CONFORMATIONAL ANALYSIS—CI

THE *GAUCHE*-HYDROGEN INTERACTION AS THE BASIS OF CONFORMATIONAL ANALYSIS[1,2]

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Abstract—It is concluded that the *gauche*-butane interaction which is one of the cornerstones of conformational analysis has been incorrectly interpreted as to origin, and that the *gauche* relationship between methyl (or methylene) groups is not the cause of the relative instability of gauche conformations. Rather, the *gauche* interactions between *vicinal*-2,3-hydrogens are mainly responsible. By the same taken, a substituent on a cyclohexane ring should not be said to have a preference for the equatorial position. Rather, the tertiary hydrogen has an energetic preference for an axial position, which leaves the substituent in the equatorial position by default. Several poorly understood phenomena are better interpreted on this basis.

Ever since D. H. R. Barton pointed out over 20 years ago[3] that the differences between axial and equatorial substituents on cyclohexane rings were of considerable chemical importance, conformational analysis has been a field of continued active interest. Two of the most useful general rules that have been developed in this field are: (1) axial substituents on a cyclohexane ring are less stable than equatorial substituents, and (2) each additional *gauche*-butane type interaction gained in going from one conformation to another is worth about 0·7 kcal/mol.

In this paper we wish to show that the reasons generally given for the origin of these two effects are probably incorrect, and the effects are in fact consequences of the van der Waals interactions between *gauche* vicinal hydrogens. The *gauche* H|H interaction, which occurs in virtually all organic compounds, is certainly the most widespread of all steric interactions. Despite the fact that organic chemists have long recognized the importance of steric interactions, the *gauche* H|H interaction has generally been ignored. The reasons for this include the ubiquitous nature of the interaction, coupled with the popular misconception[5] that the van der Waals radius of hydrogen is 1·2 Å[6] and the corresponding misleading representation of the space-filling type of model.† Whatever the reasons for not recognizing the importance of the van der Waals interactions between *gauche* hydrogens, these interactions are in our view not only the primary cause of the instability of a *gauche*-butane type in-

teraction, but are also at the root of several other poorly understood phenomena.

Experimentally[7] butane is found to exist at room temperature in two conformations—the *gauche* form where the torsional angle between the Me groups is about 60°; and the *anti* form where the torsional angle between the methyl groups is 180°. The *anti* form is found to be of lower enthalpy by about 0·7 kcal/mol.

The standard explanation for the origin of the increased energy of *gauche*-butane relative to *anti*-butane is given in *Conformational Analysis*:[8]

"In the *gauche* form there are the following individual *gauche* interactions: Me|Me, 2 Me|H and 3 H|H. The corresponding interactions in the *anti* form are 4 Me|H and 2 H|H, the difference being an Me|Me and an H|H interaction in the *gauche* form versus 2 Me|H interactions in the *anti* form. Evidently the sum of the former two interactions exceeds the sum of the latter two ... In this particular case it appears that the Me|H and H|H interactions are energetically negligible and the instability of the *gauche* form of butane may be ascribed entirely to the Me|Me interaction taken to be 0·8 kcal/mol."

We wish to show here that the H|H *gauche* interactions are *not* negligible, and in fact may be the most important contributors to the *gauche* butane effect.

A major reason why the origin of the *gauche* butane effect has been incorrectly assigned to the Me|Me interaction is the historical belief that a perfectly staggered molecular model with tetrahedral bond angles is a good approximation to a real molecule. The measurement of a perfectly staggered Fieser model of *gauche* butane indicates that the closest H|H distance by far (excluding gem-

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†A van der Waals radius for hydrogen of 1·4–1·7 Å now seems to be generally accepted.[5]

inal distance) involves the closest two hydrogens on the methyl groups. However, it is known experimentally that the bond angles in molecules are not tetrahedral. The C–C–C angles in the n-alkanes are found to be about 113°,[7,9] while the H–C–H angles are about 106·5° for methylene groups and about 108·5° for Me groups. These angular changes move the hydrogens on the *gauche* Me groups farther apart than models show. The average *gauche* H|H interaction is more serious in *gauche*-butane than is the corresponding interaction in *anti*-butane, as a result of the 106·5° H–C–H angle in the methylene group. This means that not only does *gauche*-butane have three unfavorable *gauche* H|H interactions while *anti* butane has only two, but those in *gauche* butane are more severe.

The measurement of a staggered model ignores another important point—*gauche*-butane is not rigidly locked into the staggered conformation. The barrier to interconversion of *anti*- and *gauche*-butane, and the Me rational barrier, are only about 3·0–3·6 kcal/mol in height. Rotation about either the central C–C bond or the methylene–methyl C–C bond of *gauche*-butane rapidly increases the distance between the Me hydrogens. A rotation about each of these bonds spreads out the Me|Me hydrogens and brings together the *gauche* methylene hydrogens.

If the Me|Me interaction alone were responsible for the increased energy of *gauche*-butane, then in relieving this interaction one might expect the *gauche*-butane to rotate by about 7° about each C–C bond, thereby reducing the repulation to insignificance. A 7° rotation is, however, unreasonable in our view, because it would make the 2,3 *guache*-H|H interactions much worse than they already are, and certainly much worse than the Me|Me interaction supposedly "causing" the rotation. As it is, 3° rotations are sufficient to cause the two *gauche*-H|H interactions to have between them twice the energy of the Me|Me interaction.

An examination of the methylene hydrogens, on the other hand, shows that there is no easy way to increase the distance between the 2,3-*gauche*-hydrogens. Any deviation from the staggered form makes the *gauche*-H|H interactions even worse. Another important point ignored by the usual analysis is that *gauche*-butane has one less *anti*-H|H interaction than *anti*-butane. The *anti*-hydrogens, unlike the *gauche*-hydrogens, are far enough apart

to be in the attractive region of the van der Waals curve.

Our molecular mechanics calculations indicate[†] that the interactions between the methylene hydrogens are sufficient to account for at least 75% of the calculated energy difference between *anti*- and *gauche*-butane, and consistent with this, the rotation about the central bond in *gauche*-butane only increases the C–C–C–C torsional angle to 64°. The range of experimental values (61 − 66°) is in agreement with this.[7]

Table 1. Force field (1973)

van der Waals Constants

$$E_v = -2·25\epsilon(r^*/r)^6 + 8·28(10^5)\epsilon \exp(-r/0·0736r^*)$$

Atom	r*(Å)	ε (kcal/mol)
C	1·75	0·041
H	1·50	0·063

For van der Waals calculations the electron cloud around H is centered 0·925 of the distance out along the C–H bond.

Bond Stretching

$$E_s = 71·94 \, k_s(1 - l_0)^2(1 + C_s(1 - l_0)) \quad C_s = -2·00$$

Bond	l (Å)	k_s(mdyn/Å)
C–C	1·514	4·4
C–H	1·095	4·6

Angle Bending

$$E_b = 0·021914 \, k_b(\theta - \theta_0)^2(1 + C_f(\theta - \theta_0)) \quad C_f = -0·006$$

Type		θ_0 (degrees)	
Quaternary Carbon		109·467	
Tertiary:	C–C–C	110·5	
	C–C–H	108·5	
Secondary:	C–C–C	110·2	
	C–C–H	108·5	
	H–C–H	112·8	
Primary:	C–C–H	107·9	
	H–C–H	111·1	
k_b	C–C–C	0·38	mdyn Å/rad²
	C–C–H	0·24	
	H–C–H	0·19	

Stretch-Bend

$$E_{sb} = 2·51124 \, k_{sb}(\theta - \theta_0)[(l_1 - l_0) + (l_2 - l_0)]$$

$k_{sb} = 0·12$	C–C–C
0·04	C–C–H
0·00	H–H–H

Torsion

$$E_t = (V/2)(1 + \cos(3\omega)) \, 0° \leq \omega \leq 60°$$

V = 0·53 kcal/mol for any combination of carbons and hydrogens

Torsion-Bend

$$E_{tb} = k_{tb}(1 + \cos(3\omega))[(\theta_1 - \theta_0) + (\theta_2 - \theta_0)]$$

$k_{tb} = -0·0110$ for C–C–C–C, zero otherwise.

[†]Let it be made clear at the outset that the general conclusions to be drawn here are not dependent on the exact values used for the force constants in the molecular mechanics calculations described. The calculated numbers quoted refer to our 1973 force field (see Table 1). We believe that the other popular force fields in current use will all show the *gauche*-hydrogen interaction to be at least important, if not dominating, in determining the *gauche*-anti energy difference.

If a molecule finds itself strained in a particular geometric arrangement, it will become deformed in such a way to minimize that strain by distributing it throughout the available degrees of freedom in the molecule. Up to this point our discussion has been rather general, because we have been emphasizing the concepts, not the numerical details of the *gauche* hydrogen effect. The numerical details will differ with differing force fields, but the qualitative results, and more importantly the ideas, will not.

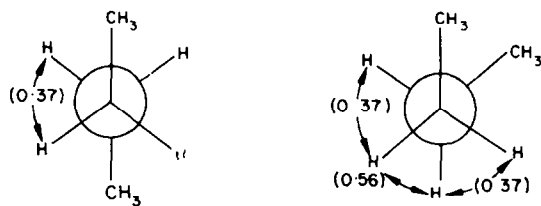For sake of completeness, we will give here some numbers from the present butane calculations (Table 2).

Table 2. Energy sums for *anti* and *gauche* butane[a]

	anti	*gauche*
Bond stretching	0·45	0·48
Angle bending	1·13	1·42
Torsion	0·01	0·09
Stretch-bend	0·12	0·15
1–4 van der Waals[b]	3·66	4·01
Other van der Waals	−0·36	−0·44
Total steric energy	5·02	5·71

[a] Numbers in parentheses in Fig are interaction energies in kcal/mol.

[b] 1,4-van der Waals are the van der Waals interactions between vicinal atoms.

The *gauche* form of butane is calculated to have a total 0·69 kcal/mol more energy than the *anti* form. The three vicinal H|H interactions in the *gauche* form are calculated to contribute 0·56 kcal/mol more energy than do the two corresponding interactions in the *anti* form (Fig). The in-

teraction between the hydrogens on the Me groups contributes only 0·26 kcal/mol. There are many other interactions contributing to the overall energy difference, with C|H interactions partly cancelling the above values, and being largely cancelled in turn by stretching, bending and torsional interactions. The best insight to the situation seems to be provided by the approximation of looking only at the H|H interactions mentioned. However, as the numbers in Table 2 show, this may be an oversimplification.

2,3-Dimethylbutane is a good illustration of how little the *gauche* Me|Me interaction itself contributes to the energy of *gauche*-butane interactions, and how important it is that it not be possible to

relieve an interaction if it is to contribute significantly to the energy of a molecule. As in *gauche*-butane, the *gauche* conformation of 2,3-dimethylbutane has one more *gauche* Me|Me interaction and one more *gauche* H|H interaction than the *anti* conformation. In contrast to n-butane, however, it is calculated[10,11] and found experimentally[11] that the two conformations are about equal in energy. The reason for this apparent anomaly is that in *gauche*-2,3-dimethylbutane the *gauche* H|H interaction can be relieved by rotation about the central C–C bond. According to our molecular mechanics calculations the torsional angle between the *gauche* hydrogens is about 72° and the *gauche* conformation is slightly lower in energy than the *anti* conformation.

Anti–2,3 – Dimethylbutane   Gauche–2,3 – Dimethylbutane
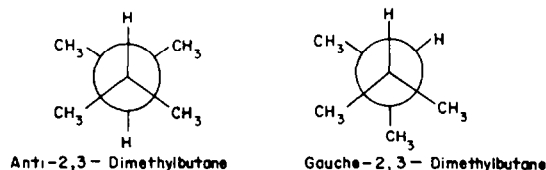
Cyclohexanes

Ever since the recognition[3] of the chemical consequences of the differences between axial and equatorial substituents, the fact that compounds with axial substituents are less stable than analogous compounds with equatorial substituents has been explained by saying that the axial position is more sterically hindered than the equatorial position. We wish to show that for a hydrogen, the *equatorial* position is much more sterically hindered than the axial position, and that the increased crowdedness of the axial position for other substituents, to the extent it exists at all, is only a small part of the reason why substituents on a cyclohexane ring prefer to be in the equatorial positon. The determining factor in conformational stability is not that the substituent prefers to be equatorial, but that the tertiary hydrogen prefers to be axial. The substituent is then left with the equatorial position by default.

Equatorial Methylcyclohexane   Axial Methylcyclohexane
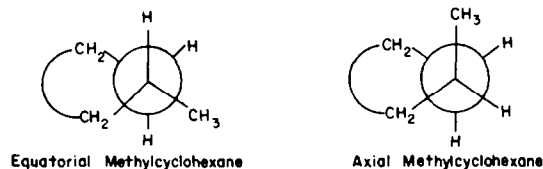
As shown by the Newman projections for methylcyclohexane there are two more *gauche*-alkane interactions in axial methylcyclohexane than there are in equatorial methylcyclohexane. The observed energy difference between the conformations of methylcyclohexane is about 1·8 kcal/mol[12]—essentially as predicted by counting the number of *gauche*-butane type interactions. It is therefore not surprising that the origin of the ob-

served energy differences between axial and equatorial groups is closely related to the origin of the difference in the energy of *gauche*- and *anti*-butane.

The "across-the-ring" interactions with the axial hydrogens shown below for axial methylcyclohexane are commonly accepted as the reason for the higher energy of the axial Me group. Measurement of models indicates that these distances are only 1·8 Å. However, these short distances cannot be expected to exist in the real molecule. The barrier to inversion of cyclohexane[13] is about 10 kcal/mol,
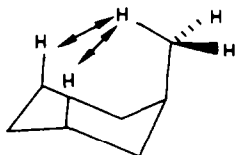
so the molecule is not rigidly held in the geometry of the models but would flatten to release the "across-the-ring" interactions. How much ring flattening might be expected? One can reason as follows. If there is 1·8 kcal resulting from the "across-the-ring" interaction, perhaps half of it would be expected to be transferred into flattening the ring, or say 0·9 kcal. If one assumes that near the bottom of the potential well, the cyclohexane inversion mode can be approximated by a cosine function, than 1 kcal corresponds to an 8–10° flattening of the ring torsional angle to which the Me is attached. In fact, it has been found experimentally that the degree of flattening of the cyclohexane ring is practically unaffected by the presence of axial substituents including axial Me groups.[14] One must therefore seek an alternative explanation for the increased energy of the axial methyl group which, unlike the "across-the-ring" interactions, will not be relieved by flattening of the ring.

Before discussing the origin of the increased energy of axially substituted cyclohexanes, it is worthwhile to look first at cyclohexane itself. Measurements on models indicate that the distance between the hydrogens *gauche* to each other is the same as the "across-the-ring" distance between the axial hydrogens (i.e. 2·50 Å). As usual, the geometry of the model is inaccurate. It has been found experimentally[15] that the C–C–C angles of

cyclohexane are opened up to about 111°, and the ring is flattened with a corresponding decrease in the C–C–C–C torsional angle to about 56°. This flattening of the ring increases the "across-the-ring" distance between the axial protons while bringing the *gauche*-hydrogens protons closer together. As is true with the n-alkanes, the H–C–H angle is noticeably smaller than the 109·5° of models, and this also pulls the axial hydrogens apart at the expense of the *gauche*-H|H distance. Our molecular mechanics calculations indicate that the H–C–H angle is slightly larger in cyclohexane than it is in the n-alkanes, mainly because the axial protons are pushed back towards the ring slightly by their vicinal equatorial neighbors. Still, the "across-the-ring" distance between *syn*-axial hydrogens is 0·1 Å greater than the distance between a vicinal axial-equatorial hydrogen pair. It thus turns out that the axial hydrogens are less sterically hindered than the equatorial ones, because with the relief of the "across-the-ring" interactions, only the *gauche*-interactions are significant. The axial hydrogen is *gauche* to only one hydrogen on the adjacent carbon, while the equatorial hydrogen is *gauche* to two. Also, the axial hydrogen benefits from an attractive *anti* H|H interaction. Thus taking an axial hydrogen and placing it in the equatorial position involves losing an attractive *anti*-H|H interaction and replacing it with an additional repulsive *gauche*-interaction with each of the methylene groups adjacent to it. This means that, for a hydrogen, *the equatorial positon is more sterically hindered than the axial position.* An interesting consequence of this fact is the systematic difference calculated for the bond lengths of axial and equatorial hydrogens (or other monoatomic substituents). Although the differences are small and have not been determined experimentally, the calculated trend is very clear; the equatorial atom in all cases has the longer bond, as it tries harder to retreat from its congested environment.

If one looks at the Newman projection of methylcyclohexane (above) one can see that in going from equatorial to axial methylcyclohexane, the axial "iso-hydrogen" of equatorial methylcyclohexane becomes the equatorial "iso-hydrogen" of axial methylcyclohexane. Our molecular mechanics calculations say that approximately 1/2 (0·9 kcal) of the energy difference between axial and equatorial methylcyclohexane comes from the intrinsic increase in the steric energy of an equatorial hydrogen relative to an axial hydrogen on a cyclohexane ring. We refer to this energy difference as the *equatorial hydrogen effect.*

Without further consideration one would be tempted to say that the other half of the energy difference between axial and equatorial methylcyclohexane comes from the "across-the-ring" interactions of the methyl group with the axial hydrogens. However, our molecular mechanics calculations indicate* that only about 25–30% of the energy comes from this

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*The reason we are not more precise in our discussion of what *causes* the energy differences between the conformations is that molecular mechanics tells one (hopefully) *what* the difference in the energy between formations is, but it does not tell what *causes* the difference in energy. One only knows from a molecular mechanics calculation what interatomic distances in the molecule *end up* being in the range of repulsive van der Waals interactions and what internal coordinates *end up* being distorted. The calculations do not tell one what *caused* these interactions. The causes are a matter of opinion which the chemist superimposes *ex post facto* on the results.

source. The remaining energy difference also comes from the "iso-hydrogen". The "iso-hydrogen" is *gauche* to two of the hydrogens on the Me group. In equatorial methylcyclohexane this hydrogen minimizes these interactions by moving away from the Me group back into the ring where the only interactions are the relatively distant "across-the-ring" axial protons. In axial methylcyclohexane the "iso-hydrogen" is unable to avoid the Me hydrogens by bending away, because of the axial hydrogens *gauche* to it. The result is what one would expect; the "iso-hydrogen" finds the best compromise it can, and the increased steric interactions of the "iso-hydrogen" in axial methylcyclohexane with both the Me group and the *gauche* axial hydrogens are together responsible for the remaining 20–25% of the energy difference between axial and equatorial methylcyclohexane.

The recognition of the fact that, for a hydrogen, the equatorial position is more crowded than the axial position, and that the equatorial hydrogen effect is the major reason that most substituents prefer to be equatorial rather than axial is of great help in explaining several well established but poorly understood phenomena. An example which has received much attention because of the failure to recognise the equatorial hydrogen effect is the apparent failure of the hydride reductions of cyclohexanones to follow Cram's rule.[16] Cram's rule states that in kinetically controlled addition reactions (except catalytic hydrogenations) the reagent will approach from the side of least hindrance. As long as one believes that the axial position of cyclohexane is the more hindered, then the hydride reductions of cyclohexanones which give the equatorial alcohol (axial attack of the hydride) are in conflict ·with this rule. Since, however, for a hydrogen the equatorial position is in fact the more hindered, these results are not an exception to Cram's rule.

This problem has recieved considerable attention in the literature[17-20] and it was suggested[19,20] that the steric interaction of the incoming hydride with the axial hydrogens on the carbon α to the carbonyl were responsible for the decreased rate of equatorial attack of hydride. This is essentially the same as our contention that the *gauche* H|H interactions are responsible. Eliel,[18] on the basis of some relative rate studies, rejected this idea and came to the conclusion that the rate difference could best be explained by Felkin's postulate of torsional strain.[17] His
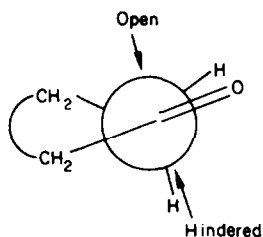
explanation was essentially that, when the hydride attacks from the equatorial side it comes in essentially eclipsed with the axial α-hydrogens. This explanation is not in serious conflict with ours, since one of the most important contributors to torsional barriers is van der Waals interactions between hydrogens. (Most of the force fields in current use attribute 30–50% of the ethane barrier to this source). We do not wish to imply that the axial position is in all possible cases less hindered than the equatorial position. If two 3-axial substituents are placed on a cyclohexanone, the equatorial position does become less hindered than the axial position (and the axial alcohol is the major reduction product[21,22]). It is interesting to note, however, that in this case the rate of the reduction drops off drastically, an experimental finding consistent with the high energy of the equatorial hydrogen.

Another experimental finding readily understood in terms of the equatorial hydrogen effect is the small size of the 3-*axial ketone effect*.[23] This effect comes about because in the axial conformation of 3-methylcyclohexanone, relative to the corresponding hydrocarbon, one of the two "across-the-ring" interactions of the Me group with the axial protons is missing. The belief that the axial protons were responsible for the instability of axial methylcyclohexane lead to the prediction that the difference between the axial and equatorial conformations of a 3-methylcyclohexanone would be reduced by 1/2 of that of methylcyclohexane, or 0·90 kcal. The experimentally determined number[23] of about 0·4–0·5 kcal was unexpectedly low. The smallness of this number is now readily explained because the most important part of the conformational energy of axial methylcyclohexane is unchanged—namely the hindered equatorial "iso-hydrogen" is still there.

Another phenomenon which we believe is better accounted for by the equatorial hydrogen effect than by the accepted explanation is the more rapid rate of oxidation of axial alcohols compared with equatorial isomers. The chromic acid oxidation of secondary alcohols proceeds by the formation of a chromate ester, followed by the removal of the carbinol H atom by base and elimination of the chromium containing fragment to give the ketone.[24] It has been found by deuterium isotope effect studies[25] that the rate-determining step is not the formation of this ester but rather the breaking of the bond to the carbinol H atom.

It has also been found that for a pair of diastereomerically related cyclohexanols the ratio of the rates (k_{ax}/k_{eq}) is a good measure of the free energy difference between the epimers being compared:[26]

$$- \Delta G^\circ_{ax\text{-}eq} = RT \ln (k_{ax}/k_{eq})$$

It has been suggested that this was because the geometry of the transition state for the reaction was

Open

Hindered

similar to that of the ketone, and the energy differences between the alcohols is diminished or nullified in the transition state. Since the axial alcohol has the higher ground state energy, the amount of additional energy it requires to get to the transition state would be less than that required by the more stable equatorial alcohol. Since, however, there appears to be very little sp^2 character at the carbinol carbon in the transition state,[27] we find it hard to rationalize why the ratio of the rates should be such a good measure of the free energy differences between the two alcohols. Even more difficult to understand is the fact that the rate for cyclopentanol is only 1·4 times faster than that for cyclohexanol.[28] The energy ($\Delta H°$) required to go from cyclohexanol to cyclohexanone[29] is 15·2 kcal, while the energy required to go from cyclopentanol to cyclopentanone is only 12·3 kcal,[29] or 2·9 kcal less. If the explanation given above for the faster rate of oxidation were correct, one would expect the ratio of the rates of oxidation of cyclopentanol to cyclohexanol to be about 125, instead of the observed 1·4.[28] We believe a better explanation for the observed rate ratio k_{ax}/k_{eq} is suggested by the fact that it is the carbinol C–H bond, which is broken in the rate-determining step, and that the carbinol hydrogen is the main source of the energy difference between the axial and equatorial alcohols. Since the gauche-H|H repulsive interactions fall off rapidly with increased C–H bond length (the repulsive part of the van der Waals function is generally taken to be either an inverse 12th power or exponential), the van der Waals repulsion for the axial and equatorial hydrogens will be the same in the transition state–namely negligible. If the above explanation is correct, one would expect the ratio of the rates to accurately reflect the energy differences between the epimeric alcohols. We estimate from our molecular mechanics calculations that the carbinol hydrogen in cyclopentanol would have about 0·2 kcal more gauche H|H repulsion energy than would the axial carbinol hydrogen of cyclohexanol. This does in fact give an estimated relative rate ratio for cyclopentanol to cyclohexanol close to 1·4.

As is well known, substituents on substituted cyclohexane rings other than alkyl groups also prefer to be in the conformation where the substituent is equatorial. Table 3 gives a list of representative

groups and their conformational free energies.

We have already discussed the Me group, and as can be seen from the Table, the preferences of conformations where the substituents are equatorial are much less for the non-alkyl groups than for Me. Since the three hydrogens on the Me group are responsible for about 50% (or 0·9 kcal) of the energy difference between an axial and an equatorial Me group, it is to be expected that the energy differences between the axial and equatorial conformations of non-alkyl groups would not be as great as that for a Me group. In most cases one might expect only the equatorial hydrogen effect to be important in determining the relative stabilities of the conformations of non-alkyl groups.

Since the equatorial hydrogen effect is 0·9 kcal, and the energy differences for all of the non-alkyl groups in Table 3 are less than 0·9 kcal it would appear that something additional needs to be considered. Let us take chlorine as an example. Propyl chloride is known to prefer the conformation where the chlorine is gauche to the Me group. The energy by which propyl chloride prefers the gauche-conformation is not accurately known. The values reported are $0·05 \pm 0·15$,[30] $0·3 \pm 0·2$,[31] and $0·0 \pm 0·5$,[32] but for the purposes of this paper we will use the average value of 0·12 kcal. In contrast to propyl chloride, chlorocyclohexane prefers the equatorial conformation over the axial by about 0·4 kcal,[33] despite the presence of two gauche-chlorine-methylene interactions in the axial conformation that are lacking in the equatorial. This apparent anomaly between propyl chloride and chlorocyclohexane can be explained on the basis of gauche H|H interactions.

To understand this matter, let us look at n-butane again. One of the most important reasons why n-butane prefers the anti-conformation is that the H–C–H angle of the methylene group is considerably reduced from the 109·5° angle of tetrahedral geometry. According to our calculations, the reason for the reduction of the H–C–H angle is that this distortion minimises the gauche-H|H interactions the methylene protons have with both the adjacent methylene group and with the adjacent Me group. In propyl chloride, the two hydrogens on the carbon attached to chlorine lack one set of these interactions, namely the Me group is removed. This allows the hydrogens not only to open up the H–C–H angle, but also to minimize the gauche H|H repulsion with the methylene hydrogens by moving away from the latter and toward the Cl atom. Our molecular mechanics calculations indicate that these changes, along with the loss of the approximately 0·2 kcal from the Me|Me interaction, allows the gauche conformation to be only 0·1 kcal less stable than the anti-, instead of 0·8 kcal as in n-butane. This means that our calculations miss the actual difference of the gauche conformation by 0·22 kcal. While the origin of this remaining

Table 3

Group	$\Delta G°_{(ax-eq)}$
CH₃	1·80
SH	0·70
OH	0·52
Cl	0·42
C≡N	0·20
F	0·15

0.22 kcal is not completely understood, there is good reason to believe that it is the result of dipolar effects which we are not yet able to take into account. In any case we will refer to this 0.22 kcal as the "*gauche*-chloride effect".

If one looks at Table 3, one will note that along any one row of the periodic table, the observed preferences of a group X for the axial position in general decrease with increasing polarity of the C–X bond. This is consistent with an increased *gauche*-polar group effect with increased group polarity. However, changes in size of X, and the number of attached hydrogens also varies, so it is not certain that the polarity trend is significant.

If we now turn our attention to chlorocyclohexane, we can see that none of the changes which allowed the *gauche*-H|H interactions in *gauche*-propyl chloride to be reduced have occurred in the axial conformation of chlorocyclohexane. The "iso-hydrogen" is still flanked by two methylene groups. This means that the equatorial hydrogen effect of about 0.9 kcal should still be operative. The estimate of 0.46 kcal for the difference in energy between axial and equatorial chlorocyclohexane that is obtained if twice the "*gauche*-chloride effect" (0.44 kcal) is subtracted from the equatorial hydrogen effect (0.9 kcal) is in good agreement with the observed value (0.4 kcal).

It is worth explaining why in our discussion we have assumed that *gauche*-Me|H and *gauche*-Cl|H interactions are much less important than *gauche*-H|H interactions. After all, are not chlorine and Me groups larger than hydrogens? They are, but they have longer bond lengths. The C–H bond length is about 1.1 Å, the C–C bond length is about 1.5 Å and the C–Cl bond length is about 1.8 Å. These increased bond lengths move these groups further away from hydrogens they are *gauche* to by more than their increased van der Waals redius makes up for. This means that despite their greater size, their interactions with *gauche*-hydrogens are smaller than the *gauche*-H|H interaction.

We would especially like to emphasize a point made implicitly several times in this paper. What causes the *gauche* H|H interaction to be so important is not so much its size, but rather the fact that unlike most of the other steric interactions one sees when one looks at a model of a compound, the *gauche* H|H interaction can generally not be significantly reduced by any kind of molecular distortion. When a hydrogen is *gauche* to two hydrogens, torsional rotations away from being staggered only increase the total *gauche* H|H interaction energy. Furthermore, the hydrogens on a methylene or methine carbon are generally *gauche* to two (or three) different sets of hydrogens, and any attempt by such hydrogens to move away from one set of hydrogens only increases their steric interactions with the other sets of hydrogens. As we have discussed in the cases of 2,3-dimethylbutane and

propyl chloride, when this butressing is not present the size of the gauche h|H interaction is greatly reduced.

In contrast to the situation with respect to the usual *gauche* H|H interaction, the typical *gauche* interaction between methyl and/or methylene groups is not similarly butressed, and the molecule can easily reduce these interactions by changing torsional and bond angles. This means that even if models indicate a large interaction, in the actual molecule this interaction will undoubtedly be considerably reduced. We have attempted with several different force fields to duplicate experimental conformational energy differences without the use of the overriding *gauche* H|H interaction, but these attempts have all failed. They always resulted in severely distorted calculated molecular geometries, and/or calculated conformational energy differences that were too small.

In conclusion, we would like to reiterate that in our view the generally ignored *gauche* H|H interaction plays an important role in conformational analysis, and in organic chemistry in general. It is in fact responsible for many of the steric effects that have previously been assigned to other sources. We believe that the recognition of the importance of *gauche* H|H interactions enables one to understand better the basic underlying feature of conformational analysis, and such recognition affords a better interpretation of several phenomena that were previously not well understood.

REFERENCES

[1]Supported in part by Public Health Service Research Grant AM-14042 from the National Institute of Arthritis and Metabolic Diseases
[2]For paper C, see N. L. Allinger and G. A. Lane, *J. Am. Chem. Soc.* in press (1974)
[3]D. H. R. Barton, *Experientia* 6, 316 (1950)
[4]A. Warshel and S. Lifson, *J. Chem. Phys.* 53, 582 (1970)
[5]See discussion by L. S. Bartell, *Ibid.* 32, 827 (1960); N. L. Allinger, M. A. Miller, F. A. Van Catledge and J. A. Hirsch, *J. Am. Chem. Soc.* 89, 4345 (1967)
[6]L. Pauling, *The Nature of the Chemical Bond*, (3rd Edition) p. 260. Cornell University Press, Ithaca, N.Y. (1960)
[7]L. S. Bartell and D. A. Kohl, *J. Chem. Phys.* 39, 3097 (1963); K. Kuchitsu, *J. Chem. Soc. Japan* 32, 748 (1959); P. B. Woller and E. W. Garbisch, Jr., *J. Am. Chem. Soc.* 94, 5310 (1972)
[8]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 13. Wiley-Interscience, N.Y. (1965)
[9]D. R. Lide, Jr., *Tetrahedron* 17, 125 (1962); D. R. Lide, Jr., *J. Chem. Phys.* 33, 1514 (1960); T. Iijima, *Bull. Chem. Soc., Japan* 45, 1291 (1972)
[10]N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van Catledge, *J. Am. Chem. Soc.* 90, 1199 (1968)
[11]T. L. Boates, Thesis, Iowa State University, 1966; E. J. Jacob, H. B. Thompson and L. S. Bartell, *J. Chem. Phys.* 47, 3736 (1967)

[12]J. A. Hirsch in N. L. Allinger and E. L. Eliel, *Topics in Stereochemistry* Vol. 1, p. 199; E. W.Garbisch, Jr., B. L. Hawkins and K. D. MacKay, in G. Chiurdoglu, *Conformational Analysis*, p. 93, Academic Press, New York, (1971)

[13]F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.* **89**, 760 (1967)

[14]C. Altona and M. Sundaralingam, *Tetrahedron* **26**, 925 (1970); H. J. Geise, F. C. Mijlhoff and C. Altona, *J. Mol. Struct.* **13**, 211 (1972) and references theirein

[15]M. Davis and O. Hassel, *Acta. Chem. Scand.* **17**, 1181 (1963); H. R. Buys and H. J. Geise, *Tetrahedron Letters* 2991 (1970)

[16]D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.* **85**, 1245 (1963), and earlier papers; G. J. Karabatsos, *Ibid.*, **89**, 1367 (1967)

[17]M. Cherest and H. Felkin, *Tetrahedron Letters* 2205 (1968)

[18]E. L. Eliel and Y. Senda, *Tetrahedron* **26**, 2411 (1970)

[19]J.-C. Richer, *J. Org. Chem.* **30**, 324 (1965)

[20]J. A. Marshall and R. D. Carroll, *J. Org. Chem.* **30**, 2748 (1965)

[21]L. H. Sarett, M. Feurer and K. Folkers, *J. Am. Chem. Soc.* **73**, 1777 (1951)

[22]S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.* **18**, 1168 (1953)

[23]E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* pp. 113–119. Interscience, New York (1965)

[24]Ref. 23, p. 114

[25]J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **38**, 1529 (1955)

[26]Ref. 23, p. 82

[27]D. G. Lee and M. Raptis, *Tetrahedron* **29**, 1481 (1973)

[28]H. G. Kuivila and W. J. Becker, III, *J. Am. Chem. Soc.* **74**, 5329 (1952)

[29]J. D. Cox and G. Pilcher, *Thermo-chemistry of Organic and Organometallic Compounds* Academic Press, New York-London (1970)

[30]N. Sheppard, *Advan. Spectr.* **1**, 295 (1959)

[31]T. N. Sarachman, *J. Chem. Phys.* **39**, 469 (1963)

[32]Y. Morino and K. Kuchitsu, *Ibid.*, **28**, 175 (1958)

[33]L. W. Reeves and K. O. Stromme, *Canad. J. Chem.* **38**, 1241 (1960)