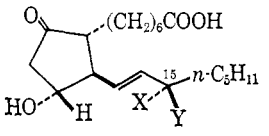
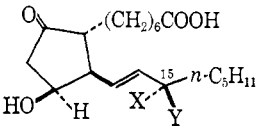
0.55.[3,5] The former pair was resolved chromatographically (silica gel; $CHCl_3$–Et_2O–CH_3OH, 5:5:0.1) after acetylation to afford the acetates **7a** (R = CH_3CO),[3] mp 56.5°, R_f 0.26, and **8b** (R = CH_3CO),[3,5] R_f 0.15. The formulation of the crystalline acetate, mp 56.5°, as **7a** follows from its identity (melting point, mixture melting point, spectroscopic) with the substance of this structure which was obtained as an intermediate in the previously described synthesis[1] of *dl*-prostaglandin E_1 (**9a**) and from its actual conversion[1] to *dl*-prostaglandin E_1.

The oily stereoisomers[9] **7b**, **8a**, and **8b** were separately transformed to prostaglandins in the E_1 series by the sequence previously described[1] with the result that **7b** produced pure *dl*-prostaglandin E_1 (**9a**) and pure *dl*-15-epiprostaglandin E_1 (**9b**) (readily separated chromatographically), and **8a** and **8b** each produced *dl*-11-epiprostaglandin E_1 (**10a**),[3] mp 92.5–93°, and *dl*-11,15-epiprostaglandin E_1 (**10b**),[3] mp 88.6–89.3°. The 11-epi formulations **10a,b** were verified by acid-catalyzed elimination of water to form, respectively, *dl*-prostaglandin A_1 and *dl*-15-epiprostaglandin A_1. Satisfactory analytical data were obtained for **10a** (*Anal.* Found: C, 67.84; H, 9.71) and for **10b** (*Anal.* Found: C, 67.54; H, 9.76).



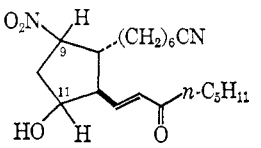
9a, X = OH; Y = H
b, X = H; Y = OH



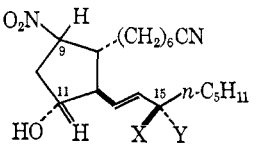
10a, X = OH; Y = H
b, X = H; Y = OH

The cyclization of **6** by the procedure described above led to C_{11}-normal and C_{11}-epi products in approximately equal amount. However, the ratio of these products depends on the conditions employed for cyclization, and, for example, use of 4% sulfuric acid in 1:1 tetrahydrofuran–water at 25° for 24 hr resulted in the formation of twice as much C_{11}-epi as C_{11}-normal cyclization product.

The synthesis of prostaglandins by direct acid-catalyzed cyclization of the nitro ketal **5** has also been accomplished. Thus, treatment of **5** with trifluoroacetic acid containing some triethylamine (initially at −10 to 25° over 1 hr and at 25° for 5 hr) followed by brief (20 sec) exposure to methanolic base at 0° produced a mixture of four stereoisomers of structure **11** which was easily separated by column chromatography on silica gel ($CHCl_3$ eluent) into a less mobile pair of C_{11}-normal alcohols epimeric at C_9 and a more mobile pair of C_{11}-epi alcohols epimeric at C_9. Reduction of the carbonyl function ($NaBH_4$) of the former pair of C_9 epimers



11



12, X = H; Y = OH
13, X = OH; Y = H

(C_{11} normal) led to a mixture of alcohols which was easily separated by chromatography on silica gel into a (less mobile) pair of C_{15}-normal alcohols epimeric at C_9 (**12**) and a (more mobile) pair of C_{15}-epi alcohols epimeric at C_9 (**13**). The pair **12** was converted to *dl*-prostaglandin E_1 by the previously described sequence[1] and, analogously, the pair **13** gave *dl*-15-epiprostaglandin E_1. Similarly, the 9-epimeric pair of nitro alcohols **11** in the C_{11}-epi series was converted after reduction and separation of C_{15} epimers into racemic C_{11}-epi- and 11,15-epiprostaglandin E_1. It is important to note that, with a nitro substituent at C_9, facile chromatographic separation of intermediates according to configuration at C_{11} and also C_{15} is possible. In addition, it has been found that 2,3-dicyano-5,6-dichloro-*p*-benzoquinone effects the selective oxidation of the Δ^{13}-15-hydroxy unit to the Δ^{13}-15-ketone unit in high yield, thus making it possible by the use of recycling of one of the isomeric C_{15} alcohols to direct the synthesis toward either C_{15}-normal or C_{15}-epi prostaglandins. Finally, since asymmetry at C_9 is removed in the later stages of synthesis, the occurrence of mixtures of C_9 epimers in this route is relatively unimportant.

Research is continuing on other modifications of the general synthetic approach to prostaglandins described herein, one objective being the complete control of stereochemistry, especially at C_{11}. A number of distinctly different synthetic routes to prostaglandins are also under study.

The racemic 11, 15, and 11,15 epimers of prostaglandin E_1 are all highly active biologically.[10] Of especial interest is the finding that *dl*-11,15-epiprostaglandin E_1 is about twice as active as *dl*-prostaglandin E_1 in tests on smooth muscle from rat uterus, but much less active in tests of vasodepression (in rats).

Acknowledgment. This work was generously supported by the National Institutes of Health.

(9) (a) For acetates **7a** and **8b** (R = CH_3CO), the molecular ions were found to have *m/e* 404.2687 and 404.2683, respectively (theory 404.2675); (b) for alcohols **7b** and **8a** (R = H), the molecular ions were found to have *m/e* 362.2564 and 362.2571, respectively (theory 362.2569).

(10) We are indebted to Drs. Peter Ramwell and Jane Shaw of the Worcester Foundation for Experimental Biology for quantitative biological measurements, the results of which will be published in full at a later time.

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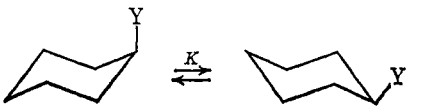
Received April 15, 1968

The Conformational Preferences of Cyclohexyl Grignard Reagents

Sir:

Probably the simplest measure of steric interactions is the difference in free-energy content of axial and equatorial cyclohexane derivatives, which, expressed in kilocalories/mole, has been defined as the *A* value[1] and

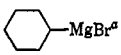
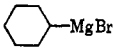
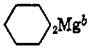
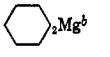
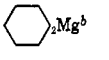
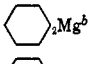
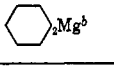


(1)

equals $-\Delta F = RT \ln K$.[2] It has been shown that these preferences are not simply related to the size

(1) S. Winstein and H. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).
(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 129.

Table I. Conformation Preferences of Magnesium Species in Ethyl and Methyl Ethers at Low Temperature

Expt	Compd	Solvent	Concn, *M*	Temp, °C	*A* value,[c] kcal/mol
1		Me_2O	1.0	−83	0.459
2		Et_2O	0.5	−75	0.784 ± 0.040
3		Me_2O	1.0	−84	0.247 ± 0.015
4		Et_2O	1.0	−82	0.525 ± 0.030
5		Et_2O	0.7	−81	0.534
6		Et_2O	0.5	−81	0.553
7		Et_2O	0.3	−83	0.537

[a] Grignard reagent. [b] Prepared by the dioxane precipitation method. [c] Uncertainty when reported represents the maximum variation observed with several samples. When no uncertainty is reported, the value represents the average of several analyses of the same sample. [d] This reagent is only moderately soluble at low temperature.

of the group; thus, the *A* values for the fluoro, chloro, bromo, and iodo groups are 0.250, 0.513, 0.480, and 0.431,[3] respectively, and the corresponding covalent radii are 0.64, 0.99, 1.14, and 1.33 Å.[4]

A knowledge of the steric requirements of organomagnesium compounds is of particular interest because of the sensitivity of their reactions to steric effects[5] and the high degree of asymmetric induction realized in some of their reactions.[6]

In this paper the conformational preferences of magnesium in the cyclohexyl Grignard reagent[7] and in dicyclohexylmagnesium in diethyl and dimethyl ethers are reported. Based on a consideration of atomic radii, the magnesium moiety and the iodo group, which have similar atomic radii,[4] might have comparable *A* values. However, magnesium complexes strongly with ethers,[8] and the actual Grignard reagent might be expected to have an *A* value approaching that of the *t*-butyl group (~4.2 kcal/mol at 220°).[9] Also, the "size" of the reagent, as defined by the *A*-value relationship, might be expected to be dependent on the ether solvent used.

Samples for nmr analysis of cyclohexyl Grignard reagents and dicyclohexylmagnesium (from the cyclohexyl Grignard reagent and dioxane) in diethyl ether and dimethyl ether were prepared using vacuum line techniques or other procedures to carefully exclude water, oxygen, and other contaminating substances. Low-temperature nmr spectra were recorded on a Varian HA-100 spectrometer. From the relative magnitudes of the α-H resonances, which are upfield from the other signals, the *A* values were calculated[3] (Table I).

The resonances of the α protons of the two conformers of the cyclohexyl Grignard reagent in dimethyl ether at −82° occur at τ 9.80 for the equatorial proton (moderately broad singlet) and τ 10.30 for the axial proton (broad triplet). The corresponding signals for dicyclohexylmagnesium in dimethyl ether at −84° are at τ 9.76 and 10.24, respectively. The spectra in ethyl ether were recorded in high-resolution operational mode and the chemical shifts were not determined. However, the general characteristics noted above were also observed in ethyl ether. To test the possible influence of concentration on *A* values, the conformational preference of the magnesium species in dicyclohexylmagnesium was tested as a function of concentration (expt 4, 5, 6, and 7 of Table I), but no dependence was found.

In both the Grignard reagent and dicyclohexylmagnesium the magnesium moiety has a larger *A* value in ethyl ether than in methyl ether solvent: Grignard reagent, 0.784 *vs.* 0.459 kcal/mol; the dialkylmagnesium compound, 0.525 *vs.* 0.247 kcal/mol. Wirth and Slick[10] have reported that boron trifluoride coordinates more strongly with methyl than with ethyl ether. If this same order of complexing holds with magnesium and if the degree of complexing is the dominant factor in determining the steric size, the opposite series would be realized. Apparently, the larger values in ethyl ether *vs.* methyl ether solvent result from coordination with a larger molecule. It appears resonable to expect that this difference in steric size with complexing solvent will be reflected in the amount of asymmetric induction and steric hindrance observed in reactions of Grignard reagents.[6] By suitable change of ether as solvent, the steric requirements of the magnesium moiety can be regulated.

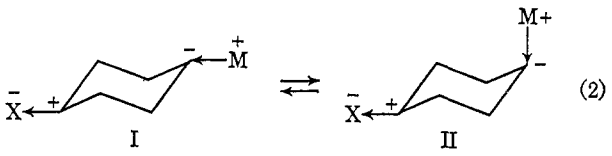
The Grignard reagent cannot be simply $(C_6H_{11})_2Mg$ because the Grignard reagent and dicyclohexylmagnesium have different *A* values. It is reasonable to expect that the magnesium in $RMgBr$[7] is more electropositive than in RMgR because of the relative electronegativities of alkyl and bromide. Therefore, $RMgBr$[7] should be complexed to a greater extent and should have greater steric requirements than R_2Mg, in accord with the observed *A* values.

As further evidence concerning the magnitude of the *A* value of the Grignard reagent, the 4-methylcyclohexyl Grignard reagent (from 4-methylcyclohexyl bromide)

(3) A. J. Berlin and F. R. Jensen, *Chem. Ind.* (London), 998 (1960).
(4) L. Pauling, "The Nature of the Chemical Bond," 2nd ed, Cornell University Press, Ithaca, N. Y., 1960, p 224.
(5) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp 170, 555, 973.
(6) D. J. Cram and D. W. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963); G. J. Karabotsos, *ibid.*, **89**, 1367 (1967).
(7) For convenience, written as RMgX. See, for example, E. C. Ashby, *Trans. N. Y. Acad. Sci.*, 27, 29 (1964).
(8) Reference 5, pp 99–102.
(9) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960).
(10) H. E. Wirth and P. I. Slick, *J. Phys. Chem.*, **66**, 2277 (1962).

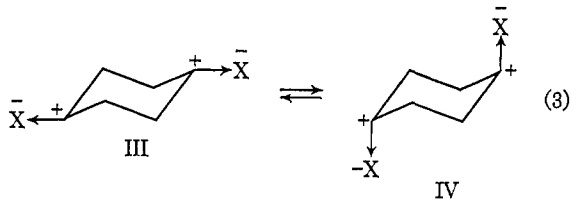
was carbonated at −78°. These acids were analyzed by glpc as the methyl esters,[11] and the isomer distribution of 83% *trans* and 17% *cis* was obtained. Identical results are obtained for reaction with mercuric bromide.[11] Assuming an *A* value for methyl of 1.8 kcal/mol[2] and utilizing the *A* value for the magnesium moiety at −83° (0.784 kcal/mol), a predicted isomer distribution of 79% *trans* and 21% *cis* is obtained. The observed isomer distribution is in accord with the distribution expected from the *A* value by low-temperature nmr spectroscopy.

In contrast, the 4-phenylcyclohexyl Grignard reagent[12] and the 4-*t*-butylcyclohexyl Grignard reagent yield only a very small amount (<4%) of *cis* acid upon carbonation at low temperature. Ring deformation[13] by the large *t*-butyl and phenyl groups may affect the conformational preferences of the magnesium moieties. In addition, dipole interactions in the phenyl



(2)

compound with phenyl equatorial and magnesium axial, as compared to the diequatorial configuration (eq 2, structure I), is expected to be less favorable because of the increased interaction of the positive charges (eq 2, structure II). An analogy for this proposal is found in the well-known phenomenon that cyclohexanes containing two electron-withdrawing groups prefer diaxial configurations,[14] presumably because of the favorable



(3)

interactions of the positive and negative charges in structure IV.

Acknowledgment. Support of this work by the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation under Grant GP-6350X is gratefully acknowledged.

(11) F. R. Jensen and K. Nakamaye, *J. Am. Chem. Soc.*, **88**, 3437 (1966).
(12) W. N. Smith, Ph.D. Dissertation, University of California, Berkeley, Calif., 1959.
(13) H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **86**, 1161 (1964).
(14) M. Hanach, "Conformational Theory," Academic Press Inc., New York, N. Y., 1965, p 121.

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Received March 15, 1968

A Reinvestigation of a Purported SH2 Reaction. The Reaction of Trichloromethyl Radicals with Organomercury Compounds. A Novel Radical-Elimination Reaction

Sir:

The benzoyl peroxide induced reactions of dialkyl- and diarylmercury compounds in carbon tetrachloride have been studied by Nesmeyanov, *et al.*[1] These authors report that this reaction follows the general path

$$R_2Hg + CCl_4 \xrightarrow{\text{peroxide}} RHgCl + RCCl_3 \quad (1)$$

The evidence presented consisted of the recovery of the alkyl- or arylmercuric chloride and the trichloromethyl compound or its corresponding carboxylic acid after alkaline hydrolysis. Significantly, no alkyl chlorides (RCl) were reported as products.

These workers suggested the formation of $RCCl_3$ arises from the reaction given by eq 2. Indeed, it is

$$\cdot CCl_3 + RHgR' \longrightarrow RCCl_3 + R'Hg\cdot \quad (2)$$
R = butyl, ethyl, cyclohexyl, aryl

difficult to conceive of a reaction mechanism to yield the reported products that does not proceed through an SH2 (bimolecular homolytic displacement) reaction. However, no examples of radical displacements on sp^3 carbon are known,[2] even though radical displacements have been reported in cyclopropane[3] and "Dewar" anthracene[4] systems where the hybridization is not truly sp^3.

In connection with studies of possible SH2 reactions, the reaction of dibutylmercury was investigated under conditions similar to those reported by Nesmeyanov, *et al.*[1] In contrast to the products expected on the basis of the earlier work, the major products found were 1,1,1,3-tetrachloropentane, 1-chlorobutane, chloroform, butylmercuric chloride, and mercury. No 1,1,1-trichloropentane, the expected product, was found. Furthermore, all attempts to repeat the reactions reported by Nesmeyanov, *et al.*, on dialkylmercury compounds failed.

In typical experiments the dialkylmercury compound (0.45 *M*), benzoyl peroxide (0.056 *M*), and carbon tetrachloride were degassed, sealed in ampoules, and heated for 7 hr at 100° or for 50 hr at 77°. In one case the reaction was carried out in a flask fitted with a Vigreux column, allowing removal of low-boiling gases. After completion of the reaction, the mercury was collected by filtration, and the alkylmercuric chloride was removed by extraction with aqueous sodium thiosulfate. Addition of potassium iodide allowed recovery of the original alkylmercuric chloride as the corresponding mercuric iodide. Analysis of the remaining solution was carried out by glpc. The 1,1,1,3-tetrachloropentane was identified by ir, nmr, and glpc comparison with known material synthesized by the free-radical addition of CCl_4 to 1-butene. The yields of the major products from the reaction of dibutylmercury are shown in Table I.

The 1,1,1,3-tetrachloropentane must arise *via* the addition of carbon tetrachloride to 1-butene under the reaction conditions, a reaction for which there is ample precedent.[5] Consequently, 1-butene was expected to be a major product. Indeed, when the low-boiling gases were allowed to escape, not only is 1,1,1,3-tetrachloropentane obtained in greatly decreased yield, but also 1-butene was trapped at −78° in 50% yield. It is also

(1) A. N. Nesmeyanov, A. E. Borisov, E. T. Golubeva, and A. I. Kovredov, *Tetrahedron*, **18**, 683 (1962).
(2) For discussion of attempts to find SH2 reactions on carbon, see: W. S. Trahanovsky and M. P. Doyle, *J. Org. Chem.*, **32**, 146 (1967); W. A. Pryor and T. L. Pickering, *J. Am. Chem. Soc.*, **84**, 2705 (1962).
(3) C. Walling and P. S. Fredricks, *ibid.*, **84**, 3326 (1962).
(4) P. E. Applequist and R. Searle, *ibid.*, **86**, 1389 (1964).
(5) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., London, 1957, p 247.