was employed as the standard for determining chemical shift values of individual proton absorptions. At least six integrations were carried out on selected proton absorptions for the competitors or their bromination products (or both) and the weighed internal standard. Integral amplitudes were maximized to obtain the highest possible accuracy. The average deviation of individual integrations from the mean was generally on the order of 1%. The average value from integration of each different proton absorption was then corrected for the number of protons contributing to the absorption. From these values, by comparison with the per hydrogen integration value obtained for the known amount of internal standard, it was possible to calculate the numbers of millimoles of each competitor which remained. In certain cases this could be done directly, and in the other cases it was done indirectly by substraction of the number of millimoles of a bromide product observed from the number of millimoles of competitor weighed into the reaction. A decision as to which one of these procedures or both were used depended on whether the individual proton absorptions necessary for nmr analysis were better separated for the starting materials or for their bromide products from other proton absorptions in the competition product mixtures. The average chemical shift values (δ in parts per million downfield from TMS), which vary slightly in different mixtures, for the various individual proton absorptions of the internal standards, competitors, and bromide products used for calculation of the product compositions are as follows: benzyl chloride, δ 4.5 (s, 2 H, CH_2Cl); diphenylmethane, 3.9 (s, 2 H, CH_2); benzhydryl bromide, 6.2 (s, 1 H, CHBr); cumene, 1.2 (d, 6 H, $J = 6.5$ Hz, CH_3); cumyl bromide, 2.1 (s, 6 H, CH_3); n-butylbenzene, 2.6 (t, 2 H, $J = 7.5$ Hz, $C_6H_5CH_2$); α-bromo-n-butylbenzene, 4.9 (t, 1 H, $J = 7.5$ Hz, C_6H_5CHBr); isobutylbenzene, 0.9 (d. 6 H, $J = 6.5$ Hz, CH_3), 2.5 (d, 2 H, $J = 7.0$ Hz, CH_2); α-bromoisobutylbenzene, 0.85 and 1.15 (for each, d, 3 H, $J = 6.5$ Hz, CH_3), 4.6 (d, 1 H, $J = 8.0$ Hz, CHBr); benzylcyclopropane, 0.2 (m, 2 H, cyclopropyl); *trans*-1-benzyl-2-methylcyclopropane, 0.4 (m, 4 H, cyclopropyl); fluorene 3.7 (s, 2 H, CH_2); 9-bromofluorene, 5.7 (s, 1 H, CHBr); 1-bromoindan, 5.3 (t, 1 H, $J = 4.0$ Hz, CHBr); indene, 3.3 (s, 2 H, CH_2), 6.3 (m,

1 H, $CH_2CH=$); cycloprop[2,3]indene, 0.0 (m, 1 H, cyclopropyl), 3.0 (m, 2 H, $C_6H_5CH_2$); 3-bromocyclohexene, 4.6 (m, 1 H, CHBr), 5.6 (m, 2 H, vinyl); and bicyclo[4.1.0]hept-3-ene, 0.3 (m, 2 H, cyclopropyl).

Calculation of Relative Reactivities.—Relative reactivities from individual competition experiments were calculated using the integrated rate equation (1), where A_0 and B_0 are the initial and A_f and B_f the final amounts of the two competitors. A

$$k_A/k_B = \log (A_0/A_f)/\log (B_0/B_f) \qquad (1)$$

summary of the results obtained from the individual competitions, along with the number of runs carried out and the internal standard used in each competition, is given in Table II. Experimental errors are average deviations from the mean. The reactivities per active benzylic or allylic hydrogen relative to toluene given in Table I were obtained by stepwise comparisons of suitable pairs using the values of Friedrich, *et al.*,[4a] for the relative reactivities of diphenylmethane to toluene (17.6 $\pm$ 0.3) and cumene to toluene (57.5 $\pm$ 1.0). The indirect comparisons were necessary for purposes of accuracy because of the marked differences in reactivity between toluene and most of the compounds investigated. Experimental errors given in Table I were obtained by use of the usual formula[10] for propagation of errors.

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The Effect of Ring Size on the Rate of Reaction of Cycloalkyl Phenyl Ketones with Sodium Borohydride

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Kinetic experiments have been carried out for the reactions of acetophenone, cyclopropyl phenyl ketone, cyclobutyl phenyl ketone, cyclopentyl phenyl ketone, and cyclohexyl phenyl ketone with sodium borohydride at 0, 25 and 35°, respectively. At 0° the relative rates of the four cycloalkyl phenyl ketones are cyclopropyl, 0.12; cyclobutyl, 0.23; cyclopentyl, 0.36; and cyclohexyl, 0.25 (relative rate constant of acetophenone is unity). The data are discussed in terms of the conformation theory.

In the study of the effect of ring size on the rate of pyrolysis of cycloalkyl phenyl sulfoxides, Kice and Campbell[1] found that the relative rates of decomposition are in the following order: cyclopentyl > cyclohexyl < cycloheptyl. The pyrolysis rate seems to be related to the physical properties of the rings. The well-known heat of combustion per methylene group is in the same order. Measurements of diffusion coefficients of medium sized monocyclic compounds in carbon tetrachloride were also shown to follow this order.[2]

In this paper we report the results of a study on the effect of different ring sizes on the reactivity of some aromatic ketones. Brown and coworkers[3] have demonstrated that sodium borohydride is an excellent reagent to study kinetically the effects of structures on the reactivity of aldehydes and ketones. They have investigated[4-6] the reaction rates of sodium borohydride with various ketones including cyclic and bicyclic ketones, as well as aromatic and aliphatic ketones.

(1) J. L. Kice and J. D. Campbell, *J. Org. Chem.*, **32**, 1631 (1967).
(2) S. F. Sun, R. J. Beshinske, and K. E. Van Holde, *J. Amer. Chem. Soc.*, **89**, 6417 (1967).

(3) H. C. Brown, E. J. Mead, and B. C. S. Rao, *ibid.*, **77**, 6209 (1955).
(4) (a) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957); (b) H. C. Brown and K. Ichikawa, *ibid.*, **1**, 221 (1957).
(5) H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **84**, 373 (1962).
(6) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).

Phenyl ketone	Temp, °C	$k \times 10^4$, l. mol^{-1} sec^{-1}
Methyl[a]	0.0	2.07
	25.0	13.6
	35.0	26.0
Cyclopropyl	0.0	0.257
	25.0	6.25
	35.0	18.7
Cyclobutyl	0.0	0.470
	25.0	2.49
	35.0	5.18
Cyclopentyl	0.0	0.740
	25.0	3.50
	35.0	7.35
Cyclohexyl	0.0	0.515
	25.0	2.38
	35.0	4.78

[a] Previous results: 2.05 at 0°, 14.0 at 25°, 26.2 at 35.15° [H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **84**, 373 (1962)].
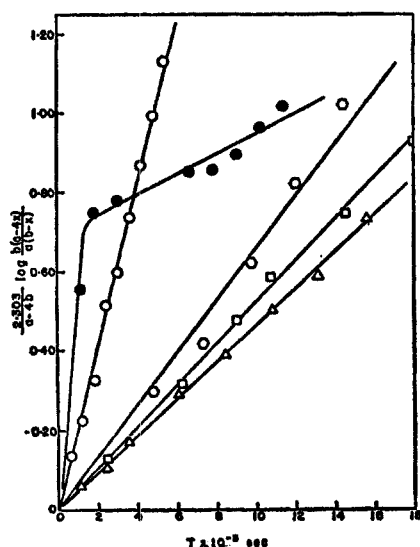

Figure 1.—Second-order reaction of sodium borohydride with cycloalkyl phenyl ketones: O, acetophenone; ●, cyclopropyl phenyl ketone; △, cyclobutyl phenyl ketone; ◇, cyclopentyl phenyl ketone; □, cyclohexyl phenyl ketone.

They did not, however, include in their list any cycloalkyl phenyl ketones.

We have carried out kinetic experiments for reactions of sodium borohydride with acetophenone, cyclopropyl phenyl ketone, cyclobutyl phenyl ketone, cyclopentyl phenyl ketone, and cyclohexyl phenyl ketone. Acetophenone is included for comparison only.

Results

The experimental data for rate constants at 0, 25, and 35°, respectively, are presented in Table I. Each kinetic experiment was carried out at least twice. The reproducibility of each rate constant was within 5%.

In all experiments the reaction is first order with respect to the ketone and first order with respect to sodium borohydride. The linearity of the second-order plots for these reactions is shown in Figure 1.

The reaction of cyclopropyl phenyl ketone was relatively slower than any other cycloalkyl phenyl ketone at 0° but faster at higher temperatures. The reaction was only followed to 50% completion, while all other compounds reacted to 100% completion. After 4 days, although some cyclopropyl phenyl ketone (initial concentration 0.136 *M*) was still found in the system, sodium borohydride (initial concentration 0.040 *M*) was completely consumed. It should be pointed out that according to the stochiometry the initial concentration of sodium borohydride was in excess by 0.006 *M*. The rate constant of cyclopropyl phenyl ketone shown in Table I was determined from the linear portion of the second-order plot.

Table II lists the activation parameters of the reactions of cycloalkyl phenyl ketones with sodium borohydride. Least-squares method was used for the

TABLE II
RELATIVE RATES AND DERIVED DATA FOR THE REACTIONS OF AROMATIC KETONES AT 0°

Phenyl ketone	Relative rates	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Methyl[a]	1.00	11.5 ± 0.3	-32.9 ± 0.3
Cyclopropyl	0.12	19.9 ± 0.1	-6.15 ± 0.3
Cyclobutyl	0.23	10.7 ± 0.1	-38.7 ± 1.8
Cyclopentyl	0.36	10.2 ± 0.6	-39.8 ± 2.0
Cyclohexyl	0.25	9.8 ± 0.6	-41.8 ± 2.0

[a] Previous results: $\Delta H^{\ddagger} = 11.70$ kcal/mol, $\Delta S^{\ddagger} = -32.4$ eu [H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, **84**, 373 (1962)].

determination of the slopes and intercepts for each of the ln *k* vs. $1/T$ data. The error limits for enthalpies of activation were calculated from the standard deviations of the slopes, whereas those of entropies of activation were determined from the standard deviations of the *y* intercepts. All the computations were carried out on the C-E-I-R Multi-Access computer service (System 420).

Discussion

The difference in the reaction rates among cycloalkyl phenyl ketones is small as found in the case of rate constants for the pyrolysis of cycloalkyl phenyl sulfoxides.[1] The small rate difference among cycloalkyl phenyl ketones is presumably due to the resonance interactions between the phenyl group and carbonyl group. Such interactions are believed to stabilize the ground states of reactants and thus possibly slow down their reaction rates.

However, the trend of change clearly follows the size of these rings. At 0° the three-membered ring reacted the slowest, while the five-membered ring reacted faster than both the four-membered and six-membered rings. The observation of the latter (three-, four-, five-membered compounds) holds at higher temperatures (25 and 35°) also and is in accord with almost all kinetic studies for reactions involving these three rings. During a reaction, if the breakage or formation of a bond directly or indirectly involves a ring atom, the rate of reaction of a five-membered-ring compound seems always in between a four-membered-ring and a six-membered-ring compound.[4]

The rate-determining step in the reaction of sodium borohydride with ketones is known to involve the transfer of the hydride ion to the carbonyl group.[3] In the transition state of cycloalkyl phenyl ketones the
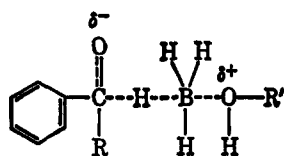
possibility exists that bond angles or torsional strains may release or enforce the strain which already exists in the ketonic carbon.[7] The relatively low rate of reaction of cyclopropyl phenyl ketone at 0° is perhaps due to the high angular strain of the cyclopropyl group. The transition of the strain from the ring to the reaction site may reduce the affinity of the ketonic carbon to the hydride ion. As the angular strain decreases from cyclobutyl phenyl ketone to cyclohexyl phenyl ketone the reaction rate likewise increases. As to why the rate of cyclohexyl phenyl ketone is slower than that of cyclopentyl phenyl ketone, there seems to be no satisfactory answer. One can only parallel the physical properties of the rings with the reactivities of ring compounds. For almost any quantitative measurements, e.g., diffusion coefficient and heat of combustion, the value of six-membered ring is always in between those of the five-membered ring and seven-membered ring, just as the five-membered ring is in between four-membered and six-membered rings. If kinetic data for cycloheptyl phenyl ketone with sodium borohydride were available, it is believed that the reaction rate for the seven-membered ring would be higher than that for the six-membered ring.

Changes in the enthalpy of activation for these reactions are expected to follow the same direction as the changes in the strain of the rings. As far as the principal values are concerned, such a trend seems to exist. But, in the first place, the change is so small, and in the second place the relative errors are so large that great significance should not be attached to the calculated data. This is also the case with the change in entropies of activation. Presumably there is not much effect of geometric configuration on the reaction rate when a ring is connected to the ketonic carbon.

The reaction of cyclopropyl phenyl ketone with sodium borohydride seems complicated. The enthalpy of activation is very high and the entropy of activation is abnormally low. In the ultraviolet absorption spectra study, Rogers[8] suggested that cyclopropyl phenyl ketone, when excited, may undergo ring breakage. Recently it was reported[9] that carbon–carbon single bonds of a cyclopropyl ring are cleaved by electrophilic reagents. This leads[10] us to suspect that the reaction of cyclopropyl phenyl ketone with sodium borohydride in isopropyl alcohol may not be a single reaction and that the product may be a mixture.

In conclusion, the characteristic features of the small rings are revealed not only in the reactions directly involved with ring atoms such as cyclanones but also in the reaction where ring atoms are not directly involved, such as cycloalkyl phenyl ketones. Relative rates depend upon a delicate balance between ring properties (e.g., bond angles and torsional strain) and resonance interactions; hence changes in reaction rates may be expected to be small.

Experimental Section

Materials.—Acetophenone was obtained from Eastman Organic Chemicals, while the four cycloalkyl phenyl ketones were obtained from Frinton Laboratories. All the ketones were purified by vacuum distillation. The physical properties of the purified ketones used for kinetic measurements are listed in Table III.

TABLE III

PHYSICAL PROPERTIES OF THE KETONES
USED IN THIS WORK

Phenyl ketone	Mp or bp, °C (mm)	$n^{25}D$
Methyl	82.8 (12)	1.5429
Cyclopropyl	60.0 (8)	1.5530
Cyclobutyl	114.5 (10)	1.5455
Cyclopentyl	118.7 (10)	1.5427
Cyclohexyl	47.2	

Isopropyl alcohol (Baker Analyzed Reagent) and sodium borohydride (Metal Halides) were purified according to the method described by Brown and coworkers.[3] All the other chemicals were reagent grade without further purification.

Kinetic Measurement.—To a standardized solution of sodium borohydride in isopropyl alcohol was added a known volume of ketone which was also dissolved in isopropyl alcohol. The mixture was prepared in a water bath at 25 or 35°, or in an ice bath at 0°, and was vigorously stirred. The accuracy of the temperature in the water bath was ±0.02° and that in the ice bath was ±0.5°. At intervals 10-ml aliquots were withdrawn and the borohydride content was analyzed by the iododate method.[11]

Product Analysis.—The solution of a ketone in isopropyl alcohol was added to the solution of sodium borohydride in the identical solvent and, after shaking, the mixture was left standing for 3 hr. The alcohol was distilled off by vacuum distillation. The infrared spectra were taken with Perkin-Elmer Infracord 137 for the product as well as for the starting material. Since NaBH₄ does not absorb in the carbonyl region, the disappearance (i.e., reduction) of the ketone stretching vibrations at ~1680 cm⁻¹ accompanied by the strong appearance of O–H bending at 3400–3600 cm⁻¹ and of C–O stretching at 950–1010 cm⁻¹ observed in the ir spectra is an indication of the reaction of the ketone with sodium borohydride.

Registry No.—Sodium borohydride, 1303-74-8; acetophenone, 98-86-2; cyclopropyl phenyl ketone, 3481-02-5; cyclobutyl phenyl ketone, 5407-98-7; cyclopentyl phenyl ketone, 5422-88-8; cyclohexyl phenyl ketone, 712-50-5.

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