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# On Conformation–Reactivity Correlations

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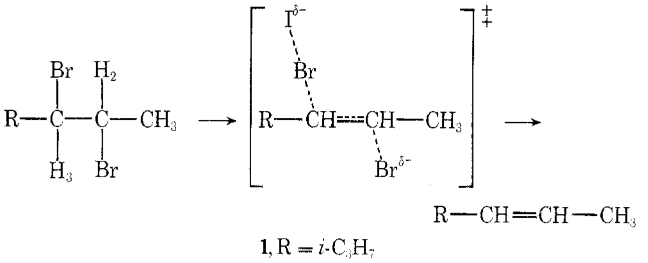
*Received September 3, 1974*

The kinetics and product studies of the reaction of 2,3-dibromo-4-methylpentanes and 2,3-dibromo-4,4-dimethylpentanes with iodide ion are reported. $^{13}C$ NMR studies, in conjunction with previous $^1H$ and dipole moment studies, strongly suggest that the erythro isomer of the *tert*-butyl compound occupies a different conformation than the erythro isomer of the isopropyl compound; yet the rates of reactions are not divergent. The bases for the frequently observed correlation between a favorable ground-state conformation and a rapid reaction rate are discussed.

A number of recent papers have commented upon the fact that substrates in which the reactive groups exist in the correct steric relationship for a given reaction frequently undergo rapid reaction.[1–16] Other studies have considered the obverse, namely, that a slow reaction is found where the preferred ground-state conformation is unfavorable for reaction. Occasionally, the suggestion is made that the ground-state conformation affects or determines reactivity. We wish to show a case in which a compound with an unfavorable ground-state conformation reacts more rapidly than a compound with a favorable conformation.[17]

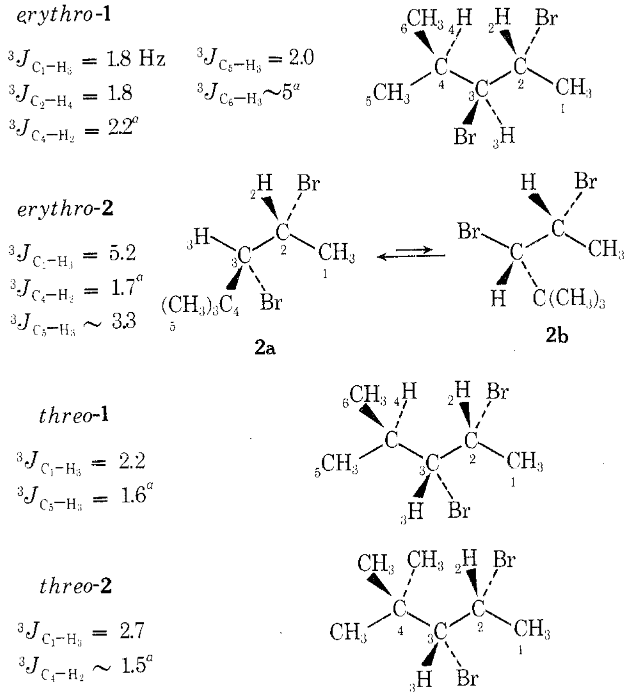
The reaction in question is the iodide-catalyzed debromination of certain acyclic dibromides 1 and 2. Earlier work on similar debrominations showed a preference for a trans elimination of the elements of bromine (Scheme I).[18]

**Scheme I**



1, R = $i\text{-}C_3H_7$
2, R = $t\text{-}C_4H_9$

**Scheme II**



2a 2b

[a] Approximate value.

The ground-state conformations of *threo*-1 and -2 are quite similar.[19] For these threo isomers, very low $^1H$ NMR $J_{23}$ values were observed, which implies a predominance of conformation(s) having gauche vicinal hydrogens. The dipole moment studies showed high resultant moments ($\mu \simeq$ 2.5 D) due to vectorially additive group moments for bromine such as expected for gauche vicinal bromines. Both lines of evidence suggest a preference for the conformers shown in Scheme II.

*erythro*-1 shows a high $J_{23}$ value (10.6 Hz) and a low dipole moment (0.9 D). In contrast, *erythro*-2 shows a lower $J_{23}$ (2.0 Hz) and a much higher dipole moment (2.6 D). Thus, the preferred conformations of these two substrates appear quite different (Scheme II). Others have noted divergent conformations for compounds containing *tert*-butyl groups compared to compounds having isopropyl or phenyl groups.[20–24] In particular, Bodot and coworkers were able to suggest numerical weights for the different conformers in certain halohydrins analogous to 1 and 2.[23] Reasons for the divergence in conformation have been suggested in earlier work.[21,25]

A third method of conformational analysis of these sub-

**Table I**
**Iodide-Catalyzed Debromination Rates and Activation Parameters**

| Registry no. | Compd | R | Isomer | $k \times 10^5$, l./mol sec | | | | $\Delta H^\ddagger$ | $\Delta S^\ddagger$ |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 60$^b$ | 70$^b$ | 80$^b$ | 85$^b$ | | |
| | | $CH_3$$^a$ | meso | 0.291 | | | | | |
| | | | dl | 0.151 | | | | | |
| | | $C_2H_5$$^a$ | erythro | 0.496 | | | | | |
| | | | threo | 0.272 | | | | | |
| 7694-00-0 | 1 | $i$-$C_3H_7$ | erythro | 0.78 ± 0.03 | 2.73 ± 0.07 | 6.8 ± 0.3 | 12 ± 1 | 24.7 ± 0.7 | −8 ± 2 |
| 7694-01-1 | 1 | | threo | 0.22 ± 0.02 | 0.61 ± 0.02 | 1.80 ± 0.09 | 3.0 ± 0.3 | 24 ± 1 | −12 ± 3 |
| 7694-04-4 | 2 | $t$-$C_4H_9$ | erythro | 3.13 ± 0.02 | 11.8 ± 0.1 | 34.3 ± 0.6 | 62 ± 2 | 26.7 ± 0.5 | −0.8 ± 1.3 |
| 7694-05-5 | 2 | | threo | 0.210 ± 0.001 | 0.572 ± 0.004 | 1.51 ± 0.02 | 2.6 ± 0.2 | 22.7 ± 0.9 | −18 ± 3 |

[a] These data are taken from ref 27. [b] Adjusted to the temperatures indicated from slightly lower temperatures for 1 and 2.

strates has recently become available, i.e., $^{13}C$–H coupling constants. Lemieux and coworkers have suggested that a correlation exists between the dihedral angel described by the $^{13}C$–C–C–H nuclei and the magnitude of $^3J_{CH}$ similar to the well-known Karplus relationship.[26] However, they caution that electronegativity effects, steric effects, and other internal factors were of concern regarding the magnitude of $^3J_{CH}$. In this work,[26] trans $^{13}C$ and H nuclei were found to have a $^3J$ value of ca. 8 Hz, whereas gauche nuclei have a $^3J$ value of ca. 1 Hz.

Scheme II shows certain $^3J_{CH}$ values found for the compounds of this study. Other $^3J_{CH}$ values could not be determined with precision, and these are not listed. The $^3J_{CH}$ values are in qualitative agreement with the results of previous methods of conformational determination. Thus, for *threo*-1 and -2, $C_1$ is predominantly gauche to $H_3$, as shown by the quite low $^3J_{CH}$ values in question.

More important is the check upon the previous data which suggested divergent conformations for *erythro*-**1** and -**2**. For *erythro*-**1**, $C_1$ and $H_3$ are predominantly gauche as indicated by the low $^3J_{CH}$ value. The larger $^3J_{CH}$ for $C_6$ and $H_3$ is qualitatively in agreement with their predominant trans geometry. In *erythro*-**2**, the $^1H$ NMR data do not distinguish between conformers **2a** and **2b** (Scheme II). However, the fairly high $^{13}C$ coupling constant for $C_1$ and $H_3$ suggests a predominant trans relationship as found in **2a** (the low $^3J_{C_4\text{-}H_2}$ is in agreement with the preference for **2a**). It is quite reasonable that **2a** should predominate over **2b** as *tert*-butyl would be very hindered in the latter.

Thus, the combination of three lines of evidence indicates that *erythro*-1 has an ideal conformation for iodide-catalyzed debromination (trans bromines) whereas *erythro*-2 predominately occupies an unfavorable conformation (gauche bromines). The rates of reaction are listed in Table I. These data show that *erythro*-**2** reacts ca. 4 times *faster* than *erythro*-**1**. Using literature values[27] for similar compounds (e.g., R = $CH_3$ and R = $C_2H_5$), a reasonably linear plot of log $k$ vs. $E_s{}^c$ (Taft's steric substituent constants) can be made.[28,29] Thus, it appears that the size of R affects reactivity through steric acceleration of debromination that is unrelated to any particular ground-state conformation. The products of reaction were >96% *trans*-4-methyl-2-pentene from 1, and 100% *trans*-4,4-dimethyl-2-pentene from **2**.

The various threo isomers are similar in reactivity. With increasing size of R, the destabilization of the ground state apparently parallels the destabilization of the transition state resulting in little net change in rate as R varies. *threo*-1 formed >90% *cis*-4-methyl-2-pentene, but *threo*-2 formed 87 ± 3 *cis*- and 13% *trans*-4,4-dimethyl-2-pentene at 85°. In the latter case, the trans alkene probably resulted from a small amount of cis elimination. We were not able to detect any isomerization of the cis alkene under the reaction conditions. Interruption of the reaction after 1 half-life revealed only the presence of *threo*-**2** and alkene. However, any isomerization to *erythro*-**2** would be difficult to detect owing to the greater reactivity of this isomer. An SN2 displacement by iodide, followed by an iodide-catalyzed debromoiodination, is also possible,[30-32] although steric hindrance to SN2 attack militates against this alternative.[30]

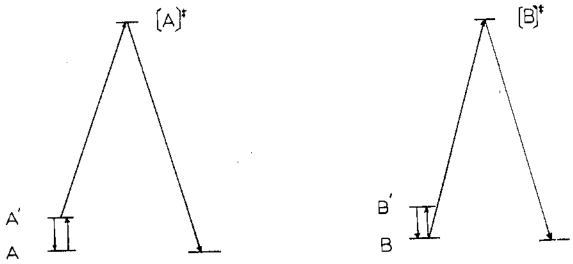


**Figure 1.**

As background for discussion of these findings and literature data, the Curtin–Hammett principle deserves special note.[33,34] This principle refers to a starting material that can form two separate products in parallel reactions. The principle states that the relative population of the various ground-state conformations in no way affects the proportions of the two products. The product ratio is dominated by the relative transition state energies. This principle assumes that the barrier to conformational interconversion (commonly a few kilocalories) is small compared to the transition state barrier (15–30 kcal). In common usage, the principle is accorded a somewhat wide range of applicability.

In a situation more directly relevant to this study, *two* hypothetical substrates A and B might be considered (Figure 1). These substrates, which have equal internal energy, form products by way of transition states of the same energy. However, substrate A must undergo internal rotation to form a less stable conformer A′ before reacting, whereas B (although it partly exists as B′) can react directly from the most stable conformer. It is easily shown by application of rate and equilibrium laws that the rates of reaction of A and B will be identical. Thus, ground-state conformation in this hypothetical case will also be irrelevant.

One might then question why so many reactions show a parallelism between preference for a particular ground-state conformation (which appears to be ideal for rapid reaction) and a high rate of reaction (or unfavorable conformation and slow reaction). In our estimation, the answer lies in the fact that if a ground state conformation is stable and highly populated, nonbonded repulsions and other internal strain factors are minimized. The transition state is even more sensitive, in many cases, to the same nonbonded repulsions and the transition state orientation in which these repulsions are minimized will also be more stable. The ground-state molecule will undergo many thousands of internal rotations, however, before the transition state is reached. Thus, the correlation between ground-state conformation and reaction rate may mean only that both phenomena are related to the same underlying factors, not that conformation per se determines reaction rate.[35] Even so, as this work indicates, the preference for an "unfavorable" conformation does not necessarily mean that the reaction rate will be slow.[36]

## Experimental Section

The compounds of this study were available from a previous study. The kinetics of reaction were determined by an ampoule technique in a manner as closely as possible approximating that of Young, Pressman, and Coryell and of Dillon.[27] The rate equation of the former group of workers was used. The solvent was 99% methanol. Rate constants were calculated by computer techniques. The average of at least two runs is reported in Table I. The observed rate constant was corrected for solvent expansion, but it was not corrected for salt effects, since the concentration of KI was virtually constant from run to run (ca. 0.22 *M*). The concentration of substate was ca. 0.038 *M* at room temperature. To check the closeness of our data to that of previous workers, the rates of reaction of *meso*-2,3-dibromobutane and *erythro*-2,3-dibromopentane were determined. The rates were within 12 and 6%, respectively, of the values reported by Young, Pressman, and Coryell.[27] The activation parameters were calculated by standard means. The kinetic data reported in Table I were actually determined at 0.1–0.2° lower temperature than those indicated. Corrections were made to the temperatures indicated using the activation enthalpy. The plot (Figure 2) uses the raw data of Young et al. in part, which were determined at slightly lower temperatures than 60 and 75°.

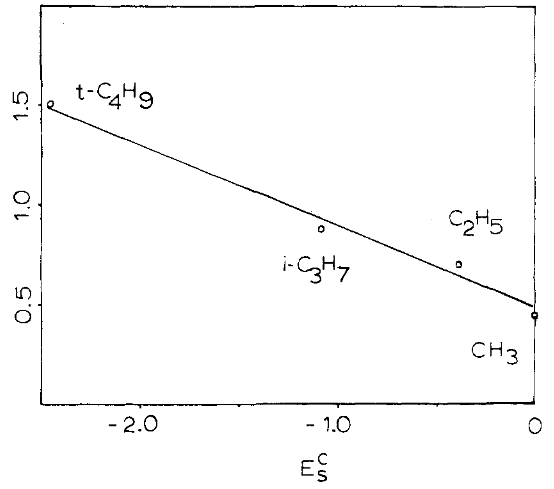


**Figure 2.** Plot of the logarithm of the rate of iodide-catalyzed debromination vs. corrected steric substituent constants ($E_s{}^c$) for the substituents indicated.

In a typical product study, 2.040 g of KI and 0.4791 g of *threo*-2 were dissolved in 25 ml of 99% methanol and heated at 85° for 59 hr in a pressure bottle. The reaction mixture was added to a large quantity of water containing a little bisulfite. This was extracted with small amounts (ca. 3 ml) of a high-boiling organic solvent (various were used). Various VPC columns adequately separated the components; an example is 7% bis(2-ethylhexyl)tetrachlorophthalate on HMDS-treated Chromosorb W (a ca. 10-ft column). At a column temperature of 50°, and a helium flow of 50 ml/min, the retention times of the *trans*- and *cis*-4,4-dimethyl-2-pentenes were 2.3 and 3.0 min, respectively. The VPC data were corrected for different thermal response factors for the two isomers determined with a mixture of known proportions. Subsequent extraction fractions of the aqueous layer showed decreasing amounts of olefins in the same ratio as the initial extract.

It was not possible to separate the *cis*- and *trans*-4-methyl-2-pentenes. The product olefins were rebrominated in cold $CCl_4$, protected from light. The rebromination was between 90 and 95% stereospecific. The resulting mixtures of 1 were analyzed on a 5% SE-30 on Var-Fort A column (5-ft stainless steel) at a column temperature of 90° and a flow of 100 ml/min. *erythro*-1 showed a retention time of 2.3 min and *threo*-1 showed a time of 3.4 min.

The $^{13}C$ NMR data was taken on ca. 1.0 g of substrate dissolved in 3 ml of $CDCl_3$. In a typical run a 1500-Hz spectral width was used along with a 2.65-sec acquisition time and a 2-sec pulse delay using the gated mode of operation of the decoupler; 4K of transient were collected. The coupling constants were taken from 100-Hz expansions or else the computer-generated listing of peak frequencies was used. The $^{13}C$ spectra were simulated using the LAOCOON III program adapted to provide a computer-generated plot of the spectrum.[37] The spectral parameters were varied until the computer simulation was superimposable on the original spectrum. In some cases, the computer program could not accommodate the number of spins required for the calculation, and a first-order analysis of the spectrum was necessary. These cases are appropriately indicated in Scheme II. The error in the $^{13}J_{CH}$ values is ±0.4 Hz.

**Registry No.**—Iodide, 20461-54-5.

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fraction, and $k_i$ is the rate constant for reaction of this conformation. For the compounds of this study, $k_{gauche} = 0$; thus $k_{obsd} = n_{anti}k_{anti}$. However, it should be noted that reservations have been expressed concerning this approach; e.g., E. L. Eliel, and J. Biros, *J. Am. Chem. Soc.*, **88**, 3334 (1966). For this approach to be valid in the case of *erythro*-**2**, the low $n_{anti}$ would require a compensatory effect in the form of a higher $k_{anti}$. This is possible if exceptional steric strains are present in the ground state that are relieved in the transition state. However, the observation of a (roughly) successful log $k$ vs. $E_s$ correlation in two cases[17] would demand an extremely fortuitous balancing of $n$ and $k$ factors.

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# *Notes*

## Determination of the Enantiomeric Purity of Isoquinoline Alkaloids by the Use of Chiral Lanthanide Nuclear Magnetic Resonance Shift Reagents

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*Received February 25, 1975*

Since the discovery[1] that lanthanide shift reagents[2] are capable of inducing simplification and enhancement of resolution in NMR spectra of various Lewis bases, many new developments and refinements have been introduced. Whitesides and coworkers[3-5] and others[6-10] have reported that chiral lanthanide shift reagents shift the resonances of many enantiomeric organic substances to different extents. This finding provides a simpler method for the determination of enantiomeric purity than others presently employed.[11-16] On the other hand, the usual procedure of adding the shift reagent incrementally to the substrate in amounts approximating an equimolar ratio to maximize the shifts results in problems. The principal ones are loss of resolution, precipitation, peak broadening, and complexity of the spectrum (especially in polyfunctional compounds) because of signal overlap due to large shifts. In addition, the significant amount of time consumed in such a method led us to investigate the reliability and reproducibility of a simpler procedure.

In essence, the method consists of the addition of the shift reagent in an approximately 1:15 molar ratio directly to the compound dissolved in a suitable solvent in an NMR tube. The procedure utilizes low-frequency NMR spectrometers, only about 25 mg of reagent, and requires less than 0.5 hr for the analysis. Because most of these alkaloids[17] are polyfunctional in nature,[18] it has been determined that, by the use of a relatively small amount of chiral shift reagent as mentioned above, the resolution of the enantiomeric signals is sufficient to permit complete analysis with a high degree of precision even at these low reagent concentrations (see Figure 1). Any signal that meets the requirement of being sufficiently separated from the others and which will respond to the chiral shift reagent is satisfactory. Thus, in one case, it was the methoxyl and/or the aromatic proton signal (glaucine, laudanosine, *N*-methylpavine, tetrahydropalmatine) and, in the other, the methyl signal (the $C_1$ methyl of salsolidine). For any specific application, the investigator can quickly determine the appropriate signal to be used.

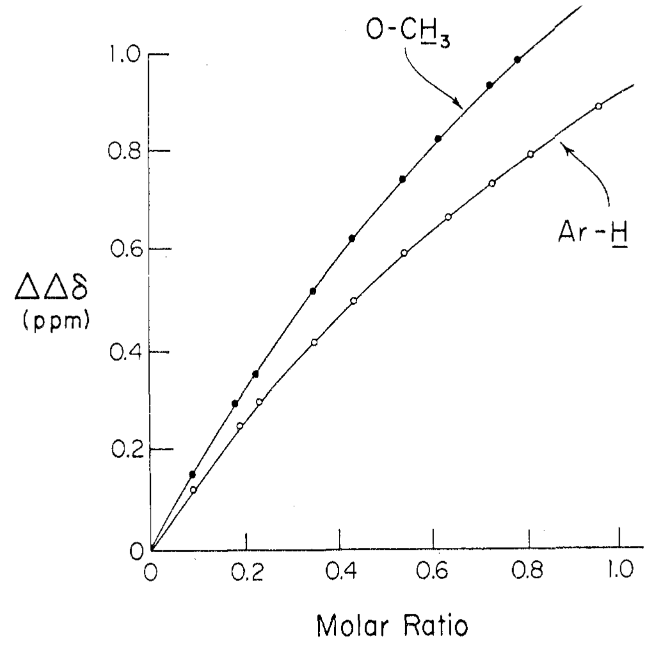

**Figure 1.** Plots of ΔΔδ (parts per million) vs. molar ratio of Eu(facam)$_3$ chiral shift reagent to compound.

Five enantiomeric pairs were studied by this method with each representing a different class of isoquinoline alkaloids: (−)-(*S*)- and (+)-(*R*)-salsolidine (a simple tetrahydroisoquinoline alkaloid), (−)-(*R*)- and (+)-(*S*)-glaucine (an aporphine alkaloid), (−)-(*S*)- and (+)-(*R*)-tetrahydropalmatine (a protoberberine alkaloid), (−)-(*S,S*)- and (+)-(*R,R*)-*N*-methylpavine (a pavine alkaloid), and (−)-(*R*)- and (+)-(*S*)-laudanosine (a benzylisoquinoline alkaloid). Because both enantiomers were available to us for each compound, several mixtures (90:10, 80:20, 70:30, 60:40, and the racemic mixture of 50:50) were made up by weighing the two enantiomers in their respective proportions and then tested by the chiral NMR shift reagent procedure. These analyses agree very well with the expected results for the weighed mixtures of enantiomers. For the cases studied, the method accurately detects an enantiomeric mixture of 95:5.

The NMR spectrum of glaucine is well known[19-22] and serves as an example of the analysis (Figure 2a). Two characteristic signals were used for the determination of its enantiomeric composition: (a) the methoxyl singlet resonance at 3.68 ppm (upfield from the three remaining methoxyl singlets) and (b) the strongly deshielded $C_{11}$ aromatic proton at 8.11 ppm. Addition of Eu(facam)$_3$ to a solution of