated pK_a's of 22.6 for **1** and 26.7 for **2**, using the method of Streitwieser.[10] The increased acidity and decreased recombination rate of the cyclopropyl ketone results in a faster hydrogen-

Table II. Rates of Deuterium and Tritium Exchange Reactions of 1-Benzoyl-2,2-diphenylcyclopropane at 75° and 0.1 *M* in Sodium Methoxide

Reaction	Solvent	k_2 (av), l. M^{-1} sec^{-1}
H-D	CH_3OD	7.45×10^{-3} 6.22×10^{-3} [b]
D-H	CH_3OH	1.23×10^{-3}
T-H[a]	CH_3OH	6.0×10^{-4}

[a] We wish to thank W. Jaeger for this determination. [b] Corrected for solvent isotope effect; see S. Andreades, *J. Amer. Chem. Soc.*, **86**, 2003 (1964).

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[8] D. J. Cram, "Fundamentals Carbanion Chemistry," Academic Press, New York, N. Y., 1965; D. J. Cram and P. Haverfield, *J. Amer. Chem. Soc.*, **83**, 2354 (1961).

[9] Under identical conditions, k_2 for H → D exchange is 11.8 times greater for **1** than for **2**.

[10] A. Streitwieser, Jr., J. I. Brauman, J. H. Hammons, and A. H. Pudjaatmaka, *J. Amer. Chem. Soc.*, **87**, 384 (1965).

deuterium exchange rate and a definite change in the rate-controlling step of the mechanism.

Tritium studies offer further support for proton abstraction by base being the rate-determining step in the exchange and racemization reactions. The rate of tritium–hydrogen exchange was determined experimentally, but the rate of the forward hydrogen–tritium could not be determined directly.

The hydrogen–tritium isotope effect can be calculated from a knowledge of the hydrogen–deuterium exchange reaction by the use of eq 4 or the Swain[11] eq 5. The value of $k_{\mathrm{H-T}}$ should not differ greatly from $k_{\mathrm{H-D}}$ since only the solvent isotope effect would be involved.

$$k_{\mathrm{H-T}}/k_{\mathrm{T-H}} = k_{\mathrm{H-D}}/k_{\mathrm{T-H}} = 10.4 \tag{4}$$

$$k_{\mathrm{H-T}}/k_{\mathrm{T-H}} = [k_{\mathrm{H-D}}/k_{\mathrm{D-H}}]^{1.442} = 10.4 \tag{5}$$

It must be concluded from the normal hydrogen–deuterium isotope effects that the proton abstraction by base is rate determining in the exchange and racemization reaction of 1-benzoyl-2,2-diphenylcyclopropane.

Experimental Section

The infrared spectra were obtained with a Perkin-Elmer infracord spectrophotometer, the nmr spectra with a Varian A-60 analytical spectrometer, and optical rotations with a Bendix automatic polarimeter using a 1.0-cm cell. Tritium counts were obtained with a Packard Tricarb liquid scintillation counter.

Solvents. Methyl alcohol-*d* was purchased from Volk Radiochemical Co. or prepared by the method of Streitwieser, *et al.*[12]

Stock Base Solutions. Stock base solutions of 1.0 *N* sodium alkoxide in alcohol (or alcohol-*d*, alcohol-*t*) were prepared by adding a weighed amount of clean sodium metal to the alcohol at −78° under an argon atmosphere. After all the sodium metal had reacted, the solution was allowed to warm to room temperature and transferred to a volumetric flask. The stock solution was standardized with hydrochloric acid and 0.1 *N* solutions were prepared by dilution.

Exchange Method. The stock solutions were prepared in volumetric flasks by adding the stock base solutions to a weighed amount of the cyclopropyl compound. These solutions were shaken until all of the cyclopropyl compound was dissolved. Five-milliliter portions were removed with a syringe and were transferred to Pyrex ampoules or Pyrex screw cap vials (with Teflon liners). The tubes were then placed in a constant-temperature bath at the appropriate temperature. Each tube was removed after a predetermined time and was quenched in a Dry Ice–acetone bath before opening. The samples were worked up using the following two methods. (1) The contents of each tube was poured into a solution of 40 ml of a 10% hydrochloric acid solution which was saturated with sodium chloride. The ether layer was separated and washed with a 5% sodium bicarbonate and three portions of water. After drying the ether solution over magnesium sulfate, the ether was removed and the residue was sublimed at 95° and 1 mm pressure. (2) The contents of each tube was shaken with 10 ml of a 10% hydrochloric acid solution. The precipitate was washed thoroughly with water and air dried before it was sublimed at 90° and 1 mm pressure. The purified compound was transferred to a small beaker and 0.5 ml of spectrograde carbon disulfide was added. The solution was warmed slightly to ensure complete solution. The infrared spectrum of the desired region was taken six to nine times, and the ratio of peak intensities was determined. From this ratio the mole % deuterium compound was determined using a standard curve. The plot of log *c vs.* time yielded straight lines in all cases. The first-order rate constants were determined by a least-squares fit of the experimental data. The average error in the first-order rate constant is approximately 5%.

Quantitative Infrared Analysis. The ratio of absorbances method was used to prepare a standard deuterium curve. A key absorption band was selected for the deuterated and nondeuterated compound, and a plot was made of the ratio of absorbances, $A_{\mathrm{D}}/A_{\mathrm{H}}$, against mole % deuterium compound. The accuracy of the calibration curve is estimated to be 0.5%. The unknown samples were run in a similar manner, and the mole % deuterated compound was read directly from the calibration curve. The infrared method was checked by combustion analysis.[13]

Racemization Method. The experimental method for the racemization reactions was identical with that for the exchange reactions except that the optical rotations were taken directly on the reaction mixtures.

Product Analysis. The mixtures of deuterated and nondeuterated compounds showed no melting point depression, and the infrared and nmr spectra indicated that no other compounds were present.

1-Deuterio-1-benzoyl-2,2-diphenylcyclopropane.[13] A 1-g sample of the ketone[3] I was heated at 100° for 24 hr in 15 ml of 1.0 *N* sodium methoxide dissolved in methanol-*d*. The methanol-*d* was recovered by distillation and the residue was taken up in ether and washed several times with water. After drying, the ether was removed and the deuterated ketone was sublimed at 95° and 1-mm pressure to yield 0.9 g, mp 133–135°.

1-Tritio-1-benzoyl-2,2-diphenylcyclopropane was prepared in a similar manner to the 1-deuterio derivative.

Table III is typical of the rate data for the tritium–hydrogen exchange.[14] Straight lines were obtained in all cases and the average of 2 runs gave an average slope 2.303 of 3.68×10^{-3} min^{-1}.

Table III. Tritium–Hydrogen Exchange for 1-Tritio-1-benzoyl-2,2-diphenylcyclopropane[a]

Time, min	Counts/min	1 mg
50	1102	347.2
100	916	290.9
150	767	246.1
200	648	209.5
250	526	167.2
300	435	137.3
350	372	119.3
400	298	93.9

[a] Temperature = 75°; ketone concentration = 3.4×10^{-2} *M*; $\mathrm{NaOCH_3}$ = 0.103 *N*.

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[11] C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Shaad, *J. Amer. Chem. Soc.*, **80**, 5885 (1958).

[12] A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

[13] A_{D} was absorption band at 1062 cm^{-1} and A_{H} at 1137 cm^{-1}. Analyses were performed by J. Nemeth, Urbana, Ill.

[14] Scintillation counting was performed using PPO (4 g/l.) and POPOP (50 mg/l.) in toluene counting solution in conjunction with a Packard Tricarb liquid scintillation counter.