than for the acetophenones, and this seems consistent with the experimental results given in Table IV. Where comparisons can be made with neutron diffraction results, the theoretically predicted positions of the hydrogen atoms agree quite well. Thus, for *o*-nitrobenzaldehyde[32] neutron diffraction gives C(carbonyl)–H = 1.12 Å and H–C(carbonyl)–O = 122°, while our theoretical optimization for benzaldehyde gives 1.11 Å and 121°, respectively.

Assignment of proton resonances in the 2,4,6-trihydroxy compounds was simplified by the nature of the exchange broadening. In both cases the upfield peak which was not broadened by the intramolecular exchange process could be assigned to the *p*-hydroxyl while the resonance furthest downfield could be assigned to the *o*-hydroxyl which is involved in the hydrogen bond. The latter assignment is based on the presumed deshielding of a proton involved in a hydrogen bond and is consistent with the Mulliken atomic charges[34] calculated for the hydroxyl hydrogens in the most stable conformation of III. The atomic charge for the hydroxyl hydrogen involved in the hydrogen bond is 0.240 e, which is to be compared with the less positive values of 0.206 and 0.202 e for the hydroxyl hydrogens in the para position and remaining ortho position, respectively. The near equality of charges on the latter two protons is consistent with the small chemical shift difference between these two hydroxyl protons. We also note a small but significant overlap population (0.045 e) consistent with a hydrogen bond between the carbonyl oxygen and one of the *o*-hydroxyl hydrogens.

The chemical shifts reported here for 2,4,6-trihydroxyacetophenone (IV) can be compared with chemical shifts of 12.85 and 9.64 ppm which have been reported[35] for the hydroxyls of 2,4-dihydroxyacetophenone. The latter values refer to an acetone solvent at ambient temperature and are about 1.3 ppm upfield from our values for the corresponding hydroxyl groups of IV measured at ~–90 °C. The discrepancy may be due in part to the rather sizable temperature coefficients of these chemical shifts. Large chemical shift differences for phenolic hydroxyls have also been reported[36] for 1-(2,5-dihydroxyphenyl)butanone in CCl_4. The 2-hydroxy proton which is involved in hydrogen bonding absorbs at 12.02 ppm while the hydrogen at the 5-position absorbs at 5.63 ppm. The chemical shift and line shape of this latter hydroxy proton are very sensitive to environmental factors while those of the hydroxy proton involved in the intramolecular hydrogen bond are less so. This behavior is consistent with our observations concerning the relative temperature and solvent dependence of the hydroxy resonances of compounds III and IV.

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Summary

Detailed analysis of the exchange-broadened ^1H NMR spectra of 2,4,6-trihydroxy derivatives of benzaldehyde and acetophenone yield activation enthalpies of 8.0 and 6.9 kcal/mol, respectively, for the exchange of the *o*-hydroxyl environments. Slightly lower barriers are surmised for the corresponding 2,6-dihydroxy compounds. Theoretical calculations using approximate molecular orbital theory indicate that the exchange process may be more complex than a simple rotation of an acyl group. The exchange may be a three-step process involving a rate-limiting initial rotation of the hydrogen-bonded hydroxyl group. The theoretical barriers are substantially higher than the experimental values. This is likely to be due to the tendency of a minimum basis set to overestimate hydrogen bond strengths as well as to the neglect of solvent interactions in the theoretical calculations.

Acknowledgment. We are grateful to Dr. John S. Ricci for helpful comments and to Mr. John Thoman for assistance with some of the calculations. Part of this research was carried out under the auspices of the U.S. Department of Energy. D.A.K. gratefully acknowledges support from the Camille and Henry Dreyfus Foundation.

Registry No. I, 387-46-2; II, 699-83-2; III, 487-70-7; IV, 480-66-0; benzaldehyde, 100-52-7; acetophenone, 98-86-2; phenol, 108-95-2; *p*-hydroxybenzaldehyde, 123-08-0; *p*-hydroxyacetophenone, 99-93-4; *p*-(dimethylamino)benzaldehyde, 100-10-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-methylbenzaldehyde, 104-87-0; *p*-isopropylbenzaldehyde, 122-03-2; *p*-fluorobenzaldehyde, 459-57-4; *p*-chlorobenzaldehyde, 104-88-1; *p*-(trifluoromethyl)benzaldehyde, 455-19-6; *p*-(dimethylamino)acetophenone, 2124-31-4; *p*-methoxyacetophenone, 100-06-1; *p*-methylacetophenone, 122-00-9; *p*-fluoroacetophenone, 403-42-9; *p*-chloroacetophenone, 99-91-2; *p*-bromoacetophenone, 99-90-1; *p*-(trifluoromethyl)acetophenone, 709-63-7; *p*-nitroacetophenone, 100-19-6; 2-nitrobenzaldehyde, 552-89-6; 2-hydroxy-3-methoxybenzaldehyde, 148-53-8; *p*-aminoacetophenone, 99-92-3.

gem-Dimethyl Effect in a Grignard Reagent Cyclization–Cleavage Rearrangement

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(2,2-Dimethyl-4-penten-1-yl)magnesium bromide (1) is in equilibrium with its cyclic isomer, [(3,3-dimethylcyclobutyl)methyl]magnesium bromide (2). The equilibrium constant for this cyclization has a value of 2×10^{-3}. The *gem*-dimethyl substitution leads to an increase of a factor of about 22 in the equilibrium constant and also retards the rate of cleavage of 2. The sources of the *gem*-dimethyl effect in this system are discussed.

Because of the strain inherent in the small ring, ring-cleavage rearrangements of the cyclobutylmethyl[1] (k'_0 in eq 1) and cyclopropylmethyl[2] Grignard reagents proceed essentially to completion.[3] Although the equilibrium

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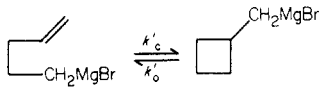
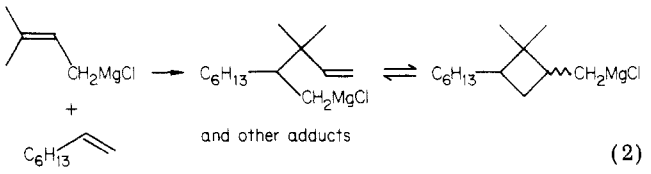


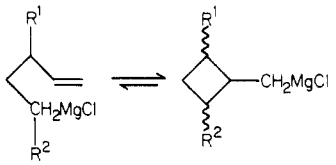
(1)

constant for cyclization is small, reaction in the cyclization direction has been demonstrated by deuterium-labeling experiments.[4,5] For instance, for the cyclobutylmethyl Grignard reagent,[4] the equilibrium constant for cyclization at 140 °C (ratio of cyclization to ring-opening rate constants) is about 4×10^{-4}. However, suitable substitution can alter the equilibrium constant so that a significant fraction of the cyclic structure is present at equilibrium. Several examples have been discovered by Lehmkuhl and co-workers[6,7] in their studies of the addition of allylic Grignard reagents to alkenes (e.g., eq 2), and we have



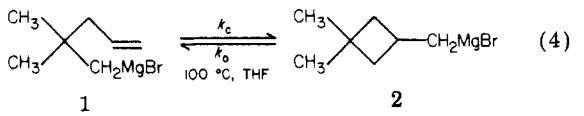
(2)

studied in detail the equilibrium involving the (2,4-dimethylcyclobutyl)methyl Grignard reagent,[8] in which the equilibrium constant for cyclization has a value of about 3 (eq 3, $R^1 = R^2 = CH_3$). A number of examples also exist



(3)

in which the three-membered ring is favored at equilibrium.[9] It appears that at least two factors may stabilize cycloalkylmethyl Grignard reagents relative to their open-chain isomers. First, cyclization of a secondary or tertiary Grignard reagent to a primary cycloalkylmethyl isomer is favored by the greater stability of the primary organometallic. Stabilization of the ring relative to the open chain by alkyl substitution (essentially the Thorpe–Ingold *gem*-dimethyl effect[10]) also appears to be involved. In this paper, we have investigated the cyclization–cleavage equilibrium of eq 4, in which only the latter factor would be present.



(4)

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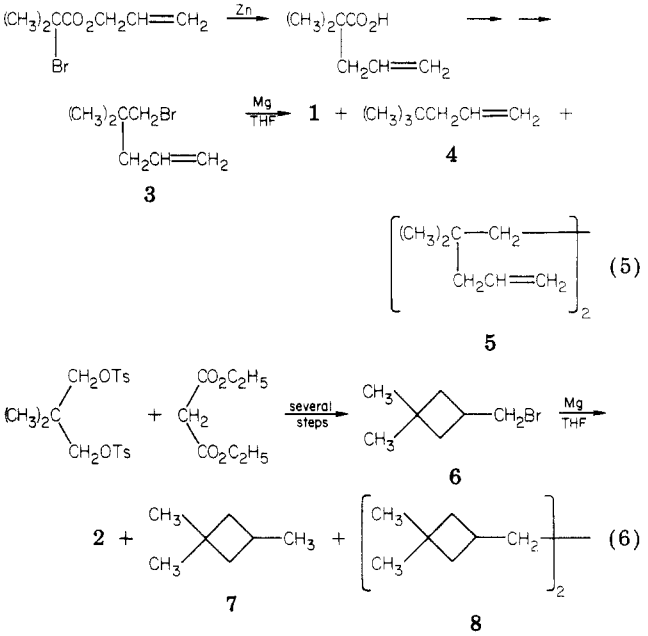
Results

The two bromides 5-bromo-4,4-dimethyl-1-pentene (**3**) and 1,1-dimethyl-3-(bromomethyl)cyclobutane (**6**) were prepared and converted to their Grignard reagents in the conventional fashion (eq 5 and 6).



(5)

(6)

Hydrolysis of the (3,3-dimethylcyclobutyl)methyl Grignard reagent (**2**) yielded only a single monomeric hydrocarbon, whose properties were consistent with the expected 1,1,3-trimethylcyclobutane (**7**). A most characteristic spectroscopic feature was the presence of an ion in the mass spectrum at m/e 56, corresponding to fragmentation of the ring to produce the isobutylene molecular ion. This was the base peak for all of the 3,3-dimethylcyclobutyl compounds encountered but was relatively weak in the acyclic compounds. Also isolated by preparative GC was a hydrocarbon **8** formed by dimerization during Grignard reagent formation. The proton NMR spectrum of the Grignard reagent had a high-field doublet at −0.31 ppm (J = 7.2 Hz), attributable to the methylene protons α to the magnesium in **2**. The methyl regions of the proton spectrum and the carbon-13 NMR spectrum were also interpreted on the basis of a mixture containing Grignard reagent and hydrocarbons **7** and **8** (see Experimental Section).

When the mixture was heated for several hours at temperatures in the vicinity of 100 °C in THF, changes occurred in the proton and ^{13}C NMR spectra which were consistent with the rearrangement process k_o in eq 4. Most prominently, the high-field doublet was replaced by a singlet at −0.34 ppm, corresponding to **1**. Hydrolysis of the Grignard reagent then yielded 4,4-dimethyl-1-pentene (**4**). With extensive heating, the NMR resonance attributed to **2** disappeared, and little of the trimethylcyclobutane **7** was found in the hydrolysis products. Analysis of the high-field NMR absorption from spectra of a sample heated for varying periods of time at 100 °C in THF led to a half-life of 10 h ($k = 1.9 \times 10^{-5}$ s^{-1}) for approach to equilibrium. Other proton and ^{13}C NMR observations consistent with this rearrangement are detailed in the Experimental Section.

The major goal of this study was to determine the amount of cyclic isomer **2** remaining at equilibrium. Because the equilibrium lies quite strongly toward the open-chain reagent **1**, it appeared that a more reliable evaluation of the equilibrium might result if it were ap-

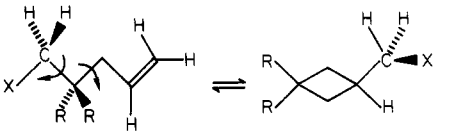
proached from the side of 1. A sample of this Grignard reagent, prepared from the corresponding bromide 3, was heated at 100 °C for 48 h. This corresponds to 5 half-lives for the equilibration of 1 with 2, so that the concentration of 2 should have attained very nearly its ultimate equilibrium value. The sample was worked up by first pumping to a cold trap the solvent and any monomeric hydrocarbons which might have been present. Fresh solvent was added, and the reagent was hydrolyzed by addition of water. Gas chromatography showed a small peak corresponding in retention time to the trimethylcyclobutane 7, which amounted to 0.20 ± 0.02% of the mixture. In addition to its retention time, it was possible to supplement the characterization of the minor component by trapping from the gas chromatograph and obtaining a mass spectrum of the trace of material so isolated. The spectrum closely resembled that of 7 (in particular the domination by m/e 56), with a small amount of 4,4-dimethyl-1-pentene being present. On this basis, the equilibrium constant for eq 4 is evaluated as 2.0×10^{-3} at 100 °C in THF. This number may represent an upper limit to the equilibrium constant, since the peak area may be enhanced by minor impurities, but should not differ greatly from the true value.

Discussion

The equilibrium constant for cyclization of Grignard reagent 1 may be compared with that for cyclization to the unsubstituted cyclobutylmethyl reagent represented in eq 1. A value of $K \leq 9 \times 10^{-5}$ has been estimated by extrapolation to 100 °C in that case.[8,11] The effect of *gem*-dimethyl substitution in the 3-position of the ring is thus to increase the equilibrium constant by a factor of 22 or more. In the equilibrium in eq 3, the effect of a methyl group at R^1 is to increase the equilibrium constant for cyclization by factors of about 42 (R^2 = H) or 5.2 (R^2 = CH_3).[8] The numbers are approximate because of uncertainties in estimating relevant rate and equilibrium constants, so no great significance should be attributed to detailed comparisons of the values given. It *is* important that *gem*-dimethyl substitution increases the degree of cyclization to the extent that the cyclic isomer may be determined.

Allinger and Zalkow have discussed the origins of the *gem*-dimethyl effect in thermodynamic terms.[12] An enthalpic factor favoring cyclization is a greater increase in the number of gauche interactions for the acyclic structure when substituents are introduced. Thus, cyclization is promoted by destabilization of the open-chain compound. This explanation is only partially equivalent to the frequently cited but less rigorous rationalization[13] that *gem*-dimethyl substitution "increases the population of conformations favorable to cyclization". Alternative conformations which are "unfavorable for cyclization" may be substantially populated in the unsubstituted acyclic compound. If they are destabilized by the substitution, then the increase in enthalpy of the open-chain compound relative to cyclic product or transition state is accompanied by an increase in the population of "favorable" conformations.

The Allinger–Zalkow explanation would appear to be appropriate to the present equilibrium. If we consider the model hydrocarbon reaction of eq 7 where X = H, the



(7)

replacement of R = H by methyl groups introduces two gauche interactions into the alkene. Interactions of the methyl groups in the cyclobutane are more difficult to evaluate. However, since the rotational barrier of propane is little greater than that of ethane,[14] the partial eclipsing of methyl and hydrogen on the ring should not generate much additional torsional strain. Puckering of the ring undoubtedly complicates the situation. Nevertheless the increase in enthalpy of the alkene on methylation should probably be greater than for the cyclobutane. If X is a group other than hydrogen, there will be, additionally, two gauche X–methyl interactions in the alkane, partially compensated by one in the cyclobutane. It is significant that in eq 3 the methyl substituent effect on the equilibrium constant appears to be an *enthalpy* effect.[8]

Allinger and Zalkow also propose an entropy contribution to the *gem*-dimethyl effect, resulting from an increase in the rotational barrier with substitution in the acyclic compound. Another sort of entropy contribution is related to the change in conformer populations discussed above. Considering eq 7 as an illustration, we might expect that the acyclic conformation shown would predominate when R = H. When R = CH_3, the populations of other conformations about the bonds indicated should increase, and the entropy of the open-chain compound would be increased by a larger entropy of mixing. With still larger groups R, a strong preference might exist, "locking" the molecule into a "conformation favorable for cyclization" and again reducing the entropy of mixing. In all cases, the cyclic isomer has little conformational mobility, so that methyl substitution would have less effect on its entropy. Thus, entropy changes resulting from substituent effects on conformer populations might work either against or for cyclization.

It is also reasonable that the original Thorpe–Ingold explanation[10] may play a role; the slightly decreased bond angle θ in the fragment 9, when R is changed from hydrogen to alkyl, would tend to lower the strain in a small ring.[15]

9

The rate constant for ring cleavage of Grignard reagent 2 is found in this work to have a value of about 1.9×10^{-5} s^{-1} at 100 °C in THF. (Cyclobutylmethyl)magnesium chloride (eq 1) has a rate constant of 2.2×10^{-4} s^{-1} under the same conditions.[4,8] In ether, the corresponding bromide reacts about 2–4 times slower than the chloride over the range 60–80 °C, but the two extrapolate to the same rate at about 120–125 °C.[3a] Thus, it appears that the cleavage rate of 2 is probably decreased by a factor of 5–10 relative to the unsubstituted (cyclobutylmethyl)magnesium bromide and that the net effect of *gem*-dimethyl substitution results from both an increase in cyclization rate and

(11) In ref 8, the values listed are twice as large as these numbers, since the discussion in that paper requires the equilibrium constant to be based on cleavage of only one of the two possible ring bonds. An alternative estimate of 2×10^{-4} is less reliable.[8]

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Table I. Spectroscopic Properties of Intermediates and Products[a]

A. 3,3-Dimethylcyclobutyl Compounds: $(CH_3)_2C(CH_2)_2CHX$

X = CO_2H: ^1H NMR 12.0 (1 H, s, CO_2H), 3.09 (1 H, approx quintet, J = 8.7 Hz, CH), 2.05 (4 H, m, CH_2), 1.17 (3 H, s, CH_3), 1.11 (3 H, s, CH_3); ^{13}C NMR 182.16 (CO_2H), 37.64 (CH_2), 31.96 (C), 31.38 (CH), 29.85 and 28.26 (CH_3); mass spectrum, 129 ($(M + 1)^+$, 0.2), 128 (M^+, 0.2), 113 (0.8), 110 (2), 95 (2), 83 (6), 73 (14), 56 (100), 55 (15), 45 (2), 43 (3.6), 41 (41), 39 (10); mass spectrum (10 eV), 129 ($(M + 1)^+$, 5), 110 (5), 83 (12), 82 (8), 73 (26), 56 (100), 41 (25)

X = CH_2OH: ^1H NMR 3.64 (2 H, d, J = 6.5 Hz, CH_2O), 3.1 (1 H, s, OH), 2.8-2.0 (1 H, m, CH), 2.1-1.2 (4 H, m, CH_2), 1.17 (3 H, s, CH_3), 1.07 (3 H, s, CH_3); ^{13}C NMR 67.72 (CH_2OH), 37.40 (CH_2), 31.39 (C), 30.71 (CH_3), 29.74 (CH), 28.85 (CH_3); mass spectrum, 99 (1), 97 (2), 96 (16), 83 (3), 81 (34), 68 (6), 67 (7), 59 (34), 58 (18), 57 (76), 56 (100), 55 (44), 43 (12), 42 (7), 41 (86), 39 (28), 31 (15)

X = CH_2OTs: ^1H NMR 7.38 (4 H, AA'BB', J_{AB} = 8.2 Hz), 3.81 (2 H, d, J = 6.3 Hz, CH_2O), 2.32 (3 H, s, CH_3), 1.95-1.13 (5 H, m), 1.04 and 0.94$_5$ (6 H, 2 s, CH_3); ^{13}C NMR 144.53 (1 C), 134.08 (1 C), 129.78 (2 C), 127.93 (2 C), 74.89 (CH_2O), 37.40 (CH_2), 31.82 (C), 30.75 and 28.72 (CH_3), 27.15 (CH), 21.53 (CH_3)

X = CH_2Br: ^1H NMR 3.41 (2 H, d, J = 7.3 Hz, CH_2Br), 2.62 (1 H, approx quintet, $J \approx$ 8 Hz, CH), 2.1-1.2 (4 H, m, CH_2), 1.14 and 1.07 (6 H, 2 s, CH_3); ^{13}C NMR 40.16 (CH_2), 39.72 (CH_2Br), 30.73, 30.59, and 28.53 (CH and CH_3's), 30.32 (C); mass spectrum, 137 (0.6), 135 (0.6), 97 (31), 81 (3), 57 (6), 56 (100), 55 (29), 41 (39), 39 (9); mass spectrum (10 eV), 137 (1.3), 135 (1.3), 97 (100), 96 (5), 81 (5), 69 (15), 56 (71), 55 (16), 41 (2.6)

X = CH_3: ^1H NMR 2.5-1.2 (5 H, m), 1.10 and 1.02 (6 H, 2 s, CH_3), 1.02 (3 H, d, J = 6.5 Hz, CH_3); ^{13}C NMR[b] 42.95, 33.26, 31.12, 28.76, 22.44, 18.51; mass spectrum, 98 (M^+, 0.3), 83 (2), 70 (7), 57 (16), 56 (100), 55 (13), 43 (3), 42 (7), 41 (39), 39 (7); mass spectrum (10 eV), 98 (M^+, 1), 83 (3), 70 (31), 57 (31), 56 (100), 55 (9), 41 (1), 39 (1)

X = C_7H_{14} (dimer): ^1H NMR 2.0-1.1 (m), 1.08 (s), 0.99 (s); singlets at about 1.09 and 1.01 ppm in THF Grignard reagent solutions; ^{13}C NMR (in THF Grignard reagent solutions) 41.6, 35.9, 30.2, 28.8, 28.6 (quaternary carbon not observed); mass spectrum, 179 (1), 138 (3), 123 (8), 110 (13), 109 (8), 97 (10), 96 (18), 95 (18), 83 (10), 82 (30), 81 (18), 69 (14), 67 (25), 57 (48), 56 (100), 55 (30), 41 (35), 39 (10)

X = CH_2MgBr:[c] ^1H NMR 1.02 and 0.97 (2 s, CH_3), 0.31 (d, CH_2Mg); ^{13}C NMR 49.7, 31.85, 30.8, 29.35, 29.10, 19.10

B. $CH_2=CHCH_2C(CH_3)_2X$

X = CH_2OH: ^1H NMR 6.2-5.5 (1 H, m, =CH), 5.2-4.7 (2 H, m, $=CH_2$), 3.7 (1 H, br, OH), 3.25 (2 H, s, CH_2OH), 1.98 (2 H, d, J = 7 Hz, CH_2), 0.87 (6 H, s, CH_3); ^{13}C NMR 135.39 (=CH), 116.90 ($=CH_2$), 71.37 (CH_2O), 43.63 (CH_2), 35.53 (C), 24.00 (CH_3); mass spectrum, 96 (6), 83 (13), 81 (10), 73 (59), 72 (9), 67 (6), 57 (7), 56 (6), 55 (100), 45 (8), 43 (29), 41 (31), 39 (15), 31 (12), 29 (15); mass spectrum (10 eV), 96 (23), 83 (9), 81 (32), 73 (100), 72 (32), 57 (3), 55 (4)

X = CH_2Br: ^1H NMR 6.3-5.5 (1 H, m, =CH), 5.2-4.8 (2 H, m, $=CH_2$), 3.24 (2 H, s, CH_2Br), 1.98 (2 H, d, J = 7.2 Hz, CH_2), 0.85 (6 H, s, CH_3); ^{13}C NMR 133.98 (=CH), 117.96 ($=CH_2$), 45.40 (CH_2Br), 44.37 (CH_2), 34.58 (C), 25.68 (CH_3); mass spectrum, 178 (0.4), 176 (M^+, 0.4), 163 (0.2), 161 (0.2), 137 (24), 135 (25), 97 (32), 83 (5), 81 (8), 57 (36), 56 (39), 55 (100), 41 (77), 39 (20)

X = CH_3: ^1H NMR 6.2-5s4 (1 H, m, =CH)15.1-4.6 (2 H, m, $=CH_2$), 1.92 (2 H, d, J = 7 Hz, CH_2), 0.89 (6 H, s, CH_3); ^{13}C NMR 135.9 (=CH), 116.24 ($=CH_2$), 48.56 (CH_2), 30.5 (C), 29.15 (CH_3); mass spectrum, 98 (M^+, 3), 83 (26), 70 (7), 58 (13), 57 (100), 56 (15), 55 (72), 43 (6), 42 (5), 41 (80), 39 (23), 29 (19)

X = C_7H_{13} (dimer): ^1H NMR 6.1-5.4 (2 H, m, =CH), 5.1-4.7 (4, H, m, $=CH_2$), 2.05 (4 H, d, J = 7 Hz, CH_2), 1.14 (4 H, s, CH_2), 0.84 (12 H, s, CH_3); singlet at 0.84 ppm in THF Grignard reagent solution; ^{13}C NMR[b] 135.78 (=CH), 116.34 ($=CH_2$), 46.42 (CH_2), 35.60 (CH_2), 32.77 (C), 26.91 (CH_3) (136.05, 116.4, 46.8, 35.95, 33.0, and 27.0 in THF Grignard reagent solutions); mass spectrum, 153 (1), 137 (1), 123 (2), 111 (7), 97 (71), 83 (54), 71 (18), 69 (52), 57 (35), 56 (9), 55 (100), 43 (30), 41 (36), 39 (7)

X = CH_2MgBr:[c] ^1H NMR 6.3-5.6 (m, =CH), 5.1-4.7 (m, $=CH_2$), 0.90 (s, CH_3); ^{13}C NMR 139.55, 114.0, 53.8 (CH_2), 35.1 (C), 33.9 (CH_3); CH_2Mg obscured by solvent.

[a] Unless otherwise noted, proton and carbon NMR spectra are for solutions in $CDCl_3$ and are reported in parts per million downfield vs. an internal $(CH_3)_4Si$ reference. Carbon NMR assignments which are given are based on off-resonance decoupling. Mass spectra were run with an electron-beam potential of 70 eV, unless a 10-eV potential is specifically noted. Results are reported as m/e (relative intensity). [b] Because of the limited amount of sample available, off-resonance decoupling could not be used for complete assignment of ^{13}C NMR spectra. [c] Proton and carbon NMR spectra in THF solution. [d] Neat sample with added $(CH_3)_4Si$.

a decrease in the rate of ring opening. The decreased rate of ring opening is consistent with other observations that the cyclization–cleavage equilibration rate is slowed by steric congestion around the reacting centers.[3a,8,16] Therefore, it is likely that the "*gem*-dimethyl effect" in eq 4 is principally an acceleration of cyclization (resulting from open-chain vs. transition-state differences in gauche interaction, entropy effects, and bond angles), with a superimposed retardation of the rate of equilibration in both directions (resulting from transition-state steric interactions). In the equilibrium of eq 3, it also appears that a "remote" methyl substituent affects largely the cyclization rate. A similar combination of a "*gem*-dimethyl effect" and steric retardation has been concluded in some other studies of cyclization reactions.[17]

Experimental Section

Melting and boiling points are uncorrected. Proton and carbon-13 nuclear magnetic resonance spectra were obtained on Varian T-60 and CFT-20 instruments, respectively, and are reported relative to internal tetramethylsilane in $CDCl_3$ solutions. In the case of Grignard reagent solutions, shifts relative to the high-field solvent resonance are corrected to Me_4Si reference by increasing the δ values by 1.79 (proton) or 25.9 ppm (carbon), as determined previously in representative Grignard reagent solutions. Carbon resonance signals were assigned in most cases by off-resonance decoupling. Mass spectra were obtained on a Hitachi RMU-6D spectrometer by Mr. Frank Laib. Data are given in Table I.

Gas chromatographic analyses and preparative separations utilized a Varian (Aerograph) A90-P chromatograph with the following columns: A, $^1/_2$ in. × 10 ft, 17% Apiezon J on 60/80-mesh Chromosorb P; B, $^1/_4$ in. × 10 ft, 25% tricresyl phosphate on 60/80-mesh Chromosorb P; C, $^1/_4$ in. × 5 ft, silver nitrate–glycerine on 30/65-mesh Chromosorb P; D, $^1/_4$ in. × 15 ft 35% of a mixture of 2,4-dimethylsulfolane and *n*-propyl sulfone on 60/80-mesh Chromosorb P; E, $^1/_4$ in. × 10 ft, 5% Carbowax 20M on 40/60-mesh Chromosorb P. Elemental combustion analyses were performed by Galbraith Laboratories and Guelph Chemical Laboratories, Ltd.

THF and ether for use in preparing Grignard reagents were distilled from $LiAlH_4$ in a slow stream of dry nitrogen. Samples of Grignard reagents were transferred by syringe to nitrogen-flushed sample or NMR tubes attached to a vacuum manifold.

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These were sealed after partial evacuation.

(3,3-Dimethylcyclobutyl)methanol was prepared as described by Conia and Gore[18] by lithium aluminum hydride reduction of 3,3-dimethylcyclobutanecarboxylic acid;[19] bp 59–60 °C (8 mm) [lit.[18] bp 84 °C (37 mm); 71 °C (14 mm)].

1,1-Dimethyl-3-(bromomethyl)cyclobutane (6). The tosylate was prepared from 3.8 g (0.033 mol) of 3,3-dimethylcyclobutanemethanol and 9.5 g (0.05 mol) of *p*-toluenesulfonyl chloride in 40 mL of pyridine. Reactants were combined at 0–5 °C, maintained at that temperature for an additional 2 h, and stirred overnight at room temperature. Decomposition with ice–water, extraction with ether, washing with dilute sulfuric acid, aqueous sodium carbonate and water, and evaporation of solvent yielded the tosylate as an oil. It was used directly in the next step, but a crystalline sample was subsequently obtained: mp 39.5–41 °C (from petroleum ether).

Anal. Calcd for $C_{14}H_{20}SO_3$: C, 62.65; H, 7.51. Found: C, 62.48; H, 7.66.

The tosylate was stirred overnight at room temperature with 9 g (0.1 mol) of lithium bromide in acetone. The product was isolated by addition of water, extraction into ether, and distillation; bp 155–157 °C.

Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40. Found: C, 47.35; H, 7.55.

2,2-Dimethyl-4-pentenoic acid was prepared by Claisen rearrangement of the Reformatsky reagent from allyl α-bromoisobutyrate, as described by Baldwin and Walker;[20] bp 60 °C (0.5 mm) [lit.[21] bp 104–108 °C (20 mm), 93–94.5 °C (9 mm)]. The acid was reduced to **2,2-dimethyl-4-penten-1-ol** with lithium aluminum hydride; bp 65 °C (10 mm) [lit.[22] bp 151–152 °C, 77–79 °C (43 mm)].

5-Bromo-4,4-dimethyl-1-pentene (3). Bromine (16.9 g, 0.106 mol) was added dropwise to triphenylphosphine (26.2 g, 0.100 mol) dissolved in 100 mL of dimethylformamide (DMF) under nitrogen at 25 °C. An orange precipitate formed, and the temperature rose by about 10 °C. To this reagent was added dropwise 2,2-dimethyl-4-penten-1-ol (10.8 g, 0.093 mol) diluted with an equal volume of DMF. The temperature rose slightly, and the precipitate dissolved. The mixture was heated for 3 h at 110 °C. It was shown by GC (column C) that the reaction stopped at about 60% conversion after about 2 h. The reaction mixture was washed twice with about 5 volumes of water and extracted with an equal volume of CH_2Cl_2. The organic phase was washed with aqueous sodium bicarbonate and chromatographed on alumina; the product was eluted with petroleum ether (bp 30–60 °C). The solvent was removed and the product distilled under vacuum.

Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40. Found: C, 47.73; H, 7.54.

Grignard Reagents 1 and 2. A Grignard reagent was prepared from 0.88 g (5 mmol) of 1,1-dimethyl-3-(bromomethyl)cyclobutane (6) and 0.3 g of sublimed magnesium in 5 mL of dried THF. The mixture was heated at reflux for 1.5 h following the initial exothermic reaction, and samples were sealed into several 5-mm NMR tubes or other tubes suitable for storage and heating. On the basis of the mode of preparation and the spectroscopic and gas chromatographic observations noted below, the Grignard reagent concentration was about 0.4 M and the total magnesium concentration about 0.7 M. Hydrolysis of the Grignard reagent yielded a single monomeric hydrocarbon product (GC columns B–D) which was isolated by preparative GC (column A) and identified as 1,1,3-trimethylcyclobutane (7) on the basis of its spectra (see Table I).

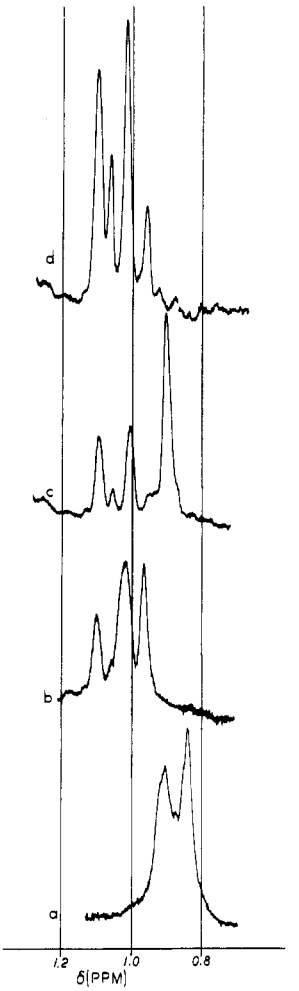

Figure 1. Methyl proton resonance of Grignard reagent solutions in tetrahydrofuran: (a) solution from 5-bromo-4,4-dimethyl-1-pentene (3); (b) solution from 1,1-dimethyl-3-(bromomethyl)-cyclobutane (6); (c) solution from 6 after heating 120 h at 100 °C; (d) solution from 6 after hydrolysis.

A small amount of a longer retention time component was eluted by raising the temperature to the vicinity of 200 °C. Its mass spectrum and a pair of methyl singlets in the NMR spectrum are consistent with expectations for the dimer 8.

The proton NMR spectrum of the Grignard reagent solution exhibited a high-field doublet at −0.31 ppm (J = 7.2 Hz), corresponding to protons α to the magnesium. A complex of peaks in the methyl region of the proton spectrum and the ^{13}C NMR spectrum could be assigned as noted below on the basis of changes produced on heating and comparison with other samples.

Heating of the Grignard reagent produced changes in the NMR spectra, most notably replacement of the doublet at −0.31 ppm by a singlet at −0.34 ppm. The change was essentially complete after about 5 h at 125 °C, and by quantitative analysis of the changes in the high-field portion of the spectrum, a half-life of 10 h at 100 °C was derived. A sample heated in a sealed tube for an extended period of time was worked up by removal of volatiles under vacuum, addition of fresh solvent, and hydrolysis with water. The monomeric hydrocarbon product from this sample had a similar retention time to that of 7 on a variety of GC columns but was separated by using columns B, C, or D. It had proton and ^{13}C NMR spectra which agreed with published spectra[23] for 4,4-dimethyl-1-pentene (4).

A Grignard reagent was similarly prepared in THF from 5-bromo-4,4-dimethyl-1-pentene (3). It had the NMR singlet at

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-0.34 ppm and yielded 4 on hydrolysis. A dimer, 5, with a longer retention time was also identified on the basis of its spectra.

By comparison of proton and ^{13}C NMR spectra from three different Grignard reagent samples, the reagent prepared from 3, and the reagent prepared from 6 before and after heating, it was possible to make assignments of methyl proton resonance signals and to assign all of the significant ^{13}C resonances. The methyl proton resonances are reproduced in Figure 1. In the Grignard reagent prepared from 3, the sharp resonance at 0.84 ppm is the hydrocarbon dimer; Grignard reagent 1 and monomeric hydrocarbon 4 overlap to give the broadened peak at about 0.90 ppm. The Grignard reagent from 6 *after heating* also has the signal from 1 at 0.90 ppm. At lower field are two strong signals which appear to result from overlap of the *gem*-dimethyl groups of monomer and dimer hydrocarbons 7 and 8. The methyl doublet from 7 is also observed. Before the reagent from 6 was heated, the two methyl singlets of Grignard reagent 2 were present at 1.02 and 0.97 ppm. In a sample which had been hydrolyzed, only the signals from 7 and 8 are observed, with the doublet from monomer 7 being more prominent.

In the ^{13}C NMR spectrum of the Grignard reagent from 3, all six resonances of dimer hydrocarbon 5 appear prominently. The methyl and methylene resonances of the monomeric hydrocarbon 4, which differ from those of 5, are present but are weak, indicating that dimerization is the principal side reaction in Grignard reagent formation. The remaining prominent resonances fall approximately in the location predicted from the parameters of Leibfritz, Wagner, and Roberts[24] for Grignard reagent 1. It is probable that the methylene carbon adjacent to the magnesium is buried in the solvent signal. The same five signals from 1 are present in the Grignard reagent prepared from 6, after heating. In the Grignard reagent from 6, several signals are prominent in the spectra both before and after heating. Most of these probably result from the dimeric hydrocarbon 8, since the resonances observed most clearly for the isolated monomer 7 in $CDCl_3$ appear rather weakly in the Grignard reagent. There remain six significant signals which disappear on heating and follow the general pattern observed for the other substituted (3,3-dimethylcyclobutyl)methyl derivatives. These may therefore be assigned to Grignard reagent 2. Table I includes NMR assignments which have been discussed above.

A sample of the open-chain Grignard reagent 1 prepared from 3 was heated for 48 h at 100 °C. The tube was opened in a drybag and connected to an adapter which permitted the solvent and other volatiles to be distilled to a trap under high vacuum. After evacuation for 1 h at about 5-μm pressure, the vacuum was broken with nitrogen, a small amount of THF was added, and the reagent was hydrolyzed by addition of an excess of water. Volatile materials were again distilled to a trap under vacuum and analyzed by GC on column B. Peak areas were assumed to be proportional to the amount of material for isomeric hydrocarbons 4 and 7. The peak corresponding in retention time to cyclized hydrocarbon 7 was trapped in a tube with liquid nitrogen cooling and analyzed by mass spectrometry.

Registry No. 1, 34164-52-8; 2, 76207-19-7; 3, 76207-20-0; 4, 76262-9; 5, 76207-21-1; 6, 76207-22-2; 7, 75017-20-8; 8, 76207-23-3; 3,3-dimethylcyclobutylmethanol, 75017-17-3; 3,3-dimethylcyclobutanecarboxylic acid, 34970-18-8; 3,3-dimethylcyclobutanemethanol tosylate, 76207-24-4; 2,2-dimethyl-4-pentenoic acid, 16386-93-9; allyl α-bromoisobutyrate, 40630-82-8; 2,2-dimethyl-4-penten-1-ol, 3420-42-6.

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Rates of Formation of Some Phenazines by Cyclization of Di- and Monoimines of *N*-(2-Aminophenyl)-*p*-benzoquinone[1]

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The spectrophotometrically determined rates for cyclization of *N*-(2-aminophenyl)-*p*-benzoquinonediimine and its 5-methyl and 5-chloro derivatives in buffered aqueous media are reported in Table I for the pH range 6–9. The first-order rate equation involves protonated diimine. At higher pH these diimines hydrolyze to the corresponding monoimines which then undergo cyclization. The first-order rate expression for cyclization for monoimine 3 (k_L) involves the neutral monoimine and under the conditions used for the reaction is faster than the second-order hydrolysis (k_h) of diimine 1a. Around pH 1 the diimines hydrolyze at the nonterminal imine nitrogen to the corresponding *p*-benzoquinone monoimine and *o*-phenylenediamine, which react further. Monoimine 3 undergoes a similar hydrolysis.

Mechanisms have been proposed for cyclization reactions which result in phenazines by formation of a nitrogen–carbon bond.[2] However, more data are needed to reduce the speculative nature of the proposed mechanisms and to eliminate possible alternatives. Rate-limiting steps have been observed that involve cationic, neutral (or zwitterionic), and/or anionic species. Presented here are the results of some rate studies of the cyclization of *N*-(2-aminophenyl)-*p*-benzoquinonimine (3) and -diimine and the 5-methyl and 5-chloro derivatives of the diimine (1a–c).

Diimines. Diphenylamines were synthesized by condensing *o*-fluoronitrobenzene with the appropriately substituted *p*-phenylenediamine followed by reduction of the nitro group with hydrogen and palladium. The resulting amines were recovered as the dihydrochlorides.

The diimines 1 (see Chart I) are prepared in dilute solution by potassium ferricyanide oxidation of the corresponding diphenylamines (6a–c). Within the pH range

(1) Taken in part from the M.S. Thesis of N. P. Loveless, University of Bridgeport, 1977, and presented in part at the 175th National Meeting of the American Chemical Society, Anaheim, CA, Mar 1978, Abstract No. ORGN 71.

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