

It is quite probable that the effect of drying at 75° is to bring about a reaction sequence similar to the above. In this case olefin and diiodide are both found in the black reaction product.

Drying by evacuation at room temperature to 10⁻⁴ mm. and over phosphorus pentoxide follows a course of reaction which probably involves a pathway which is a one-electron transfer and which is reversible. It may be that this pathway also occurs in the benzene extraction and the 75° drying of I.

At present the nature of the free radicals formed by dehydrating and heating I is not clear. However, the fact that the line width decreases with increasing temperature and that the radical content remains constant as a function of temperature suggests that the radicals may be due to a type of donor-acceptor complex formation.⁹ In the case of III the complex involves iodide, as shown in the reaction just postulated. In the case of IV, obtained by heating I, the complex probably involves triiodide. The connection between the nature of these species and the temperature dependence of the e.s.r. absorption is not apparent.

Acknowledgment.—We are very grateful to Dr. Nelson J. Leonard, who suggested a free radical study of these compounds.

[CONTRIBUTION FROM THE CENTRAL BASIC RESEARCH LABORATORY, ESSO RESEARCH AND ENGINEERING CO., LINDEN, N. J.]

Studies in Magnetic Nonequivalence. N.m.r. Spectra of Two-Spin and Two-Spin-Group Systems

BY E. I. SNYDER

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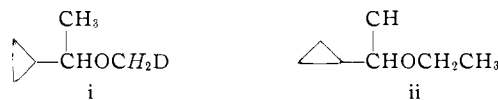
Nuclear magnetic resonance spectra have been obtained for several simple spectral systems whose methylene groups contain magnetically nonequivalent hydrogens, or whose isopropyl groups contain nonequivalent methyl hydrogens. The variation of the chemical shift between nonequivalent hydrogens of saturated systems varies with solvent in the same way as does the chemical shift between the terminal methylenes of the corresponding olefins. This behavior is interpreted as demonstrating the insufficiency of the chemical shift *per se* as a reliable measure of conformational equilibria. Also presented are data which demonstrate a small, but real, solvent dependence of geminal coupling constants.

Introduction

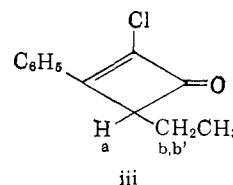
It is known that in systems of the type A-CX₂-B, where A is an atom or group of atoms and B is a group which lacks a plane of symmetry, the X nuclei are sometimes magnetically nonequivalent. This phenomenon has been observed for the methylene hydrogens in the ethyl group of esters,¹ sulfites,² sulfoxides,^{3,4} diethyl sulfide-borane,⁵ diethylmethylammonium iodide,⁶ a thiophosphonate,⁵ carboxylic esters,⁶ for the methylene hydrogens of variously substituted 1,1,1,2-tetrasubstituted ethanes,^{1,7} in the difluoromethylene group of appropriately substituted ethanes,^{1,8-10} and for the methyls of various systems containing an isopropyl skeleton.¹¹ The origin of such nonequivalence has

usually been ascribed to differences in conformer population.^{8,12} However, Waugh and Cotton have explicitly mentioned⁴ that a symmetry argument alone, completely independent of any facets of conformational isomerism, could equally well account for such nonequivalence, although some have not seemed to take cognizance of this latter alternative.

Recently Roberts and co-workers¹³ have interpreted both the lack of nonequivalence in the deuteriomethyl group of i (*vs.* the observed nonequivalence in the ethyl



analog ii) and the inequality of vicinal couplings $J_{ab}, J_{ab'}$ between the nonequivalent methylene hydrogens and



- (1) P. R. Schafer, D. R. Davis, M. Vogel, K. Nagarajan, and J. D. Roberts, *Proc. Natl. Acad. Sci. U. S. A.*, **47**, 49 (1961).
- (2) H. S. Finegold, *Proc. Chem. Soc.*, 283 (1960).
- (3) T. D. Coyle and F. G. A. Stone, *J. Am. Chem. Soc.*, **83**, 4138 (1961).
- (4) J. S. Waugh and F. A. Cotton, *J. Phys. Chem.*, **65**, 562 (1961).
- (5) H. S. Finegold, *J. Am. Chem. Soc.*, **82**, 2641 (1960).
- (6) E. I. Snyder, unpublished results.
- (7) (a) D. R. Davis and J. D. Roberts, *J. Am. Chem. Soc.*, **84**, 2252 (1962); (b) D. R. Davis, R. P. Lutz, and J. D. Roberts, *ibid.*, **83**, 246 (1961).
- (8) P. M. Nair and J. D. Roberts, *ibid.*, **79**, 4565 (1957).
- (9) J. J. Drysdale and W. D. Phillips, *ibid.*, **79**, 219 (1957).
- (10) J. N. Shoolery and B. Crawford, Jr., *J. Mol. Spectry.*, **1**, 270 (1957).
- (11) S. Goodwin, J. N. Shoolery, and L. F. Johnson, *J. Am. Chem. Soc.*, **81**, 3065 (1959); H. O. House and W. F. Gilmore, *ibid.*, **83**, 3980 (1961); T. H. Siddall, III, and C. H. Prohaska, *ibid.*, **84**, 2502 (1962).

- (12) J. A. Pople, *Mol. Phys.*, **1**, 3 (1958).
- (13) G. M. Whitesides, F. Kaplan, K. Nagarajan, and J. D. Roberts, *Proc. Natl. Acad. Sci. U. S. A.*, **48**, 1113 (1962).

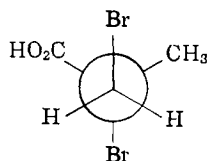
the tertiary hydrogen in iii as constituting proof that nonequivalence arises from conformational effects.¹⁴

The term "magnetic nonequivalence" leads to semantic confusion which needs clarification. In general, the only two criteria which can be conveniently applied to differentiate magnetically between nuclei are the chemical shift difference between the nuclei and the spin coupling constant of these nuclei with some third one. It would therefore be preferable to classify nuclei as magnetically nonequivalent in the chemical shift or spin coupling sense. As shall become clear in subsequent papers, nuclei which are nonequivalent by one criterion may be equivalent according to the other. It must be emphasized that in suitable A-CX₂-B systems the X nuclei are *always stereochemically nonequivalent* but *not necessarily magnetically nonequivalent*. Unless otherwise stated in this paper and subsequent ones, the term "nonequivalent" will invariably refer to magnetic nonequivalence.

As it appears to us, the subject of magnetic nonequivalence has a number of distinct, but not wholly independent, aspects: (A) What are the broad characteristics of systems which have nonequivalent nuclei? (B) What sort of behavior is exhibited by the criteria of nonequivalence? (C) What is (are) the origin(s) of nonequivalence? (D) What quantitative relations can be developed linking information gathered from systems possessing nonequivalent groups and conformational (rotational) isomerism? We shall defer treatment of point D to some later time. The sum of our observations will contribute to point A and conclusions based on their interpretation will bear on C. Because the present paper deals exclusively with simple spectral systems, *viz.*, two-spin and two-spin-group systems, insofar as magnetic nonequivalence is concerned the work described herein bears only on the criterion of chemical shift.

Results

All n.m.r. spectra of a compound were recorded at the same concentration (usually 40% weight/volume) in several solvents. For α,β -dibromoisobutyric acid (I) each of the low-field signals of the AB pattern was further split into a quadruplet by spin coupling with the methyl protons ($J \sim 0.5$ c.p.s.). Similar long-range couplings had previously been observed in the methyl ester of this acid.^{7b} In analogy with the stereochemistry of such couplings recently elucidated^{7a} in the related dibromide, 1,2-dibromo-2-phenylpropane, the low field signals presumably arise from the hydrogen *trans* to the -CH₃ groups in the conformation¹⁵



Chemical shifts (δ) between the methylene protons in the dibromide and in the unsaturated acid α -methylacrylic acid (II), from which I is formally derived, are included in Table I and are plotted in Fig. 1. Also tabulated are the geminal coupling constants for the dibromide. Similar data for 2,3-dibromo-2-phenylpropionic acid (III), its corresponding olefin, atropic acid (IV), and their methyl esters (V, VI), all of which give

(14) In future publications we shall show that such inequality of vicinal coupling constants is not always observed.

(15) If the conformation having bromines *trans* oriented is the most important one, then the observation by Freeman and Pachler¹⁵ that long-range coupling is present in *erythro*-2,3-dibromobutyric acid would lead to the opposite assignment.

(16) R. Freeman and K. Pachler, *Mol. Phys.*, **5**, 85 (1962).

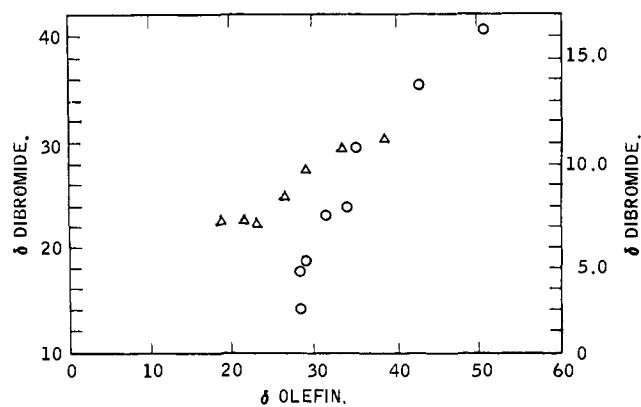


Fig. 1.—Plots of chemical shift difference (δ) in c.p.s. between methylenes of dibromide and the olefin from which it is derived. O, CH₂BrCBrCH₃CO₂H-CH₂=CCH₃CO₂H system, y-scale on left; Δ , CH₂BrCBrC₆H₅CO₂CH₃-CH₂=C₆H₅CO₂CH₃ system, y-scale on right.

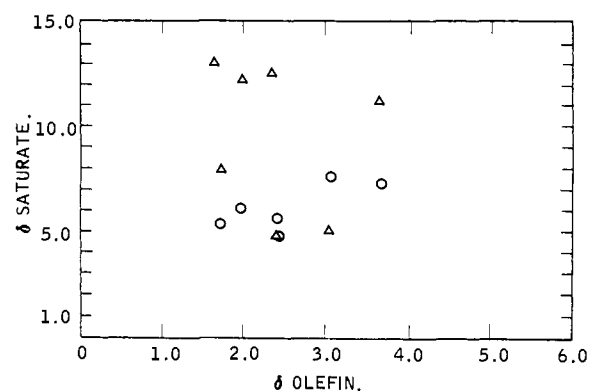


Fig. 2.—Plots of chemical shift difference (δ) in c.p.s. between methyls of saturates *vs.* δ of methyls in C₆H₅CH=C(CH₃)₂: O, C₆H₅CHBrCB₇(CH₃)₂; Δ , C₆H₅CHOHCH(CH₃)₂.

unperturbed AB spectra, are also included in Table I. The entries of Table II are systems in which the hydrogens of methylenes have been replaced by methyls, and all furnish additional examples of nonequivalent methyls in an isopropyl unit.¹¹ Since long range coupling between the methyl and 2-hydrogen has been observed in *erythro*-2,3-dibromobutyric acid,¹⁶ it is noteworthy that no fine structure was resolved in *either* of the two methyls of 2,3-dibromo-3-methylbutyric acid (X). That each of the methyl resonances has a half-width of ~ 1.1 c.p.s. (compared to 0.3 c.p.s. for internal TMS) might indicate that the doublet structure from long range CH₃-H coupling is diffused by a superimposed quartet arising from CH₃-CH₃ coupling. Similarly, the methyls of 1,2-dibromo-1-phenyl-2-methylpropane (VII) have a half-width of about 1 c.p.s. (0.3 c.p.s. for internal TMS) but no fine structure was resolved. Figure 2 shows plots of δ_{CH_3} in VII and in 2-methyl-1-phenylpropanol-1 (IX) *vs.* δ_{CH_3} in the olefin 1-phenyl-2-methylpropene-1 (VIII).

Discussion

Although differences are small, the solvent variation of the coupling constant between the methylene hydrogens of I is unquestionably real. This observation is not unique, for comparable variation has been noted in several three-spin systems containing nonequivalent methylene hydrogens.⁶ Rationalization of this variation on the basis of a changing HCH angle is somewhat uncertain in view of the state of flux of theoretical considerations regarding the relation be-

TABLE I
 N.M.R. PARAMETERS AT 60 MC. IN VARIOUS TWO-SPIN SYSTEMS

Compound		Benzene (2.28) ^a	Chlorobenzene (5.94)	Chloroform (5.05)	Nitrobenzene (36.1)	Methanol (33.1)	Acetone (21.4)	Acetonitrile (38.8)	Dimethyl- formamide (36.7)
CH ₃	δ^b	40.3	35.3	29.2	24.1	23.0	18.6	18.0	13.5
CH ₂ BrCBrCO ₂ H I	$\bar{\nu}^c$	218	227	241	245	243	247	243	250
	$\nu_{\text{CH}_3}^d$	108	118	124	126	121	122		121
	J_{gem}	9.8	10.00	9.8	10.04	9.6	9.71	10.13	9.68
CH ₂ =C(CO ₂ H) II	δ	50.8	43.3	35.0	34.2	30.8	29.0	28.2	28.2
	$\bar{\nu}$	346	352	358	360	360	354	358	351
CH ₂ BrC(C ₆ H ₅)BrCO ₂ H III	δ			11.3			8.3	7.8	
CH ₂ =C(C ₆ H ₅)CO ₂ H IV	δ			31.2			26.4	23.7	
CH ₂ BrCBrCO ₂ CH ₃ V	δ	11.3	10.6	9.8	8.5		7.5	7.4	7.6
	$\bar{\nu}$	245	249	256	263		264	262	271
	ν_{OCH_3}	202	214	232	233		231	230	233
CH ₂ =C(CO ₂ CH ₃) VI	J_{gem}	10.69	10.65	10.69	10.76		10.88	10.95	10.98
	δ	37.5	33.4	29.0	26.1		21.6	22.5	18.0
	$\bar{\nu}$		357	365	366		366	366	368
CH ₂ =C(CO ₂ CH ₃) VI	ν_{OCH_3}		214	225	226		225	225	227
	J_{gem}	1.37	1.39	1.33	1.19		1.23	1.03	1.09

^a The number in parentheses is the dielectric constant of the solvent. ^b δ is the chemical shift difference in c.p.s. between methylene protons. ^c $\bar{\nu}$ is the mean chemical shift of the methylene protons (in c.p.s. referred to internal TMS). ^d ν_X is the chemical shift of the X group (in c.p.s. referred to internal TMS).

 TABLE II
 N.M.R. PARAMETERS AT 60 MC. IN VARIOUS TWO-SPIN-GROUP SYSTEMS

Compound		Solvent						
		CCl ₄	Cyclohexane	Chlorobenzene	Dioxane	Chloroform	Benzene	Dimethyl- formamide
C ₆ H ₅ CHBrCBr(CH ₃) ₂ (VII)	δ^a	7.1	7.4	5.5	4.9	5.9	5.9	<0.6
	$\bar{\nu}^b$	115	113	107	115	116	103	117
C ₆ H ₅ CH=C(CH ₃) ₂ (VIII)	δ	3.7	3.1	2.4	2.4	2.0	1.7	1.6
	$\bar{\nu}$	109	108	106	110	111	103	111
C ₆ H ₅ CHOHCH(CH ₃) ₂ (IX)	δ	10.9	4.9	12.5	4.9	12.2	13.1	7.8
	$\bar{\nu}$	47	46	50	51	50	50	52
(CH ₃) ₂ CBrCHBrCO ₂ H (X)	δ					6.0	6.5	
(CH ₃) ₂ C=CHCO ₂ H (XI)	δ					15.3	28.7	

^a δ is the chemical shift difference between the nonequivalent methyl groups. ^b $\bar{\nu}$ is the mean chemical of the methyl protons (in c.p.s. referred to internal TMS).

tween such an angle and the corresponding geminal coupling constant.¹⁷ A similar solvent dependence of geminal coupling constants has been noted in 1,2-dichloro- and 1,2-dibromopropane¹⁸ and in 2-methoxyethanol.¹⁹

Variation of the chemical shift (δ) between nonequivalent hydrogens of methylenes with solvent is dramatic, ranging between 13 and 50 c.p.s. in I.²⁰ The data also clearly demonstrate that such variation is related to the dielectric constant of the solvent, with the higher chemical shift being associated with the solvent of lower dielectric constant. One might ascribe such a variation in chemical shift to changes in conformational population by the following reasoning. Let us make the assumption that the most stable conformer is the one in which bromines are *trans* oriented. The dipole-dipole repulsion energy between bromines *gauche* oriented would decrease with increasing dielectric constant of the solvent insofar as the latter is related to the dielectric medium in which the molecule is imbedded. Therefore, should electrostatic interactions largely determine the position of equilibrium, one would then expect differences in population of the various conformers to decrease as the dielectric constant of the solvent increases. Association of the chemical shift between the methylene hydrogens with differences in

conformer populations would now lead to the observed variation of δ with solvent. However, such a hypothesis seems to be negated by the one-to-one correspondence between δ in the dibromide I and δ in the olefin II.²¹ The latter is a rigid system whose geometry is invariant with solvent to a high degree of approximation. Since differences in δ of the methylenes cannot reflect differences in geometry at the adjacent carbon, it is reasonable to associate changes of δ with magnetic properties

(21) Such a correlation between the chemical shift differences of fixed and mobile proton pairs tempts one to conclude that in these cases no large variation in conformational population is occurring. This conclusion is supported by our data on three-spin systems of the type XCH₂CHYZ, where the values of the two vicinal coupling constants are usually quite solvent insensitive. However, many cases have been observed in three-spin systems where solvent invariance of the vicinal coupling constants is not attended by a correlation between chemical shift differences of fixed and mobile proton pairs. This suggests that such a correlation is more of a special case than a general one and that the absence of a correlation of the type described need not imply significant variation in conformational population. (Historically, the finding of this correspondence in some two-spin systems spurred efforts in three-spin systems where both the coupling constants and chemical shifts could be brought to bear independently upon the same problem. Our experience in three-spin systems subsequently forced us to abandon chemical shift data as a reliable probe of conformational effects.) M. T. Melchior of this company has suggested that the one-to-one correspondence in chemical shift differences noted for acid and ester pairs cited above may result from intramolecular hydrogen bonding between the carbonyl oxygen and a β -hydrogen in both the unsaturated and saturated derivative. Such an interaction, for which molecular models indicate a quite favorable H...O distance, would favor a particular conformation of the saturated derivative. It is quite reasonable to expect that the chemical shift difference between the methylene protons in this conformation would closely parallel the corresponding chemical shift difference in the olefin, such that if variations in conformer population were small (or, what amounts to the same thing, if the conformation in which hydrogen bonding is present is greatly preferred) the over-all chemical shift difference correlation between mobile and fixed proton pairs can be rationalized.

(17) M. Karplus, Symposium on High-Resolution NMR, Boulder, Colo., July, 1962; *J. Am. Chem. Soc.*, **84**, 2458 (1962).

(18) H. Finegold, *Proc. Chem. Soc.*, 213 (1962).

(19) R. J. Abraham, private communication.

(20) A check of concentration effects on δ in I indicated that in benzene the chemical shift at infinite dilution was approximately 10% higher than that observed in the standard 40% solution.

of solvent, degree, and kind of solvation, etc. The conclusion drawn from the observed correspondence between δ in dibromide and that in the olefin is that the chemical shift between nonequivalent hydrogens in methylenes *need not accurately reflect changes in rotational equilibrium*, but instead may merely reflect those magnetic properties of the solvent which affect chemical shift differences between hydrogens of a vinylic terminal methylene group.

Should the chemical shift difference between nonequivalent hydrogens in methylene groups arise mainly from a "solvent effect," as is suggested above, then one might expect some relation between δ and the mean resonance position of the methylene protons, $\bar{\nu}$.²² The data demonstrate that not only is $\bar{\nu}$ solvent dependent, but that, at least in the case of I–II, the correspondence between $\bar{\nu}$ and δ is as good as that between δ (dibromide) and δ (olefin). That equally good correspondence between $\bar{\nu}$ or ν_{OCH_2} in the olefin IV and these same parameters in the dibromide V is observed lends further support to the notion that *all* of the chemical shift values and differences can be interpreted as arising from properties of solvent related to local magnetic field anisotropy rather than any properties of solvent influencing conformational equilibria.

In the compounds VI–VII, where nonequivalent methyls are observed, the chemical shift differences in the saturated systems also seem to be related to the chemical shift between methyls of the olefin. Plots of δ saturate *vs.* δ olefin (Fig. 2) demonstrate much scatter, but a trend seems to be present. Interestingly, whereas the larger chemical shift difference between the methylene hydrogens of the dibromide VII is usually associated with the solvent in which the chemical shift difference in the olefin VIII is the larger, the inverse relation seems to hold for the alcohol IX and olefin VIII.

It is noteworthy that δ of the nonequivalent methyls in VII are *larger* than the δ of the nonequivalent-methylenes in $\text{C}_6\text{H}_5\text{CHBrCH}_2\text{Br}$.⁶ Quite naively, should conformational effects largely determine chemical shift differences, one might expect δ of the methyls to be less than that of the methylenes, for substitution of bulky methyl groups for the methylene hydrogens in $\text{C}_6\text{H}_5\text{CHBrCH}_2\text{Br}$ would tend to decrease differences in conformer populations, as is observed for the couple $\text{BrCH}_2\text{CH}_2\text{Br}$ – $\text{Br}(\text{CH}_3)_2\text{CC}(\text{CH}_3)_2\text{Br}$.²³ Such specious reasoning completely neglects what may well be the most important factor determining the chemical shift difference between nonequivalent nuclei, *viz.*, the anisotropy of the magnetic field about the carbon atom bearing the nonequivalent atoms or groups. Although detailed considerations might eventually invalidate this suggestion, it does not now seem unreasonable to suggest that the magnetic field gradients in those re-

gions of space corresponding to methyl hydrogens in the grouping $\text{AC}(\text{CH}_3)_2\text{B}$ may be greater than in those regions corresponding to the methylene hydrogens of the similar grouping ACH_2B . The greater field gradient could well be expected to cause the larger chemical shift difference irrespective of whether nonequivalence has its origins in conformational population differences or an inherent magnetic asymmetry. Similarly, it should be obvious that in a series ACX_2B , where the B group is varied, profound differences in chemical shift could occur which arise *solely* from changes in the magnetic anisotropy of the B groups.

It is clear that our data do not preclude some contribution to chemical shift differences from changes in conformational equilibria. But we cannot over-emphasize the inadequacy of the chemical shift as a valid criterion of conformational equilibria. The present state of our knowledge makes any such correlation exceedingly hazardous, and the results obtained therefrom²⁴ should be viewed with extreme reservation.

Summary

The unequivocally demonstrated variation of a geminal coupling constant with solvent necessitates that solvent effects on spin coupling constants be considered before ascribing changes in coupling constants to other origins.

Correspondence of the chemical shift between nonequivalent hydrogens of methylene and methyl groups with that found in corresponding olefins suggests magnetic properties of solvents produce changes in chemical shift which override those caused by differences in rotational equilibria, thereby making the chemical shift an inadequate measure of the equilibrium constant.

Experimental

All n.m.r. spectra were obtained on a Varian Associates model A-60 spectrometer. Unless otherwise noted, the compounds studied were either purified commercial chemicals or were prepared according to literature methods. Methyl esters were prepared from the purified acids by the addition of diazomethane. Methyl atropate had n_D^{20} 1.5398. Methyl dibromohydratropate melted at 60.1–60.7° (methanol).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{Br}_2\text{O}_2$: C, 37.30; H, 3.13; Br, 49.64. Found: C, 37.09; H, 3.00; Br, 49.55.

Addition of bromine to 2-methyl-1-phenylpropene-1 in carbon disulfide followed by distillation afforded the 1,2-dibromo-2-methyl-1-phenylpropane, n_D^{20} 1.5871.

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{Br}_2$: C, 41.12; H, 4.14; Br, 54.73. Found: C, 41.08; H, 4.43; Br, 54.65.

Acknowledgment.—The author wishes to acknowledge technical assistance provided by Messrs. M. Buza and T. Sara. He also wishes to thank Esso Research and Engineering Co. for permission to publish these results.

(24) T. H. Siddall, 111, and C. A. Prohaska, *J. Am. Chem. Soc.*, **84**, 2502, 3467 (1962). Although the authors successfully correlate "resonance doubling" in certain organophosphorus compounds with distinct conformations using little "special case" theory, it seems possible to explain virtually all of the data without recourse to conformational considerations.

(22) We wish to thank both M. T. Melchior, who first suggested this corollary, and a referee for pointing out this possibility to us.

(23) S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, Inc., New York, N. Y., 1954, p. 64.