The Gauche Effect. Some Stereochemical Consequences of Adjacent Electron Pairs and Polar Bonds

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Theoretical and Experimental Bases for the Postulate of the Gauche Effect

The scope of theoretical conformational analysis has been broadened considerably in recent years by the development and accessibility of computer programs for *ab initio* molecular orbital calculations on polyatomic systems.[1] These developments are of interest to organic chemists because of the expectation that a coherent, theoretically based, set of rules may emerge to guide the application of qualitative and phenomenological concepts of molecular structure.

A particularly advantageous feature of a quantum mechanical calculation is its ability[2] to provide both the total energy and the components of the total energy of a system as a function of molecular geometry. Thus it becomes possible to justify, in a more rigorous way, a conclusion that a given stereochemical phenomenon is governed, for example, by attractive effects or repulsive effects, by kinetic energy changes or potential energy changes, and to understand why a molecule or a reactive intermediate exists in a particular conformation.

The purpose of this Account is to illustrate, apply, and attempt to explain a phenomenon associated with the presence of adjacent electron pairs or polar bonds in a molecule or reactive intermediate. In agreement with the predictions of *ab initio* molecular orbital calculations, but not with current qualitative and phenomenological concepts, such species exhibit a *"gauche effect,"* i.e., *a tendency to adopt that structure which has the maximum number of gauche interactions between the adjacent electron pairs and/or polar bonds.* The data collected in Table I show the experimentally determined and theoretically computed stable structures of N_2H_4,[3,4] P_2H_4,[5,6] H_2O_2,[7,8] H_2S_2,[9,10] and FCH_2OH.[11] Table II provides additional examples (given in ref 12–27) of the gauche effect of adjacent electron pairs which demonstrate that the effect is not restricted to simple compounds nor to a particular row of the periodic table.

It is evident that the computed rotational behavior of the compounds of Table I anticipates in each case the experimentally observed gauche effect. The theoretical results thus also "contain the explanation" of the effect, but to discover this explanation it is necessary to devise methods to dissect and systematize the analysis of the data. Such methods exist[2,28] and are

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Table I
Molecules Which Exhibit the Gauche Effect and for Which Theoretical Data Are Available[a]

Compd	Conformation	Dihedral angle (ϕ), deg Exptl	Dihedral angle (ϕ), deg Theor
N_2H_4		90–95[3]	116[4]
P_2H_4		90–100[5]	Stabilities are $C_2 > C_{2v} > C_{2h}$[6]
H_2O_2		111[7]	123[8]
H_2S_2		90° 36'[9]	91° 16'[10]
FCH_2OH		60[11]	60[11]

[a] In this table, depiction of the electron pairs as directed ligands allows these to be employed as convenient reference points in the visualization of a particular conformation. However (see text), the most meaningful physical picture is that which describes the relative positions of the *nuclei*.

responding to the three equivalent eclipsed structures, and three identical minima, corresponding to the three equivalent staggered structures. The rotational curves associated with the energy components also show threefold barriers, but the phases of T, V_{nn}, and V_{ee} are opposite to that of V_{ne}. In one result,[29] the total barrier in the attractive term was 19.7 kcal mole^{-1} and in the repulsive term it was 22.4 kcal mole^{-1}. Since both of these are much larger than the barrier associated with the total energy (2.7 kcal mole^{-1}), it follows that the rotational barrier in ethane is a *balance* of attractive and repulsive forces. As the molecule rotates from the staggered to the eclipsed conformation the repulsive interactions increase (*i.e.*, V_{rep} becomes more positive) and the attractive interactions also increase (*i.e.*, V_{att} becomes more negative); the increase in the repulsive interactions is greater, so that the barrier is "repulsive dominant." Repulsive-dominant threefold barriers are also found in propane,[30] ethyl fluoride,[2] methanol,[29] methylamine,[29] and methanethiol.[31] It

Table II
Further Examples of the Gauche Effect of Adjacent Electron Pairs

Compd	Dihedral angle, deg	Method	Ref
RO–OR	100–125	Dipole moment	12
RCO_2–OH	72 ± 4	Dipole moment	13
RCO_2–OR′	Skewed	Dipole moment	14
RCO_2–OCOR	100	Dipole moment	15a
	123	X-Ray	15b
FO–OF	87.5 ± 0.5	Microwave spectroscopy	16
$(C_6H_5CH_2)_2N$–$N(CH_2C_6H_5)_2$	Gauche	Low-temperature nmr	17
$R_2C{=}N{-}N{=}CR_2$	90–135	Dipole moment	18
	80–85	X-Ray	19
$(CH_3)_2P$–NCl_2	Gauche	Low-temperature nmr	20
$(CH_3)_3CS$–$SC(CH_3)_3$	110	Dipole moment	12
	110	Absorption spectroscopy	21
ArS–SAr	103	X-Ray	22
$R(S)_nR$	~90	Various	23
FS–SF	87.9	Microwave spectroscopy; gauche and trans isomers formed in equal amounts from monomeric form	24
$(C_6F_5)_2As$–$As(C_6F_5)_2$			25
CH_3Se–$SeCH_3$	82	Vibrational spectroscopy	26
HalSe–SeHal	C_2 symmetry	Vibrational spectroscopy	27

outlined in the first part of this Account. It now seems possible to state[2,11] that the reasons for the fundamentally different nature of the rotation–inversion behavior associated with *adjacent* electron pairs and polar bonds are understood.

The total energy of a system, E_T, is a sum of four terms: V_{ne}, the nuclear–electron attraction; V_{nn}, the nuclear–nuclear repulsion; V_{ee}, the electron–electron repulsion; and T, the kinetic energy of the electrons. The attractive component of E_T is V_{ne}, and the repulsive component is $V_{nn} + V_{ee} + T$. The potential energy term is $V_{ne} + V_{nn} + V_{ee}$.

The rotational potential energy curve for ethane displays a threefold barrier, *i.e.*, in a 360° rotation about the C–C bond, there are three identical maxima, cor-

seems reasonable to conclude that the physical nature of the rotational barriers of each of these compounds is similar and that the introduction of a polar bond or the replacement of a carbon atom by a heteroatom containing one or two lone pairs does not change this picture.

Pyramidal inversion has also been studied.[28b,c,32,33] The computed inversion curves of ammonia and fluor-

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amine show double minima; in each case the stable structure is the pyramidal one, the planar structure is the transition state for interconversion of the two invertomers,[34] and, as expected,[11,28c,35] fluoramine shows the higher barrier (20.3 kcal mole^{-1} vs. 5.08 kcal mole^{-1}). The barrier in ammonia is repulsive dominant.[28b,c,32] The attraction is greatest (i.e., lowest value of V_{att}) in the planar structure and the repulsion is also greatest (i.e., highest value of V_{rep}) in the planar structure. Consequently, as the molecule proceeds from the ground state to the transition state for inversion, there is an increase in the attractive interactions and an accompanying increase in the repulsive interactions. The change in the repulsive term is greater, the largest change (95.3 kcal mole^{-1}) being observed in V_{ee}. Qualitatively this suggests that the barrier exists because of repulsion between the nitrogen lone pair and the N–H bonding electron pairs.

Such qualitative interpretations are reminiscent of the analysis employed so successfully in the localized-electron-pair theory[36] (also known as the valence-shell electron-pair repulsion theory (VSEPR[37])) of molecular structure. According to this theory, ammonia has a pyramidal structure because the preferred arrangement of bonded and nonbonded electron pairs about a central atom is that which maximizes their distance apart in accordance with the assumptions that lone-pair–lone-pair repulsions are greater than lone-pair–bond-pair repulsions, which in turn are greater than bond-pair–bond-pair repulsions.

The existence of the gauche effect seems initially to be in conflict with the basic assumption of the VSEPR theory. However, the apparent contradiction is resolved by the results of the theoretical calculations. As seen, the arrangement of bonding and nonbonding electron pairs about a single uncharged atom is decided mainly by the repulsive interactions, but when nonbonding electron pairs or electronegative ligands are placed on adjacent atoms, for some geometries the nuclear–electron attraction becomes sufficiently important to alter the balance between attractive and repulsive effects. Thus, whereas ammonia has a repulsive-dominant inversion barrier, fluoramine has an attractive-dominant barrier,[33] i.e., the change in V_{att} is now greater than the change in V_{rep} on proceeding from the pyramidal ground state to the planar transition state, and, as exemplified by the gauche effect, energy minima are often found for structures that should have been destabilized if the repulsive interactions alone were considered.

For example, CH_3OH and CH_3SH have threefold barriers both in the total energy and in the individual components, and the barrier in E_T is repulsive-dominant. However, when adjacent electron pairs or a polar bond is present, as in FCH_2OH,[11] $^-CH_2OH$,[38] and $^-CH_2$-SH,[31,38] a gauche effect is observed, the total energy

displays a twofold barrier (one attractive and one repulsive), and the attractive and repulsive components display only a single barrier. Similar behavior is seen in H_2NOH,[4] H_2O_2,[8] and H_2S_2.[10]

Qualitatively, we tend to think of an electron pair as a directed ligand which is capable of displaying stereochemical properties. On this basis, each of the compounds shown in Table I might be viewed in terms of the general structure abcMNxyz, where M and N are the central atoms (carbon, nitrogen, oxygen, sulfur), and abcxyz are "ligands" (hydrogen, fluorine, electron pairs). We might then have expected, as with compounds XCH_2CH_2X,[39] each eclipsed conformation and each staggered conformation to have a maximum or minimum associated with it. Since this is not the case, some "ligand"–"ligand" interactions appear to have a more important effect upon molecular geometry than others. In the case of FCH_2OH,[11] the most important interactions are those between the C–F and O–H bonds. When these are syn-periplanar (1), the nuclear–nuclear and electron–electron repulsion terms are more important than the nuclear–electron attraction. The structure represents an energy maximum, and the barrier is repulsive-dominant. In the course of rotation from 1 to the anti-periplanar structure 2, both attraction and repulsion are decreased. In the early stages of this rotation ($\theta = 0° \to \theta = 60°$), ΔV_{rep}, the change in the repulsive interactions, is greater than ΔV_{att}, the change in the attractive interactions. However, by the time the anti-periplanar structure is reached ($\theta = 0° \to \theta = 180°$), the change in the attractive term has overcome the change in the repulsive term and is greater by 4.38 kcal mole^{-1}. This latter structure is an energy maximum, the barrier being attractive-dominant because the destabilization caused by loss of the attractive H---F interaction is greater than the stabilization gained by the decrease in the repulsive interactions. The energy minimum, corresponding to structure 3, is reached when the difference in the change of the attractive and repulsive terms ($\Delta V_{rep} - \Delta V_{att}$) has reached its maximum value.

1   2   3
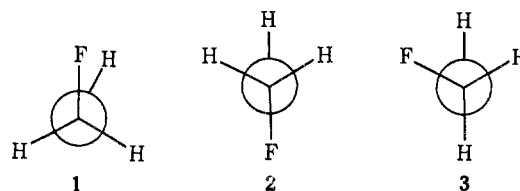
This analysis of the theoretical result for FCH_2OH illustrates, first, how the gauche effect may result from the balance between attraction and repulsion, and second, that the interaction associated with adjacent polar bonds (in this case the C–F and O–H bonds) may be a more important structural factor than the interaction of a polar bond with adjacent lone pairs.

In most discussions of the effects of adjacent polar

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bonds upon conformational properties,[40] electrostatic repulsion between the dipoles has been thought to play an important, if not decisive, role. On this basis, and taking group electronegativity as a relevant criterion for the polarity of a C–X bond,[41] the gauche structures should be disfavored progressively in the series XCH_2-CH_2X in the direction I → F, and in the series XCH_2-CH_2X → X_2CHCH_2X → X_2CHCHX_2. However, for the 1,2-disubstituted ethanes there is a gradual *increase* in the proportion of the gauche conformation in the direction I → F, so that in the gas phase the gauche and trans forms of 1,2-difluoroethane have equal stability.[42,43] Consequently, the preference for the anticoplanar structures in XCH_2CH_2X (X = Cl, Br, I) is more properly ascribed to "size" effects or "steric" effects[44] than to polar effects. An alternative viewpoint, for which both experimental and theoretical support can be found (see later), is that the importance of the gauche effect becomes less as the distance between the interacting ligands *increases*. The subtle balance between attractive and repulsive interactions may be seen in 1,1,2-trisubstituted ethanes. In compounds X_2CHCH_2X (X = Cl, Br) the gauche conformation is less stable than the trans both in the gas phase and in solution,[42] but in solution the analogous cyclohexanes 1,1,2-trichloro- and 1,1,2-tribromocyclohexane favor the gauche conformation.[45] With one additional polar bond (X_2CHCHX_2; X = F, Cl, Br, O), the gauche conformation is more stable both in the gas phase and in solution.[11,42,43]

The gauche effect of adjacent polar bonds is not restricted to systems that contain only carbon–halogen bonds. In nonpolar solvents 2-chloro-, 2-bromo-, and 2-methoxyethanol favor the gauche structures.[46] Intramolecular hydrogen bonding is not responsible for these properties since 2-chloro- and 2-methoxyethyl acetate,[46] 1,2-dimethoxyethane,[47] polyoxymethylene, and related compounds[47] also have gauche structures. In the vapor phase, 1,2-dicyanoethane has the gauche structure.[48]

When both adjacent electron pairs and adjacent polar bonds are present, the situation is more complex and there is evidence that the observed structure depends not only on the number of gauche interactions but on the distance between the interacting ligands.

In molecules M_2X_2 (M = O, S, Se; X = halogen) the gauche structure (g) contains three electron-pair–electron-pair, two electron-pair–polar-bond, and one polar-bond–polar-bond interaction (3e/e + 2e/X + X/X). The interactions in the trans structure (t) are (2e/e + 4e/X). Although the geometries of the two structures (and, consequently, the magnitudes of the interactions) are not the same, several qualitative conclusions may be reached by equating the difference between the above two expressions to the difference in the energy contents of the two structures. In all cases the gauche structure is more stable, *i.e.*, $\Delta E = E_g - E_t = e/e + X/X - 2e/X < 0$. It follows that either the stabilizing effect of one or both of e/e and X/X is more important than any stabilizing effect of e/X, or that e/X is destabilizing. The converse of this statement, that destabilization of e/e and X/X is less than the destabilization of 2e/X, seems to be ruled out by the data on molecules M_2X_4. In these compounds the relative numbers of adjacent electron pairs (two) and adjacent polar bonds (four) are reversed from those in M_2X_2, but ΔE, the difference in the interactions, has the same form, *i.e.*, e/e + X/X − 2e/X. Structural data are available for tetrafluorohydrazine (N_2F_4)[49] and tetrafluorodiphosphine (P_2F_4).[50] The former is a 53:47 mixture of trans and gauche structures at room temperature (the gauche structure has a dihedral angle of 67.1°); the latter appears to have the trans structure. Thus in these compounds e/e + X/X − 2e/X $\geqslant$ 0.

Since a consistent description results from the postulate that the e/e interactions in the hydrides O_2H_2, S_2H_2, Se_2H_2, N_2H_4, and P_2H_4 and the X/X interactions in the tetrahaloethanes X_2CHCHX_2 are stabilizing, it seems reasonable to expect the same behavior in the M_2X_2 and M_2X_4 compounds. The observed progressive reversal of isomer stabilities in the series N_2H_4, N_2F_4, P_2F_4 is then consistent only with the additional postulates that electron-pair–polar-bond interactions are stabilizing, and the magnitude of this stabilizing interaction depends upon both the total number of electron pairs and the M–M distance. It is interesting that an analysis in terms of the distance between the interacting ligands has been suggested to account for the differing rotational barriers in the series CH_3CH_3 (2.8 kcal), CH_3SiH_3 (1.67 kcal), CH_3GeH_3 (1.24 kcal), and CH_3SnH_3 (0.65 kcal).[51] Although the merits of this type of empirical correlation have been questioned,[43] it does have the advantages of providing a concept that is both easy to grasp and capable of experimental and theoretical tests.

A recent study of $^-CH_2$–CH_2^- provides theoretical support for this concept and, as well, insight into the origins of the gauche effect.[38a] Following optimization of the C–C bond length (r), the pyramidal angles (HCH

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= HCC = ϕ), and the dihedral angle (θ), energy minima were found for r = 1.6 Å, ϕ = 105°, and θ = 79° (gauche) and 180° (trans). The gauche structure is 2.54 kcal mole^{-1} more stable than the trans. As the C–C bond length is shortened to 1.3 Å, there is a small change in the pyramidal angles (105° → 110°) and a more pronounced gauche effect (θ_{min} = 79, 180°; $E_{trans} - E_{gauche}$ = 10.6 kcal mole^{-1}). These results were considered to have physical meaning only if it is assumed that the lone-pair–lone-pair interactions are invariant with dihedral angle, i.e., as in the case of FCH$_2$OH,[11] the nonbonding electron pairs create a quasispherical potential field in which the true ligands (or bonding electron pairs) move. This conclusion is supported by the component analyses and means that the structures of molecules containing adjacent electron pairs are decided by the balance of attraction and repulsion between the *bonding electron pairs* and *the nuclei*. Heuristic descriptions based on repulsive interactions alone are necessarily incomplete.[38b]

For ethylene dicarbanion the barriers to single inversion (15.4 kcal mole^{-1}) and double inversion (28.9 kcal mole^{-1}) are both attractive dominant, i.e., the attractive and repulsive interactions are *least* at the transition states, in contrast to ammonia,[32] in which attraction and repulsion are both a *maximum* at the transition state.

Some Applications of the Gauche Effect

Organosulfur Stereochemistry. In the course of our theoretical studies of the structures of carbanions adjacent to S,[31] SO,[52] and SO$_2$,[53] we have obtained, by *ab initio* SCF methods, rotation–inversion surfaces for $^-$CH$_2$SH (4), $^-$CH$_2$SHO (5), and $^-$CH$_2$SHO$_2$ (6), and several rotational cross sections of the hypersurface of $^-$CH$_2$SCH$_2^-$ (7). In all cases the structure containing the maximum number of gauche interactions between adjacent electron pairs (4, 7) or between electron pairs adjacent to polar bonds (5, 6) was found to be an energy minimum. *These results are now seen to be manifestations of the gauche effect.* Where unambiguous structural data are available on these systems, these are in agreement with the theoretical predictions.

The α-sulfonylcarbanion has received much attention in recent years, and most workers conclude that the stable structure has the carbanion on the bisector of the OSO angle.[54] In the related compounds RSO$_2$-OR′, the R and R′ groups are gauche, corresponding to a gauche arrangement of the two lone pairs and the two polar bonds.[55]

Ready formation of the dicarbanion of dimethyltetra-

thiaadamantane (8)[56] has been reported; quenching with methyl iodide yields a tetramethyltetrathiaadamantane (9). Thus this latter compound is formed by alkylation of a carbanion which contains the maximum number of gauche interactions between adjacent electron pairs. The kinetic acidity of the bridgehead proton of 10 is greater by a factor of 10^3 than that of the tertiary proton of the open-chain analog 11.[57]
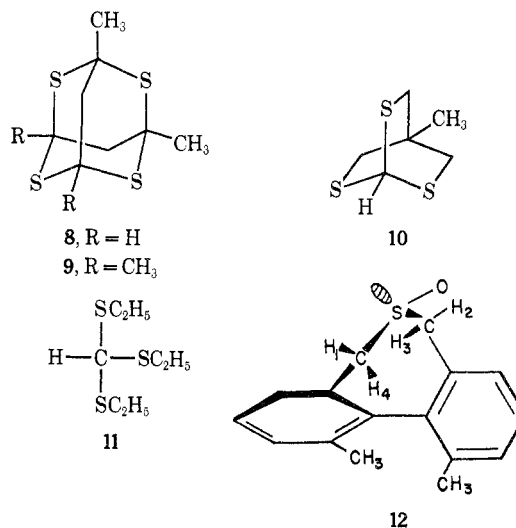
This difference may be taken as a reflection of the acceleration to be expected when the gauche orientation is imposed by conformational constraints.

Unambiguous evidence for stability of the gauche structure of an α-sulfinyl carbanion is seen in the observation that in 12 H$_2$, a proton in the oxygen–sulfur-sulfur lone-pair sector, undergoes ready base-catalyzed hydrogen–deuterium exchange in several solvent systems.[58] In sulfinates, R–SO–OR′, the R and R′ groups are gauche.[59] One of the oxygen lone pairs is on the bisector of the oxygen–sulfur–sulfur lone-pair angle; the other lone pair is trans to the S–O bond.

At the beginning of our studies it seemed reasonable to suppose that stabilization of the gauche structures of carbanions 4–7 was the result of some effect associated with the availability for bonding of low-lying d orbitals of sulfur.[60] However, in no case have the calculations revealed a contribution to the ground states of these species from the sulfur d orbitals. It is conceivable that the calculations have represented the sulfur d orbitals incorrectly; however, since the calculations are otherwise in harmony with experimental data, and both are in harmony with the gauche effect of adjacent electron pairs and polar bonds, the possibility cannot be ignored that the d orbitals of sulfur are not as important from a stereochemical standpoint as has been thought.

(52) A. Rauk, S. Wolfe, and I. G. Csizmadia, *Can. J. Chem.*, **47**, 113 (1969).

(53) S. Wolfe, A. Rauk, and I. G. Csizmadia, *J. Amer. Chem. Soc.*, **91**, 1567 (1969).

(54) See (a) F. G. Bordwell, E. Doomes, and P. W. R. Corfield, *ibid.*, **92**, 2581 (1970); (b) G. Maccagnani, F. Montanari, and F. Taddei, *J. Chem. Soc. B*, 453 (1968); (c) R. R. Fraser and F. J. Schuber, *Chem. Commun.*, 1474 (1969); (d) J. N. Roitman and D. J. Cram, *J. Amer. Chem. Soc.*, **93**, 2225 (1971); (e) see also footnote 5 of ref 53.

(55) O. Exner, Z. Fidlerová, and V. Jehlicka, *Collect. Czech. Chem. Commun.*, **33**, 2019 (1968).

(56) K. C. Bank and D. L. Coffen, *Chem. Commun.*, 8 (1969); see also A. A. Hartmann and E. L. Eliel, *J. Amer. Chem. Soc.*, **93**, 2572 (1971).

(57) S. Oae, W. Tagaki, and A. Ohno, *ibid.*, **83**, 5036 (1961).

(58) R. R. Fraser and F. J. Schuber, *Can. J. Chem.*, **48**, 633 (1970). Also personal communications from Professors R. R. Fraser and T. Durst.

(59) O. Exner, P. Dembach, and P. Vivarelli, *J. Chem. Soc. B*, 278 (1970).

(60) D. L. Coffen, *Rec. Chem. Progr.*, **30**, 275 (1969); K. A. R. Mitchell, *Chem. Rev.*, **69**, 157 (1969); C. A. Coulson, *Nature (London)*, **221**, 1106 (1969).

Although pictorial representations of $d\pi$–$p\pi$ bonding (cf. **13**) are esthetically pleasing, they need not be correct.

There are a number of experimental and theoretical consequences of this conclusion. The rate constants for hydrogen exchange at the benzylic positions of **14** and **15** differ by a factor of 5×10^5 in favor of the di-

Scheme I

18

19   **20**

13   **14**   **15**
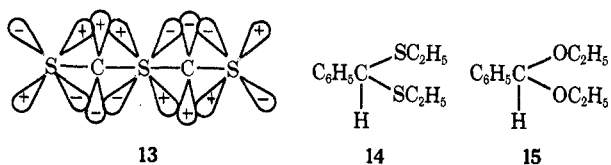
thioacetal, and this has been attributed to d orbital conjugation.[61] However, if this conjugative effect is not present, it is necessary to provide an alternative explanation for this enormous rate difference between the oxygen and sulfur systems. One approach which is under investigation[62] involves calculation of proton affinities for the reactions $CH_3OH \rightarrow {}^-CH_2OH + H^+$ and $CH_3SH \rightarrow {}^-CH_2SH + H^+$. We hope that these calculations will reveal (i) a difference between the two, in the proper direction and of the correct magnitude; (ii) whether any difference is related to the presence of d orbitals on sulfur; (iii) alternate explanations of the difference if d orbitals are found to be unimportant.

From an experimental standpoint abandonment of d-orbital explanations of sulfur stereochemistry in favor of the gauche effect and its consequences reveals the existence of a number of novel stereochemical possibilities. Several of these can be discerned in the case of sulfonium ylides. It is known that the barrier to pyramidal inversion in a sulfonium salt, e.g., **16**, is 25–30

$$R_1CH_AH_B\overset{+}{-}\overset{..}{S}R_2R_3 \quad\quad R_1\overset{-}{C}H\overset{+}{-}\overset{..}{S}R_2R_3$$
16   **17**
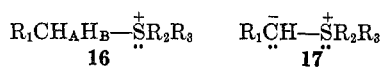
kcal/mole,[63] and that base treatment of **16** will generate the ylide **17**.[64] If the dominant influence upon the rotational curve of this compound is the presence of the two adjacent electron pairs, **17** should resemble a hydrazine or $^-CH_2CH_2^-$ in its rotational curve, and the energy minimum will correspond to that structure in which the electron pairs are gauche. Furthermore, in the representation shown in **17**, the ylide carbon carries a negative charge and sulfur carries a positive charge. Continuing the analogy with ethylene dicarbanion, both carbon and sulfur can be expected to be pyramidal, with different barriers to inversion. The known effects of substituents upon barriers to pyramidal inversion[28c] allow the predictions that the electron-withdrawing
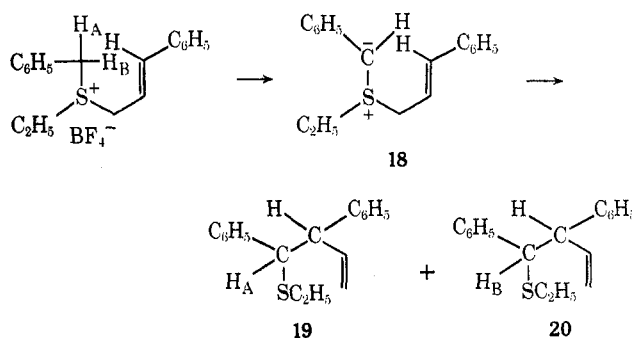
sulfonium substituent will raise the barrier to inversion at carbon relative to that in a simple carbanion (ca. 5 kcal mole^{-1}),[65] and the electron-releasing carbanionic substituent will lower the barrier to pyramidal inversion at sulfur relative to that in the parent sulfonium cation. Finally, H_A and H_B of **16** are diastereotopic because of the adjacent chiral center, and these protons can be expected to exhibit diastereotopic reactivity in the formation of the ylide if their orientation with respect to the sulfur lone pair is different.

In the conversion of **16** to **17**, the following sequence of observations can, therefore, be anticipated: (i) selective removal of that methylene proton which is gauche to the electron pair on sulfur; (ii) an induction of asymmetry at the carbon atom; (iii) a decrease in the barrier to inversion at sulfur; (iv) if the barrier to inversion at carbon is sufficiently increased, and that at sulfur decreased, an effective transfer of asymmetry from sulfur to carbon so that racemization of the ylide will proceed by pyramidal inversion at carbon.

The available experimental data appear to be compatible with these predictions. Scheme I summarizes some recent work by Ollis and coworkers.[66] The ylide **18** undergoes an electrocyclic rearrangement to the mixture of diastereomeric sulfides **19** and **20**, and these are formed in unequal amounts. Since the rearrangement step is stereospecific, the formation of two diastereomers implies the intervention of two distinct sulfonium ylides, one from removal of H_A and the other from removal of H_B. Since the diastereomers are formed in unequal amounts, it follows that the two ylides are produced at different rates, i.e., that H_A and H_B exhibit diastereotopic reactivity. Stereochemical identification of H_A and H_B was not made in this work, but Fava and coworkers[67] have observed a second example of diastereotopic reactivity, in the case of hydrogen-deuterium exchange of **21**. The reaction **21** → **22** is at least 500 times faster than the reaction **22** → **23**. It was found that the proton removed in the fast exchange (with retention of configuration) is gauche to the sulfur lone pair.

(61) S. Oae, W. Tagaki, and A. Ohno, *Tetrahedron*, **20**, 417 (1964).

(62) S. Wolfe, L. M. Tel, J. H. Liang, and I. G. Csizmadia, research in progress.

(63) D. Darwish, S. H. Hui, and R. Tomilson, *J. Amer. Chem. Soc.*, **90**, 5631 (1968); D. Darwish, *Mech. React. Sulfur Compounds*, **3**, 33 (1968).

(64) D. Darwish and R. Tomilson, *J. Amer. Chem. Soc.*, **90**, 5938 (1968).

(65) R. E. Kari and I. G. Csizmadia, *J. Chem. Phys.*, **50**, 1443 (1969).

(66) R. W. C. Cose, A. M. Davies, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 293 (1969).

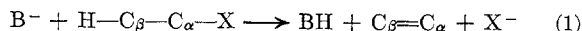(67) G. Barbarella, A. Garbesi, and A. Fava, *Helv. Chim. Acta*, **54**, 341 (1971).

Racemization of the sulfonium salt **24** proceeds with a $\Delta H^{\ddagger}$ of 29 kcal mole^{-1};[63] the derived ylide **25** racemizes with a $\Delta H^{\ddagger}$ of 23 kcal mole^{-1}.[64] Since the conjugative

21, R = R' = H
22, R = D; R' = H
23, R = R' = D

24

25
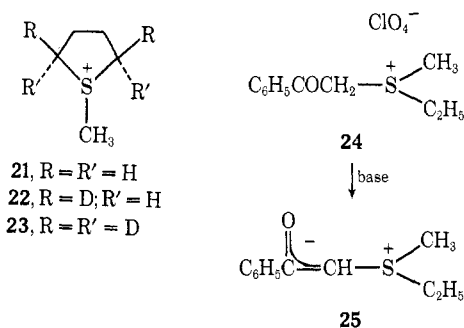
effect of the adjacent carbonyl group will tend to stabilize the planar structure at carbon, racemization of **25** can reasonably be assumed to proceed by pyramidal inversion at sulfur. Therefore, formation of the ylide has caused a decrease of 6 kcal mole^{-1} in the barrier to inversion at sulfur.

Syntheses of 1,3-bissulfonium salts, **26**, and conversion of these salts to 1,3-bissulfonium ylides, **27**, have been described.[68] The stereochemical capabilities of **26** and **27** were not discussed, but the presentation of structure **28** for the ylides indicates that d-orbital conjugation (with a planar ylide carbon atom) was assumed. The description of these compounds in terms of adjacent electron pairs predicts the zwitterionic structure **27** to be the more accurate description. The implications of this representation are that the negative charge remains localized on the ylide carbon which should then be demonstrably pyramidal because of the cumulative electron-withdrawing effects of the two sulfonium substituents.[28c] Formulation **27** is strongly supported by the observations[69] of much larger upfield shifts (2.5–3 ppm) of the B protons compared to that of the A protons (0.5 ppm) upon deprotonation of **26**. The effect is seen even more clearly upon examination of the chemical shift changes for the overall process $RCH_2{}^{A}SCH_2{}^{B}SCH_2{}^{A}R \rightarrow$ **27**. Although this sequence transforms a neutral molecule into a cation, only the A protons reflect this fact (downfield shift of 0.3–0.6 ppm); the B protons are shifted *upfield* by 1–1.5 ppm. The pyramidal character of the ylide carbon in these compounds, as well as a demonstration of the gauche effect, are seen in the observation that the bistetrafluoroborate of **29** undergoes stereoselective hydrogen-deuterium exchange (**29 → 30 → 31**).
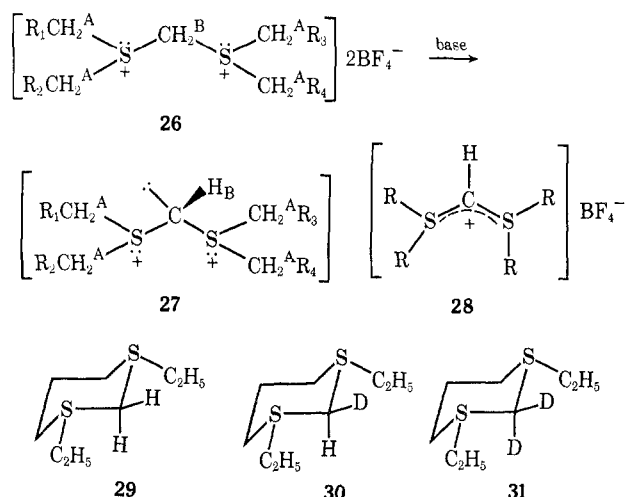
The Syn–Anti Dichotomy. There is an extensive literature on the mechanisms of olefin-forming β elimination reactions[70] (eq 1). Because two bonds are

$$B^{-} + H{-}C_{\beta}{-}C_{\alpha}{-}X \longrightarrow BH + C_{\beta}{=}C_{\alpha} + X^{-} \quad (1)$$

26

27

28

29

30

31

made and two broken in the overall process, a host of mechanistic variations can be realized by an appropriate combination of substrate and medium according to whether the transition state is reactant-like or product-like, or is influenced by steric effects or electronic effects. Experimental observations of second-order kinetics may be associated either with a variable E2 transition state[70a] classified as paenecarbanion, central, or paenecarbonium according to the degree of $H{-}C_{\alpha}$ and $C_{\beta}{-}X$ bond breaking, or with a carbanionic intermediate (E1cb, eq 2, with $k_2 \gg k_{-1}$ (nonreversible E1cb[70b,71]) or $k_{-1} > k_2$ (reversible E1cb[70b,71]).

$$B^{-} + H{-}C_{\beta}{-}C_{\alpha}{-}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^{-}C_{\beta}{-}C_{\alpha}{-}X \overset{k_2}{\longrightarrow} C_{\beta}{=}C_{\alpha} + X^{-}$$

$$(2)$$

When a carbanionic intermediate or a carbanion-like transition state is involved, an electron pair is formed or developed adjacent to a polar bond. It should now be asked whether, *in these circumstances*, the gauche effect might play some role in deciding the stereochemical course of an elimination. In order to place this possibility within the context of recent work, let us first review the stereochemistry of olefin-forming bimolecular eliminations.

At the present time the stereochemical course of an elimination reaction is defined[72a] to be syn (**32**) or anti
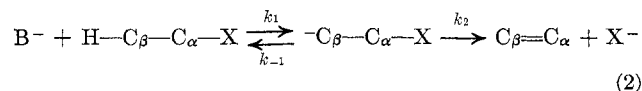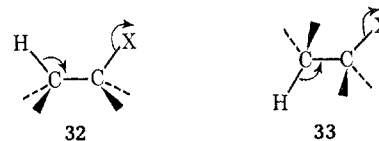

32

33

(68) C. P. Lillya and P. Miller, *J. Amer. Chem. Soc.*, **88**, 1559, 1560 (1966); I. Stahl, M. Hetschko, and J. Gosselck, *Tetrahedron Lett.*, 4077 (1971).

(69) S. Wolfe and P. Chamberlain, Abstracts, 54th National Conference of the Chemical Institute of Canada, Halifax, N. S., 1971.

(70) (a) J. F. Bunnett, *Surv. Progr. Chem.*, **5**, 53 (1969); (b) D. J. McLennan, *Quart. Rev., Chem. Soc.*, **21**, 490 (1967); (c) C. K. Ingold, *Proc. Chem. Soc. London*, 265 (1962); (d) D. V. Banthorpe, "Elimination Reactions," Elsevier, New York, N. Y., 1963.

(71) (a) Z. Rappoport, *Tetrahedron Lett.*, 3601 (1968); F. G. Bordwell, M. M. Vestling, and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5950 (1970).

(72) (a) J. Sicher, J. Závada, and J. Krupicka, *Tetrahedron Lett.*, 1619 (1966); (b) J. Závada, J. Krupicka, and J. Sicher, *Chem. Commun.*, 66 (1967); (c) J. Sicher and J. Závada, *Collect. Czech. Chem. Commun.*, **32**, 2122 (1967); (d) J. Závada and J. Sicher, *ibid.*, **32**, 3701 (1967); (e) M. Svoboda, J. Závada, and J. Sicher, *ibid.*, **33**, 1415 (1968); (f) M. Svoboda, J. Závada, and J. Sicher, *ibid.*, **32**, 2104 (1967); (g) J. Sicher and J. Závada, *ibid.*, **33**, 1278 (1968); (h) J. Závada, M. Svoboda, and J. Sicher, *ibid.*, **33**, 4027 (1968); (i) J. Závada, J. Krupicka, and J. Sicher, *ibid.*, **33**, 1393 (1968); (j) M. Pánková, J. Sicher, and J. Závada, *Chem. Commun.*, 394 (1967); (k) M. Pánková, J. Závada, and J. Sicher, *ibid.*, 1142 (1968); (l) J. Závada, M. Pánková, and J. Sicher, *ibid.*, 1145 (1968); (m) J. Sicher, J. Závada, and M. Pánková, *ibid.*, 1147 (1968).
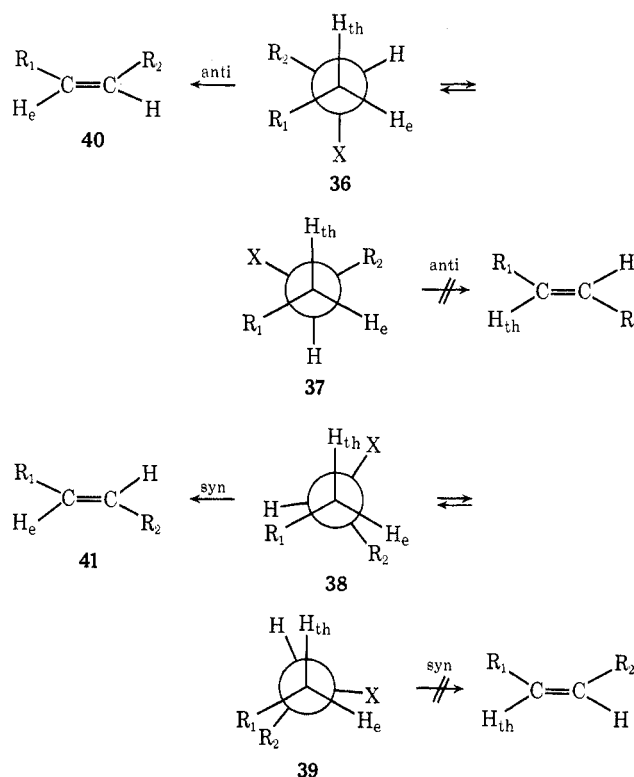
Scheme II

34

35

Scheme III

40

36

37

41

38

39
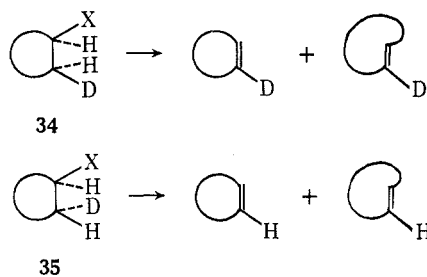
(33) according to whether the two vicinal groups depart from the same side (32) or from opposite sides (33) of the developing double bond, irrespective of whether these groups are configurationally cis or trans to one another or whether the reaction leads to a cis or trans olefin. Anti elimination may be viewed conceptually[70c] as an S_E2 substitution upon C_β (with retention of configuration) followed by an S_N2 substitution by the resulting electron pair upon C_α. Syn elimination may be viewed conceptually as an S_E2 substitution with inversion upon C_β, followed by an S_N2 substitution upon C_α. Thus anti elimination will proceed most favorably from the anti (staggered) conformation, and syn elimination from the syn-periplanar (eclipsed) conformation. Until recently it was thought[70d] that the double-inversion path (syn elimination) would be demonstrable only when special steric effects permitted the syn periplanar conformation to be achieved more readily than the anti,[73] or when strong activation at C_β permitted C_β–H bond breaking to be well advanced in the transition state, as in the case of a reaction shifted toward the E1cb path.

However, an important series of papers by the late Professor Sicher and his coworkers[72] has forced a reevaluation of these views. In Sicher's work, employing initially medium-ring compounds,[72a–d] a study of the rate profiles (i.e., variation of rate with ring size in a homologous series of compounds) for cis- and trans-olefin formation revealed that these differed from one another. Cis- (34) and trans- (35) β-deuterium labeled substrates were then employed[72e–h] in these studies to determine the nature of the difference. In general (Scheme II), it was found that both olefins retained deuterium when the cis compounds were employed and that (after correction for the isotope effect[73b]) both olefins had lost deuterium when the trans compounds were employed. These observations were discussed in terms of syn and anti mechanistic paths and revealed that cis olefins are formed by anti, and trans olefins by syn elimination. The phenomenon has become known[72d] as the "syn–anti dichotomy." When the deuterium-labeling results are analyzed in terms of syn and anti stereochemical paths it is found that the proportion of the syn → trans route is increased by an increase in the base strength,[72g] by a decrease in the dielectric constant

of the medium[72d,g,i] and, other factors being equal, in the direction $^+N(CH_3)_3$[72g] > OTs[72e,74] > Br.[72i,75]

It will be noted that the observations summarized in Scheme II show that the trans C_β–H(D) is lost in the formation of both olefins. Although special conformational features in the medium rings can be invoked[72g] to demonstrate that the trans proton is sterically more accessible in both the syn and anti transition states, Sicher considered that such steric effects could not represent the sole cause of the syn–anti dichotomy. To demonstrate this point the studies were extended to open-chain compounds with very similar results[72j,k,l] (Scheme III). When the syn–anti dichotomy is observed experimentally, it is always in the direction anti → cis, syn → trans, i.e., the threo proton (H_{th}) is lost preferentially in the formation of both olefins. From a steric standpoint it is possible to understand why syn elimination from 38 (loss of H_{th}) could be favored over syn elimination from 39 (loss of H_e), but there seemed to be no obvious reason why anti elimination from 36 (loss of H_{th}) should be favored over anti elimination from 37 (loss of H_e).

Recently Saunders has developed[76a,b] a steric theory of the syn–anti dichotomy which is consistent with the effects of chain branching in a series of compounds $R_1CH_2CH(^+N(CH_3)_3)CHCH_2R_2$ (42). This theory is

(73) J. L. Coke and M. P. Cooke, Jr., J. Amer. Chem. Soc., 89, 2779 (1967); (b) M. P. Cooke, Jr., and J. L. Coke, ibid., 90, 5556 (1968); (c) J. L. Coke and M. C. Mourning, ibid., 90, 5561 (1968).

(74) D. H. Froemsdorf, W. Dowd, W. A. Gifford, and S. Meyerson, Chem. Commun., 449 (1968).
(75) R. A. Bartsch, Tetrahedron Lett., 297 (1970).
(76) (a) D. S. Bailey and W. H. Saunders, Jr., J. Amer. Chem. Soc., 92, 6904 (1970); (b) D. S. Bailey, F. C. Mountgomery, G. W. Chodak, and W. H. Saunders, Jr., ibid., 92, 6911 (1970); (c) W. H. Saunders, Jr., D. G. Bushman, and A. F. Cockerill, ibid., 90, 1775 (1968).

founded on the argument that increasing base strength leads to less stretching rather than more stretching of the C_β–H bond and hence to a more reactant-like transition state whose geometry can be examined with the aid of molecular models. To support this argument it was noted that, with 2-phenylethyltrimethylammonium ion,[76c] the hydrogen isotope effect increases, and the Hammett ρ value decreases with increasing base strength. If the hydrogen isotope effect is a maximum when the proton is half-transferred in the transition state, and decreases when the proton is more or less than half-transferred,[77] the combination of the isotope and substituent effects does imply a decrease in the extent of proton transfer with increasing base strength in the latter system. However, extension of this conclusion to the series 42 does not seem compelling, for three reasons: the existence of a syn–anti dichotomy in the 2-phenylethyl system has not been demonstrated, so that a discussion of the two systems in terms of an analogous response to changes in base strength may not be warranted. Secondly, and more significantly, the Westheimer model, relating observed isotope effect to extent of proton transfer,[77] has recently been challenged:[78] "the hope, which at one time seemed bright, for a simple general correlation of Brønsted coefficients, kinetic isotope effects, and solvent isotope effects with the extent of proton transfer in the transition state has proved vain." Thirdly, a steric analysis of the elimination reaction would require that the size of the base be a significant factor affecting orientation;[79] however, a study of orientation in elimination from 2-butyl bromide with $CF_3CH_2O^-$ and $C_2H_5O^-$ has revealed[80] that, from the standpoint of the base, steric control of orientation is a less important factor than base *strength*.

It seems worthwhile, therefore, to explore further a suggestion put forward by Sicher[72g,m] that the syn–anti dichotomy is the result of "the operation of some effect which has so far escaped notice." Sicher pointed out that in a compound $R_1CH_{th}H_eCHXR_2$, the protons H_{th} and H_e are diastereotopic and could, under appropriate conditions, exhibit diastereotopic reactivity. This idea was, unfortunately, not developed very far, but in principle it cannot be dismissed provided that the effect which has escaped notice is one which predicts H_{th} to be the more reactive proton. In this sense, the main issue then becomes not the explanation of a syn–anti dichotomy but an explanation of the preferred reactivity of H_{th}. This is the question to which the relevance of the gauche effect in bimolecular elimination reactions may be addressed.

In applying the gauche effect, the following assumptions are made: (1) the syn–anti dichotomy is characteristic of E1cb or paenecarbanion transition states;

Scheme IV
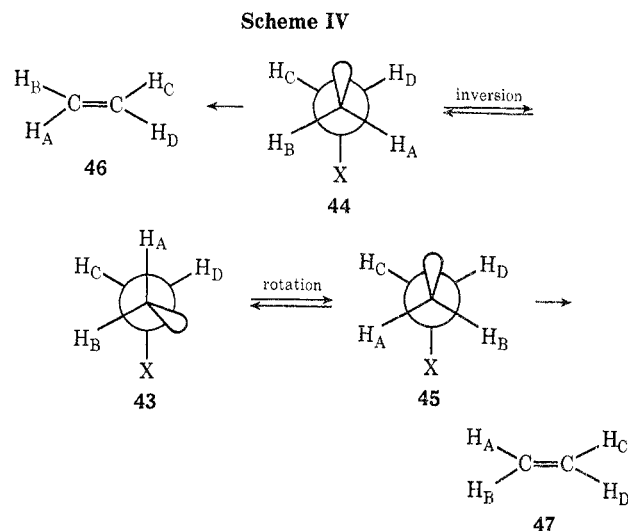
(2) the overall process is not concerted,[81] *i.e.*, (3) the intermediate carbanion may undergo rotation–inversion[52] prior to (4) the breaking of the C_α–X bond, in an exergonic process, by an internal S_N2 displacement.

It is clear that a chemical distinction between H_{th} and H_e is possible if and only if the protons are diastereotopic in the C_β–H bond-breaking step. In an E1 reaction these protons are enantiotopic in the C_β–H bond-breaking step and, in the absence of gegenion effects,[82] are chemically indistinguishable. Similarly, if the transition state for C_β–H bond breaking is olefin-like (achiral), the distinction between the two protons will be greatly diminished. The maximum difference in reactivity between H_{th} and H_e should occur when the C_β–H bond is broken *prior to* the loss of asymmetry at the adjacent chiral center, irrespective of the actual degree of bond breaking in the transition state for this process.[76a] That diastereotopic protons may exhibit differing reactivities in nonenzymatic reactions is now well documented, both in systems for which the gauche effect is considered to be the origin of the difference[54c,67,83] and in others.[84]

The rotation–inversion behavior of a carbanion adjacent to a chiral center has been treated theoretically in detail.[52] Extension of this theoretical description to the system $^-CH_AH_BCH_CH_DX$ is shown in Scheme IV. Carbanions 43–45 represent minima on the rotation–inversion surface, so that interconversion is an endergonic process. Carbanion 44 forms olefin 46, and 45 forms the geometric isomer 47. If carbanions 44 or 45 were formed preferentially, a single olefin would result in each case. However, if carbanion 43 were formed

(77) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

(78) F. G. Bordwell and W. J. Boyle, Jr., *J. Amer. Chem. Soc.*, **93**, 512 (1971).

(79) H. C. Brown, I. Moritani, and Y. Okamoto, *ibid.*, **78**, 2193 (1956); H. C. Brown and R. L. Klimisch, *ibid.*, **87**, 5517 (1965).

(80) R. A. Bartsch, C. F. Kelly, and G. M. Pruss, *Tetrahedron Lett.*, 3795 (1970).

(81) (a) J. W. Cornforth, *Angew. Chem., Int. Ed. Engl.*, **7**, 903 (1968); (b) F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(82) P. S. Skell and W. L. Hall, *J. Amer. Chem. Soc.*, **85**, 2852 (1963).

(83) S. Wolfe and A. Rauk, *Chem. Commun.*, 778 (1966); R. R. Fraser and F. J. Schuber, *ibid.*, 397 (1969); B. J. Hutchinson, K. K. Andersen, and A. R. Katritsky, *J. Amer. Chem. Soc.*, **91**, 3839 (1969); M. Cinquini, S. Colonna, U. Folli, and F. Montanari, *Boll. Sci. Fac. Chim. Ind. Bologna*, **27**, 203 (1969).
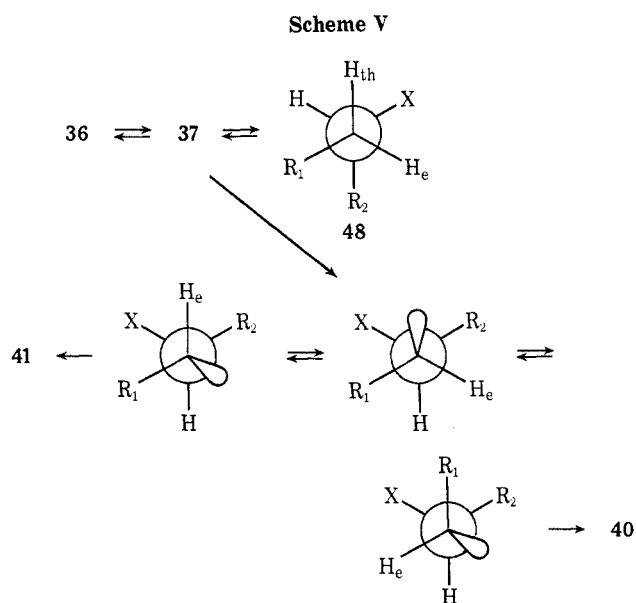
(84) P. T. Lansbury, *Accounts Chem. Res.*, **2**, 210 (1969); W. Tochtermann, H.-O. Horstmann, C. Degel, and D. Kraus, *Tetrahedron Lett.*, 4719 (1970).

Scheme V

preferentially (because of the gauche effect), both olefins would result, their proportions depending on the rates of the two interconversion processes.

The more general case of a substrate $R_1CH_{th}H_e$-$CHXR_2$ is considered in Scheme V. If the gauche effect is invoked, then, in **37**, H_{th} will be more reactive than H_e; in **36**, H_e will be more reactive than H_{th}. In **48**, the gauche effects are equal so that any difference would result from the superposition of a steric effect, e.g., H_{th} should be more accessible to the base (it should be noted that **48** approximates the conformation found in the medium ring compounds). We now assume that the gauche effect is the most important stereochemical determinant, i.e., that $\Delta G^{\ddagger}$ for removal of H_{th} from **37** or **48** is equal to $\Delta G^{\ddagger}$ for removal of H_e from **36** or **48**. Whether H_{th} or H_e will be seen to be more reactive will then depend upon the free energies of **36**, **37**, and **48**.[85] Since **37** and **48** are expected to be more stable than **36**, the conversion of $R_1CH_{th}H_eCHXR_2$ to the mixture of olefins *should be observed to proceed with loss of H_{th}* (only the conversion of **37** to olefins is shown in detail). Moreover, any factor that further destabilizes **36**, such as an increase in the size of the R groups,[76a,b]

(85) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1963, p 238.

should increase the observed difference in reactivity between the two protons.

We believe that the theory of bimolecular elimination just outlined deserves consideration, both as an explanation of the syn–anti dichotomy and as a rationale for the development of a novel stereochemical procedure to complement those already available[70a,71b] for the detection of carbanionic intermediates. A number of experimental tests of the theory can be suggested and are being undertaken in our laboratory. These include (1) a study of the syn–anti dichotomy in elimination from a *primary* carbon;[86] (2) a study of the effect of temperature upon the kinetic difference between H_{th} and H_e; (3) a study of the effect of the leaving group X; (4) recalculation of kinetic isotope effect data.[87] The results presented in the first part of this Account suggest that the magnitude of the gauche effect will depend upon the C_α–X bond length in the direction $C-N<^+$, $C-OTs > C-Cl > C-S<^+ > C-Br$. The data presently available[72-75] indicate that the relative positions of $N(CH_3)_3$ and Br in this sequence are correct ($N(CH_3)_3$ shows a gauche effect and Br does not), and that the behavior of OTs is intermediate.[88]

(86) Cf. W. F. Bayne and E. I. Snyder, Tetrahedron Lett., 571 (1971).

(87) R. A. Bartsch, J. Amer. Chem. Soc., 93, 3683 (1971).

(88) Further examples of stereochemical phenomena which appear to be interpretable in terms of the ideas presented herein, but could not be discussed within the constraints of this Account, include aldolization reactions,[89] the α effect (supernucleophiles[90]), and lone pair effects in ir spectroscopy.[91]

(89) M.-C. Roux-Schmitt, J. Seyden-Penne, and S. Wolfe, Tetrahedron, submitted for publication.

(90) J. O. Edwards and R. G. Pearson, J. Amer. Chem. Soc., 84, 16 (1962). We thank Professors R. F. Hudson and J. O. Edwards, and Dr. R. Curci for bringing this work to our attention.

(91) P. J. Krueger and J. Jan, Can. J. Chem., 48, 3236 (1970). We thank Professor Krueger for bringing this work to our attention and for a helpful discussion.