Conformations. V. Conformational Analysis of 2-Bromocyclohexanone by Nuclear Magnetic Resonance Spectroscopy
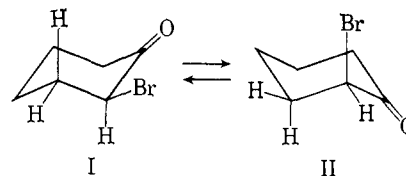
BY EDGAR W. GARBISCH, JR.[1]

Conformational analysis of 2-bromocyclohexanone using both proton spin coupling and chemical shift parameters shows that the conformational isomer with the axial bromine (II) is preferred to the extent of 52–91 ± 4% over the concentration range of 100–0 mole %, respectively, of ketone in carbon tetrachloride.

Mobile systems under conformational equilibria often are amenable to quantitative or semiquantitative conformational analysis by n.m.r. spectroscopy[2,3]; however, the success of this approach (as well as others) often relies on the availability of conformationally homogeneous model substrates from which the nuclear spin coupling and/or chemical shift parameters for the various possible conformational isomers are derived. In the absence of model substrates, the problem of conformational analysis is reduced to the qualitative, or at best, semiquantitative level, for the necessary parameters then must be estimated for the hypothetical conformationally homogeneous isomers from theoretical or empirical relationships (structural deformations and magnetic effects arising from the substituent being presumed negligible) or be obtained from "frozen out" conformational isomers at reduced temperatures (temperature independence of chemical shifts being assumed). Ideally, conformational analysis of a substance may be successful employing either the time-averaged coupling constants or the chemical shift parameters of appropriate nuclei. In practice, however, coupling patterns are often complex or obscured by long range virtual coupling, and model chemical shift parameters may be rendered unreliable because of the magnetic effects of the additional group or groups positioned so as to ensure model conformational homogeneity. Using the technique of nuclear spin decoupling, coupling patterns conceivably may be simplified often to the extent where they could be used successfully.

As an example illustrating both the nuclear spin coupling and the shielding parameter approach to conformational analysis, 2-bromocyclohexanone has been chosen, since this material has been investigated extensively by other methods and data are available for comparison.[4]

Results

For rapidly equilibrating systems, observed couplings (and chemical shifts) are time averages of the couplings (and chemical shifts) in the various components under equilibrium. In order to estimate the equilibrium between the two conformational isomers of 2-bromocyclohexanone, I and II, the proton spin couplings between H_2 and H_{3a}, H_{3e} and the chemical shifts of the

(1) Address correspondence to University of Chicago.

(2) (a) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962); (b) W. C. Neikam and B. P. Dailey, *J. Chem. Phys.*, **38**, 445 (1963); (c) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

(3) A. A. Bothner-By and C. Naar-Colin, *ibid.*, **84**, 743 (1962); F. A. L. Anet, *ibid.*, **84**, 747 (1962); and H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *J. Chem. Phys.*, **36**, 3353 (1962).

(4) (a) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958); (b) N. L. Allinger, J. Allinger, and N. A. Le Bel, *J. Am. Chem. Soc.*, **82**, 2926 (1960); (c) B. Waegell and G. Ourisson, *Bull. soc. chim. France*, 496 (1963).

$$\text{I} \rightleftharpoons \text{II}$$

C_2-protons in I and II must be known. With regard to the proton couplings, these three spin systems in I and II are of the ABX type[5] where X is the C_2-proton whose resonance is isolated downfield from the other ring proton resonances. Neglecting the weak combination transitions which are not often observed, the separation between the terminal peaks of the X resonance is equal to $J(H_2, H_{3a}) + J(H_2, H_{3e})$.[5] If this coupling constant sum is designated J_I and J_{II} for I and II, respectively, $J° = J_I N_I + J_{II} N_{II}$ where $J°$ is the observed separation between the terminal lines of the C_2-proton resonance for 2-bromocyclohexanone. It follows that

$$N_I = J° - J_{II}/J_I - J_{II} \qquad (1)$$

Equation 2 gives the mole fraction of I utilizing the chemical shifts of H_{2a} (δ_I) and H_{2e} (δ_{II}) of I and II, respectively, and the observed chemical shift of H_2 ($\delta°$) of 2-bromocyclohexanone.

$$N_I = \delta° - \delta_{II}/\delta_I - \delta_{II} \qquad (2)$$

In order to estimate values of J_I and J_{II}, representative couplings were determined for a number of conformationally homogeneous model compounds. The results are summarized in Table I. The H_{2a} resonance of no. 1 is slightly perturbed from the expected X-part of an ABX absorption, probably because of virtual coupling to H_{4a}.[6] In no. 2 and 3 where the chemical shift of the C_4 axial proton is shifted to lower field as compared to that of no. 1, the $H_{\alpha,a}$ resonance is seen to be normal. The H_{2e} absorption of no. 4 and 5 appear as triplets with each component of the triplet being split into doublets by about 1.5 c.p.s. This splitting has been found to arise from a stereospecific long range coupling to H_{6e}.[7] From the couplings in Table I, average values of 18.2 and 5.7 c.p.s. are estimated for J_I and J_{II}, respectively.

Values of $J°$ as a function of the mole percentage of 2-bromocyclohexanone in carbon tetrachloride were determined and are shown in Fig. 1. There was no

(5) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 134; and R. T. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

(6) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

(7) E. W. Garbisch, Jr., Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., September 9–13, 1963, p. 36Q.

TABLE I

COUPLING PARAMETERS FOR MODEL SUBSTRATES

No.	Model	Proton resonance	$J(H\alpha,H\beta a)$ + $J(H\alpha,H\beta e)$, c.p.s.
1			17.9
2			18.4
3			18.3 (αa) and 5.7 (αe)
4			5.8
5			5.6

concentration dependence of the couplings representative of J_I and J_{II} in no. 1 and 5 of Table I. In Fig. 2 are shown δ_I, δ_{II}, and δ° as a function of concentration.[8] Using the data in Fig. 1 and 2, J_I and J_{II}, and eq. 1 and 2, the percentage of I at conformational equilibrium as a function of concentration in carbon tetrachloride may be estimated from either chemical shift or proton spin coupling measurements. The percentages of I at several selected concentrations are shown in Table II along with reported results from other approaches for comparison.

TABLE II

CONFORMATIONAL ANALYSIS OF 2-BROMOCYCLOHEXANONE[a]

Mole % 2-bromocyclo-hexanone	Mole % I using eq. 1[b]	Mole % I using eq. 2[b]	Mole % I, lit.
100	48	...	Ca. 50 (infrared)[4a]
50	43	...	...
33	37	31 (35)[d]	...
15	27	26 (31)[d]	...
8	20	22 (29)[d]	...
0	9	8 (18)[d]	15 (heptane, dipole moment)[c]
			17 (CCl₄, ultraviolet)[4c]

[a] $25 \pm 2°$ in CCl₄.   [b] $\pm 4\%$.   [c] Ref. 4b and W. D. Kumler and A. C. Huitric, J. Am. Chem. Soc., **78**, 3369 (1956).   [d] Empirically corrected (see text).

As *trans*-2,6-dibromocyclohexanone (III) represents a model for the case of $N_J = 0.5$, it is of interest to

(8) The α-axial protons (α to both the carbonyl and halogen) in α-halo-ketones are known to resonate at lower magnetic field than the α-equatorial protons: A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, J. Am. Chem. Soc., **85**, 2185 (1963); and K. M. Wellman and F. G. Bordwell, *Tetrahedron Letters*, 1703 (1963). This is in contrast to what is normally observed for cyclohexane systems.[2]
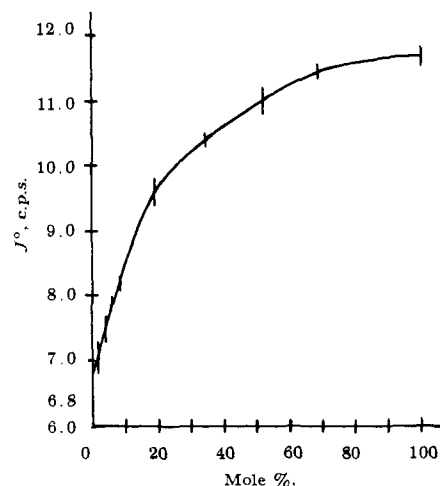

Fig. 1.—Values of J° as a function of the mole percentage of 2-bromocyclohexanone in carbon tetrachloride.
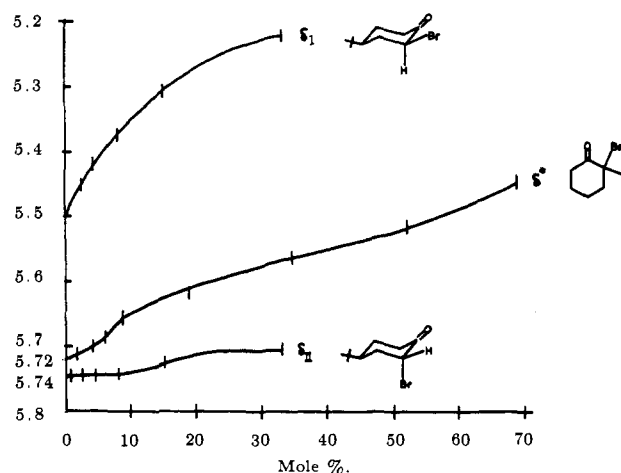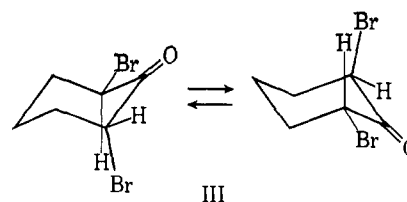

Fig. 2.—Values of δ_1, δ_{II}, and δ° as a function of the mole percentage of ketone in carbon tetrachloride.

determine whether or not eq. 1 leads to a comparable result. Rapid chair–chair interconversion of III should

III

lead to a time-averaged coupling of the 2,6-protons representative of $(J_I + J_{II})/2$ or 11.9 c.p.s. The observed separation between the terminal lines of the α-proton resonance of III is 11.1 c.p.s. which leads to $N_I = 0.43$ in only fair agreement with expectation. Possibly, a slight structural deformation of III could account for this discrepancy; however, the normal α-proton resonances of no. 3 in Table I suggest that this may not be an adequate explanation.

Discussion

Mole percentages of I derived from eq. 1 and 2 appear to be in good agreement over the concentration range of 2-bromocyclohexanone in carbon tetrachloride shown in Table II. The dependence of N_I on the concentration of 2-bromocyclohexanone is expected, as it has been shown from previous work[4] that N_I (I

having a larger dipole moment than II) increases as the dielectric constant of the solvent increases. At infinite dilution, $N_I = 0.09 \pm 0.04$ as determined by n.m.r. spectroscopy employing both proton spin coupling (eq. 1) and chemical shift (eq. 2) parameters is in fair agreement with $N_I = 0.15$ (in heptane) as determined by dipole moment measurement.[4b] Although there appears to be good agreement between the results employing eq. 1 and 2 (Table II), there exists a possibility that model compounds used to obtain values of δ_I and δ_{II} (no. 1 and 5 in Table I) are not totally satisfactory because of long range shielding effects arising from the t-butyl group.[2b,c,9] Eliel and co-workers[10] have tabulated empirical corrections for the shielding effects of alkyl groups on the α-carbinol protons of alkylated cyclohexanols. From their results, a correction of $+0.03$ p.p.m. for the δ_{II} values and no correction for the δ_I values (Fig. 2) can be estimated. Using the "corrected" δ_{II} values, new values of N_I were derived from eq. 2 and these are shown as parenthetical entries in Table II. It is difficult to justify

(9) J. I. Musher, *J. Chem. Phys.*, **35**, 1159 (1961); **37**, 192 (1962).

(10) E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962).

the need for these corrections in this instance, since agreement between the uncorrected values of N_I (Table II) obtained from eq. 1 and 2 appears satisfactory.

Experimental

(11) N. L. Allinger and J. Allinger, *J. Am. Chem. Soc.*, **80**, 5476 (1958).

(12) E. J. Corey, *ibid.*, **75**, 3297 (1953). The procedure used for the synthesis of both *cis*- and *trans*-2,6-dibromocyclohexanones was that described by R. Metze and P. Schreiber, *Chem. Ber.*, **89**, 2470 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIF.]

Infrared Spectral Studies of Grignard Solutions

BY RUDOLF M. SALINGER AND HARRY S. MOSHER

The infrared spectra of the Grignard and dialkyl- or diphenylmagnesium reagents prepared from methyl, ethyl, and phenyl halides in ethyl ether and in tetrahydrofuran have been investigated. The R–Mg absorption shows as a rather wide band between 500 and 535 cm.$^{-1}$ for R = Me or Et and between 365 and 383 cm.$^{-1}$ for R = Ph. The spectra of the Grignard solutions prepared in THF from methyl chloride, methyl bromide, ethyl chloride, ethyl bromide, and phenyl bromide and the corresponding dialkylmagnesium solutions in THF are noticeably different and can be interpreted in terms of the equilibrium, $R_2Mg + MgX_2 \rightleftarrows 2RMgX$, where the species may be in part ionized. The infrared spectra of *ether* solutions of the same reagents, in contrast to those of the THF solutions, are not definitive and do not warrant such a conclusion. In every case the infrared spectrum of an equimolecular mixture of dialkylmagnesium (or diphenylmagnesium) and magnesium halide was identical with that of the corresponding solution of Grignard reagent. Reactions of alkyl iodides with magnesium in THF gave heterogeneous mixtures, the solutions from which were rich in dialkylmagnesium and contained but little iodide. It is evident from these data that conclusions drawn concerning the nature of any one Grignard reagent cannot be safely extrapolated to other such reagents because of the varying effects of R, X, and solvent on the Grignard system.

Introduction

The problem of the precise nature of the Grignard reagent has attracted renewed interest since the definitive experiments of Dessy, *et al.*[1] demonstrated that there was essentially no magnesium exchange between diethylmagnesium in ether solvent and radioactive magnesium bromide. Recently Ashby and Becker[2] showed that in tetrahydrofuran (THF), monomeric species predominate in some simple Grignard reagents, in contrast to the dimeric species existing in ethyl ether. Vreugdenhil and Blomberg[3] reported that *dilute* solutions (*ca.* 0.01 *M*) of ethylmagnesium bromide in ethyl ether *or* in THF contain only monomeric species. Stucky and Rundle,[4] by X-ray studies, found that phenylmagnesium bromide etherate crystals contain PhMgBr·2Et$_2$O units. Nuclear magnetic resonance studies[5] have been very revealing but not definitive concerning the species RMgX *vs.* R$_2$Mg·MgX$_2$. The demonstration by Walborsky[6] of the stereochemical stability of the Grignard reagent from 1-bromo-1-methyl-2,2-diphenylcyclopropane establishes the integrity of the carbon–magnesium bond in this specific case. This body of diverse and partially conflicting data suggests that the nature of the Grignard reagent may be very dependent upon the variables of solvent, R group, and halide, and that a comparative study of several reagents by some suitable physical method should be made. It should be emphasized that physical methods may reveal the composition of the Grignard solution but may reveal little or nothing concerning the reactive species of the Grignard reagent.

Infrared spectroscopy should serve as a useful tool,

(1) R. E. Dessy, J. H. Wotiz, and C. A. Hollingsworth, *J. Am. Chem. Soc.*, **79**, 3476 (1957).

(2) E. C. Ashby and W. E. Becker, *ibid.*, **85**, 118 (1963).

(3) A. D. Vreugdenhil and C. Blomberg, *Rec. trav. chim.*, **82**, 453, 461 (1963).

(4) G. D. Stucky and R. E. Rundle, *J. Am. Chem. Soc.*, **85**, 1002 (1963).

(5) G. M. Whitesides, F. Kaplan, and J. D. Roberts, *ibid.*, **85**, 2167 (1963), and papers cited therein.

(6) H. M. Walborsky and A. E. Young, *Record Chem. Progr.*, **23**, 75 (1962).