which was identical in all respects with that obtained by methanolic iodination of **1** (see above).

*trans*-**4-Methoxy-2-pentene.** Sodium hydride (5.29 g, 0.126 mol) as a 56% by weight suspension in mineral oil was first washed with dry ether and then covered with 50 ml of dry ether. To the stirred hydride suspension was slowly added 9.0 g (0.105 mol) of *trans*-3-penten-2-ol[36] with cooling. When evolution of hydrogen ceased, methyl iodide (17.9 g, 0.126 mol) was added and the mixture stirred at room temperature for 24 hr. After dropwise addition of water to destroy excess hydride, the mixture was extracted with water and ether. The ether extract was dried over magnesium sulfate and filtered. The ether was distilled off through a 9-in. column packed with metal helices. The residue was distilled through the same column giving 4.27 g (0.043 mol, 43%) of *trans*-4-methoxy-2-pentene, **10**, bp 89–91° (lit.[21a] bp 90°). The nmr spectrum in carbon tetrachloride showed a two-proton multiplet centered at 5.7 ppm, a one-proton multiplet centered at 3.5 ppm, a three-proton singlet at 3.32 ppm, and two three-proton doublets at 1.75 and 1.13 ppm.

Optically active **10** was obtained in the following manner. *trans*-3-Penten-2-ol was converted into the acid phthalate ester and resolved *via* the brucine salt according to the method of Hill, Kenyon, and Phillips.[21a] The (+)-acid phthalate ester, $[\alpha]^{22}D$ +22.2 ± 0.2° (*c* 4, $CHCl_3$), which is estimated to be 58% optically pure,[23] was reduced with lithium aluminum hydride in ether to give (+)-*trans*-3-penten-2-ol. Treatment of this alcohol with sodium hydride and methyl iodide as described for the racemic alcohol gave (−)-4-methoxy-2-pentene, $[\alpha]^{23}D$ −54.2° (*c* 3, $CHCl_3$).

**2-Methoxypentane.** The procedure and apparatus used to effect catalytic hydrogenation of 4-methoxy-2-pentene to 2-methoxypentane was that described by Brown and Brown.[37] In the reaction flask (B) was placed 35 ml of ethanol, 1 ml of 5% chloroplatinic acid, and 1 g of activated charcoal. In the generator flask (A) was placed 10 ml of 1.0 *M* sodium borohydride, 1 *M* in sodium hydroxide. The system was purged with nitrogen. Basic sodium borohydride solution (5 ml, 1 *M*) in ethanol and 0.7 ml of glacial acetic acid were injected separately into B while the contents were stirred magnetically. Concentrated hydrochloric acid (10 ml) was injected into A which effectively replaced nitrogen with a hydrogen atmosphere. Into B was injected 3.0 g of 4-methoxy-2-pentene. As hydrogen was absorbed, sodium borohydride solution was automatically drawn into A as required. After about 10 hr the theoretical amount of borohydride solution had been consumed. The contents of B were filtered into 50 ml of 5% sodium carbonate solution and extracted with 50 ml of ether. The ether extract was washed repeatedly with water, dried, and distilled. Distillation through a 9-in. column packed with metal helices gave, after removal of the solvent, 1.38 g of 2-methoxypentane, **11**, bp 88–89°. The nmr spectrum of this product showed *no* vinyl resonances. The O-methyl singlet was superimposed on the one-proton methine resonance at 3.4 ppm; a methyl doublet was evident at 1.12 ppm, and the remaining signals were complex multiplets in the region 0.7–1.6 ppm.

Catalytic hydrogenation (by the procedure described above) of (−)-**10**, $[\alpha]D$ −54.2° (*c* 3, $CHCl_3$), obtained by methylation of (+)-*trans*-3-penten-2-ol, gave (+)-**11**, $[\alpha]D$ +9.9° (*c* 5, $CHCl_3$). Catalytic hydrogenation of an 82:18 *trans–cis* mixture of (−)-**10**, $[\alpha]^{23}D$ −5.33° (*c* 33, $Et_2O$), obtained by borohydride reduction of (−)-**8**, gave (+)-**11**, $[\alpha]^{24}D$ +1.2° (*c* 11, $CHCl_3$).

(36) E. R. Coburn, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 696.

(37) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966).

# Lack of Steric Hindrance and of Stereoelectronic Control in Proton Removal from 4,4-Disubstituted Cyclohexanones

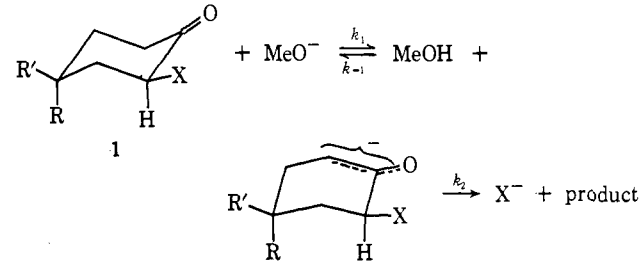
**F. G. Bordwell and Richard G. Scamehorn**[1]

*Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201.* *Received April 13, 1968*

**Abstract:** Comparison of the rates of base-catalyzed deuterium exchange at the α positions of 4,4-diphenyl-, 4-methyl-4-phenyl-, and 4,4-dimethylcyclohexanones with that of cyclohexanone itself failed to reveal steric hindrance to proton abstraction by the 4-axial substituents. Since the original evidence for stereoelectronic control in proton abstraction is based on the assumption that the steric effect of a 4-axial substituent is substantial, these results cast doubt on the importance of this factor.

The kinetic data presented in an earlier paper[2] revealed a sizable rate retardation for Favorskii reactions of 2-chloro-4,4-disubstituted cyclohexanones relative to 2-chlorocyclohexanone itself. From studies of deuterium exchange and Br/Cl leaving group effects it was concluded that the reactions proceeded by loss of halide ion from an enolate ion rather than by a concerted 1,3 elimination of a hydrogen and a halogen atom.

The rate retardation was found to be associated with the presence of the axial group, since the rate for 2-chloro-4-phenylcyclohexanone was not retarded. Two explanations for this axial effect are possible: (a) the axial group interferes in some way with the loss of $X^-$ ($k_2$ (and $k_{obsd}$) will then decrease relative to 2-chlorocyclohexanone), or (b) the axial group causes a shift in the equilibrium resulting in a lower concentration of enolate ion ($k_{obsd}$ will then decrease since $k_{obsd} = K_{eq}k_2$). Shift of the **1** ⇄ **2** equilibrium away from **2** conceivably could result from a decrease in $k_1$ caused by steric hindrance to removal of the C-6 axial proton from **1**. In fact, it has been suggested that a similarly




(1) National Institutes of Health Predoctoral Fellow, 1966–1968.

(2) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).

situated axial methyl group has a sizable retarding effect on proton removal in an acid-catalyzed enolization.[3-5]

In order to obtain evidence on this point the rates of exchange for a number of 4,4-disubstituted cyclohexanones were examined (Table I).

**Table I.** Rates of Methoxide Ion Catalyzed Exchange of Cyclohexanone and 4,4-Disubstituted Cyclohexanones in $CH_3OD$ at 25°

| 4,4-Disubstituted cyclohexanone R | R′ | $k$,[a] $M^{-1}$ sec$^{-1}$ |
|---|---|---|
| H | H[b] | $1.05 \times 10^{-1}$ |
| Ph | Ph[c] | $3.4 \times 10^{-1}$ |
| Ph | Me[c] | $8.9 \times 10^{-2}$ |
| Me | Me[d] | $5.7 \times 10^{-2}$ |

[a] Rate constants for total exchange at the $\alpha$ positions ($k^{group}$); see C. Rappe and W. H. Sachs, *J. Org. Chem.*, **32**, 4127 (1967), for a discussion of terminology. [b] Average of five runs (±0.014 average deviation). [c] Average of two runs. [d] One run only.

The data in Table I show that 4-axial substituents exert very little effect on the rate of proton abstraction at the 2 position. The 3.2-fold *faster* rate for 4,4-diphenylcyclohexanone, as compared to cyclohexanone, is the result that might be expected for the inductive effect of the phenyl groups. There is no evidence for a steric effect here, and the effect appears to be negligible in the other ketones also.

The failure of an axial 4-methyl or even an axial 4-phenyl group to retard appreciably the removal of a proton from the C-2 position of cyclohexanones casts doubt on the importance of stereoelectronic control in influencing the rate of proton abstraction since the evidence to support this theory collapses in the absence of such a steric effect. The direct evidence for stereoelectronic control is actually slight. The original postulate rested mainly on the fact that the 6$\beta$ axial proton in 3$\beta$-acetoxycholestan-7-one is removed preferentially, relative to the 6$\alpha$ equatorial proton. The rate preference was small (1.2–1.5-fold) but the supposition was made that this preference would be much larger in the absence of the hindering effect of the axial methyl group at C-10.[3] The idea is an attractive one and has been widely accepted but, as has been recently pointed out,[6] in most subsequent instances the steric and stereoelectronic effects also have been in conflict and "it is not possible to assess the contribution of each toward the stereochemical course of enolization and ketonization." If the steric effect proves to be of minor importance this will be true also for the stereoelectronic effect. The data in Table I indicate that this is the situation, at least for proton abstraction by methoxide ion in methanol. It is of course conceivable that stereoelectronic control could be of importance with other bases and solvents or in acid-catalyzed enolization, but it would seem that additional evidence is required to establish this point.

Stereoelectronic control requires that the proton be removed most readily when the C–H bond is at right angles to the plane of the C=O group and, therefore, parallel to its $p$ orbitals.[3] The axial H–C bond in cyclohexanone actually does not meet this optimum condition in the ordinary chair form. As an alternative it has been suggested that the transition state structure will be that which minimizes steric repulsions.[7] For an acyclic system the preferred transition state will then be that in which the C–H bond of the proton being removed and the C=O bond are *trans* and coplanar.[7] Our own view is that the steric hindrance to proton abstraction noted by Feather and Gold[7] and elsewhere[8] is most likely caused by steric hindrance to solvation,[9] and that the geometry of the transition state is still open to question.

## Experimental Section

**Kinetic Materials.** 4,4-Diphenylcyclohexanone,[10] 4-methyl-4-phenylcyclohexanone,[2] and 4,4-dimethylcyclohexanone[10] were purified by washing with sodium bicarbonate solution and with water, drying, and recrystallizing. Cyclohexanone was purchased commercially, washed as above, and distilled. The methanol-O-$d_1$ was prepared by the method of Streitwieser, Verbit, and Stang[11] (>98.5% $d$).

**Kinetic Procedure.** The rate of exchange of the $\alpha$-hydrogen atoms with deuterium was measured by removal of aliquots from a methanol-O-$d_1$ solution of known base concentration, isolation of the ketone, and analysis of the number of $\alpha$ protons remaining by nmr spectroscopy. In a typical run, 50 ml of a 0.078 $M$ solution of 4,4-diphenylcyclohexanone in methanol-O-$d_1$ and 10 ml of a $1.382 \times 10^{-2}$ $M$ sodium methoxide in methanol-O-$d_1$ solution were thermostated for 30 min at 25 ± 0.03° (Aminco No. 4-8600 constant-temperature bath). The solutions were combined and mixed. Aliquots (5 ml) were withdrawn at timed intervals and delivered into a quenching solution consisting of 1 ml of 0.25 $N$ nitric acid and 10 ml of water. The ketone precipitated immediately and was either filtered, washed with water, and dried, or taken up in carbon tetrachloride, dried, and concentrated to ~250 $\mu$l.

The number of $\alpha$ protons remaining was determined from integrated nmr spectra. The nmr spectrum of the unexchanged ketone was taken with each run, and in each instance the value was ±0.03 protons of theoretical. The data obtained from a typical run are shown in Table II. The rate constant was calculated from the slope of a plot of log $(a - x)$ *vs.* $t$. Division of the first-order rate constant by the base concentration gave the second-order rate

**Table II.** Data Obtained from a Typical Deuterium Exchange Reaction of 4,4-Diphenylcyclohexanone

| $t$, sec | $\alpha$ protons remaining |
|---|---|
| 83 | 3.38 |
| 186 | 3.22 |
| 298 | 2.96 |
| 400 | 2.65 |
| 512 | 2.44 |
| 651 | 2.30 |
| 912 | 1.78 |
| 1220 | 1.40 |
| 1536 | 1.04 |
| 1810 | 0.90 |
| ∞ | 0.03 |

(3) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).
(4) An example where methyl substitution causes a shift in equilibrium due principally to a decrease in $k_1$ (presumably due to steric hindrance) may be found in the $10^2$ decrease in $K_a$ for $(MeCO)_2CHCH_3$ relative to $(MeCO)_2CH_2$. Here methyl substitution causes a 210-fold decrease in $k_1$ and only a 2.1-fold decrease in $k_{-1}$.[5]
(5) See the values of $k_1$ and $k_{-1}$ compiled by R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).
(6) J. Fishman, *J. Org. Chem.*, **31**, 520 (1966), and references cited therein.
(7) J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).
(8) See J. Hine, J. G. Huston, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, **87**, 5050 (1965), for references and a discussion.
(9) E. S. Lewis and J. D. Allen, *ibid.*, **86**, 2022 (1964), footnote 6.
(10) F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 2544 (1963).
(11) A. Streitwieser, L. Verbit, and P. Stang, *ibid.*, **29**, 3706 (1964).

constant. The plots remained linear until 2.5–3.0 of the four $\alpha$ protons were exchanged, after which the rate gradually dropped off, presumably due to isotope effects. The rate constants were reproducible within 5%.

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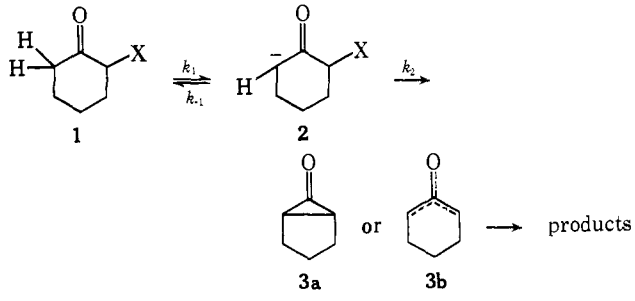
# Favorskii Reactions. II. Evidence Concerning the Nature of Halide Release

**F. G. Bordwell and Richard G. Scamehorn**[1]

*Contribution from the Chemistry Department, Northwestern University, Evanston, Illinois 60201.* *Received May 4, 1968*

**Abstract:** The rates and products of the reaction of various *meta*- and *para*-substituted $\alpha$-chlorobenzyl methyl ketones ($ArCHClCOCH_3$) with sodium methoxide in methanol have been studied. For the parent compound, $PhC^{\alpha}HClCOC^{\alpha'}H_3$, 79% of deuterium exchange at C-$\alpha'$ occurred prior to reaction. The yield of Favorskii ester increased from 9% at 0° with <0.05 *M* NaOMe to 61% at 65° with 2 *M* NaOMe. Evidence is presented to show that this increase is due to a higher activation energy and a greater acceleration in rate with increased ionic strength for the Favorskii reaction relative to a competing reaction to form hydroxy methyl ketal. The Hammett $\rho$ for methoxyoxirane formation (leading to hydroxy methyl ketal) was found to be −0.9. The Hammett $\rho$ for the Favorskii reaction was found to be −2.37. The yield of Favorskii ester was increased to 68% for Ar = *p*-MeOPh (0.05 *M* NaOMe) and was decreased to 0% for Ar = *p*-$NO_2Ph$. The relatively large negative value for $\rho$ in the Favorskii reaction indicates a high degree of ionic character in the C–Cl bond at the transition state. A mechanism is suggested whereby the ionization of the halogen is aided by $\pi$-bond participation from the parallel p orbitals of the enolate ion. Evidence is presented to show that the $COCH_2^-$ grouping promotes bromide ion release from $PhCHBrCOCH_2^-$ *ca.* $10^5$ more effectively than does the $CO_2^-$ grouping from $PhCHBrCO_2^-$, but *ca.* $10^5$ less effectively than does the $SO_2CH_2^-$ grouping from $PhCHBrSO_2CH_2^-$.

It has recently been shown that in several cyclohexanone systems the Favorskii reaction can be described as shown below, where reversible carbanion formation precedes the formation of a reactive intermediate **3**.[2] The formation and nature of **3** has been the subject of considerable discussion.[3-8] Direct displacement of halide ion by the $\alpha'$-carbanion leading to a cyclopropanone (**3a**) was proposed by Loftfield[3] and supported by Stork and Borowitz.[4] Recent work has




shown that cyclopropanones are indeed quantitatively converted to Favorskii products in the presence of base.[9] On the other hand, solvolysis of halide ion leading to a delocalized intermediate species (**3b**) has been suggested to account for stereochemical studies[7] and for methoxy ketone formation.[8] Theoretical arguments have also been advanced in support of the delocalized intermediate, and the difficulty of attaining the correct geometry for SN2 displacement in the cyclohexanone system has been pointed out.[6]

To date, however, no systematic study of the effect of electronic and structural variations on the rate and products of the Favorskii reaction has appeared. In order to learn more about the nature of the step in which the halide ion is lost, we have turned our attention to the acyclic system $ArCHClCOCH_3$. Here the electronic effect of *meta* and *para* substituents in the aromatic ring on the rate of loss of chloride ion would be expected to provide important information concerning the nature of the transition state.

It was imperative to the success of this project that the halide ion be lost in the rate-controlling step of the reaction. In other words, it is necessary that at least partial equilibrium be established between the halo ketone **4** and the enolate ion **5**. This will be true if $k_{-1}$ [MeOH] $\gg k_2$. If this condition does not hold, $k_1$ will be rate determining and changing the electronic nature of Ar will have but little effect on the rate of the Favorskii reaction.

**Deuterium Exchange.** Deuterium exchange studies similar to those used previously[2] showed that extensive deuterium exchange had occurred at the $\alpha'$ position of $\alpha$-chlorobenzyl methyl ketone **4** (Ar = Ph). The Favorskii ester obtained from a reaction of **4** (Ar = Ph) with sodium methoxide in methanol-O-*d* was shown by

(1) National Institutes of Health Predoctoral Fellow, 1966–1968. This paper was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, paper no. 119.
(2) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).
(3) R. B. Loftfield, *ibid.*, **73**, 4707 (1951).
(4) G. Stork and I. J. Borowitz, *ibid.*, **82**, 4307 (1960).
(5) J. G. Aston and J. D. Newkirk, *ibid.*, **73**, 2900 (1951); A. A. Sacks and J. G. Aston, *ibid.*, **73**, 3902 (1951).
(6) J. G. Burr and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).
(7) H. O. House and W. F. Gilmore, *J. Amer. Chem. Soc.*, **83**, 3980 (1961).
(8) A. W. Fort, *ibid.*, **84**, 2620 (1962).
(9) N. J. Turro and W. B. Hammond, *ibid.*, **87**, 3258 (1965).