At high pH or at high concentrations of certain ionic species, the internal hydrogen bonding is thought to be disrupted, with the amylose adapting a random-coil conformation.[23] To investigate the effect of this phenomenon on the cmr spectrum of amylose, we have measured the carbon chemical shifts of amylose as a function of basicity (Table VI). It is observed that the changes are rather minor except when 1 *N* sodium hydroxide was used. In 6.5 *M* lithium bromide, a system known[23] to have significant effects upon the optical rotation of amylose, there were only small changes in the cmr spectrum compared to neutral solutions.

The interpretation of the spectrum of soluble starch is difficult in that we have no really adequate model for comparison. Once the resonances of C-1, -4, and -6 have been assigned in the usual way, there can be no more specific assignments. It is interesting, however, to observe that the positions of the three specifically assigned resonances of amylose are very similar in chemical shift to the analogous nuclei of maltose (**3a**, **b**) and methyl β-maltoside (**3c**). Furthermore, the changes observed in these chemical shifts in 1 *N* sodium hydroxide approximate closely those changes observed in the spectrum of **3c** in the same milieu. It therefore seems probable that similar changes in conformation are being observed in both cases.

The constancy in the chemical shift of the C-6 resonance throughout the systems studied is also interesting. While in a helical conformation such as the one described above, the hydroxymethyl group would be expected to experience no intramolecular steric interactions. The disruption of the helix, however, could lead to increased interactions of this carbon and, hence, to changes in its chemical shift. In fact, no significant changes are observed.

An attempt was also made to measure the chemical shifts of the carbons of glycogen. After some 2400 spectral accumulations, peaks were evident at approximately 119.7, 120.9, and 121.7 ppm. However, no resonances corresponding to C-1, -4, and -6 could be detected.

Finally, the cmr spectrum of cellulose acetate was measured (Table VI). In this case, the peaks other than the easily assigned resonances of C-1, -4, and -6 overlap in one large broad peak at about 120.3 ppm. As often observed in the glucose and cellobiose acetates, the acetate methyl resonances could not be resolved. The resonances due to the acetate carbonyl carbons, however, were clearly resolved and easily observable. Again, it is recognized that the spectrum of this polysaccharide closely approximates that of its closest disacharide relative, β-cellobiose octaacetate.

While these results present no really new data about the conformations of these molecules, the fact that the spectra were measurable heralds a new and important method in carbohydrate chemistry. The development of pulse spectroscopic methods in conjunction with variable-temperature capabilities should make the cmr spectra of disaccharides routinely available to chemists concerned with their study.

Nuclear Magnetic Resonance Spectroscopy. Barriers to Internal Rotation in Some Halogenated Methylbutanes[1]

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Abstract: Barriers to internal rotation about the C(2)–C(3) bonds have been determined for ten closely related halogenated methylbutanes by detailed line-shape analysis of their nuclear magnetic resonance spectra. The experimental barriers range from 9 to 16 kcal/mol. In addition, for some of the compounds investigated, free-energy differences were obtained for rotational isomers under conditions of slow conformational exchange. The results are discussed in terms of possible contributing nonbonded interactions.

Molecular structure and reactivity are governed to a large extent by both attractive and repulsive nonbonded interactions between atoms or groups of atoms within the molecule. Extensive studies of conformational equilibria have been especially informative in revealing the nature and magnitudes of intramolecular interactions.[2] Nuclear magnetic resonance (nmr) spectroscopy is particularly well suited for studying conformational equilibria and equilibration because, in favorable cases, it provides not only barriers to conformational equilibration, but also direct measurements of ground-state conformational energy differences.[3]

Rotation about C–C bonds in substituted ethanes is of considerable current interest,[4,5] and has been

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(1) Supported by the National Science Foundation; presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif. March 31, 1971.

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965; M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965.

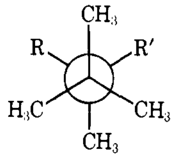
(3) (a) G. Binsch, *Top. Stereochem.*, 3, 97 (1968); (b) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Elmsford, N. Y., 1965, Chapter 9.

(4) (a) F. J. Weigert, M. B. Winstead, J. I. Garrels, and J. D. Roberts, *J. Amer. Chem. Soc.*, 92, 7359 (1970); (b) W. J. Orville-Thomas, *J. Mol. Struct.*, **6**, 1 (1970); (c) N. Sheppard, *ibid.*, **6**, 5 (1970); (d) A. V. Cunliffe, *ibid.*, **6**, 9 (1970); (e) P. N. Brier, *ibid.*, **6**, 23 (1970); (f) N. L. Owen, *ibid.*, **6**, 37 (1970); (g) R. J. Abraham, *ibid.*, **6**, 49 (1970); (h) J. Bailey and S. Walker, *ibid.*, **6**, 53 (1970); (i) E. Wyn-Jones, *ibid.*, **6**,

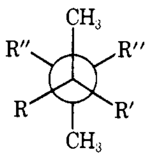
the subject of a vast number of experimental[4,6] and several theoretical[5,6] investigations concerning relative conformational energies and barriers to their interconversion. The great majority of these studies were concerned with molecules bearing several halogen substituents. In contrast, few investigations of rotational barriers have been heretofore reported for substituted ethanes in which alkyl–alkyl or alkyl–halogen interactions are involved.[7] We have obtained relative free energies of rotational isomers and barriers to internal rotation about the carbon–carbon single bond in several closely related ethane derivatives containing both halogen and alkyl substituents.

Results

The following compounds were investigated: 3-chloro-2,2,3-trimethylbutane (**1**), 3-bromo-2,2,3-trimethylbutane (**2**), 3,3-dichloro-2,2-dimethylbutane (**3**), 3,3-dibromo-2,2-dimethylbutane (**4**), 3-chloro-3-bromo-2,2-dimethylbutane (**5**), 3-chloro-2,2,3-trimethylpentane-*4,4,5,5,5-d*$_5$ (**6**), 3-chloropentamethylpentane (**7**), 2,3,3-tribromo-2-methylbutane (**8**), 2,2,3,3-tetrachlorobutane (**9**), and 2,2,3,3-tetrabromobutane (**10**). Except for commerically available **1** and **3**, the samples were prepared by more or less standard methods as shown in Chart I. Purification of the products was accomplished by either recrystallization or preparative gas–liquid partition chromatography (glpc). Treatment of pinacolone with phosphorus trichloride dibromide gave a mixture of **4** and **5**. Increasing the reaction temperature from 0 to 30° increased the relative amount of **5** from about 5 to about 25%, thus facilitating its efficient isolation by glpc.

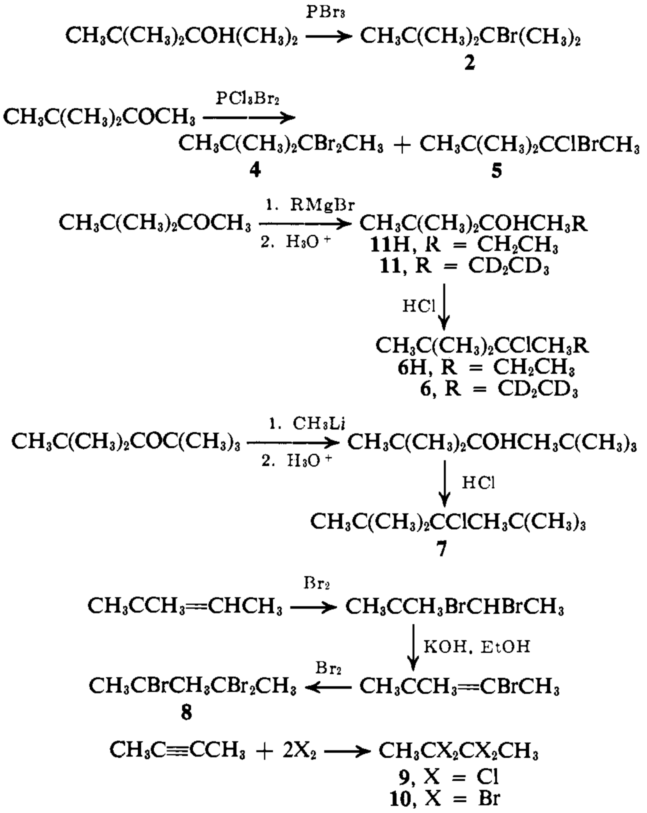


1, R = Cl; R′ = CH$_3$
2, R = Br; R′ = CH$_3$
3, R = R′ = Cl
4, R = R′ = Br
5, R = Cl; R′ = Br
6, R = Cl; R′ = CD$_2$CD$_3$
7, R = Cl; R′ = C(CH$_3$)$_3$



8, R = CH$_3$; R′ = R″ = R‴ = Br
9, R = R′ = R″ = R‴ = Cl
10, R = R′ = R″ = R‴ = Br

Chart I



$$\mathrm{CH_3C(CH_3)_2COH(CH_3)_2 \xrightarrow{PBr_3} \underset{\mathbf{2}}{CH_3C(CH_3)_2CBr(CH_3)_2}}$$

$$\mathrm{CH_3C(CH_3)_2COCH_3 \xrightarrow{PCl_3Br_2} \underset{\mathbf{4}}{CH_3C(CH_3)_2CBr_2CH_3} + \underset{\mathbf{5}}{CH_3C(CH_3)_2CClBrCH_3}}$$

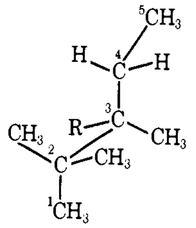
$$\mathrm{CH_3C(CH_3)_2COCH_3 \xrightarrow[2.\ H_3O^+]{1.\ RMgBr} CH_3C(CH_3)_2COHCH_2R}$$
$$\mathbf{11H},\ \mathrm{R = CH_2CH_3} \qquad \mathbf{11},\ \mathrm{R = CD_2CD_3}$$
$$\downarrow \mathrm{HCl}$$
$$\mathrm{CH_3C(CH_3)_2CClCH_2R}$$
$$\mathbf{6H},\ \mathrm{R = CH_2CH_3} \qquad \mathbf{6},\ \mathrm{R = CD_2CD_3}$$

$$\mathrm{CH_3C(CH_3)_2COC(CH_3)_3 \xrightarrow[2.\ H_3O^+]{1.\ CH_3Li} CH_3C(CH_3)_2COHCH_2C(CH_3)_3}$$
$$\downarrow \mathrm{HCl}$$
$$\underset{\mathbf{7}}{\mathrm{CH_3C(CH_3)_2CClCH_2C(CH_3)_3}}$$

$$\mathrm{CH_3CCH_3{=}CHCH_3 \xrightarrow{Br_2} CH_3CCH_3BrCHBrCH_3}$$
$$\downarrow \mathrm{KOH,\ EtOH}$$
$$\mathrm{\underset{\mathbf{8}}{CH_3CBrCH_3CBr_2CH_3} \xleftarrow{Br_2} CH_3CCH_3{=}CBrCH_3}$$

$$\mathrm{CH_3C{\equiv}CCH_3 + 2X_2 \longrightarrow CH_3CX_2CX_2CH_3}$$
$$\mathbf{9},\ \mathrm{X = Cl} \qquad \mathbf{10},\ \mathrm{X = Br}$$

The physical and spectral properties of all the products and synthetic intermediates in Chart I were in full accord with their assigned structures (see Experimental Section). It is noteworthy that the ambient temperature nmr spectra of both **6H** and **11H** showed doublets for the 3-methyl group. The splittings (0.6 Hz at both 60 and 100 MHz) must result from a stereospecific four-bond coupling to one of the protons at C(4). It is not unreasonable to expect the ethyl group (C(4) and C(5)) to adopt a conformation anti to the *tert*-butyl group. Such an arrangement provides favorable geometry for four-bond coupling to one, but not both hydrogens at C(4).[8] For **6** and **11** wherein deuterium has been substituted for hydrogen on C(4) and C(5), the splitting was not observed, as expected from the diminished magnitudes of proton–deuterium couplings.[9]



11H, R = OH
6H, R = Cl

For compounds **1**–**7**, rotational barriers were determined by line-shape analyses of the temperature-dependent *tert*-butyl resonances. At ambient temperature, singlets are observed and on lowering the sample temperature, broadening occurs and eventually separation is observed into either two or three resonances depending on the molecular symmetry. If two equivalent groups are attached at C(3) (as in **1**–**4**), two peaks with relative intensities 2:1 emerge. The spectra of **4** are shown in Figure 1 and serve to illustrate this type of behavior. Spectra of **3** are entirely analogous, as are those obtained for **1** and **2**. However, for the latter two compounds which bear two methyl groups at C(3) rather than two halogens, the doubly degenerate transition is downfield, in contrast to what is observed

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65 (1970); (j) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970); (k) F. Heatley and G. Allen, *Mol. Phys.*, **16**, 77 (1969).

[5] (a) R. J. Abraham and K. Parry, *J. Chem. Soc., B*, 539 (1970); (b) G. Heublein, R. Kühmstedt, P. Kadura, and H. Dawczynski, *Tetrahedron*, **26**, 81, 91 (1970); (c) J. D. Roberts, Abstracts of the 20th National Organic Chemistry Symposium of the American Chemical Society, Burlington, Vt., June 1967, p 63.

[6] For reviews, see ref 4j and (a) J. P. Lowe, *Progr. Phys. Org. Chem.*, **6**, 1 (1968); (b) R. A. Pethrick and E. Wyn-Jones, *Quart. Rev., Chem. Soc.*, **23**, 301 (1969); (c) N. Sheppard, *Advan. Spectrosc.*, **1**, 288 (1959); (d) E. B. Wilson, Jr., *Advan. Chem. Phys.*, **2**, 367 (1959); (e) S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York, N. Y., 1954.

[7] A. Rieker and H. Kessler, *Tetrahedron Lett.*, 1227 (1969).

[8] S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).

[9] L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 142

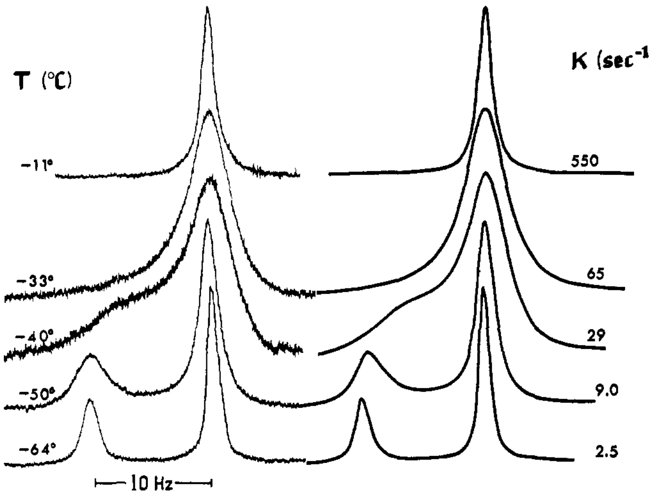


Figure 1. Experimental (left) and calculated (right) proton spectra of the *tert*-butyl resonance of 3,3-dibromo-2,2-dimethylbutane (4) at various temperatures. The low-field temperature-independent methyl resonance is not shown.

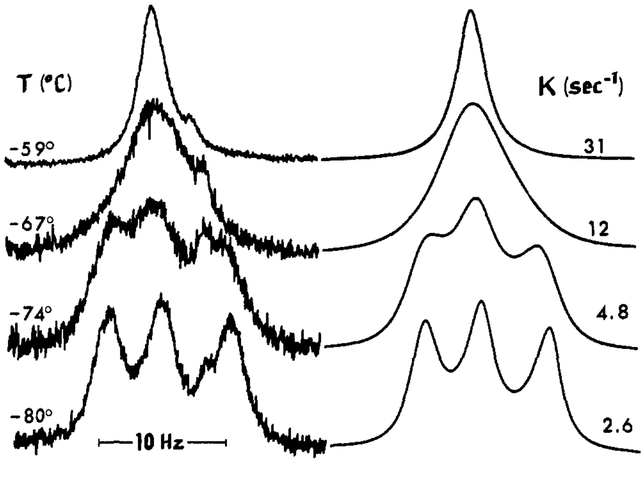


Figure 2. Experimental and computer-simulated proton spectra of the *tert*-butyl group of 3-chloro-2,2,3-trimethylpentane-4,4,5,5,5-d_5 (6) at various temperatures. The transition assigned to the 3-methyl group is not shown.

for **3** and **4**. When three different groups are attached to C(3), as in **5**, **6**, and **7**, three separate peaks corresponding to each methyl group of the *tert*-butyl groups are expected when rotation about the C(2)–C(3) bond is slow, as is illustrated for **6** in Figure 2. Actually, for **7** in carbon disulfide, two of these resonances are accidentally degenerate at low temperatures as shown in Figure 3. However, in chlorobenzene, a solvent shift allows separate observation of all three bands at about −60°.

Immediate and unequivocal peak assignments are possible for the low-temperature spectra of **1**–**4** as a result of molecular symmetry, the less intense peak being assigned, of course, to the methyl group gauche to both identical C(3) substituents, and the more intense peak being assigned to the two remaining 2-methyl groups. Peak assignments for **5**, **6**, and **7** in which three separate resonances are possible below coalescence are neither as readily made, nor in fact necessary for interpretation of the rate data.

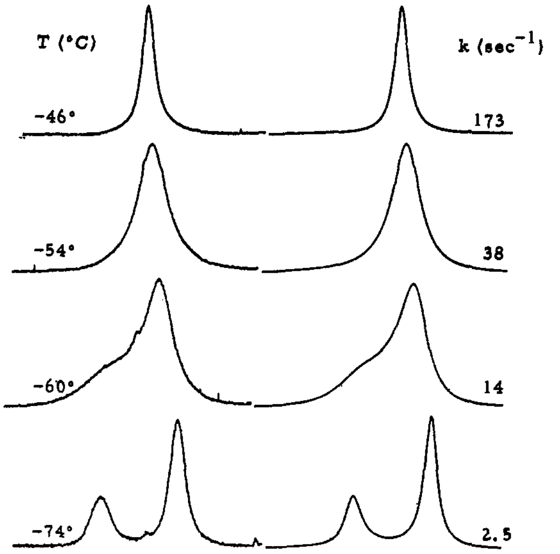


Figure 3. Experimental (left) and calculated (right) proton spectra of the *tert*-butyl resonance of 3-chloropentamethylpentane (7) in carbon disulfide. The more intense upfield peak below the coalescence temperature results from an accidental degeneracy of two methyl groups attached to C(2) and C(4). The resonance for the 3-methyl group is not included.

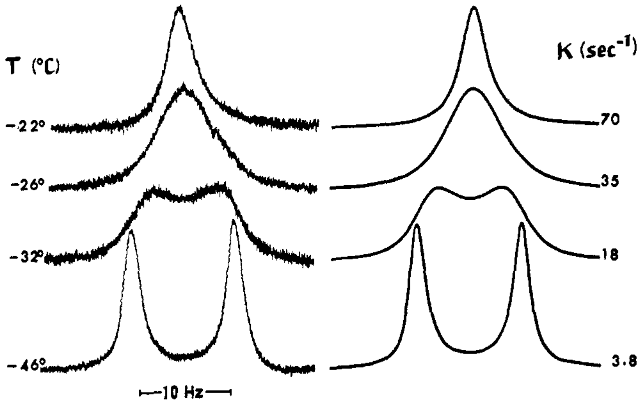
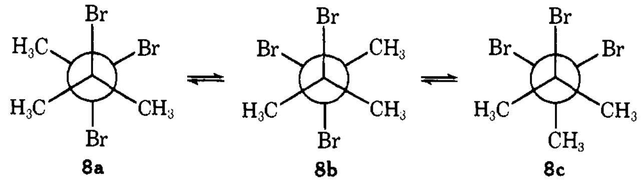


Figure 4. Temperature-dependent observed and calculated spectra of the high-field methyl resonance of 2,3,3-tribromo-2-methylbutane (8). The low-field methyl band (C(4)) was temperature independent.

The temperature dependence of the spectra of **8** are especially informative as to the nature of the rotational equilibrium. The ambient-temperature proton spectrum of **8** in carbon disulfide consists of two singlets: δ 2.73 (3 H) and 2.09 (6 H). The high-field peak corresponding to the two geminal methyl groups broadens and gradually separates into two equally intense bands as the temperature is lowered to −54.7° (see Figure 4). At the same time, the low-field band remains essentially unchanged. This behavior is most probably the consequence of hindered conformational exchange between **8a** and its enantiomer **8b**, which



8a **8b** **8c**

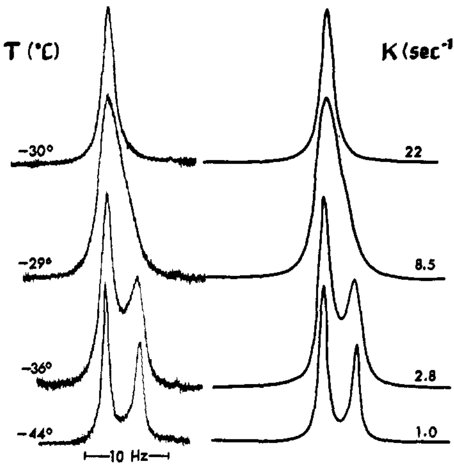


Figure 5. Observed and calculated proton spectra of 2,2,3,3-tetrachlorobutane (**9**) in acetone-d_6 at several temperatures.

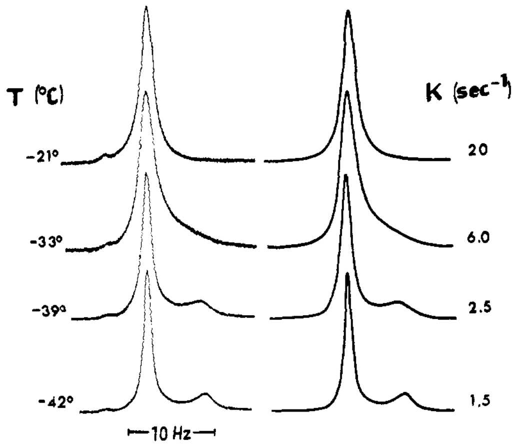
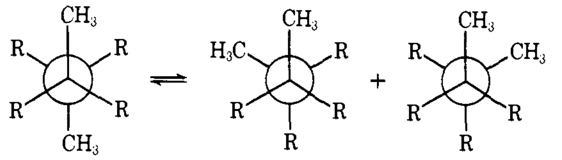


Figure 6. Observed and calculated proton spectra of 2,2,3,3-tetrachlorobutane (**9**) in carbon disulfide–acetone-d_6 (10:1 v/v) at various temperatures.

causes the geminal methyl groups to undergo mutual exchange. A significant population of **8c** can be ruled out because it would result in a temperature dependence of the low-field peak and an additional band in the high-field region at low temperatures. Furthermore, below coalescence, the rate of conversion of **8a** or **8b** to **8c** must be slow on the nmr time scale because otherwise a low-energy path would be available for conversion of **8a** to **8b** (*via* **8c**) and the observed temperature dependence would not result.

Compounds **9** and **10** are unique in this study in that the relative populations of the rotational isomers are not fixed by molecular or group symmetry. Spectra of **9** in acetone-d_6 shown in Figure 5 are representative of these compounds. As the temperature is lowered, the singlet broadens and then separates eventually into two unequally intense singlets. In both **9** and **10**, below the coalescence temperature the more intense peak is at lower field. The low-temperature spectra of **9** and **10** show a marked solvent dependence. Thus, for **9**, when the solvent is changed from acetone-d_6 to carbon disulfide–acetone-d_6 (10:1 v/v), the relative intensity of the high-field peak diminishes (see Figures 5 and 6). Exactly analogous behavior is noted for **10** when chlorobenzene–acetone-d_6 (2:1 v/v) is replaced by carbon disulfide as the solvent. Because a decrease in the dielectric constant of the medium is expected to reduce the relative stability of the rotamer possessing the largest dipole moment,[4g,10,11] the upfield resonances are assigned to the gauche rotamers, **9g** and **10g**.



(1)

9t, R = Cl **9g** **9g′**
10t, R = Br **10g** **10g′**

Additional evidence in favor of these assignments is derived from chemical-shift data. As noted above, for compounds in which assignments were unequivocally established (**1–4**), the 2-methyl groups in each compound which were gauche to the largest number of halogen atoms on C(3) appeared at lowest field. Generalizing, one would then predict the methyl resonances of **9t** and **10t** to be at lower field than **9g** and **10g**, respectively. The free-energy changes for the trans to gauche isomerization (eq 1) of **9** and **10** were calculated from the relative populations obtained in the line-shape analyses, and the results are given in Table I.

Table I. Conformational Free-Energy Difference for Tri- and Tetrahalobutanes (**8–10**)

Compd	Solvent	Temp, °C	ΔG, cal/mol
8	CS$_2$	−55	≥2,000[a]
9	Acetone-d_6	−44	170[b,c]
9	CS$_2$-acetone-d_6 (10:1 v/v)	−50	630[b,c]
10	C$_6$H$_5$Cl-acetone-d_6 (2:1 v/v)	−25	680[b,c]
10	CS$_2$	−30	~1,800[b,d]

[a] For **8a** + **8b** → **8c**. Lower limit because **8c** was not observed. [b] For trans to gauche interconversion. [c] Obtained from relative populations derived from line-shape analysis. [d] Estimated from relative peak intensities (~2% gauche).

Line shapes were calculated simulating the temperature-dependent resonances of **1–10** for one nucleus exchanging between either two (**1–4**, **7–10**) or three (**5**, **6**) nonequivalent sites. One-nucleus calculations are appropriate because no couplings were observed between the methyl groups and all of the protons on a given methyl group are magnetically equivalent as a result of rapid methyl rotation.

The calculations used the DNMR program.[12] The line widths, in the absence of exchange, were taken either as those of the nonexchanging methyl resonances or from side bands on the TMS used for calibration. These values gave equivalent values of $T_2{}^*$ when comparisons were made. Rate constants were obtained by either visual fitting of the computer-plotted to experimental spectra or by an iterative least-squares procedure on digitized spectra. Typical fits are shown in Figures 1–6. No significant temperature dependence of the intramolecular chemical shifts was noted below the coalescence temperature and therefore these

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(10) R. J. Abraham, *J. Phys. Chem.*, **73**, 1192 (1969), and earlier papers.

(11) F. Heatley and G. Allen, *Mol. Phys.*, **16**, 77 (1969).

(12) G. Binsch, *J. Amer. Chem. Soc.*, **91**, 1304 (1969).

Table II. Barriers to Internal Rotation in Halobutane Derivatives (**1–10**)[a]

Compd	Solvent	T_c,[b] °C	ln A	E_a, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol[c]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
1	CF_2Cl_2	−81	34.1 ± 0.5	11.8 ± 0.2	9.82 ± 0.01	11.4 ± 0.2	8.1 ± 1.0
2	CS_2	−68	36.0 ± 0.7	13.6 ± 0.3	10.80 ± 0.02	13.2 ± 0.3	11.9 ± 1.4
3	CF_2Cl_2	−61[d]	29.3 ± 0.4	10.9 ± 0.2	10.81[d] ± 0.01	10.5 ± 0.2	−1.6 ± 0.7
4	$CF_2{=}CCl_2$	−38	28.9 ± 0.4	11.8 ± 0.2	12.27 ± 0.01	11.4 ± 0.2	−3.8 ± 0.7
5	$CF_2{=}CCl_2$	−45	30.0 ± 0.2	12.3 ± 0.1	11.90 ± 0.01	11.8 ± 0.1	−0.4 ± 0.5
6	CS_2	−71	27.6 ± 0.6	10.3 ± 0.2	10.87 ± 0.01	9.9 ± 0.2	−5.0 ± 1.1
7	CS_2	−58	36.1 ± 0.8	14.1 ± 0.4	11.42 ± 0.02	13.7 ± 0.4	10.4 ± 1.6
8	CS_2	−30	28.7 ± 0.4	12.3 ± 0.2	12.61 ± 0.01	11.8 ± 0.2	−3.2 ± 0.7
9	CS_2–acetone-d_6 (10:1, v/v)	−31	32.2 ± 0.4	14.6 ± 0.2	13.47 ± 0.01	14.1 ± 0.2	2.6 ± 0.7
	Acetone-d_6	−30	34.6 ± 0.4	15.8 ± 0.2	13.54 ± 0.01	15.3 ± 0.2	7.2 ± 0.9
10	C_6H_5Cl–acetone-d_6 (2:1, v/v)	+18	26.9 ± 0.4	14.1 ± 0.2	15.96 ± 0.01	13.5 ± 0.2	−8.4 ± 0.7

[a] The barriers correspond to the process wherein the rear carbon rotates clockwise by 120°. The uncertainties are 50% confidence intervals determined from a statistical analysis of random errors in temperature and rate-constant measurements. Any systematic errors could result in much larger errors in the derived parameters. [b] Coalescence temperature. [c] Calculated at T_c. [d] A. Rieker and H. Kessler[7] report T_c = −70.5° and $\Delta G^{\ddagger}$ = 11.1 kcal/mol for **3** in CS_3.

chemical shifts were used throughout the entire temperature range.

A statistical least-squares fitting[13] of the temperature dependencies of the rate constants to the Eyring rate equation, assuming a transition coefficient of unity, gave $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ from which the remaining activation parameters were calculated using the appropriate equations.[3a,13] A typical Eyring plot of ln k/T *vs.* $1/T$ from the least-squares analysis is shown in Figure 7, and the activation parameters are collected in Table II. The reported uncertainties are 50% confidence intervals obtained from the statistical analysis by considering random errors in both the rate constants and temperature measurements. Any systematic errors encountered, however, could result in errors several times the magnitudes of these estimates.

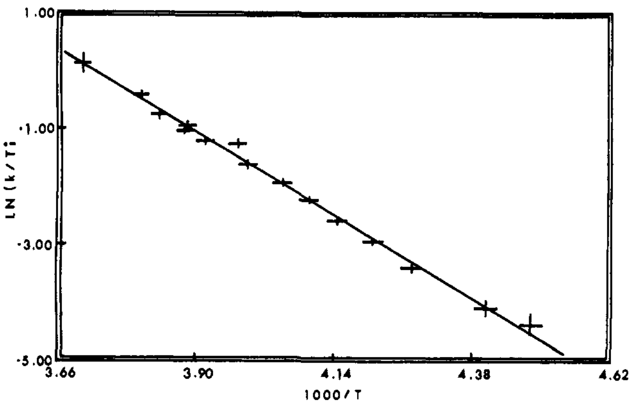

Figure 7. Eyring plot of the rate of rotation about the C(2)–C(3) bond of 2,3,3-tribromo-2-methylbutane (**8**).

Except for **8**, the processes to which the experimental barriers correspond are unambiguous. As was mentioned previously, two conceivable paths exist for conversion of **8a** to **8b**. The first is a direct 120° rotation about the C(2)–C(3) bond. The second is a rotation in the opposite direction by 120° to form **8c**, followed by another 120° rotation giving **8b**. If the potential barrier for the first process is considerably larger than for the second, the dominant path would be the one in which **8c** is an intermediate. In studying rotational barriers in unsymmetrical ethane derivatives containing halogen substituents, a correlation was observed between the rotamer populations and the three possible potential barriers.[4a] The smallest barrier was found to separate the two most stable rotamers, while the largest barrier separated the least stable rotamers. Since **8c** is the least populated conformer of **8** (to the extent of not being observable), the direct path for conversion of **8a** to **8b** is thought to predominate.

The observed barriers in **9** and **10** must correspond to the trans to gauche process (eq 1) because exchange between the enantiomeric gauche rotamers is not observable in achiral solvents.

Discussion

The application of a simple additive gauche interaction scheme for calculating ground-state conformational energy differences in **8**, **9**, and **10** (Table I) from pairwise interactions derived from simpler compounds seems unwarranted in light of previous unsuccessful attempts for related molecules.[6c,14] Furthermore, because of the observed solvent dependence for **9** (see Table I), it would be necessary to account for effects of the medium for any quantitative or semiquantitative agreement. A qualitative prediction is, however, possible in terms of the gauche interactions involved. Literature values for the gas-phase trans to gauche free-energy differences in some 1,2-disubstituted ethanes are tabulated in Table III. The larger values for 1,2-dichloroethane, 1,2-dibromoethane, and n-butane than for 1-chloro- and 1-bromopropane imply

Table III. Gas-Phase Energy Differences between Gauche and Trans Conformations of 1,2-Disubstituted Ethanes

Compd	ΔE, kcal/mol
$CH_3CH_2CH_2CH_3$	0.8[b]
$CH_3CH_2CH_2Cl$	−0.05[b]
$CH_3CH_2CH_2Br$	−0.1, −0.28[b]
$ClCH_2CH_2Cl$	1.2[c]
$BrCH_2CH_2Br$	1.77[c]

[a] $\Delta E = E_{\text{gauche}} - E_{\text{trans}}$. [b] Reference 6c. [c] Reference 6a.

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(13) W. E. Wentworth, *J. Chem. Educ.*, **42**, 96, 162 (1965).

(14) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **43**, 602 (1965).

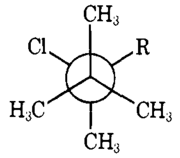
that gauche halogen–halogen and gauche methyl–methyl interactions are more severe than gauche halogen–methyl interactions.[15] On conversion of **9t** and **10t** to **9g** and **10g**, respectively (eq 1), two gauche methyl–halogen interactions are replaced by one methyl–methyl and one halogen–halogen arrangement, and we would predict a loss in stability, as is observed. Similar reasoning predicts **8a** (and **8b**) to be energetically favored over **8c**.

Some trends are apparent in the rotational barriers in Table II. Without exception, substitution of bromine for chlorine results in increased values of $\Delta G^{\ddagger}$ (compare **1** with **2**, **3** with **4**, **5** with **4**, and **9** with **10**). Moreover, in the majority of cases, the increases in $\Delta G^{\ddagger}$ are accompanied by increases in the less reliable[3a] values of the Arrhenius activation energy and the enthalpy of activation (E_a and $\Delta H^{\ddagger}$, respectively). This substituent effect was not observed in a study of a series of halogenated ethanes.[4a] The suggested reason was that effects of the larger bromine tend to cancel with the effects of the longer carbon–bromine bond distances. In the present case, the presence of larger and less symmetrical methyl groups, compared to halogen atoms, could offset any such cancellation. For **9** and **10**, an increase in $\Delta G^{\ddagger}$ is not accompanied by a corresponding increase in E_a and $\Delta H^{\ddagger}$. Also, relatively large variations are seen in $\Delta S^{\ddagger}$ for these two compounds. Possibly this is a result of the larger inherent uncertainties in $\Delta H^{\ddagger}$, E_a, and $\Delta S^{\ddagger}$ than in $\Delta G^{\ddagger}$, or, alternatively, because of the use of different solvents.[18,19] Solvent effects should be more pronounced in **8**, **9**, and **10** than in the other molecules studied, because internal rotation results in a larger change in dipole moment with both C(2) and C(3) carrying halogen substituents. Evidence supporting this contention has been obtained from equilibrium studies.[11] The larger barriers observed for the bromo compounds than for the chloro analogs probably are a result of increased steric strain in an eclipsed, or very nearly eclipsed, transition state resulting from a larger effective size of bromine as opposed to chlorine.

When halogen is substituted for methyl, an increase in the free energy of activation for rotation is observed (compare **1** with **3**, **1** with **5**, **2** with **4**, **2** with **5**, **4** with **8**, **3** with **9**, **4** with **10**, and **8** with **10**). However, in some cases, opposite changes in E_a and $\Delta H^{\ddagger}$ occur which render difficult any simple explanation of the consistent changes in $\Delta G^{\ddagger}$. Substitution of chlorine or bromine atoms for methyl groups gives decreased values of $\Delta H^{\ddagger}$ and E_a for **3** as compared with **1**, **4** as compared with **2**, and **5** as compared with **2**. Corresponding decreases are not observed in the free energies of activation, apparently because of the large experimental entropies of activation of **1** and **2**. If these latter values are real, these two compounds are to be considered somewhat anomalous. Both **1** and **2** are, in fact, structurally similar, containing a single halogen substituent and five methyl groups on the C(2)–C(3) ethane fragment. Similarly, **3**, **4**, and **5** are related, each containing two geminal halogen atoms and four methyl groups, and their entropies of activation are all small and negative. A convincing explanation of the large positive entropies of activation of **1** and **2** is not readily apparent. The absence of clear, consistent, and predictable changes in the E_a and $\Delta H^{\ddagger}$ values when methyl groups are replaced by halogen atoms may be because no single effect predominates in contributing to the overall barriers.

The effect of increasing the number of bromine atoms on the C(2)–C(3) fragment is of particular interest in the series of compounds **4**, **8**, and **10**. A small and perhaps insignificant increase is observed in $\Delta G^{\ddagger}$, E_a, and $\Delta H^{\ddagger}$ on comparing **8** with **4**. However, a much larger difference is noted between **8** and **10**. If the interpretation discussed above for rotamer exchange in **8** is correct, the major structural difference in the transition states for **8** and **10** is that **10** contains a bromine atom eclipsing (or nearly so) another bromine, while the transition state for **8** contains only bromine–methyl eclipsings. Apparently, bromine–bromine eclipsing is less favorable than bromine–methyl eclipsing interactions. Similarly, the sharp increase in barrier between **3** and **9** is probably due to an eclipsed chlorine–chlorine arrangement in the transition state of **9**, indicating that eclipsed chlorine–chlorine repulsions are stronger than chlorine–methyl repulsions. Sharp increases in the barriers have also been noted in chloroethanes when the transition states contain additional chlorine–chlorine eclipsing interactions.[4e]

Compounds **1**, **6**, and **7** were investigated for the purpose of examining the effects of the size of alkyl substituents on the barrier heights. The protons attached to C(5) of **6H** obscured the *tert*-butyl resonance and prevented an accurate line-shape treatment. The pentadeuterio analog **6** was therefore prepared. A significant isotope effect on the rate of conformational inversion could not be detected, as both **6** and **6H** showed approximately equal coalescence temperatures (±3°). The expected increase in $\Delta G^{\ddagger}$ with group size is observed in comparing **1**, **6**, and **7**; however, the magnitude of the changes are surprisingly small. This is all the more striking because substituting a bromine atom for a *tert*-butyl group *increases* the free energy of activation (compare **7** with **5**). Generally, a bromine atom is considered approximately comparable in size to a methyl group with van der Waals radii of 1.95 and 2.0 Å, respectively.[20] A plausible explanation of the relatively small $\Delta G^{\ddagger}$ value for **7** may arise from the ab-



1, R = CH_3
6, R = CD_2CD_3
6H, R = CH_2CH_3
7, R = $C(CH_3)_3$

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[15] The reason for this is not well understood. Abraham and Parry[5a] have calculated these effects using an electrostatic term for coulombic attractions arising from bond polarization, while Allinger, *et al.*,[16] and Kreevoy and Mason[17] have obtained reasonable agreement without such assumptions.

[16] N. L. Allinger, J. A. Hirsch, M. A. Miller, and J. Tyminski, *J. Amer. Chem. Soc.*, 91, 337 (1969).

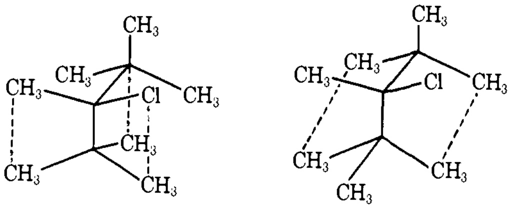
[17] M. M. Kreevoy and E. A. Mason, *ibid.*, 79, 4851 (1957).

[18] Ideally, comparisons should be made using the same solvent; however, low solubilities or unfavorable rotamer populations severely limit the possible choices of solvent.

[19] For a discussion of solvent effects on rotational barriers, see G. Govil and H. J. Bernstein, *J. Chem. Phys.*, **48**, 285 (1968).

[20] "Handbook of Chemistry and Physics," 49th ed, The Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p D-107.

sence of spherical symmetry of the *tert*-butyl group and a resulting cog-wheeling type of arrangement in the transition state **7e** which reduces the effective group size. Rather severe methyl–methyl repulsions in the ground-state **7g** may also serve to decrease the barrier. The values of $\Delta H^{\ddagger}$, E_a, and $\Delta S^{\ddagger}$ for **6** are somewhat lower than expected when compared to **1** and **7**. Here, most confidence probably should be placed on the experimentally more reliable values of the free energies of activation.



7e **7g**

Experimental Section

Nmr spectra were taken on a Varian A-56/60A spectrometer operating at 60 MHz and equipped with a V-6040 temperature controller. Sample temperatures were determined by the methanol chemical-shift method, with a methanol capillary centered in the sample tube. Each trace of the variable-temperature spectra was calibrated, using the audio side-band technique. Spectra were obtained using 10–20% solutions with about 3% added TMS. Solvents for the variable-temperature studies are given in Table II. Reported melting points and boiling points are uncorrected and nmr chemical shifts, δ, are in parts per million downfield from internal TMS, at an ambient probe temperature of about 38°.

Caution! Most of the following compounds are potent lachrymators—care should be exercised in preparing and handling them.

3-Bromo-2,2,3-trimethylbutane (2). Phosphorous tribromide (2.5 g) was added to vigorously stirred 2,3,3-trimethylbutan-2-ol (1.0 g) at 0°. The resulting solid mass was taken up in ether and poured into about 10 g of cracked ice, and the mixture was stirred and allowed to warm to room temperature. The ether layer was washed with water and dried over sodium sulfate, and the solvent was removed under aspirator pressure. The yield of crude bromide **2** was 1.34 g (87%). Recrystallization from methanol afforded white crystals: mp 154–155° (s); reported[21a] mp 150–152°. The nmr shifts in CS$_2$ were δ 1.76 (6 H, s), 1.10 (9 H, s); ir (CCl$_4$) no OH.

3,3-Dibromo-2,2-dimethylbutane (4). Bromine (16.0 g) was added dropwise to stirred phosphorous trichloride (20.0 g) at 0°. Then 10.0 g of pinacolone was added dropwise to the stirred, cooled mixture. After the addition was complete, the mixture was allowed to warm to room temperature and was hydrolyzed by careful, dropwise addition of about 75 ml of water. The product was extracted with ether and the ethereal extract was washed with water, sodium bicarbonate solution, and again with water, and then dried over magnesium sulfate. The solvent was removed under aspirator pressure and the residue was recrystallized from ethanol. The major component was isolated, using preparative glpc (3.05 m × 0.95 cm, 10% poly-*m*-phenyl ether on Chromosorb W at 100°; 200 ml/min of He). Recrystallization from ethanol gave pure **4**: mp 194–194.5°, reported[21b] mp 191.5°. The nmr shifts in dichlorodifluoroethene were δ 2.51 (3 H, s), 1.28 (9 H, s). The ir in CCl$_4$ showed no carbonyl absorption.

3-Chloro-3-bromo-2,2-dimethylbutane (5). The preparation of **5** was accomplished using the procedure described for **4**, except that the addition of pinacolone was conducted at room temperature and the minor product with the shorter retention time was isolated. The shifts in dichlorodifluoroethene were δ 2.31 (3 H, s), 1.26 (9 H, s).

2,2,3-Trimethylpentan-3-ol (11 H). A previously reported[22] procedure gave a 49% yield of **11H** with bp 50–55° (25 mm); reported[22] bp 149–152° (760 mm); reported[23] bp 76° (40 mm). The shifts in CS$_2$ were δ 1.2–1.8 (2 H, m), 1.41 (1 H, s), 0.6-1.1 (3 H, m), 1.02 (3 H, d, J = 0.6 Hz), 0.90 (9 H, s). The ir of the neat liquid showed absorption at 3470 cm^{-1} (broad, intense) and no carbonyl.

2,2,3-Trimethylpentan-3-ol-*4,4,5,5,5-d$_5$* (11). The deuterio alcohol **11** was prepared using the procedure for **11H**, except that ethyl-d_5 bromide was used in place of the undeuterated analog. The product, **11**, had bp 55–65° (24 mm). The nmr in CCl$_4$ showed: δ 1.13 (1 H, s), 1.04 (3 H, s), 0.92 (9 H, s). The ir (neat) had absorptions at 3480 cm^{-1} (broad, intense), 2080-2240 cm^{-1}, and negligible carbonyl.

3-Chloro-2,2,3-trimethylpentane (6H). Concentrated hydrochloric acid (5 ml) was added dropwise with stirring to 1.0 g of **11H** at 0°. After the addition was complete, stirring was continued for 15 min. Cracked ice (2 g) was then added and the product was extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate, and concentrated at atmospheric pressure. The residue was distilled, affording about 0.5 g (30%) of the chloride (**6H**) having bp 77–79° (54 mm), n^{24}D 1.4412; reported[24] bp 87° (62 mm), n^{20}D 1.4441. The nmr spectrum in CCl$_4$ showed δ 1.4–2.2 (2 H, m), 1.54 (3 H, d, J = 0.6 Hz), 0.8–1.2 (3 H, m), 1.07 (9 H, s). The ir (neat) showed no OH absorption.

3-Chloro-2,2,3-trimethylpentane-*4,4,5,5,5-d$_5$* (6). The procedure for **6H** was also used in the preparation of **6**, except for the starting material which was the deuterated alcohol **11**, and purification was accomplished using preparative glpc (1.52 m × 0.95 cm 10% Carbowax 20 M on 60–80 Chromosorb P at 65° with 120 ml/min of He). The nmr (CS$_2$) showed δ 1.41 (3 H, s), 1.04 (9 H, s).

Pentamethylpentan-3-ol. A solution of 5 g of tetramethylpentan-3-one in an equal volume of anhydrous ether was added dropwise to a stirred, cooled (ice bath) solution of methyllithium (24 ml, 2.4 *M*, 0.058 mol) in ether under nitrogen. After the addition was complete, the reaction mixture was hydrolyzed with aqueous saturated ammonium chloride. The product was extracted with ether, and the ethereal extract was washed with water, dried over magnesium sulfate, and concentrated under the aspirator pressure. Distillation of the residue gave 5 g (90%) of a material which solidified in the receiver. The bp was 105–108° (60 mm); reported[23] bp 122.5–123° (100 mm). The nmr (CCl$_4$) showed δ 1.12 (3 H, s), 1.04 (18 H, s), 0.97 (1 H, s), while the ir (CCl$_4$) had absorptions at 3625 (sharp) and 3520 cm^{-1} (broad), and no carbonyl.

3-Chloropentamethylpentane (7). A solution of pentamethylpentan-3-ol (2 g) in ether (1 ml) was added to cooled (ice bath), concentrated hydrochloric acid (10 ml). The mixture was vigorously stirred for 30 min and then poured into about 10 g of cracked ice. The product was extracted with ether; the ethereal extract was washed with water and dried over magnesium sulfate, and the solvent was removed under aspirator pressure. The residue was purified by preparative glpc; 1.52 m × 0.95 cm 10% Carbowax 20 M on 60–80 Chromosorb P at 100° with 200 ml/min of He, using a 30 cm × 5 mm i.d. collection tube at room temperature. Higher column temperatures or slower flow rates were found to cause excessive decomposition while more efficient condensors would collect the volatile decomposition product: nmr (CS$_2$) δ 1.56 (3 H, s), 1.18 (18 H, s); ir (CCl$_4$) no OH, no C═C.

2,3-Dibromo-2-methylbutane was prepared as described earlier.[25] The product had bp 67–69° (28 mm); reported[26] bp 72-73° (30 mm). The nmr (CCl$_4$) showed δ 4.33 (1 H, g, J = 7 Hz), 1.91 (3 H, s), 1.86 (3 H, d, J = 7 Hz), 1.76 (3 H, s).

3-Bromo-2-methyl-2-butene. 2,3-Dibromo-2-methylbutane (14.2 g) was added to a solution of potassium hydroxide (10 g) in methanol (150 ml) and the resulting mixture was stirred for 4 hr. An equal volume of water was then added and the product was extracted with ether. The ethereal extract was washed with water and dried over magnesium sulfate. The solvent was removed under atmospheric pressure. Distillation of the residue afforded 6.30 g (87.4%) of the bromoalkene: bp 52–54° (76 mm); reported[27] bp 118–120°. The nmr (CCl$_4$) showed δ 2.19 (3 H, m), 1.76 (6 H, m).

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(21) (a) G. Chavanne and B. Lejeune, *Bull. Soc. Chim. Belg.*, **31**, 100 (1922); (b) A. V. Grosse and V. N. Ipatieff, *J. Org. Chem.*, **8**, 444 (1943).

(22) L. Clark and W. N. Jones, *J. Amer. Chem. Soc.*, **34**, 173 (1912).

(23) F. N. Whitemore and K. E. Laughlin, *ibid.*, **55**, 3733 (1933).

(24) F. L. Howard, T. W. Mears, A. Fookson, P. Pomerantz, and D. B. Brooks, *J. Res. Nat. Bur. Stand.*, **38**, 379 (1947); *Chem. Abstr.*, **41**, 5291 (1947).

(25) C. M. Suter and H. D. Zook, *J. Amer. Chem. Soc.*, **66**, 741 (1944).

(26) J. Boeseken, *Recl. Trav. Chim. Pays-Bas*, **54**, 662 (1935).

(27) J. K. Farrell and G. B. Bachman, *J. Amer. Chem. Soc.*, **57**, 1282 (1935).

2,3,3-Tribromo-2-methylbutane (8). The preparation of **8** was accomplished using a modification of a reported procedure.[28] Bromine (1.07 g) was added dropwise to a stirred, ice-cooled solution of 3-bromo-3-methyl-2-butene (1.00 g) in carbon tetrachloride (10 ml). The solution was then allowed to warm to room temperature and the solvent was removed under aspirator pressure. The resulting solid residue was recrystallized from ethanol to give white crystals which sublime before melting (1.30 g, 64.5%). The nmr (CCl_4) showed δ 2.73 (3 H, s), 2.09 (6 H, s).

2,2,3,3-Tetrachlorobutane (9). Chlorine was bubbled slowly into a stirred, cooled (ice bath) solution of dimethylacetylene (0.59 g) in carbon tetrachloride (10 ml) for 3 hr. The solvent was removed under aspirator pressure and the solid residue recrystallized from ethanol. The material was purified by glpc (3.05 m × 0.95 cm 10% poly-*m*-phenyl ether on 60–80 Chromosorb W at 100° with 200 ml/min of He). The nmr in CCl_4 showed δ 2.42 (s) with no other peaks. **Caution!** Violent reaction may occur after several minutes if chlorine accumulates. Preparation on a large scale should be avoided.

2,2,3,3-Tetrabromobutane (10). Bromine (3.2 g) was added dropwise to a stirred, ice-cooled solution of dimethylacetylene (0.59 g) in pentane (10 ml). After the addition was complete, the ice bath was removed and stirring was continued for 30 min. The solvent was removed under aspirator pressure and the residue recrystallized from ethanol: mp 246–248° (s); reported[29] mp 243°. The nmr (CCl_4) showed δ 2.87 (s), no other peaks. The ir (CCl_4) showed no double-bond absorption.

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(28) J. Schmidt and F. Leipprand, *Chem. Ber.*, 37, 548 (1909).

(29) J. Wislicenus and P. Schmidt, *Ann.*, 313, 225 (1900).

1,3-Dipolar Addition Reactions of Reissert Compounds

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Abstract: The mesoionic intermediate, **2**, produced by loss of fluoroboric acid from 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (**1**) is essentially a munchnone imine. As such, it can undergo 1,3-dipolar addition reactions with suitable dipolarophiles. The reaction of **1** with ethyl phenylpropiolate was especially significant in that both the bridged intermediate, 2-carbethoxy-1,3-diphenyl-3-hydroxy-13-cyano-3,13-dihydrobenzpyrrocoline-3,13-lactim (**3**), and the aromatic heterocyclic compound, ethyl 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (**6**), were isolated. The formation of a bridged intermediate such as **3** had been postulated to occur in the various 1,3-dipolar addition reactions of sydnones, sydnone imines, and munchnones; however, this type of structure had always remained a theoretical concept only, since the elimination of carbon dioxide or isocyanic acid to form the final aromatic heterocyclic product had occurred rapidly. The bridged adduct **3** was found to undergo thermolysis at a high temperature to give **6** plus a polymer of isocyanic acid. The proof of structure of **6** consisted of its hydrolysis and decarboxylation to give 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline (**10**). In an independent synthesis, 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**11**) was prepared by the condensation of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with cinnamonitrile. Hydrolysis of the amide and decarboxylation of the resulting acid gave **10**. Reaction of **1** with dimethyl acetylenedicarboxylate gave dimethyl 3-phenylpyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (**8**). The structure of **8** was established in two different ways. First of all, the ester was subjected to hydrolysis and the resulting acid to decarboxylation to give 3-phenylpyrrolo[2,1-*a*]isoquinoline (**17**), which was also obtained by cyclodehydration of β-(1-isoquinolyl)propiophenone (**18**) in polyphosphoric acid. In the second proof of structure, dimethyl 2-(1-isoquinolyl)-3-benzoylmaleate (**19**) was prepared by the reaction of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile with dimethyl acetylenedicarboxylate. Treatment of **19** with 100% phosphoric acid gave **8**.

A mechanism for the acid-catalyzed hydrolysis of a Reissert compound (a 1-acyl-1,2-dihydroquinaldonitrile or a 2-acyl-1,2-dihydroisoquinaldonitrile) has been proposed[1] in which a mesoionic compound is postulated to be an intermediate. Since such a mesoionic intermediate is essentially a munchnone imine, and since munchnones, sydnones, and sydnone imines are known to undergo 1,3-dipolar addition reactions readily,[2] it was anticipated that a 1,3-dipolarophile might be used to capture the intermediate. This expectation was realized, as described below.[3]

When 2-benzoyl-1,2-dihydroisoquinaldonitrile was treated with fluoroboric acid in glacial acetic acid, a yellow precipitate (**1**) of the Reissert salt was obtained. The reactions of **1** with ethyl phenylpropiolate, ethyl tetrolate, and dimethyl acetylenedicarboxylate were examined. Exceptionally promising results were obtained in the case of the reaction with ethyl phenylpropiolate; the anticipated, initial, bridged intermediate **3** could actually be isolated as a moderately stable, crystalline compound. This appears to be the first example of the isolation of such an intermediate among all of the known 1,3-dipolar addition reactions of the same general type involving munchnones, sydnones, and sydnone imines.

Two colorless compounds of molecular formulas $C_{28}H_{22}N_2O_3$ (**3**) and $C_{27}H_{21}NO_2$ (**6**), respectively, were obtained by the reaction of **1** with ethyl phenylpropiolate in boiling methylene chloride–ethanol solution.

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(1) (a) R. L. Cobb and W. E. McEwen, *J. Amer. Chem. Soc.*, 77, 5042 (1955); (b) E. K. Evanguelidou and W. E. McEwen, *J. Org. Chem.*, 31, 4110 (1966), and papers cited therein.

(2) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 2, 565 (1963); (b) R. Huisgen, H. Gotthardt, H. Bayer, and F. Schaefer, *ibid.*, 3, 136 (1964).

(3) A preliminary account of a small portion of this work has been published: W. E. McEwen, I. C. Mineo, Y. H. Shen, and G. Y. Han, *Tetrahedron Lett.*, 5157 (1968).