tions were determined by titration of 10-ml aliquots with standard acid to a phenolphthalein end point.

Equilibrium Studies.—Solutions were prepared in heavy-walled tubes fitted with metal caps with butyl rubber liners or in glass tubes fitted with serum caps. The tubes were baked for 2 days at 130°, capped, evacuated, and filled with dry nitrogen through a hypodermic needle. Liquid ketone, followed by 10.0 ml of sodium diarylamide solution, was introduced by means of a dry syringe. The amount of ketone was determined by direct weighing of the capped tube.

Spectra were measured in a 0.016-cm cell at 32° by a Model 21 Perkin-Elmer ir spectrophotometer. Monoglyme and diglyme solutions of the amines and ketones obeyed Beer's Law at the C=O and N—H stretching bands. No appreciable absorbance was exhibited at these frequencies by the corresponding anions. Equilibrium concentrations were obtained from the Beer's Law plots and initial concentrations. Data are listed in Table I.

Elimination Studies.—Enolate solutions were prepared in a manner similar to that for sodium diarylamide solutions from 5 g of sodium hydride dispersion, 0.04 mol of ketone, and 250 ml of dry solvent. Sodiodeoxybenzoin was prepared in both monoglyme and diglyme, other enolates in diglyme only. Stirring at room temperature was continued until absorbance in the carbonyl region was negligible.

The elimination reactions were conducted in glass tubes by the technique described for the equilibrium studies. Halide (1 ml) and 10 ml of 0.15 *M* enolate were allowed to stand at room temperature until reaction was complete. Reactions with *n*-propyl chloride were carried out at 45°. The vapor over the reaction mixture was analyzed at 30° on a 20-ft column packed with 30% hexamethylphosphoramide on Chromosorb P. Hydrocarbons were identified by relative retention times with respect to pentane which was added to each sample. The liquid mixtures were diluted with 100 ml of water and extracted with *n*-butyl bromide. The bromide layer was washed with water to remove most of the diglyme and analyzed by glpc on a column of phenyl silicon on Gas-Chrom Z. The percentage of elimination was calculated from the areas under the peaks corresponding to alkylated ketone and original ketone. Thermal response values for homologous ketones have been shown to be equal within experimental error.[16]

Ebulliometric Studies.—Boiling point elevations were determined in a differential ebulliometer as described previously.[12] Reproducible temperatures were obtained quickly by forcing the stream of dry nitrogen through a bubbler containing mineral oil and then removing the bubbler to restore atmospheric pressure. The molal boiling point constant for monoglyme was determined for solutions of triphenylmethane in this solvent. A plot of ΔT *vs.* molality was linear and passed through the origin. The slope of the line $\Delta T/m = k = 3.05 \pm 0.04$. The constant was checked by a determination of the molecular weight of benzil. Also, the boiling point elevation of a 0.146 *M* (0.172 *m*) monoglyme solution of potassium *t*-butoxide was 0.153° indicating an aggregation number of 3.4, only slightly lower than that reported for 0.0077–0.0971 *M* solutions in benzene (3.6–3.9) where a structure with four *t*-butoxide ions at four corners of a cube has been suggested as a somewhat stable entity.[20] Boiling point elevations for 0.112, 0.173, and 0.407 *M* solutions of sodium diphenylamide were 0.337, 0.511, and 1.096° corresponding to aggregation numbers of 1.18, 1.24, and 1.41. Free amine could not be detected by ir analysis in the solutions following the ebulliometric measurements

Registry No.—*n*-Propyl chloride, 540-54-5; *n*-propyl bromide, 106-94-5; *n*-propyl iodide, 107-08-4; isopropyl bromide, 75-26-3; isopropyl iodide, 75-30-9; *n*-butyl bromide, 109-65-9; *s*-butyl bromide, 78-76-2; *t*-butyl bromide, 507-19-7; sodiodeoxybenzoin, 17003-50-8; sodiobutyrophenone, 17003-51-9; sodiopinacolone, 17003-52-0; sodiodeoxybenzoin with monoglyme, 17010-22-9.

(20) W. von E. Doering and R. S. Urban, *J. Amer. Chem. Soc.*, **78**, 5940 (1956).

Conformational Equilibria in the 2-Amino-1,2-diphenylethanol System. I. Nuclear Magnetic Resonance Studies

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Conformational preferences in a series of 2-(N,N-dialkylamino)-1,2-diphenylethanols and their derivatives have been investigated utilizing the relationship between the vicinal coupling constant and the dihedral angle described by H–C–C–H of the ethane backbone. For the N,N-dialkylamino groups considered, *i.e.*, morpholino, piperidino, pyrrolidino and dimethylamino, the *anti* rotamer A is dominant in all compounds of the *threo* series and in all but eight compounds of the *erythro* series. This observation serves to emphasize the important stabilizing influence of the division of the four bulkiest groups into two pairs separated from one another by hydrogens. An examination of those *erythro* compounds in which the *gauche* rotamer (eB) dominates suggests the importance of (1) intramolecular hydrogen bonding (OH···N) in the *erythro* amino alcohols **1a–d**, (2) the large steric requirement of the N-methylpiperidino group in the *erythro* methiodides **5** and **6**, and (3) the special steric requirements of the pyrrolidino group.

In the preparation of the isomeric enamines, *cis*- and *trans*-1-(4-morpholino)-1,2-diphenylethylene, rather striking differences were noted in the reactivity of the precursors, *dl-erythro*- and *dl-threo*-2-(4-morpholino)-1,2-diphenylethyl mesitoate, respectively, toward strong base.[2] The amino alcohols from which these esters were derived also demonstrated some marked differences in reactivity. Observations such as these prompted, as part of a larger study, an investigation of the factors controlling the position of conformational equilibria in the 2-amino-1,2-diphenylethanol system.

The diastereomeric N,N-dialkylamino alcohols, *threo* and *erythro*[3] **1a–d** (Table I), possessing a high degree of configurational homogeneity, were prepared *via* nucleophilic scission of the C–O bond of *cis*- and *trans*-stilbene oxide, respectively, by the appropriate amine. The *trans* nature of the epoxide opening[4] was verified by the conversion of *threo* and *erythro* amino alcohols **1a** and **1b** back into the epoxides from which they were derived by treatment of the corresponding methiodides with sodium hydride in tetrahydrofuran.[5]

(1) (a) NDEA Fellow 1963–1966. (b) Participant in the Undergraduate Research Program supported by National Science Foundation Grant No. GY-817.

(2) M. E. Munk and Y. K. Kim, *J. Org. Chem.*, **30**, 3705 (1965).

(3) The terms *threo* and *erythro* as used in this paper indicate *dl-threo* and *dl-erythro*.

(4) (a) R. E. Lutz, J. A. Freek, and R. S. Murphy, *J. Amer. Chem. Soc.*, **70**, 2015 (1948); (b) W. Stuhmer and G. Messwarb, *Arch. Pharm.*, **286**, 19 (1953).

(5) The *trans* nature of the ring closure is well documented. See A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA[a]

$PhCH_a(OR)-CH_bPh(X)$

Compd	Chemical shift[b] H_a thr[e]	H_a er[e]	H_b thr	H_b er	OH thr	OH er	J_{ab}, Hz[c] thr	J_{ab}, Hz[c] er	[anti]/[gauche][d] thr	[anti]/[gauche][d] er
Amino alcohols										
1, R = H										
a, X = 4-morpholino	304	318	213	202	300	200	10.3	4.3	*f*	0.28
b, X = 1-piperidino	302	320	212	202	305	205	10.4	4.8	*f*	0.41
c, X = 1-pyrrolidino	300	313	228	197	290	222	10.0	3.7	*f*	0.16
d, X = N,N-dimethylamino	301	317	213	192	295	190	10.5	4.4	*f*	0.30
Esters										
2, R = mesitoyl										
a, X = 4-morpholino	403	~400[g]	247	227			10.4	8.0	*f*	2.3
b, X = 1-piperidino	405	402	248	233			10.4	9.6	*f*	*f*
c, X = 1-pyrrolidino	400	397	249	216			8.9	5.2	4.6	0.52
b, X = N,N-dimethylamino	401	403	244	238			10.5	9.3	*f*	6.7
3, R = acetyl										
a, X = 4-morpholino	391	387	237	220			10.1	7.1	*f*	1.4
b, X = 1-piperidino	389	386	234	225			10.7	8.7	*f*	3.8
c, X = 1-pyrrolidino	379	382	230	206			7.1	4.4	1.4	0.30
d, X = N,N-dimethylamino	382	383	234	214			10.0	7.1	*f*	1.4
Ethers										
4, R = CH_3; X = piperidino	277	287	228	212			9.2	7.7	6.1	1.9
Methiodides										
5, R = H; X = 1-(N-methylpiperidino)[h]	344	378	305	317			10.7	2.9	*f*	*i*
6, R = CH_3; X = 1-(N-methylpiperidino)[h]	343	345	326	300			10.4	2.2	*f*	*i*

[a] Spectra were determined at room temperature on a Varian Model A-60 (60 MHz) spectrometer in $CDCl_3$ solution at a concentration of 15%. [b] In $-$hertz relative to internal tetramethylsilane. [c] An average of 6–10 runs. Measurements made on signals for both H_a and H_b where no overlapping with other signals occurs. Values accurate to an estimated ±0.1 Hz. [d] Ratio of population of rotamer A to rotamer B. [e] thr = *threo*; er = *erythro*. [f] >90% *anti*. [g] Overlapping the aromatic proton signals. [h] Run in dimethyl sulfoxide-d_6. [i] >90% *gauche*.

The *threo* and *erythro* amino alcohols **1a–d** served as precursors of the corresponding esters (**2** and **3**), ethers (**4**), and methiodides (**5** and **6**) shown in Table I. The conditions employed in the preparation of these derivatives were designed to retain their configurational integrity (see Experimental Section).

The power of nuclear magnetic resonance as a tool of conformational analysis in acyclic systems is now well established.[6] In particular, the observed vicinal coupling constant, J_{ab}, affords an *estimate* of the position of rotational conformational equilibria because of the

$PhCH_a(OR)-CH_bPh(NR_2)$

relationship of the dihedral angle described by H–C–C–H to the vicinal coupling constant. Since a high frequency of interconversion between the three possible rotamers is to be expected in the acyclic systems studied the observed vicinal coupling constant J_{ab} reflects a weighted mean dependent on the relative populations of *anti* (A) and *gauche* (B and C) rotamers.[7]

The observed vicinal coupling constants, J_{ab}, recorded in Table I, are conveniently determined by direct measurement since the signals for the protons of the ethane backbone, H_a and H_b, each appear as a doublet, as expected of the simple AX system. In all compounds the most deshielded ethane proton is undoubtedly that attached to carbon bearing the more electronegative oxygen atom.

These data, as recorded in Table I, *permit a rough approximation* of rotamer population at equilibrium using the simple relationship[6h,6i,9]

$$J_{ab} = p_A J_{anti} + p_{(B+C)} J_{gauche}$$

where p = rotamer population expressed as a mole fraction. In the system under study, it is suggested that populations of rotamers tC and eC (Chart I) are small compared with those of tB and eB, respectively. Because of the large steric requirements of Ph and NR_2

(6) (a) G. M. Whitesides, J. P. Sevenair, and R. W. Goetz, *J. Amer. Chem. Soc.*, **89**, 1135 (1967); (b) C. A. Kingsburgy and D. C. Best, *J. Org. Chem.*, **32**, 6 (1967); (c) C. A. Kingsburgy and W. B. Thorton, *ibid.*, **31**, 1000 (1966); (d) M. Buza and E. I. Synder, *J. Amer. Chem. Soc.*, **88**, 1161 (1966); (e) E. I. Synder, *ibid.*, **88**, 1165 (1966); (f) J. C. Randall, R. L. Vaulx, M. E. Hobbs, and C. R. Hauser, *J. Org. Chem.*, **30**, 2035 (1965); (g) J. W. Huffman and R. P. Elliot, *ibid.*, **30**, 365 (1965); (h) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962); (i) F. A. L. Anet, *ibid.*, **84**, 747 (1962); (j) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961).

(7) Although it may be understood, it seems desirable to emphasize that the term "rotamer" as used in this paper is not confined to the "pure-staggered" arrangement; rather the term is intended to embrace those conformations with "reasonable" deviations from the pure-staggered as well.[8] Such lattitude in definition appears compatible with our present ability to determine the conformation of acyclic molecules in solution.

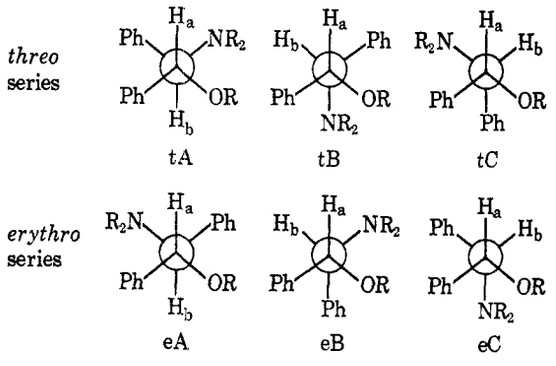
(8) See, for example, E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers Inc., New York, N. Y., 1965, p 11.

(9) Although strictly speaking, the J_{gauche} values may vary slightly for tB, tC, eB and eC,[6e] it will be assumed for the examination of trends that they are equal. The same argument applies to J_{anti} in tA and eA.

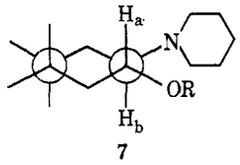
compared with those of OR and H, rotamers with Ph at C-1 *gauche* to *both* Ph and NR_2, *i.e.*, tC and eC, would be expected to be more sterically encumbered than tB and eB, respectively.[10] The *approximate* relationship can be further simplified to eq 1.

$$J_{ab} = p_A J_{anti} + p_B J_{gauche} \quad (1)$$

CHART I
ROTAMERS IN THE *threo* AND *erythro* SERIES

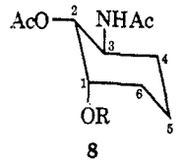


Previous investigations of acyclic systems[6] suggest 10–13 and 1–4 Hz as "working ranges" for J_{anti} and J_{gauche}, respectively. In order to narrow the range and obtain a "working value" of J_{anti} for the system under study, model compounds were examined in which the vicinal protons are constrained in an *anti* relationship. A J value of 10.0 Hz is observed for both *trans*-2-(1-piperidino)cyclohexanol (**7**, R = H) and its acetate **7**, R = $COCH_3$, compounds expected to reside in that chair conformer with H_a and H_b axial to one another.



7

Since J_{ab} is identical for both compounds it appears that intramolecular hydrogen bonding in **7**, R = H,[11] produces little or no distortion of the H_a–C–C–H_b angle.[12] Anet, Bannard, and Hall[13] report $J_{2,3}$ (*i.e.*, $J_{180°}$) = 10.4, 10.7, and 10.5 Hz for the trisubstituted cyclohexane compounds **8**, R = CH_3, $COCH_3$, and C_2H_5,



8

respectively. Although the cyclohexane system is far from an ideal model for the acyclic system under study, these observations do suggest that with few exceptions the *threo* compounds (Table I) are highly populated as the *anti* rotamer tA. A *minimum* "working value," J_{anti} = 10.3 Hz,[14] is therefore obtained by averaging J_{ab} for all of the *threo* compounds with the exception of esters **2c** and **3c** (see below).

Suitable model systems with vicinal protons constrained in a *gauche* relationship are less easily accessible. In the cyclohexane series, $J_{1,2}$ (equatorial–axial) values of 2.3, 2.8, and 2.5 Hz are reported for compounds **8**, R = CH_3, CH_3CO, and C_2H_5,[13] respectively. Although these values point to the predominance of *gauche* rotamer eB for the *erythro* methiodides **5** and **6** (J_{ab} = 2.9 and 2.2 Hz;[16] Table I), the tenuous value of the model cited cannot be ignored. The suggested conformational bias, however, appears consistent with the large steric requirements of the N-methylpiperidino (comparable with that of a *t*-butyl group) and phenyl groups, and, consequently, the severe *gauche* interaction expected between these groups in rotamer eA.[17,18] In constrast, in rotamer eB the bulky N-methylpiperidino at C-2 (as well as the phenyl group at C-1) is *gauche* to the two smallest groups on the adjacent carbon atom. Electrostatic ion-dipole attraction could further stabilize rotamer eB relative to eA.[19] A *maximum* "working value," J_{gauche} = 2.6 Hz,[14] is, therefore, obtained by averaging J_{ab} for the *erythro* methiodides **5** and **6**.

Using the *minimum* and *maximum* "working values" for J_{anti} and J_{gauche}, respectively, the relative populations of *anti* (A) and *gauche* (B) rotamers were calculated (Table I). The *approximate* nature of the [*anti*]/[*gauche*] ratio derived in this manner is to be emphasized; however, the approach is consonant with the stated objective of this paper, namely, *to formulate and evaluate trends*.

An examination of J_{ab} (Table I) reveals the dominance of values greater than 6.5 Hz; thus it follows from eq 1 that the *anti* rotamer (A) is most highly populated (*i.e.*, >50%) in *all* compounds of the *threo* series and in all but eight compounds of the *erythro* series. For convenience in discussion, the compounds are grouped according to the dominance of the *anti* (A) or *gauche* (B) rotamer. Attention is focused on the former group first.

The preponderance of compounds in which the *anti* rotamer (A) is most highly populated serves to emphasize the importance of 1,2 nonbonded repulsive interactions in controlling rotamer preference in the 2-(N,N-dialkylamino)-1,2-diphenylethanol system. Specifically, it would appear that the division of the four bulkiest groups into two pairs separated from one another by hydrogens contributes to a reduction in the

(10) If the steric requirements of OR and H are *small by comparison* to those of Ph and NR_2 there is some resemblance to the XCH_2CHYZ system in which it has been suggested[6e] that the rotamer with X *gauche* to both Y and Z is negligibly populated.

(11) Supported by preliminary high dilution infrared studies: M. Meilahn, experimentation in progress.

(12) Since the C–C–C angles in the cyclohexane ring are reported to be about 111.5° [see V. A. Atkinson and D. Hassel, *Acta Chem. Scand.*, **13**, 1737 (1959) and V. A. Atkinson, *ibid.*, **15**, 599 (1961)], dihedral angle H_a–C–C–H_b in **7** deviates slightly from 180°.

(13) F. A. L. Anet, R. A. B. Bannard, and L. D. Hall, *Can. J. Chem.*, **41**, 2331 (1963).

(14) A. A. Bothner-By [*Advan. Magnetic Resonance*, **1**, 195 (1965)] reports J_{anti} = 13 Hz and J_{gauche} = 4 Hz for ethane systems with carbon substituents. With an electronegative atom on each carbon atom of the ethane system, slightly lower values would be expected.[15]

(15) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(16) Because of solubility difficulties it was necessary to obtain the nmr spectra of **5** and **6** in *d*$_6$-DMSO.

(17) Possible solvation of the cationic site (quaternary nitrogen) by dimethyl sulfoxide could further accentuate the steric requirement of the N-methylpiperidino group. We are indebted to Professor Dodson of the University of Minnesota for this suggestion.

(18) The energy difference (ΔE) between *gauche* and *anti* rotamers of 1-phenyl-3,3-dimethylbutanes is reported[6a] to be 1.7 ± 0.09 kcal/mol.

(19) The large steric requirements of the water-solvated NH_3^+ group and electrostatic ion-dipole attraction could also account for the dominance of the *gauche* conformer reported by Huffman and Elliot[6g] for *dl-erythro*-2-amino-1,2-diphenylethanol in dilute acid solution. As expected, the *anti* conformer dominates the corresponding *dl-threo* isomer.[6g]

energy of the system. The findings of Mateos and Cram[20] in the system RCH(Ph)CH(OH)R and Everett and Hyne[21] in the ephedrine system further underscore the stabilizing influence of this steric factor.

In the case of the *threo* amino alcohols **1a–d**, intramolecular hydrogen bonding (OH···N) undoubtedly contributes to the dominance of the *anti* rotamer in chloroform solution.[22] Dreiding molecular models of those rotamers with a *gauche relationship between the hydroxyl and amino groups* clearly display an arrangement of atoms conducive to intramolecular hydrogen bond formation. The measured *intramolecular* O—N distance of 2.8 ± 0.5 Å compares favorably with the average O—N distance, 2.80 ± 0.09 Å, reported for *intermolecular* OH···N bonding in the crystalline state,[23] although it should be noted that the O–H–N angle probably differs significantly in the two cases.

Although the nmr data do not permit an accurate assessment of the role of dipole–dipole interactions,[24] it would appear that the effect of such forces are not profound. For example, in the *threo* amino alcohols **1a–d** and the *threo* ether **4**, CO—CN dipole–dipole repulsion would be expected to destabilize rotamers tA and tB relative to tC, thus acting in opposition to the steric factor and intramolecular hydrogen bonding. With the presence of the carbonyl group in the esters **2** and **3** the dipole–dipole interaction could be repulsive (CN—CO) or attractive (CN—C=O). Since the *anti* rotamer (A) dominates both the *threo* (NR_2 and OR *gauche*) and *erythro* (NR_2 and OR *anti*) series of esters (**2c** and **3c** excepted), it appears as though the effects of dipole–dipole interaction are overshadowed by the steric factor.

In those compounds where the *anti* rotamer (A) is most heavily populated in *both diastereomers* (compounds **2**, **3**, and **4**; pyrrolidino esters **2c** and **3c** excepted), it should be noted that J_{threo} is consistently higher than $J_{erythro}$ (Table I), leading to a greater [*anti*]/[*gauche*] value in the *threo* series. This observation suggests the following order of decreasing rotamer stability: tA > eA > eB > tB. The proposed order of stability is in accord with that proposed by Mateos and Cram[20] for the RCH(Ph)CH(OH)R system and indicates the following orders of steric requirement: Ph > OR (R = acyl or CH_3) > H and R_2N > Ph > H. Although the factors responsible for the "large" steric requirement of the R_2N group in this system still require clarification, it is interesting to note that Kingsbury and Best[6b] assign a *larger* steric requirement to cyclohexyl than to phenyl in the $CH_3CH(OH)CH(R)CH_3$ system.

Turning next to those eight *erythro* compounds in which the *gauche* rotamer eB predominates, three conspicuous subgroups are evident; the *erythro* methiodides **5** and **6** (discussed above), the *erythro* amino alcohols **1a–d**, and the *erythro* pyrrolidino esters **2c** and **3c**.

In the case of the *erythro* amino alcohols **1a–d**, an examination of the relative spatial arrangements of amino and hydroxyl groups in rotamers eA and eB suggests that it is the energy gained in intramolecular hydrogen bonding (OH···N)[22]—possible in eB but not eA—that offsets the steric factor favoring the *anti* rotamer (eA). The solvent dependence of the observed vicinal coupling constant, J_{ab}, provides support for the role ascribed to intramolecular hydrogen bonding in controlling the conformational preference of the *erythro* amino alcohols (Table II). The increases

TABLE II
EFFECT OF SOLVENT ON THE MAGNITUDE OF J_{ab} FOR AMINO ALCOHOL **1b**

Solvent	J_{ab}, Hz[a,b] *threo*	J_{ab}, Hz[a,b] *erythro*	[*anti*]/[*gauche*][c] *threo*	[*anti*]/[*gauche*][c] *erythro*
$CDCl_3$	10.4	4.8	*d*	0.41
CCl_4	10.1	4.7	*d*	0.37
CH_3CN	10.4	6.4	*d*	0.96
CH_3SOCH_3[e]	10.2	7.9	*d*	2.2

[a] Determined at room temperature at a concentration of 15%. [b] Values accurate to an estimated ±0.1 Hz. [c] Ratio of population of rotamer A to B. [d] >90% *anti*. [e] One drop of D_2O added to effect loss of hydroxyl hydrogen resonance.

in J_{ab} of 1.6 and 3.2 Hz (compared with the chloroform-*d* value), respectively, for the *erythro* amino alcohol in acetonitrile and dimethyl sulfoxide is consistent with the expected increase in *intermolecular* hydrogen bonding in these proton-acceptor solvents (OH···N≡C and OH···OS)[25] and concomitant decrease in *intramolecular* hydrogen bonding (OH···N). In these solvents the steric factor assumes a more influential control of conformational preference. In carbon tetrachloride, a solvent similar to chloroform in proton-acceptor ability, the balance of factors controlling rotamer preference should resemble that achieved in chloroform and lead to comparable values for J_{ab}.[26] In the *threo* series of amino alcohols the hydroxyl hydrogen resonance uniformly appears at lower field than in the *erythro* series. This suggests (but does not require) that there exists a higher population of intramolecularly hydrogen-bonded species (OH···N) in the *threo* amino alcohols in chloroform-*d* solution, an observation consistent with the reported [*anti*]/[*gauche*] ratios (Table I).[27]

One of the more surprising and striking observations of the present study is what appears to be "abnormally" low J_{ab} values for the *erythro* pyrrolidino esters **2c** and **3c** (Table I). Whereas the *anti* rotamer (eA) is heavily populated in the other six *erythro* esters reported the *gauche* rotamer eB clearly dominates in these two compounds. Since the basicity of the pyrrolidino group closely approximates that of the piperidino and dimethylamino group, the magnitude of the polar forces operating on the ground states of these *erythro* esters should be comparable.

(20) J. L. Mateos and D. J. Cram, *J. Amer. Chem. Soc.*, **81**, 2756 (1959).
(21) D. H. Everett and J. B. Hyne, *J. Chem. Soc.*, 1636 (1958).
(22) The values of J_{ab} for the *threo* and *erythro* amino alcohols **1a–d** remain unchanged in the concentration range 15–0.5%, the latter value being the limit of available instrumentation. High dilution infrared studies (M. Meilahn, in progress) indicate the operation of intramolecular hydrogen bonding (OH···N).
(23) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, p 289.
(24) S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press Inc., New York, N. Y., 1954.
(25) A. Allerhand and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 866 (1963).
(26) The similarity of J_{ab} values in chloroform-*d* and carbon tetrachloride suggests that the deuterium-donor ability of the former (basic nitrogen as the acceptor) does not play a significant role in the control of conformation in this system. See C. G. Cannon, *Spectrochim. Acta*, **10**, 429 (1958).
(27) The role of intermolecular hydrogen bonding (OH···N) cannot be excluded; however, see footnote 22. The sensitivity of the chemical shift of hydroxyl hydrogen to the extent of hydrogen bonding, intramolecular and intermolecular, is well known: J. B. Hyne, *Can. J. Chem.*, **38**, 125 (1960).

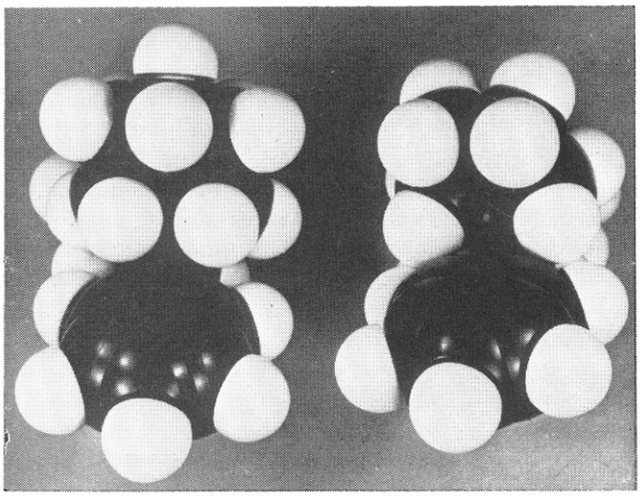


Figure 1.—CPK molecular models of the *anti* rotamer (eA) of *erythro* amino alcohols **1b** and **1c** (left to right) in their "most favorable arrangements."

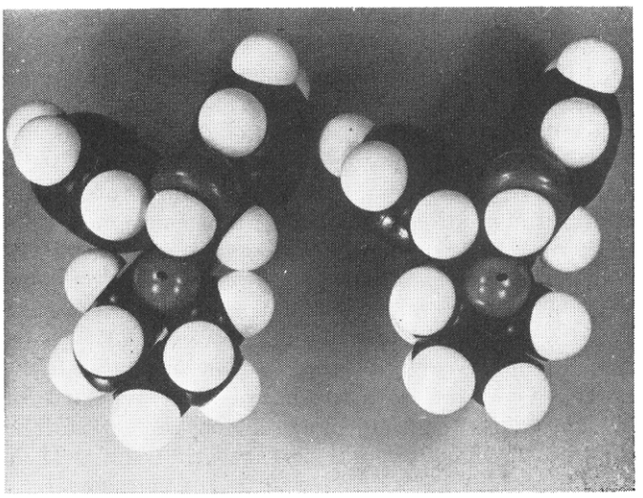


Figure 2.—CPK molecular models of the *gauche* rotamer (eB) of *erythro* amino alcohols **1b** and **1c** (left to right) in their "most favorable arrangements."

Attention was therefore focused on the possible role of subtle steric requirements, unique to the pyrrolidine ring, acting to destabilize the *anti* rotamer eA and/or stabilize the *gauche* rotamer eB, relative to the corresponding *erythro* piperidino compound as the standard of comparison. If some steric factor does does operate in the *erythro* pyrrolidino esters **2c** and **3c**, the same factor could operate in the *erythro* pyrrolidino alcohol **1c**, thus reinforcing the influence of intramolecular hydrogen bonding that favors rotamer eB. Indeed, it can be observed that J_{ab} for *erythro* **1c** is slightly, but consistently, less than J_{ab} for *erythro* amino alcohols **1a**, **1b**, and **1d**.

An examination of space-filling CPK[28] models of *erythro* amino alcohols **1b** and **1c** revealed small differences in the steric requirements of the piperidino and pyrrolidino groups, the impact of which is probably of little consequence *except in cases of sterically encumbered molecules such as those considered in the present study.* The presence of a phenyl group on each carbon atom of the ethane backbone contributes measurably to this encumbrance as does the bulk of the dialkylamino group.

In comparing the degree of crowding in the *anti* and *gauche* rotamers of *erythro* **1b** and **1c** the groups on the ethane backbone were oriented in a way to minimize the steric interactions suggested by the models. In the *gauche* arrangement (eB) it was found that the orientation of the "plane" of the cyclic amino group favorable to intramolecular hydrogen bonding (OH$\cdots$N) was also favored from a steric point of view. In each rotamer it was noted that the "planes" of the phenyl and cyclic amino groups were similarly oriented in space whether the molecule contained a piperidine or a pyrrolidine ring.

Viewing the *anti* rotamer (eA) of *erythro* amino alcohols **1b** and **1c** from the vantage point suggested in Figure 1, greater steric repulsion is evident between the pseudo-axial hydrogens at positions 2 and 5 of the pyrrolidino group (at C-2 of the ethane backbone) and the carbon atoms of the phenyl group also attached at C-2, than between the axial hydrogens at positions 2 and 6 of the piperidino group and the carbon atoms of the phenyl group. In contrast, in the *gauche* rotamer eB (Figure 2), greater steric repulsion is observed between the equatorial hydrogens at positions 2 and 6 of the piperidino group and both the phenyl group attached to the same carbon atom and the hydrogen atom H_a,[29] than between the pseudo-equatorial protons at positions 2 and 5 of the pyrrolidino group and the rest of the molecule. The same description applies equally well to the *erythro* esters, *i.e.*, **2b** *vs.* **2c** and **3b** *vs.* **3c**, since models indicate that the acyl group of the ester can orient in space without increasing the crowding in the molecule. Implicit in the foregoing analysis are the limitations imposed by the diagnostic power of the molecular models.

Models suggest, although not as clearly, since here we appear to be operating at their maximum "resolving power," that the same steric factors are implicated in the similar, but less dramatic deviation of J_{ab} values in the *threo* pyrrolidino esters **2c** and **3c**, *i.e.*, J_{ab} for *threo* **2c** and **3c** is consistently lower than for the other six *threo* esters studied.

In this connection, the failure to observe a similar downward trend in J_{ab} in the *threo* pyrrolidino amino alcohol **1c** is pertinent. It can be argued that here the influence of intramolecular hydrogen bonding (OH$\cdots$N) is more profound in the *anti* rotamer (tA) than in the more encumbered *gauche* rotamer (tB) and that it is this influence that offsets the effect of the special steric requirements of the pyrrolidino group. If such is the case, a reduction in the importance of intramolecular hydrogen bonding should lead to a decrease in J_{ab} (*i.e.*, a shift toward the *gauche* rotamer tB) for the *threo* pyrrolidino amino alcohol, **1c**, *but not for the corresponding threo piperidino amino alcohol* **1b**. Table II demonstrates that the dramatic increase in proton-acceptor ability of dimethyl sulfoxide compared with chloroform does not cause any decrease in J_{ab} of the *threo* piperidino amino alcohol **1b**; however, the same change of solvent, from chloroform to dimethyl sulf-

(28) Corey–Pauling–Koltun space-filling molecular models.

(29) The photograph of the model may suggest that rotation about the C–N bond would relieve the steric repulsion shown. However, the newly formed conformations develop new steric repulsions that appear to be equal to or greater than in the conformation pictured.

oxide, in the case of the *threo* pyrrolidino amino alcohol **1c** effects a reduction in J_{ab} from 10.0 to 8.2 Hz.

Experimental Section[30]

Amino Alcohols 1a–d.—The *dl-threo* and *dl-erythro* amino alcohols **1a–c** were prepared according to the procedure of Munk and Kim.[2] A heated (100°), sealed, heavy-wall Pyrex tube was employed in the preparation of the N,N-dimethylamino alcohols **1d**. Dioxane was employed as a solvent in this case. Configurational homogeneity was demonstrated by gas chromatography in all cases. Pertinent data are recorded in Table III.

TABLE III

PROPERTIES OF THE AMINO ALCOHOLS AND THEIR ESTERS

Compd	Yield, %	Mp, °C	Anal, %[a] Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
threo **1a**[b]	80	151–152						
erythro **1a**[b]	75	125–126.5						
threo **1b**[c]	85	100–101						
erythro **1b**[c]	94	109–110						
threo **1c**	80	91.5–92.5	80.86	7.92	5.34	81.15	8.12	5.00
erytho **1c**	85	92.5–93.5	80.86	7.92	5.34	80.76	8.14	5.04
threo **1d**[d,e]	85	98–99						
erythro **1d**[d,e]	90	87.5–89.0						
threo **2a**[b]	42	160–161.5						
erythro **2a**[b]	32	193–194.5						
threo **2b**	83	162.5–164	81.46	7.78	3.28	81.28	7.72	3.29
erythro **2b**	25	115–116	81.46	7.78	3.28	81.57	7.67	3.21
threo **2c**[f]	80	124.5–125.5	81.32	7.56	3.39	81.22	7.49	3.44
erythro **2c**[f]	27	104.5–105.5	81.32	7.56	3.39	81.44	7.51	3.49
threo **2d**[d]	53	137–138	80.59	7.54	3.61	80.47	7.58	3.66
erythro **2d**[d]	50	97–98	80.59	7.54	3.61	80.86	7.57	3.78
threo **3a**	79	142–143	73.82	7.12	4.30	73.80	7.22	4.32
erythro **3a**	68	110–111	73.82	7.12	4.30	73.77	7.24	4.57
threo **3b**	80	125.5–126.5	77.98	7.79	4.33	77.83	7.92	4.33
erythro **3b**	83	109–110	77.98	7.79	4.33	77.72	7.75	4.60
threo **3c**	59	86–87	77.64	7.49	4.53	77.91	7.29	4.66
erythro **3c**	55	86–87	77.64	7.49	4.53	77.57	7.65	4.66
threo **3d**	40	90.5–92	76.30	7.47	4.94	76.21	7.70	5.15
erythro **3d**	54	102–103	76.30	7.47	4.94	76.50	7.60	4.94

[a] Reported only in the case of new compounds. [b] Reference 2. [c] Reference 4a. [d] Prepared by T. A. Treat. [e] G. Drefahl and H.-H. Horhold, *Chem. Ber.*, **94**, 1657 (1961). [f] Prepared by Dr. J.-L. Derocque.

Mesitoate Esters 2a–d.—The *dl-threo* and *dl-erythro* mesitoate esters **2a–d** were prepared according to the procedure of Munk and Kim.[2] Configurational homogeneity was demonstrated by gas chromatography. Pertinent data are recorded in Table III.

Acetate Esters 3a–d.—The *dl-threo* and *dl-erythro* acetate esters **3a–d** were prepared from the corresponding amino alcohol by warming on a steam bath with acetic anhydride in pyridine as a solvent. Configurational homogeneity was demonstrated by gas chromatography. Pertinent data are recorded in Table III.

***dl-erythro*-2-(1-Piperidino)-1,2-diphenylethanol Methiodide (5).**—A solution of 0.56 g (0.002 mol) of the *dl-erythro* amino alcohol **1b** in 10 ml of methyl iodide was refluxed in the dark for 33 hr. A white solid, 0.82 g (96%) was filtered from the solution and washed with ether. The solid was recrystallized from methanol–ether: mp 222.5–224.5° dec.

Anal. Calculated for $C_{20}H_{26}INO$: C, 56.74; H, 6.19; N, 3.31. Found: C, 56.69; H, 6.16; N, 3.03.

***dl-threo*-2-(1-Piperidino)-1,2-diphenylethanol Methiodide (5).**—Using the above procedure for *dl-erythro*-2-(1-piperidino)-1,2-diphenylethanol methiodide, 0.54 g (0.0019 mol) of the *dl-threo* amino alcohol **1b** afforded 0.34 g (41%) of the crude methiodide. Crystallization from methanol–ether afforded an analytical sample, mp 206–207° dec.

Anal. Calcd for $C_{20}H_{26}INO$: C, 56.74; H, 6.19; N, 3.31. Found: C, 56.98; H, 6.29; N, 3.31.

***dl-erythro*-2-(1-Piperidino)-1,2-diphenylethyl Methyl Ether (4) and Its Methiodide (6).**—To a magnetically stirred, ice-cold solution of 2.03 g (0.0072 mol) of the *dl-erythro* amino alcohol **1b** in 10 ml of freshly distilled tetrahydrofuran (from $LiAlH_4$) was added 6.3 ml (0.01 mol) of *n*-butyllithium solution (hexane).[31] After stirring for 5 min, 5 ml of methyl iodide was added and the temperature adjusted to 50°. The reaction was monitored *via* gas chromatography and, after 9.5 hr a white solid, the methiodide of the methyl ether (**4**) was filtered from the solution and washed with ether. The filtrate was washed and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Chromatography of the oily residue over alumina (developed with benzene) afforded 0.48 g (23%) of the gas chromatographically homogeneous oily ether.

Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.41; H, 8.70; N, 4.96.

Crystallization of the crude solid methiodide **6** from methanol afforded 0.33 g (10%) of the pure product, mp 216–218° dec. Recrystallization yielded an analytical sample, mp 218.5–220° dec.

Anal. Calcd for $C_{21}H_{28}INO$: C, 57.67; H, 6.45; N, 3.20. Found: C, 57.74; H, 6.44; N, 3.47.

***dl-erythro*-2-(1-Piperidino)-1,2-diphenylethyl Methyl Ether Methiodide (6).**—Using the procedure described above for the preparation of *dl-erythro* **4** with a reaction period of 14 hr, 1.02 g (0.0037 mol) of the *dl-erythro* amino alcohol **1b** afforded 0.70 g (44%) of the pure methiodide, mp 218.5–220° dec.

***dl-threo*-2-(1-Piperidino)-1,2-diphenylethyl Methyl Ether (4) and Its Methiodide (6).**—Using the procedure described above for the preparation of *dl-erythro* **4** with a reaction period of 4 hr, 2.03 g (0.0072 mol) of the *dl-threo* amino alcohol **1b** afforded 1.08 g (51%) of the methyl ether as a gas chromatographically homogeneous oil.

Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.08; H, 8.54; N, 4.62.

The methyl ether methiodide **6** was crystallized from methanol to afford 0.99 g (31%) of the pure product, mp 223–224° dec.

Anal. Calcd for $C_{21}H_{28}INO\cdot(CH_3OH)$: C, 55.92; H, 6.84; N, 2.97. Found: C, 56.05; H, 6.87; N, 2.83.

***dl-threo*-2-(1-Piperidino)-1,2-diphenylethyl Methyl Ether Methiodide (6).**—Using the procedure described above for the preparation of *dl-threo* **4** with a reaction period of 11 hr, 1.02 g (0.0036 mol) of the *dl-threo* amino alcohol **1b** afforded 1.27 g (80%) of the pure methiodide, mp 223–224° dec.

***trans*-2-(1-Piperidino)cyclohexanol (7, R = H).**—A solution of 21.6 g (0.246 mol) of cyclohexene oxide and 23.2 g (0.274 mol) of piperidine was refluxed for 22 hr. The solution was vacuum distilled to afford 28.8 g (72%), bp 67–90° (1.2 mm). The alcohol crystallized from acetone, mp 37–38° (lit.[32] mp 34–35°).

***trans*-2-(1-Piperidino)cyclohexyl Acetate (7, R = CH_3CO).**—Using the procedure described under acetate esters, 2.0 g (0.011 mol) of the *trans* alcohol **7**, R = H, yielded 1.2 g (49%) of the crystalline acetate, mp 56–57°. Recrystallization from acetone afforded an analytical sample.

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.27; H, 10.31; N, 6.22. Found: C, 69.21; H, 10.34; N, 6.32.

Registry No.—**1a** (*threo*), 4176-70-9; **1a** (*erythro*), 4176-71-0; **1b** (*threo*), 17278-18-1; **1b** (*erythro*), 17244-78-9; **1c** (*threo*), 17244-79-0; **1c** (*erythro*), 17244-80-3; **1d** (*threo*), 17244-81-4; **1d** (*erythro*), 17244-82-5; **2a** (*threo*), 17244-83-6; **2a** (*erythro*), 4176-73-2; **2b** (*threo*), 17244-83-6; **2b** (*erythro*), 17244-86-9; **2c** (*threo*), 17244-87-0; **2c** (*erythro*), 17244-88-1; **2d** (*threo*), 17244-89-2; **2d** (*erythro*), 17244-90-5; **3a** (*threo*), 17244-91-6; **3a** (*erythro*), 17244-92-7; **3b** (*threo*), 17244-93-8; **3b** (*erythro*), 17244-94-9; **3c** (*threo*), 17244-95-0; **3c** (*erythro*), 17244-

(30) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared absorption spectra were determined as potassium bromide pellets or thin liquid films and recorded on a Perkin-Elmer Model 137 or 237B Infracord. Nuclear magnetic resonance spectra were run in an appropriate solvent on a Varian Associates Model A-60 spectrometer with tetramethylsilane as an internal or external standard. All gas chromatographic analyses were obtained on a 6-ft stainless steel column packed with 5% XE-60 on Anakrom ABS support using a thermal conductivity detection system and helium as the carrier gas. Microanalyses were determined by Midwest-Microlab, Inc., Indianapolis, Indiana.

(31) Supplied by Foote Mineral Co., Exton, Pa.

(32) F. N. Hayes, L. C. King, and D. E. Peterson, *J. Amer. Chem. Soc.*, **78**, 2528 (1956).

96-1; **3d** (*threo*), 17244-97-2; **3d** (*erythro*), 17244-98-3; **4** (*threo*), 17244-99-4; **4** (*erythro*), 17243-72-0; **5** (*threo*), 17243-73-1; **5** (*erythro*), 17243-74-2; **6** (*threo*), 17243-75-3; **6** (*erythro*), 17243-76-4; **7** (R = CH_3CO), 17243-99-1.

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The Acid-Catalyzed Equilibration of 1,3-Diarylallyl Alcohols

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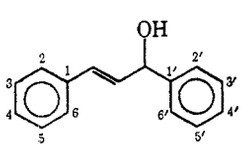
The equilibrium and rate constants for the acid-catalyzed (HCl in 60% aqueous dioxane) equilibrations of three 1,3-diarylallyl alcohols (chalcols) have been measured at 30°. Both ends of the allyl group are in identical environments, with the possible exception of the electronic environment which is determined by the pattern of substitution on the aromatic rings. The equilibrium constants are nearly insensitive to the *para* substituents. For the isomerizations of the 4- to the 4′-substituted chalcol, K_{eq} = 0.805, 1.16, and 0.71 for nitro, bromo, and methoxy, respectively. The rate constants are quite sensitive to the substituents. The forward rate constants for the substituents (nitro and bromo, respectively) are 4.75×10^{-3} and 2.89×10^{-1} (min M)$^{-1}$. The reverse rate constants are 5.87×10^{-3} and 2.49×10^{-1} (min M)$^{-1}$. Both the forward and reverse rate constants for 4- and 4′-methoxychalcol are estimated to be 84 (min M)$^{-1}$. Apparently two different kinds of resonance effects are operative. One effect, which is pronounced, involves the interaction of the substituent with the charge in the transition state. The other effect, which is minimal, is the conjugation of the substituent with the allylic double bond.

There are several studies in the literature concerned with substituent effects on the chemical properties of allylic systems.[1] Few of these studies deal with symmetric systems in which all factors (steric, etc.) except electrical effects are constant at the termini of the allylic cation under consideration.

The required symmetry can be found in the 1,3-diarylallyl (chalcol) system. There have been two previous studies of the allylic rearrangement in chalcols. Burton and Ingold[2] in 1928 isomerized 4- and 4′-methylchalcol and 4- and 4′-chlorochalcol in refluxing acetic anhydride. Because of the limited techniques available at that time, the authors were able to indicate only that the equilibrium mixtures seemed to contain more of the 4 isomer in both cases.



Braude and Waight[3] compared rate and equilibrium constants for the three reactions listed in Figure 1. The rate constants for reaction 3 were estimated rather than measured (see footnote *e*, Table I).

A comparison of the data for reactions 1 and 3 indicated that the nitro group has little effect on the equilibrium position, but a large retarding effect on the rate of equilibration. The former effect is attributed to the lack of resonance stability when a nitro group is conjugated with a double bond, and the latter effect is attributed to the destabilization of a positively charged species (presumably the transition state for the reaction) by the nitro group.

The *p*-nitrophenyl group changes the equilibrium constant from greater than 10 for reaction 2 to 0.83 for reaction 1. This illustrates the conjugative properties of an aromatic group. On the other hand, the *p*-nitrophenyl group has little effect on the rate of the reaction. This, in the opinion of Braude and Waight, is due to a balancing of the rate-retarding effect of the nitro group and the rate acceleration due to delocalization of charge into the phenyl ring.

In a later paper in the same series Braude and Gore[4] measured rate and equilibrium constants for the acid-catalyzed isomerizations of 1-naphthyl-3-phenylallyl alcohols. The equilibrium constants are close to unity reflecting the nearly identical conjugated abilities of the phenyl and (α- and β-) naphthyl groups.

The work of Braude and Waight[3] seems to establish a dichotomy of resonance effects for the nitro group. On the one hand resonance definitely retards the build-up of positive charge in the allyl group. On the other hand, resonance plays little role in determining the more favorable position for the allylic double bond in 4- and 4′-nitrochalcol. In order to test the applicability of this dichotomy of resonance effects to other groups, the rate and equilibrium constants for the acid-catalyzed isomerizations of three pairs of chalcols have been measured.

Results

The chalcols were synthesized by a modification of the procedure of Davey and Hearne.[5] The base-catalyzed condensation of the appropriate benzaldehyde and acetophenone gave the chalcone, and borohydride reduction gave the chalcol. 4′-Methoxychalcol and 4-bromochalcol have not previously been obtained as crystalline compounds. These structures were verified by elemental and spectral analyses. It should be noted that 4- and 4′-methoxychalcol and 4- and 4′-bromochalcol were quite unstable. The methoxy compounds decomposed to oils in a few days, whereas the bromo compounds became oils in a few weeks. These

(1) See, for instance, R. Sneen, *J. Amer. Chem. Soc.*, **82**, 4261 (1960); R. Sneen and A. Rosenberg, *ibid.*, **83**, 895, 900 (1961).
(2) H. Burton and C. K. Ingold, *J. Chem. Soc.*, 904 (1928).
(3) E. A. Braude and E. S. Waight, *ibid.*, 419 (1953).
(4) E. A. Braude and P. H. Gore, *ibid.*, 41 (1959).
(5) W. Davey and J. A. Hearne, *ibid.*, 4978 (1964).