CHEMICAL REVIEWS

VOLUME 68, NUMBER 4 July 25, 1968

ALLYLIC STRAIN IN SIX-MEMBERED RINGS

FRANCIS JOHNSON

The Dow Chemical Company, Eastern Research Laboratory, Wayland, Massachusetts 01778

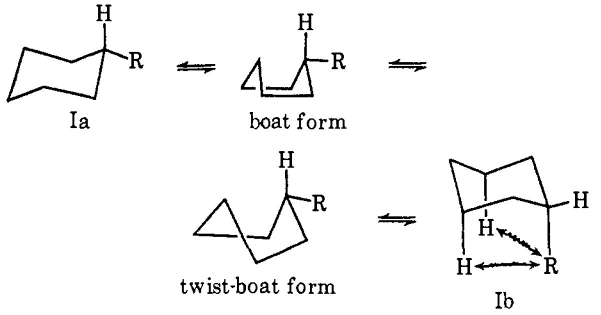
Received December 11, 1967

CONTENTS

I. INTRODUCTION

In the realm of cyclic organic compounds, the six-membered ring has been a source of both challenge and entertainment to the stereochemist. Quite apart from the frequency of its occurrence in isolable compounds, it appears to be one of the most highly preferred forms in transition states. As such it has come to be looked upon as one of the more intrinsically strain-free systems in organic chemistry, and it is not surprising that since the inception of modern stereochemistry the monocyclic six-membered ring has been under intensive investigation.

Under particularly heavy attack during the past 20 years have been cyclohexane and its substituted derivatives, and from this a fairly lucid picture has emerged. In fact, the conformational model of chair–boat–twist-boat forms (eq 1) which has been developed, together with a knowledge of the $\Delta G_x°$ values associated with various substituted groups, allows rational predictions to be made in more complicated cases. In the main, the chair form (Ia) is by far the more stable, and substituents, in all but a few cases, tend to occupy equatorial positions because of the rather severe strain associated with 1,3-diaxial interactions such as those depicted in Ib.



(1)

On the basis of these principles, which have been reviewed recently,[1-3] it is possible both to anticipate or to explain conformational and isomerizational equilibria, relative rates of reaction, and structural instabilities in many *saturated* cyclic systems.

However, the same can scarcely be said of the corresponding unsaturated compounds containing an endo- or an exocyclic double bond (with the possible exception of cyclohexanone). Only very recently has any logical

---

(1) E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 6.

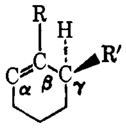
(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, Chapter 2.

(3) M. Hanack, "Conformation Theory," Academic Press Inc., New York, N. Y., 1965, pp 87–149.

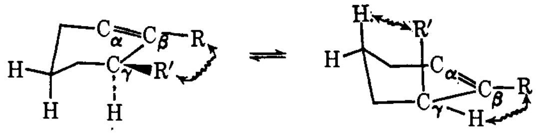
pattern concerning conformational effects begun to take shape. The purpose of this review is (a) to try to clarify the situation that pertains to methylenecyclohexanes and cyclohexenes substituted at, and allylically to, the double bond and (b) to attept to correlate these results with the chemical behavior of related systems.

In 1965, the author, in collaboration with Malhotra, put forward two propositions[4] in an attempt to deal with these endo- and exocyclic double-bond cases. These were formulated as a result of past experiences with the stereochemical behavior of enamines, enolate anions, and imines together with a considerable number of literature examples of related systems that seemed to fall into the same category.

The first proposal, dealing with the endocyclic case, stated that *in a cyclohexene such as II, if R and R′ are moderately large, they will interfere with each other sterically to such an extent that that conformer, IIb, having the axial substituent will be the favored form.* Conversely, if R and R′ are small in size, IIa will be the favored conformer. This suggestion was based on the idea that in such a system as IIa the dihedral angle between $C_\gamma R'$ and $C_\beta R$ is smaller (originally estimated from models to be $\sim$35°) than the ideal value of 60° and that, accordingly, the energy of interaction of R with R′ would be greater in IIa than that of R′ with the transannular axial hydrogen at C-4 plus the C-6 equatorial hydrogen–R interaction, in IIb.



II

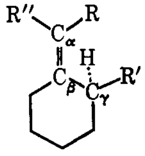


IIa IIb

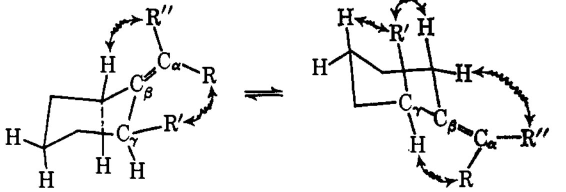
This type of strain for the sake of semantic simplicity was given the trivial designation of A$^{(1,2)}$ since the groups involved are substituted on the 1 and 2 positions of an allylic group.

One of the more interesting aspects of the conformational change (IIa → IIb, when the substrate is a reactive species, *e.g.*, enamine or enolate anion) concerns the steric resistance that might be afforded an approaching reagent. As we have noted before, the group R′ of II can be equatorial or axial depending on the sizes of R and R′. Reagent attack on II would undoubtedly be controlled by two factors, *viz.* (a) the stereoelectronic effect which would demand as much continuous π-orbital overlap as possible in the transition state and (b) the steric resistance to the reagent's approach. In IIa there is little conflict since no severe hindrance to axial approach of the reagents exists. Thus electrophilic attack, for instance, might be expected to take place at C_α on the lower face of the molecule. In the case of IIb, however, one might anticipate that attack on the upper face at C_α would be favored by the stereoelectronic effect, but opposed by the steric resistance of R′ (the latter argument assumes that R′ does not behave as a coordinating group for the attacking reagent; otherwise attack on the upper face could be highly favored). Thus if R′ is very large, attack on the lower face might be expected to prevail. This would demand the adoption by the ring of a boatshape at some point during the reaction coordinate with the implicit high-energy demands of such a course. Thus this can be expected to be favored only if this energy requirement is lower than that required by the reagent to pass by the R′ group on the upper face of IIb.

The second proposal outlined by Johnson and Malhotra deals with a methylenecyclohexane such as III (exocyclic double-bond case) and states that *where R and R′ are* moderate in size *they will interfere with each other drastically, in fact more so than if they were 1,3 diaxially related in a cyclohexane ring.*



III



IIIa IIIb

Thus it could be expected that the conformational equilibrium should favor that form having the axial substituent (i.e., IIIb). Conversely if the groups R and R′ are small and do not interfere with one another, then conformation IIIa should be favored. This proposal was predicated on the basis of an ideal near-planar arrangement of the grouping $R'C_\gamma C_\beta{=}C_\alpha RR''$. The type of strain involved here, as shown in IIIa, was termed A$^{(1,3)}$ strain, since it involved groups *syn* to one another on the C-1 and C-3 positions of an allylic (A) system. Again it is important to point out that in considering the attack of a reagent on a molecule such as III, where the transition state resembles starting material, its conformational composition must be taken into account. If the dominant conformer is IIIa, steric resistance to attack by a reagent at C_α or C_β would be encountered from the axial hydrogen atoms at C-3 and

---

[4] F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.*, **87**, 5492 (1965).

C-5 of the ring on the upper face, whereas little if any resistance to a reagent's approach would be expected from the lower face of the molecule. Thus attack on the lower face should be preferred. On the other hand, reagent attack on conformer IIIb at C_α or C_β would be resisted to a substantial degree by the group R′ on the upper face, whereas attack on the lower face would encounter resistance, if any, only from the axial hydrogen atoms at C-3 and C-5 of the ring. Attack on the lower face then is much to be preferred from the point of view of transition-state energies. It should be noted that stereoelectronic effects do not operate in this case since continuous overlap in the transition state is possible no matter from which side the reagent attacks. Thus in this system there is no opposing stereoelectronic effect as was noted in the case of II discussed above.

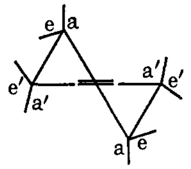
Before examining these proposals in the light of experimental results, it seems only fair to mention that the ideas embodied in $A^{(1,2)}$ and $A^{(1,3)}$ strain are not new. The literature contains a number of examples where the author in question offered one or other of the above explanations to rationalize the observed phenomenon. Since we plan to discuss some of these examples later, no further mention will be made of them here. However, what perhaps has been lacking in the past is the recognition that *these effects are real and that they are the general property of allylic and pseudo-allylic systems whether the latter be in an alicyclic or an acyclic system.*

To begin with we shall confine our remarks to cyclic systems and for the sake of a complete picture will record for each of the above cases what is known concerning the geometry of both II and III in the vicinity of the double bond. To do this it is necessary to transpose nonbonding distances from unsubstituted to substituted cases, in an *idealized* way. Although this is far from satisfactory, it at least gives some idea of the nonbonded interactions involved and the way they change when R and R′ are made increasingly larger.

II. $A^{(1,2)}$ STRAIN

A. THE GEOMETRY OF CYCLOHEXENE

There can be little doubt concerning the conformational preference of cyclohexene. X-Ray work on a variety of molecules such as morphine[5] and cholesteryl iodide,[6] and on the *cis,trans,cis*-1,3,4,5,6 isomer of pentachlorocyclohexene,[7] has confirmed the earlier conclusions of Beckett, Freeman, and Pitzer.[8] They had concluded that the molecule exists largely as the half-chair and differs from the half-boat by 2.7 kcal/mole. Relative to cyclohexane, cyclohexene has the shape of a flattened chair, and Barton, *et al.*,[9] suggested that only C-4 and C-5 bear truly axial (*ax*) and equatorial (*eq*) bonds. Bonds located at C-3 and C-6 were regarded as being somewhat differently oriented (A) and were termed pseudo-axial (a′) and pseudo-equatorial (e′). Corey and Sneen[10] carried out a vector analysis of the system using regular bond lengths but were forced, however, to employ distorted classical bond angles in order to close the ring in the mathematical model. They found that both allylic and homoallylic bonds (not associated with ring formation) suffered displacement, the axial allylic bonds being displaced through an arc of 23° away from the vertical axis whereas the axial bonds at the homoallylic positions were displaced through an arc of 11° away from the vertical axis and slightly toward the ring center. Thus they concluded that all of these bonds should be considered as e′ or a′. Nevertheless, for the sake of simplicity, in this article they will simply be termed equatorial and axial. In addition it was found that cyclohexene possessed 1 kcal/mole of strain energy over and above that which might be expected by comparison with *trans*-butene-2.



A

From their data it can be calculated that the dihedral angle between a substituent at C-1 on the double bond and one at the 6-*eq* allylic position is ~39°.

Recently a more advanced calculation has been made by Bucourt[11] using machine computation. In this analysis modern bond lengths and bond angles were used. By deforming the dihedral angles of the ring selectively, it was possible to calculate a structure of minimum energy for cyclohexene. This comprises a half-chair conformer having the internal dihedral angles $\psi_{x,y}$ between ring carbons x and y as shown in IV. Similar but later calculations[12] for 3,4-dimethylcyclohexene afforded the values shown in V. The deviations from the normal are based on a rounded-off value of 55° taken from cyclohexane. For the latter molecule Davis and Hassell[13] found the C–C–C angle to be 111.55 ± 0.15° and the dihedral angle to be 54.5°. Some reliance can undoubtedly be placed in the calculated figures for cyclohexene since further machine

---

(5) J. M. Lindsay and W. H. Barnes, *Acta Cryst.*, **8**, 227 (1955).

(6) C. H. Carlisle and D. Crowfoot, *Proc. Roy. Soc.* (London), **A184**, 64 (1945).

(7) R. A. Pasternak, *Acta Cryst.*, **4**, 316 (1951).

(8) C. W. Beckett, N. K. Freeman, and K. S. Pitzer, *J. Am. Chem. Soc.*, **70**, 4227 (1948).

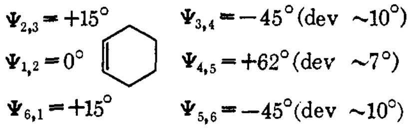
(9) D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shoppee, *Chem. Ind.* (London), 21 (1954).

(10) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **77**, 2505 (1955).

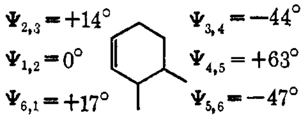
(11) R. Bucourt, *Bull. Soc. Chim. France*, 2080 (1964).

(12) R. Bucourt and D. Hainaut, *ibid.*, 1366 (1965).

(13) M. Davis and O. Hassell, *Acta Chem. Scand.*, **17**, 1181 (1963).

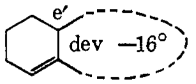


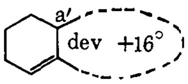
IV



V

computation by Bucourt for cyclohexane gave values of 111.1 and 55.5° for the ring C–C–C and dihedral angles, respectively, in excellent agreement with the experimental values noted above. The ring strain calculated for cyclohexene in its half-chair form was 1.57 kcal/mole, being composed of ring or Baeyer strain, 0.15 kcal/mole, and Pitzer strain, 1.42 kcal/mole. In assessing the external dihedral angle that is important to us, Bucourt[14] chose a deviation of ±16° from an arbitrary normal value for cyclohexane.





Under *ideal* circumstances then, the dihedral angle between two substituents at the 1- and 6-*eq* positions will be about 43–44°, based on an arbitrary value of 60° for cyclohexane, rather than the 35[4] or 39°[10] used previously. For two methyl groups attached at these points (II, R = R′ = CH_3), this represents an increased interaction between them of approximately 0.5–0.6 kcal/mole. This value is realistic only if the methyl groups in the system can be related to the CH_3–CH_3 skew interaction in butane since it is calculated using the equation $V\psi = V_0/2(1 - \cos 3\psi)$. The latter is the usual form used to describe possible energy variations in Pitzer strain with change in the dihedral angle.[15] The transannular diaxial strain in the 1,6-*ax* conformer can be taken as 0.9 kcal/mole. Although the 6-*ax*-methyl group and the 4-*ax*-hydrogen atom are perhaps a little further apart than such 1,3-diaxial groups would be in cyclohexane, we assume that the greater tendency to conformational change from IIa to IIb would be compensated for by the loss of hyperconjugation with the 6-*ax*-hydrogen atom. The interaction between the C-1 methyl and the 6-*eq*-hydrogen atom can be estimated as 0.25 kcal/mole (work mentioned later suggests this value may be somewhat higher, ~0.6 kcal/mole) based on a methyl–hydrogen interaction in propane, again calculated from the $V\psi = V_0/2(1 - \cos 3\psi)$ formula. Using these very approximate figures it can be seen that the 1,6-*eq* conformer is 0.35 kcal/mole more energetic than the 1,6-*ax* conformer. 1,6-Dimethylcyclohexene then could be expected to exist as a 64:36 mixture of axial and equatorial conformers. It should be mentioned also at this point that a conformational change of the ring to the boat form serves only to increase the interaction between substituents at C-1 and C-6 as judged from models so that only the half-chair form will be considered in the examples discussed below.

One may expect, therefore, that $A^{(1,2)}$ strain (a) will make itself felt when the groups at C-1 and C-6 are bulky, (b) will, from literature evidence, operate best when the C-1 substituent conjugates with the double bond, and (c) will not exert a controlling effect unless all other major steric factors in the system cancel one another. *It is not a very powerful effect.*

B. GENERAL CASES OF $A^{(1,2)}$ STRAIN

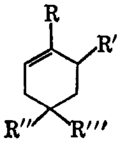
1. Conformational Preference

The outstanding examples of $A^{(1,2)}$ strain in simple systems are provided by the work of Garbisch.[16–18] By nmr spectroscopy he was able to show that in many 1,6-disubstituted cyclohexene derivatives the dominant conformation is that with the substituent at C-6, axially oriented. He concluded that in 1-arylcyclohexenes the 6-*eq* substituents were held more nearly in the C-2–C-1–C-6 plane than were the 6-*ax* substituents, and that the interaction between the aryl group and the C-6 substituent was, at least in part, the impetus leading to a preference for conformation IIb. Garbisch's results for specific examples of the general case VI are shown in Table I. Several very interesting points emerge from these findings. First, although no direct comparison of the same groups (*e.g.*, R = R′ = CH_3) is available, it is obvious that the well-known 1,3-diaxial interaction has a greater effect than $A^{(1,2)}$ strain in these compounds. Otherwise in cases d, k, and l the conformation having the C-6 substituent (R′) in the axial orientation might have been expected to prevail. Secondly, since it has been shown that the NO_2 group is not much larger than methyl, as judged from conformational energies[19–21] (the difference between their $\Delta G_x°$ values being ~0.25 kcal/mole), the estimation made above for the conformational composition of 1,6-dimethylcyclohexene does not seem unreasonable in the light of experimental results with VI. If anything, the calculation errs in the direction of the equatorial conformation (*i.e.*, the calculated energy difference between conformers is probably too low). One other point deserves comment, and this concerns the

---

(14) R. Bucourt, *Bull. Soc. Chim. France*, 1262 (1963).
(15) F. H. Westheimer, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 12.
(16) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4243 (1962).
(17) E. W. Garbisch, Jr., *ibid.*, **27**, 4249 (1962).
(18) E. W. Garbisch, Jr., *ibid.*, **30**, 2109 (1965).
(19) R. J. Ouellette and G. E. Booth, *ibid.*, **30**, 423 (1965).
(20) R. J. Ouellette and G. E. Booth, *ibid.*, **31**, 3065 (1966).
(21) W. F. Trager and A. C. Huitric, *ibid.*, **30**, 3257 (1965).

TABLE I
CONFORMATIONAL STUDY OF VI

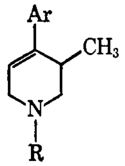


	R	R'	R''	R'''	Preferred conformer of R'
a	C_6H_5	$(CH_3)_3C$	H	H	*ax*
b	C_6H_5	C_6H_5	H	H	*ax*
c	C_6H_5	$(CH_3)_2COH$	H	H	*ax*
d	C_6H_5	$(CH_3)_2COH$	CH_3	CH_3	*eq*
e	C_6H_5	$COCH_3$	H	H	ncp[a]
f	C_6H_5	$COCH_3$	CH_3	CH_3	*eq*
g	CH_3	$COCH_3$	H	H	ncp[a]
h	C_6H_5	NO_2	H	H	*ax*
i	$CH_3C_6H_4$	*trans*-NO_2	$(CH_3)_3C$	H	*ax*
j	C_6H_5	*trans*-NO_2	CH_3	H	*ax*
k	C_6H_5	*cis*-NO_2	CH_3	H	*eq*
l	C_6H_5	NO_2	CH_3	CH_3	*eq*
m	CH_3	NO_2	H	H	*ax*
n	CH_3	Br(2-NO_2)	H	H	*ax*
o	OCH_3	Br	H	H	*ax*

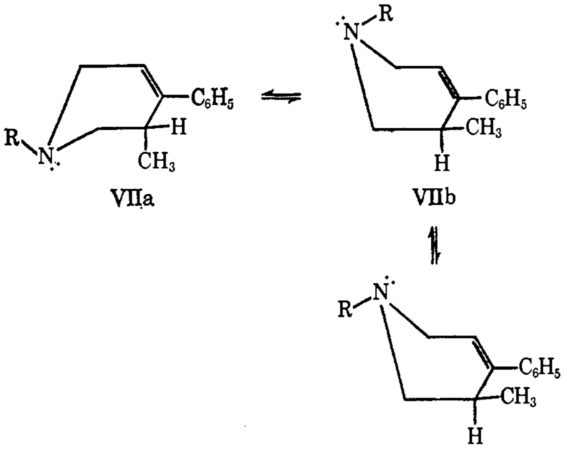
[a] ncp = no conformational preference.

lack of preference displayed in cases e and g. Based on size considerations alone, it would have been anticipated that the axial orientation of the acetyl group would have been preferred, especially since the nitro group has recently been estimated[19-21] to be the same size as acetyl. Why no conformational preference is displayed in these cases remains a mystery.

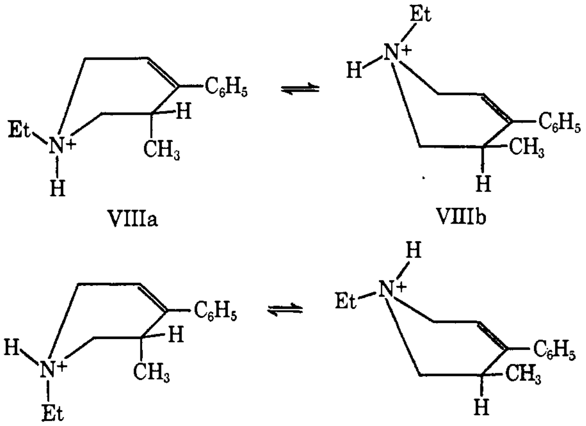
Most interesting examples of this type of strain, closely related to the work of Garbisch, are the cases of VII reported by Beckett, *et al.*[22-24] In all of these molecules, that conformation VIIa which possesses an axial methyl group appears to be preferred over the other possible forms VIIb and VIIc. Evidence for this conclusion was derived largely from intrinsic ultraviolet absorption data (hypsochromic shift of 10.5–12.5 mμ) and by comparison of their nmr and ultraviolet spectra with those of 1-phenyl-6-substituted cyclohexenes. The destabilizing 1,3-diaxial interaction in VIIa between the lone pair on nitrogen and the 5-methyl group was considered to be small. However, it was found that protonation of these compounds reduces the population of the conformer with the 5-*ax*-methyl group to ~50% of the total (nmr evidence in deuteriochloroform). It is interesting that, in the case of the N-ethyl salt (VIII), only the forms VIIIa and VIIId in a ratio of about 43:57 could be detected in solution. The authors have ascribed the increased interaction of the proton on nitrogen versus the lone pair with the 5-*ax*-methyl group as being primarily responsible for this. It seems more likely that superimposed in this effect there must also be steric effects of the gegenion and perhaps also of molecular association. These would drive the equilibrium in the same direction and account for the rather large change in the equilibrium position, rather than attributing it completely to the difference in size between a proton and a lone pair of electrons on nitrogen.



VII



VIIa VIIb VIIc



VIIIa VIIIb VIIIc VIIId

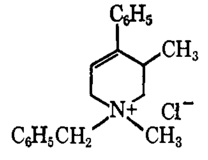
In connection with this the same authors showed that quaternization of VII with alkyl halides further reverses the conformational equilibrium, and in compounds such as IX the conformer with an equatorial methyl group at C-5 predominates. Ultraviolet data indicate that in IX there is a decrease in the coplanar nature of the styrenoid chromophore by comparison with the free base VII (R = $CH_2C_6H_5$).

---

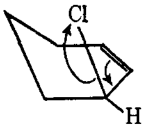
[22] A. H. Beckett, A. F. Casy, and M. A. Iorio, *Tetrahedron*, **22**, 2745 (1966).

[23] A. H. Beckett, A. F. Casy, and H. Z. Youssef, *Tetrahedron Letters*, 537 (1965).

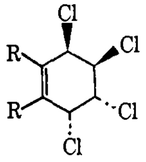
[24] A. F. Casy, A. H. Beckett, M. A. Iorio, and H. Z. Youssef, *Tetrahedron*, 3387 (1966).

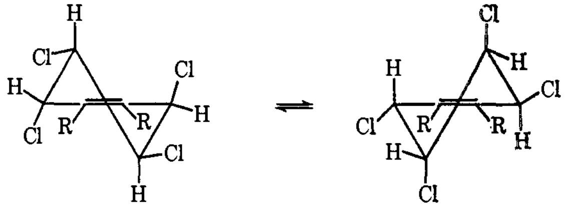

IX

Two other monocyclic cases which appear to be examples of A$^{(1,2)}$ strain are those of 3-bromo- and 3-chlorocyclohexene. These substances have been shown both by Raman and infrared spectroscopy[25] to exist preferentially in the conformation with the halogen atom axially oriented in the liquid or gaseous state, the chloro compound to the extent of 74.5% and the bromo compound to the extent of 79.5%. The same author also found[26] that in the liquid or vapor state the isomeric 4-bromocyclohexane exists as a mixture of conformers, that with the axial bromine atom slightly predominating. The energy difference between the two forms here was estimated to be about 50 cal/mole. This figure compares excellently with the value 77 ± 15 cal/mole found by Jensen and Bushweller[27] in their determination of the energy barrier to ring inversion in 4-bromocyclohexane (the latter being calculated to be 5.93 kcal/mole at −116.1°K). These authors consider that the rather large amount of the axial bromo conformer present is due to the reduction of transannular interactions *vis-à-vis* bromocyclohexane. If 4-bromocyclohexene is considered to be normal, the difference between the conformational preferences of the 3-halo- and 4-halocyclohexenes could thus be ascribed to A$^{(1,2)}$ strain. However, a more plausible explanation may be that of allylic participation in which the double bond contributes to a slightly more ionic C–halogen bond in the ground state when the halogen is axial (X) than when it is equatorial, thus lowering the energy of the system when in this conformation.


X

Another similar example where A$^{(1,2)}$-strain effects become noticeable involves the conformational state of *cis,trans,cis*-1,2,3,4-tetrachlorotetrahydronaphthalene (XI) (R, R = –CH=CHCH=CH–). This has been shown by de la Mare, *et al.*,[28] to exist almost entirely as the conformer XIa rather than XIb in solution whereas previous X-ray work[29] had concluded that in the solid state it was exclusively XIa. However, in the case of the corresponding cyclohexene derivative XI (R = R = H) the conformational equilibrium mixture was found to contain a considerable amount of XIb as determined from dipole and electron diffraction measurements[30,31] even though the transannular interactions that the axial chlorine atoms encounter must be the same in both systems and despite the fact that the Cl–Cl interactions must be greater in XIa than XIb. The additional factor contributing to the displacement to the left of the above equilibrium is undoubtedly the interaction between the C-1 and C-4 chlorine atoms and the hydrogens in the C-6 and C-8 *peri* positions in the isomer on the right, in effect a form of A$^{(1,2)}$ strain. The mechanism of hydrolysis of both the above tetralin and cyclohexene compounds is thought to proceed through the conformations represented by XIb; accordingly the tetralin reacts more slowly[32] than the cyclohexene.


XI


XIa XIb

An outstanding manifestation of A$^{(1,2)}$ strain occurs in the province of enamines. Generally speaking a *pyrrolidine* enamine of structure XII exists largely as that conformer (XIIb) having R in the quasi-axial orientation.[33,34] In XIIa the steric interference between R and a CH$_2$ group of the amine is substantial because of the tendency of the lone pair on nitrogen to conjugate with the double bond and for which a planar state of the atoms concerned is highly desirable. That


XIIa XIIb

---

[25] K. Sakashita, *Nippon Kagaku Zasshi*, 81, 49 (1960).
[26] K. Sakashita, *ibid.*, 80, 972 (1959).
[27] F. R. Jensen and C. H. Bushweller, *J. Am. Chem. Soc.*, 87, 3285 (1965).
[28] P. B. de la Mare, M. D. Johnson, J. S. Lomas, and V. Sanchez del Olmo, *J. Chem. Soc., B*, 827 (1966).
[29] M. A. Lasheen, *Acta Cryst.*, 5, 593 (1952).
[30] O. Bastiansen, *Acta Chem. Scand.*, 6, 875 (1952).
[31] O. Bastiansen and J. Markali, *ibid.*, 6, 442 (1952).
[32] P. B. D. de la Mare, R. Koenigsberger, and J. S. Lomas, *J. Chem. Soc., B*, 834 (1966).
[33] F. Johnson and A. Whitehead, *Tetrahedron Letters*, 3825 (1964).
[34] S. K. Malhotra and F. Johnson, *ibid.*, 4027 (1965).

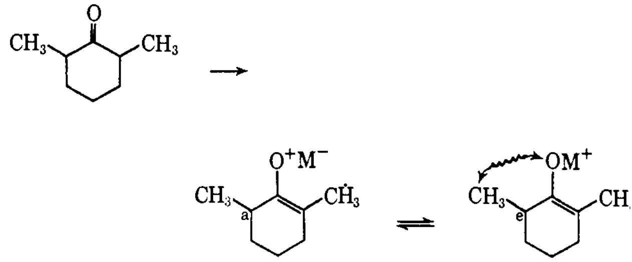
this type of enamine exists preferably as XIIb was suggested first by Williamson.[35] However, a full discussion of his reasoning is postponed to a later section where the formation, proof of structure, and reactivity of enamines will be dealt with in detail.

Another example closely related to the case of XII, in which $A^{(1,2)}$ strain is thought to control the conformational composition, concerns the enolate anions of certain substituted cyclohexanones. It has been found that[36] the ratio of conformers XIIIa and XIIIb in the potassium enolate salt of 2,6-dimethylcyclohexanone is solvent dependent (Table II). To a rough approximation, the bulkier the solvent the greater the amount of XIIIb. This has been interpreted as being due to the interaction of the solvated ion pair O^-M^+ with the methyl group at C-6. The greater this interaction the greater the amount of XIIIb produced at equilibrium. This of course must have a limit because eventually interference will begin to occur even between the solvated ion pair and the axial methyl group. A leveling effect can thus be expected as the solvent becomes bulkier, and a point will be reached where further increase in solvent size will not affect the ratio of the two conformers. This may well have been reached in the case of triglyme since tetraglyme changes the ratio but little.

TABLE II

Solvent	$cis^{a,b}$	$trans^{a,b}$
Tetrahydrofuran	63.7	36.3
N,N-Dimethylacetamide	61.7	38.3
Benzene	61.6	38.4
Ether	59.1	40.9
Monoglyme	56.2	43.8
Diglyme	55.0	45.0
Dioxane	52.4	47.6
Hexamethylphosphoramide	50.8	49.2
Dimethylformamide	47.8	52.2
Dimethyl sulfoxide	44.9	55.1
Sulfolane	44.8	55.2
Triglyme	38.6	61.4
Tetraglyme	45.0	55.0

[a] In these solvents the equilibrium percentage of the *cis* (Va) isomer is in the range of 90–92% (*cf.* ref 7) as determined by glpc. [b] Corrected percentages based on the isomeric distribution of free ketone under equilibrating conditions.



XIIIb XIIIa

It is pertinent that the ratios quoted in Table II were obtained by quenching one part of the equilibrated reaction product in acetic anhydride. The ratio of enol acetate to ketone in the product (by glc) was used as a direct measure of enolate anion formation. The other part of the reaction mixture was quenched with aqueous acetic acid using high-speed stirring and the ratio of *cis* and *trans* ketone again determined by glpc analysis. This ratio was corrected for ketone not in the enolate state (as computed from the acetic anhydride quenching) to give the ratios cited. The whole argument rests of course on there being stereoelectronic control of the protonation in the acid-quenching process. Evidence for this was derived from the quenching of the enolate anion of 2,6-dimethyl-4-*t*-butylcyclohexanone, with deuterioacetic acid–deuterium oxide under irreversible conditions. The infrared spectrum of the product showed principal absorption in the C–D stretching region characteristic of axial C–D. This result seems to imply that the bulk of the protonation occurs with stereoelectronic control, thus confirming the above conclusions.

An alternative proposal has been put forward by House, Tefertiller, and Olmstead.[37] As a result of careful deuterium-labeling studies on the protonation of the lithium enolate of 4-*t*-butylcyclohexanone and of the 1,2 enolate of 2-ethyl-4-*t*-butylcyclohexanone by acetic acid, they have proposed that both O and C protonation occur to an equal extent. Furthermore, they have suggested that C protonation in the absence of steric effects is not subject to stereoelectronic control (*i.e.*, protonation from either side of the molecule is equally probable), whereas the further conversion to ketone of the enol derived from O protonation, proceeds with a high degree of stereoelectronic control (*i.e.*, axial protonation at C-2). Confirmation of the latter point was elicited from deuterioacetic acid hydrolysis experiments with 1-ethoxy-4-*t*-butylcyclohexene. The monodeuterated 4-*t*-butylcyclohexanone obtained was composed of more than 90% of the axial deuterio isomer.

Despite this interpretation of the mechanism of protonation of enolate anions, it cannot account for the production of *trans*:*cis* 2,6-dimethylcyclohexanone in a ratio greater than 1:3. It does however suggest that $A^{(1,2)}$ strain associated with the enolate anion XIIIa is less than previously postulated.[33]

A similar effect involving an enolate system has been noted by Ringold and coworkers.[38] From kinetic studies they have concluded that the introduction of a methyl group at the 2 position of testosterone destabilizes the potassium enolate salt with respect to that of testosterone. This is best accounted for on the basis

---

(35) W. R. N. Williamson, *Tetrahedron*, **3**, 314 (1958).

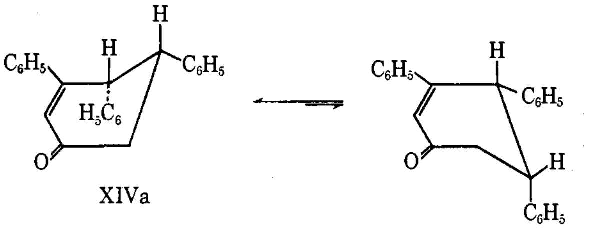
(36) S. K. Malhotra and F. Johnson, *J. Am. Chem. Soc.*, **87**, 5513 (1965).

(37) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

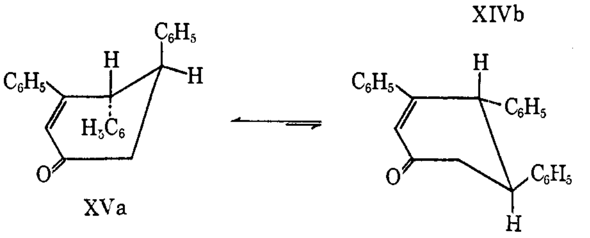
(38) G. Subrahmanyam, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **88**, 1332 (1966).

of a steric interaction between the C-2 methyl group and the solvated O^-M^+ system at C-3.

Lastly a very interesting case has been reported recently by Baradel and his associates.[39] They found from nmr studies that the isomeric cyclohexenones XIV and XV both exist largely in the conformations having an axial phenyl group at C-3 (XIVa and XVa, respectively) in accordance with $A^{(1,2)}$-strain predictions.


XIVa

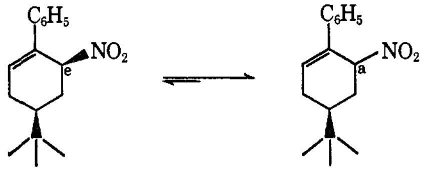
XIVb


XVa

XVb

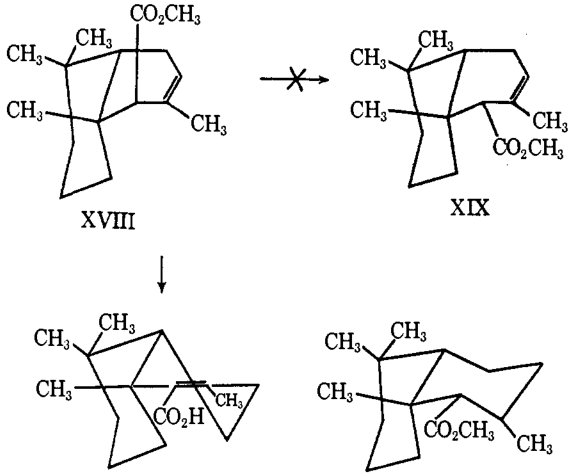
2. *Isomerizational Preference*

Since by definition isomers are closely related to conformers, it might be expected that $A^{(1,2)}$ strain also could control the equilibrium composition of the former, other factors being equal. An example of such a case is the base-catalyzed equilibration of *cis*- and *trans*-4-butyl-6-nitro-1-phenylcyclohexenes (XVI and XVII, respectively) which leads to an equilibrium composition of 85–95% of the *trans* stereoisomer (*i.e.*, axial nitro group).[40]


XVI

XVII

A most interesting example in a more complicated system is that reported by Stork and Burgstahler,[41] who found that the bicyclofarnesic acid methyl ester (XVIII) was unchanged when treated with sodium methoxide at 150–160° for 24 hr.

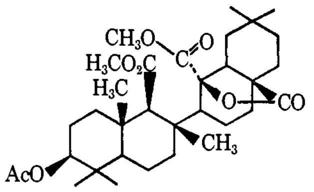

XVIII

XIX

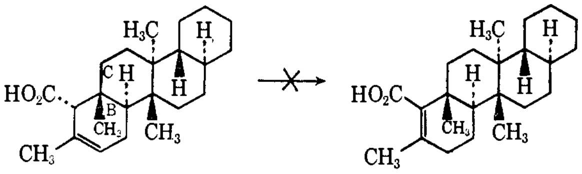
XXI

XXII

Barton[42] pointed out that in severely crowded systems such as XXIII the axial orientation of the carboxyl function will probably be the more stable. However, as noted by Stork,[41] most of the compulsion in XVIII for an axial carbomethoxy group appears to be the interaction between the methyl group on the double bond and the carbomethoxyl in the equatorial isomer XIX since XXII fails to undergo any isomerization when treated with base. Surprisingly perhaps, it proved possible to move the double bond into conjugation, by first preparing the acid chloride and then hydrolyzing the latter. The product was formulated as XXI. Further discussion of this system is deferred to the section below on carbanions.


XXIII

A very closely related example has been described by Corey and Ursprung.[43] They isolated a degradation product from friedelin having structure XXIV in which the carboxyl group was found to be more stable in the axial orientation. In this instance, however, acid-catalyzed isomerization of the double bond to give the α,β-unsaturated system XXV could not be accomplished. This was explained as being due to the *trans*-fused relationship of the B–C junction. In the decalin series such a relationship favors a Δ^2 over a Δ^1 double bond.


XXIV

XXV

---

[39] A. M. Baradel, J. Dreux, and R. Longeray, *Bull. Soc. Chim. France*, 3543 (1966).

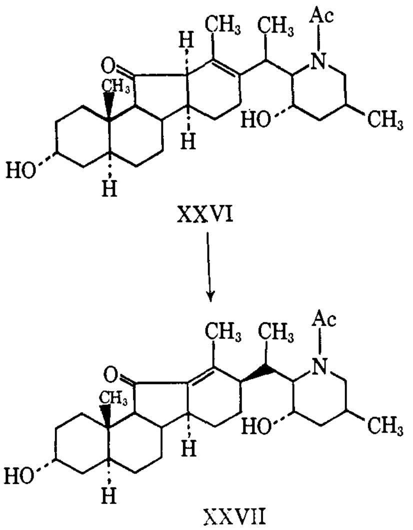
[40] Unpublished work quoted in footnote 17 of ref 17.

[41] G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955).

[42] D. H. R. Barton and G. A. Morrison, *Fortschr. Chem. Org. Naturstoffe*, **19**, 165 (1961).

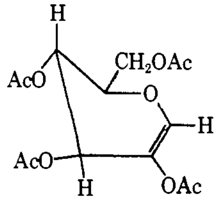
[43] E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.*, **78**, 5041 (1956).

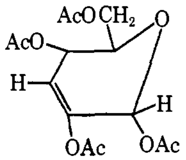
Another example of this phenomenon has been described by Wintersteiner and Moore[44] in the jervine series. They found that base-catalyzed isomerization of XXVI led to compound XXVII in which the large side chain of ring D is axially oriented.

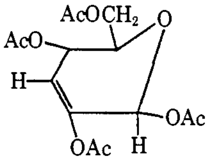

XXVI

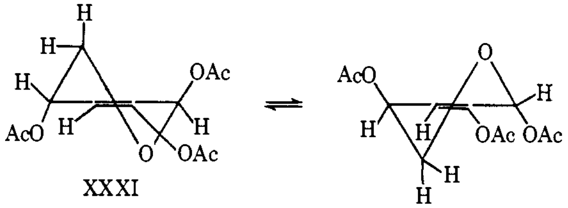
XXVII

A case of simple isomerization, where allylic strain has been invoked as an explanation,[45] is the rearrangement of XXVIII to XXIX together with smaller amounts of XXX when treated at room temperature with zinc chloride in acetic anhydride for 10 min.[46] Models suggest that there is little geometrical difference in the allylic systems of cyclohexene and 2H-3,4-dihydropyran. In XXVIII strain exists between the acetates at C-3 and C-4 because the latter acetoxyl group is equatorial. In the product, XXIX, where the corresponding acetate now has an axial orientation this interaction has been lost.


XXVIII


XXIX

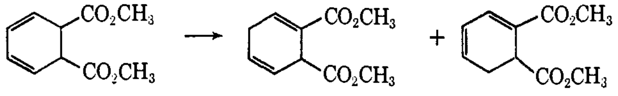

XXX

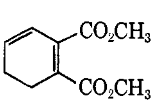

XXXI

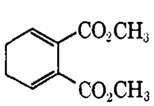
XXXII

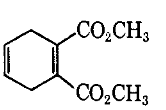
Ferrier and Sankey[45] have also investigated the conformational equilibrium between XXXI and XXXII and have concluded that the energy difference between them is 0.8 kcal/mole (at 118°) in favor of XXXII. In the case of compounds having benzoyloxy groups instead of acetoxyls, the energy difference rises to 1.3 kcal/mole.

Finally in this section attention should be drawn to equilibration studies with the diene XXXIII.[47] The only two products that can be isolated are XXXIV and XXXV. Although it was not studied, the orientation of the 6-carbomethoxy group in both of these compounds is undoubtedly quasi-axial. Particularly in XXXV this must be the case since in this cyclohexadiene system the dihedral angle between the 1- and 6-*eq* positions is reduced to ~25°. Of interest also is the fact that none of isomers XXXVI–XXXVIII were found in the equilibration mixture, a testimony to the repulsion that must exist between the two carbomethoxy groups in such planar systems. This type of strain undoubtedly is present in dimethyl phthalate as it is in aspirin[48] and 1-bromo-2,4,6-trichlorobenzene.[49,50] In the latter case the aromatic ring itself is distorted.


XXXIII XXXIV XXXV


XXXVI


XXXVII


XXXVIII

Further aspects of $A^{(1,2)}$ strain are discussed below in the sections on enamines, enolate anions, and metal-ammonia reduction.

III. $A^{(1,3)}$ STRAIN

A. THE GEOMETRY OF METHYLENECYCLOHEXANE

The only calculations concerning the geometry of methylenecyclohexane are those of Corey and Sneen[10] who computed the shape of a ring having a single sp^2-hybridized carbon atom. The latter was assumed to have an angle of 120° in the ring, and coordinate analysis revealed a unique solution in which there was significant distortion from the cyclohexane molecule. In fact the ring assumes the shape of a flattened chair. The dihedral angle of importance for our purposes, that between the exocyclic sp^2 bond and the 2-*eq* bond, was

---

(44) O. Wintersteiner and M. Moore, *Tetrahedron*, **21**, 779 (1965).

(45) R. J. Ferrier and G. H. Sankey, *J. Chem. Soc., C*, 2345 (1966).

(46) R. U. Lemieux, D. R. Lineback, M. L. Wolfrom, F. B. Moody, E. G. Wallace, and F. Komitsky, Jr., *J. Org. Chem.*, **30**, 1092 (1965).

(47) P. Courtot and J.-M. Robert, *Bull. Soc. Chim. France*, 3362 (1965).

(48) P. J. Wheatley, *J. Chem. Soc., Suppl.*, 6036 (1964).

(49) A. I. Kitaygorodsky, *Tetrahedron*, **9**, 183 (1960).

(50) J. T. Struchkov and S. L. Solenova, *Proc. Moscow State Univ.*, **12**, 1228 (1959).

calculated to be 15.36°.[51] However, it was later noted that an angle of this magnitude would cause a 2-*eq* substituent on a cyclohexanone ring to make a considerable contribution to the ORD curve of the optically active form, contrary to experiment. In view of this, a new computation was made[52] in which the angle in the ring at the sp^2 carbon was given the experimental value found for acetone, namely 116°.[53] This led to the conclusion that the cyclohexanone ring is little distorted from that of cyclohexane and that the dihedral angle which the 2-*eq* (and the 6-*eq*) bond makes with the carbonyl plane is only 4.3°. This thus confirmed Barton's earlier empirical conclusion[54] that a 2-*eq* substituent in cyclohexanone would almost eclipse the carbonyl group. The bext model for methylenecyclohexane is undoubtedly isobutylene. Recent microwave measurements[55,56] on this molecule reveal the C–C–C angle to be $115.5 \pm 0.2°$ which is probably more accurate than the 112° (approximately) determined by electron diffraction.[57] Thus the later calculations[52] using acetone as a model seem eminently satisfactory for methylenecyclohexane.

No machine calculations have been made, for a six-membered ring with an exocyclic double bond, to determine the exact geometry of the conformation with minimum energy. However, Allinger, *et al.*,[58,59] have concluded from a consideration of all possible interactions in a series of conformations that the flexible form of cyclohexanone is more energetic than the chair form by 2.0 kcal/mole, and we may reasonably expect the same to be true for methylenecyclohexane.

For the purposes of further argument, the five centers involved in $A^{(1,3)}$ strain (*i.e.*, $R'—C_\gamma—C_\beta{=}C_\alpha—R$) will be regarded as lying in the same plane. This approximation seems justified since small lateral displacements of R′ or R perpendicular to the $C_\gamma—C_\beta{=}C_\alpha$ plane do little to reduce the nonbonded interaction between the groups. By adopting this simplification and using the most recently determined bond lengths and angles derived from isobutylene,[55,57] propene,[60,61] and long-chain hydrocarbons,[62–64] it is easy trigonometrically to compute the distances separating the central atoms of R and R′.

If $R = R' = H$, then the distance $R\cdots R' = r_{H/H} = 2.35$ Å. Similarly, if $R = H$ and $R' = CH_3$, then $R\cdots R'' = r_{H/CH_3} = 2.38$ Å, and, if $R = CH_3$ and $R' = H$, $R\cdots R' = r_{CH_3/H} = 2.50$ Å. Finally when $R = CH_3$ and $R' = CH_3$, $R\cdots R' = r_{CH_3/CH_3} = 2.45$ Å.

In methylenecyclohexane then, the ethylenic hydrogen atom *syn* to the 2-*eq* proton is slightly closer than the usually accepted van der Waals H–H distance (2.5 Å). However, calculations according to Hendrickson's form[65] of the interaction function $E = Be^{-ur} - (A/r^6)$ leads to a value of $\simeq$-85 cal per pair of H atoms indicating a very slight attraction between them. It is pertinent to note that if the C–C–C angle of methylenecyclohexane is given Bartell's value[57] of 112°, the $H\cdots H$ distance becomes 2.38 Å, and again the atoms attract one another ($\simeq$-94 kcal/mole. Using a "harder" curve such as that of Bartell,[66] the $H\cdots H$ interaction becomes a slight repulsion of about 0.2 kcal/mole while the curve of Bucourt and Hainaut[67] leads to a value of $\sim$0.4 kcal/mole. Whichever of the more acceptable forms[68] of the function is used, the interaction between the hydrogen atoms in question appears to be quite small.

On the other hand, in the case where $R = R' = CH_3$ ($r = 2.45$ Å), there is a large steric interaction and here there is a good literature case for comparision, namely, that of 1,8-dimethylnaphthalene (XXXIX). In the latter compound the experimentally determined strain energy[69] between the methyl groups is 7.6 kcal/mole, and using a nondistorted model (*ideal case*) the carbon atoms of the methyl groups can be calculated to be 2.49 Å apart based on X-ray data on naphthalene[70,71] for the ring dimensions. The nonbonded interaction of the methyl groups in IIIa ($R = R' = CH_3$) could be expected to be somewhat larger since not only are the methyl groups in XXXIX slightly further apart, but the latter system benefits from larger hyperconjugation effects than does IIIa ($R = R' = CH_3$). However, to a first approximation a value of 7.6 kcal/mole could be expected to represent the strain energy in the latter system.

Calculations according to the various forms of the energy curves for $C\cdots C$ nonbonded interactions at a distance of 2.45 Å give values ranging from $\sim$0.7 to $\sim$4 kcal/mole.[65] These calculations necessarily ignore $H\cdots H$ nonbonded interactions which are undoubtedly

---

(51) C. W. Shoppee, T. E. Bellas, R. E. Lack, and S. Sternhell, *J. Chem. Soc.*, 2843 (1965).

(52) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961); see ref 10.

(53) J. D. Swalen and C. C. Costain, *J. Chem. Phys.*, 31, 1562 (1959).

(54) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(55) V. W. Laurie, *J. Chem. Phys.*, **34**, 1516 (1961).

(56) L. H. Scharpen and V. W. Laurie, *ibid.*, **39**, 1732 (1963).

(57) L. S. Bartell and R. A. Bonham, *ibid.*, **32**, 824 (1960).

(58) N. L. Allinger, J. Allinger, and M. A. DaRooge, *J. Am. Chem. Soc.*, **86**, 4061 (1964).

(59) N. L. Allinger, J. G. D. Carpenter, and M. A. DaRooge, *J. Org. Chem.*, **30**, 1423 (1965).

(60) D. R. Lide and D. Christensen, *J. Chem. Phys.*, **35**, 1374 (1961).

(61) D. R. Lide and D. E. Mann, *ibid.*, **27**, 868 (1957).

(62) L. S. Bartell, *J. Am. Chem. Soc.*, **81**, 3497 (1959).

(63) R. A. Bonham and L. S. Bartell, *ibid.*, **81**, 3491 (1959).

(64) R. A. Bonham, L. S. Bartell, and D. A. Kohl, *ibid.*, **81**, 4765 (1959).

(65) J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).

(66) L. S. Bartell, *J. Chem. Phys.*, **32**, 827 (1960).

(67) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. France*, 501 (1966).

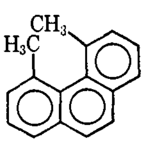
(68) C. A. Coulson and C. W. Haigh, *Tetrahedron*, **19**, 527 (1963).

(69) J. Packer, J. Vaughan, and E. Wong, *J. Am. Chem. Soc.*, **80**, 905 (1958).

(70) F. R. Ahmed and D. W. J. Cruickshank, *Acta Cryst.*, **5**, 852 (1952).

(71) D. W. J. Cruickshank, *ibid.*, **10**, 504 (1957).

the more important in this case. If the strain between the methyl groups of IIIa ($R = R' = CH_3$) is considered as a methane–methane interaction, then the value of *E*, according to the relationship suggested by Mason, *et al.*,[72,73] approximates 30 kcal/mole. This value must be far too large since the nonbonded interaction between the methyl groups in 4,5-dimethylphenanthrene (XL) has been shown to be ~12–15 kcal/mole,[74] and here by inspecting a model the methyl groups can be seen to be much closer than in IIIa.

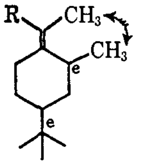


XL

In any case the methyl–methyl nonbonded interaction in IIIa ($R = R' = CH_3$) is certainly large enough to ensure that the conformational state of III must be very close to 100% IIIb. Available evidence suggest that the interaction appears to be even greater than that which exists between two methyl groups that are situated 1,3 diaxially in a cyclohexane ring (the latter has been assessed in all as ~3.6 kcal/mole[75]) and greater than that of an axial *t*-butyl group for which the $\Delta G_x{}^\circ$ has been estimated as 5.6 kcal/mole.[2,76]

On the basis of the above reasoning then, the strain energy difference between IIIa and IIIb can be calculated to be approximately 4.5 kcal/mole in favor of IIIb. This is derived empirically from the difference in nonbonded strain associated with the various interactions in each conformer, $\approx [1(A^{(1,3)}\ CH_3\text{–}CH_3$ interaction) $-$ 2(1,3-diaxial CH_3–H interactions) $-$ 1(*cis*-butene interaction)] $\approx [7.6 - 2 \times 0.9 - 1.3] = 4.5$ kcal/mole. No quantitative data are available to support such a large number. Whether experimentally the value will be found to be closer to ~4.5 kcal/mole or to the 1.0 kcal/mole calculated by the author[4] by equating the $A^{(1,3)}$ strain in IIIa with a 1,3-diaxial CH_3–CH_3 interaction must await further research. Qualitative data that are available would suggest a somewhat intermediate number.

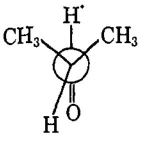
The conformational composition of molecules such as XLI, where the *t*-butyl and methyl groups are *cis* related, should prove most interesting since the $CH_3 \cdots CH_3$ interaction is relieved in the boat or twist-boat form, and this conformer should be anticipated as the dominant one.



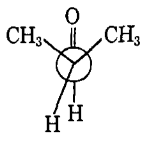
XLI

The intermediate cases of III where $R = CH_3$ and $R' = H$ or $R = H$ and $R' = CH_3$ are of interest for comparison purposes only. In the instance where $R = CH_3$ and $R' = H$, the system is very much like that of *cis*-2-butene so that the nonbonded interaction between the methyl group and the 2-*eq*-H atom may be assessed as ~1.3 kcal/mole. Conformational inversion here has no meaning since it leads to the same molecule. On the other hand, in the case where $R = H$ and $R' = CH_3$, there is an opportunity for conformational inversion to give a different form, namely 2-*ax*-methylmethylenecyclohexane. In view of the distance involved ($r = 2.38$ Å), one would expect the $A^{(1,3)}$ strain to be somewhat greater than 1.3 kcal/mole. However, several other factors complicate the issue. The segment of III under discussion conforms to 1-butene, and in the latter molecule *the conformation with the methyl group eclipsed with a C-1 hydrogen atom appears to be as well populated as the other two staggered forms where there is no eclipsing.*[77] This indicates that this nonbonded interaction is not important despite the fact that it could be compared to a 1,3-diaxial methyl–hydrogen interaction in a cyclohexane ring. Robinson,[78] in an extension of his paper on the reactivity of cyclohexanone,[79] has suggested that the eclipsed conformer of 1-butene is important in the conformational equilibrium because in this case *the hydrogen atoms at C-3 are in the best position for hyperconjugation.* This same factor undoubtedly operates to prevent conformational inversion of IIIa ($R = H$; $R' = CH_3$) to IIIb ($R = H$; $R' = CH_3$) since it is 2-*ax*-H and not 2-*eq*-H hyperconjugation with the double bond that is important.

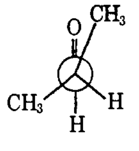
An alternative explanation for the eclipsing of a methyl group with the terminus of a π system has been offered by Bartell.[80] He found by electron diffraction that isobutyraldehyde exists as a conformational mixture of *gauche* and *trans* forms in the ratio of 10:1. The *cis* form appears to be absent. The preference for



trans



cis



gauche

---

[72] I. Amdur and A. E. Mason, *J. Chem. Phys.*, **23**, 415 (1955).

[73] A. E. Mason and W. E. Rice, *ibid.*, 22, 843 (1954).

[74] H. A. Karnes, B. D. Kybett, M. H. Wilson, J. L. Margrave, and M. S. Newman, *J. Am. Chem. Soc.*, **87**, 5554 (1965).

[75] N. L. Allinger and M. A. Miller, *ibid.*, **83**, 2145 (1961); see also C. W. Beckett, K. S. Pitzer, and R. Spitzer, *ibid.*, **69**, 2488 (1947).

[76] S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

[77] A. A. Bothner-By, C. Naar-Colin, and H. Gunther, *ibid.*, **84**, 2748 (1962).

[78] M. J. T. Robinson, Oxford University, England, private communication.

[79] W. D. Cotterill and M. J. T. Robinson, *Tetrahedron Letters*, 1833 (1963).

[80] J. P. Guillory and L. S. Bartell, *J. Chem. Phys.*, **43**, 654 (1965).

the *gauche* form thus approximates 1 kcal/mole and Bartell has suggested that this is due to an attraction between the carbonyl and methyl groups. He has further commented on the similarity of the conformational preference of isobutyraldehyde to that of 2-methylcyclohexanone. This explanation of methyl-carbonyl attraction would have to be made into a generality, *i.e.*, π-bond–alkyl group attraction, to explain all cases including that of 1-butene.[77] On electronic grounds this does not seem very likely.

The author considers that the hypothesis advanced by Robinson seems the more attractive since it can, without too much stretching of the imagination, cover all cases with reasonable ease. The Achilles heel of the argument, however, lies at the core, namely the concept of hyperconjugation, an ill-understood phenomenon which has been much disputed if not often discredited in the past.

Although theoretically a discussion of the acid-catalyzed equilibration between methylenecyclohexane and 1-methylcyclohexene might be placed in the section below on isomerization equilibria, it seems more pertinent to mention it here.

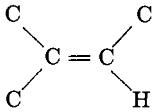
At equilibrium the system contains on the average 99.6% of 1-methylcyclohexene, and the free energy for the change *exo* to *endo* is -3.24 kcal/mole while the enthalpy is -2.4 kcal/mole.[81]

This change can be examined on a nonexperimental basis by using appropriate nonbonded interaction strain values. However, even when minimum values are chosen for methylcyclohexene and maximum values are considered for methylenecyclohexane to obtain the most favorable values for the isomerization, theory runs contrary to fact.

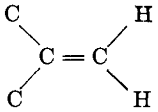
This strain in cyclohexene relative to cyclohexane as mentioned earlier has been computed to be 1.57 kcal/mole, being composed of Baeyer strain (0.15 kcal/mole) and Pitzer strain (1.42 kcal/mole). The introduction of a methyl group at the 1 position will lead to an $A^{(1,2)}$-strain interaction with the 6-*eq*-H atom of at the least 0.25 kcal/mole. There will also be an $A^{(1,3)}$ interaction (0.4 kcal/mole) between one of the hydrogen atoms of the methyl group and the hydrogen atom at C-2 since it must be expected that the methyl group will adopt the same orientation found in isobutylene. Thus the strain energy of 1-methylcyclohexene can be estimated to be 2.22 kcal/mole with respect to cyclohexane.

On the other hand, the introduction of a single sp^2-hybridized carbon atom into cyclohexane cannot be expected to lead to more angle strain than there is in cyclohexene (where by comparison two sp^2 carbon atoms have been introduced). Maximal additional strain of ~0.8 kcal/mole (see earlier discussion) comes from the nonbonded interactions of the 2-*eq*- and 6-*ax*-hydrogen atoms with the methylene hydrogen atoms (a destabilizing type of interaction that was emphasized by Turner[82]). All in all, the strain here does not appear to be greater than 1 kcal/mole, again with respect to cyclohexane. Thus one could reasonably expect that at equilibrium methylenecyclohexane should predominate to the extent of ~86%, quite contrary to experimental fact. One other major difference, however, that does exist between the two systems and which has been mentioned by Turner in his excellent paper[82] on the subject, is the number of hydrogen atoms available for hyperconjugation in each compound, two in methylenecyclohexane and four in 1-methylcyclohexene. Nevertheless, it does not seem likely that even this difference can be the ultimate driving force which controls the equilibrium between methylenecyclohexane and 1-methylcyclohexene. If it were, each of these hydrogen atoms would have to contribute ~2 kcal/mole to the system to explain the equilibrium. Such a value for hyperconjugation by hydrogen does not appear realistic.

Whatever the controlling effect is, however, it would seem to be remarkably constant. An examination of the equilibria of the homologous methylenecycloalkanes with the isomeric 1-methylcycloalkenes has shown[81] that they all lie almost completely on the side of the latter. This suggests that angle strain, tortional strain, and nonbonded interactions merely act as secondary effects modifying the ΔF and ΔH values concerned but not changing them drastically. The possibility exists that quite apart from hyperconjugation, the bonding situation in i is much to be preferred over that of ii being, in fact, related to a variation in the hybridization differences of the two systems.[83,84]



i



ii

B. GENERAL CASES OF $A^{(1,3)}$ STRAIN

1. *Conformational Preference*

No systematic investigation of a series of compounds has been carried out to assess the importance of this type of strain in six-membered monocyclic systems, and, in fact, even in related polycyclic systems one is hard pressed to find quantitative data.

One of the best documented examples involves the geometric isomers of 2-methylcyclohexylideneacetic

---

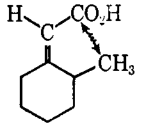
[81] A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and C. Jacura *J. Am. Chem. Soc.*, **82**, 1750 (1960).

[82] R. B. Turner and R. H. Garner, *ibid.*, **80**, 1424 (1958).

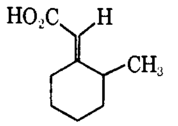
[83] M. J. S. Dewar and H. N. Schmeising, *Tetrahedron*, **5**, 166 (1959).

[84] S. W. Staley, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S146.

acid. Nmr studies[85] on these compounds have indicated that the *syn* isomer (XLII) exists as the conformer with an axial methyl group whereas the *anti* isomer (XLIII) largely is constituted of the conformer

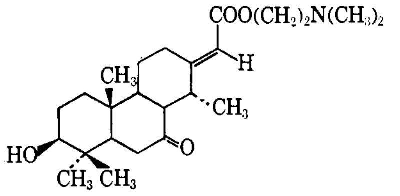


XLII



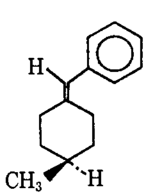
XLIII

with an equatorial methyl group. The compounds were used as models for the determination of the stereochemistry of the C-14 methyl group in cassain (XLIV). As it turned out this methyl group has the axial orientation.

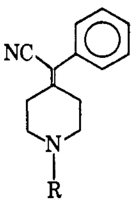


XLIV

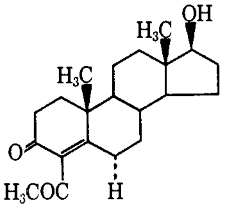
More subtle aspects of $A^{(1,3)}$ strain are to be found in examples XLV and XLVI. In the former, measurements on the optically active molecule[86] revealed that



XLV



XLVI



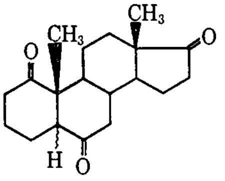
XLVII

the phenyl ring is twisted to a small degree out of the plane of the double bond, and this was ascribed, correctly it would seem, to interference between the phenyl ring and the *syn*-2-*eq*-hydrogen atom of the cyclohexyl ring.

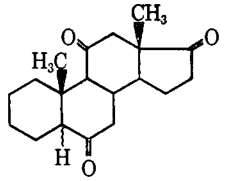
In the closely related XLVI (R = alkyl), ultraviolet spectral measurements have shown[87] that the benzene ring is twisted out of the plane of the double bond by as much perhaps as 35°. A similar effect has been noted[88] with 4-acetyltestosterone (XLVII), the acetyl group being twisted somewhat out of conjugation with the double bond. This result is undoubtedly due in part to the nonbonded interaction that would result between the acetyl group and the 6-*eq*-hydrogen atom if this carbonyl group were planar with the double bond. The same phenomenon involving 4-carbomethoxy-4-cholesten-3-one, has been recorded by Julia and Moutonnier.[89]

A number of interesting examples of allylic strain can be found among compounds in which one of the atoms of the allylic group has been replaced by an atom other than carbon. Provided that bond distances in the system remain approximately the same, the facts of $A^{(1,3)}$ strain should not be altered. Such systems have been termed pseudo-allylic and several examples of this type are noted below. First and foremost, the 2-alkyl ketone effect[90-93] can be placed in this category. Here the interaction can be looked upon as an interaction of the 2-*eq*-alkyl group with a nonbonding pair of electrons on oxygen. When the alkyl group is methyl, no nonbonded repulsive interaction can be noted since the conformational equilibrium is almost the same as that of α-methylcyclohexane. However, 2-*t*-butylcyclohexanone exists to the extent of ~15–18% in that conformer with an axial 2-*t*-butyl group. An interesting series to be studied for comparison with these results, would be the corresponding 2-alkylmethylenecyclohexanes. No work in this area has yet been reported.

Nevertheless, Jones and his coworkers[94] have shown recently that 1,6,17-trioxo-5α-androstane (XLVIIIa) is isomerized to the 5β isomer (XLIX) in 82% yield. They have also observed a similar isomerization with 1,6-dioxo-5α-androstane. On the other hand, it is known that *trans*-A/B-6-oxo compounds lacking the 1-oxo function are more stable than their *cis*-A/B isomers. It was concluded[94] that the isomerizations were driven by the severe nonbonded interaction that occurs with the 11α-hydrogen atom when a 1-oxo function is introduced into the *trans*-A/B system.



XLVIIIa (5α-H)
XLVIIIb (5β-H)



XLIXa (5α-H)
XLIXb (5β-H)

This repulsion is relieved in the *cis*-A/B form because the C-11-C-9-C-8 moiety in these compounds can assume an axial orientation with respect to ring A. These results represent perhaps an extreme case of the 2-alkyl ketone effect. By comparison XLIXa does

---

(85) H. Hauth, D. Stauffacher, P. Nicklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965).

(86) J. H. Brewster and J. E. Privett, *J. Am. Chem. Soc.*, **88**, 1419 (1966).

(87) C. M. Lee, A. H. Beckett, and J. K. Sugden, *Tetrahedron Letters*, 2721 (1966).

(88) M. Gorodetsky and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5213 (1964).

(89) S. Julia and C. Moutonnier, *Bull. Soc. Chim. France*, 3211 (1965).

(90) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Am. Chem. Soc.*, **88**, 2999 (1966).

(91) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, **20**, 765 (1964).

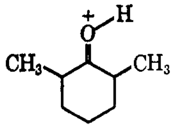
(92) W. D. Cotterill and M. J. T. Robinson, *ibid.*, **20**, 777 (1964).

(93) B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962).

(94) J. E. Bridgeman, P. C. Cherry, W. R. T. Cottrell, E. R. H. Jones, P. W. Le Quesne, and G. D. Meakins, *Chem. Commun.*, 561 (1966).

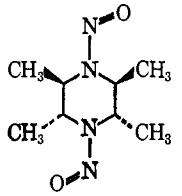
not isomerize to XLIXb under alkaline conditions. In the former the interference exists with the 1α-H atom whereas in the latter a similar interference would exist with the 5β-H atom. Since there would be no net change in nonbonded interactions, the normal stability order (*trans*-A/B > *cis*-A/B) prevails.

Work, related to both the above papers by Jones, *et al.*,[94] and to the anionic enolization studies[36] mentioned earlier, has been published recently by D'Silva and Ringold.[95] They observed that in 97.7% sulfuric acid at 27°, 2,6-dimethylcyclohexanone exists as a 56:44 mixture of the *cis* and *trans* isomers, respectively, rather than the normal 92:8 ratio found in the presence of dilute acid or base. In explaining this shift in equilibrium, they adopted the ideas of Malhotra and Johnson[36] that the solvent shell surrounding the protonated carbonyl group of L interacts with an equatorial methyl substituent. Apparently this interaction does not exist when the methyl group becomes axial, and the equilibrium therefore shifts in the direction of the *trans* isomer.

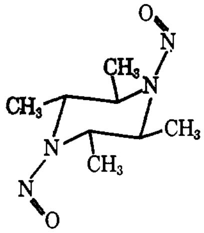


L

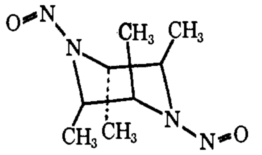
Another interesting example of $A^{(1,3)}$ strain concerns N,N′-dinitroso-2,3,5,6-tetramethylpiperazine (LI). Nmr evidence[96] indicates this compound *to exist in conformation LIb in which all methyl groups are axial.* By



LI

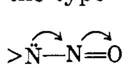


LIa



LIb

virtue of conjugation of the type

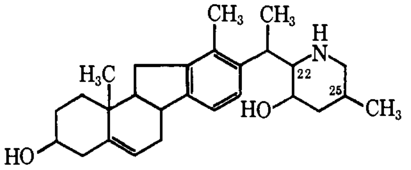


$$>\ddot{N}-N=O$$

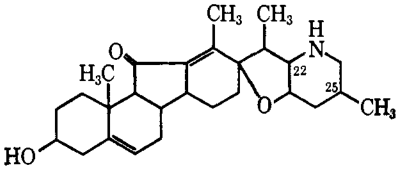
the atoms of the system $CH_3-\overset{|}{C}H-\overset{|}{N}-N-O$ are held in a plane, and thus severe steric interference could be expected between the oxygen of the nitroso group and the *syn*-methyl group in the conformer LIa—hence the conformational preference for LIb, despite the fact that the latter contains two 1,3-diaxial methyl-methyl interactions. More than likely though, the twist-boat conformation makes a large contribution to the state of LIb, because of the diminution in strain to be expected in this form.

This particular case raises the possibility that 2-substituted N-acylpiperidines might exist in that conformation with the 2-substituent axially oriented. That such is the case has been shown recently by Paulsen and Todt,[97] who found that N-trifluoroacetyl-2-methylpiperidine exists preferentially in that conformation with an axial methyl group. Again Nagarajan, *et al.*,[98] have demonstrated that N-acyl-2-methyl-1,2,3,4-quinolines exhibit similar behavior in that the conformation with an axial methyl group is preferred.

Perhaps the most outstanding example in this category concerns the stereochemistry of jervine and veratramine at C-22 and C-25. By nmr studies Johnson, *et al.*,[99] have shown recently that the substituents at



veratramine



jervine

these two centers are *trans* related, both having equatorial orientations. Previously they had been assigned a *cis* relationship by both Augustine[100] and Masamune, *et al.*[101] Working with the triketoamide LII derived from jervine, Augustine showed that on base treatment it led to a diastereoisomer in 75% yield. Since N-acetyl-5α,6,12,13-tetrahydrojervine was unaffected by the same treatment, he concluded that isomerization had occurred exclusively at C-22 to give the presumably more stable system with the C-22 and C-25 substituents *trans* related (diequatorial). Masamune and

---

[95] T. D. J. D'Silva and H. J. Ringold, *Tetrahedron Letters*, 1505 (1967).

[96] R. Harris and R. K. Spragg, University of East Anglia, private communication; see also R. K. Harris and R. A. Spragg, *J. Mol. Spectry.*, **23**, 158 (1967).

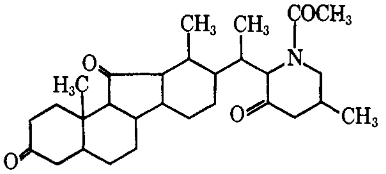
[97] H. Paulsen and K. Todt, *Angew. Chem. Intern. Ed. Engl.*, **5**, 899 (1966).

[98] K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967).

[99] J. W. Scott, L. J. Durham, H. A. P. deJongh, U. Burckhardt, and W. S. Johnson, *Tetrahedron Letters*, 2381 (1967).

[100] R. L. Augustine, *Chem. Ind.* (London), 1448 (1961).

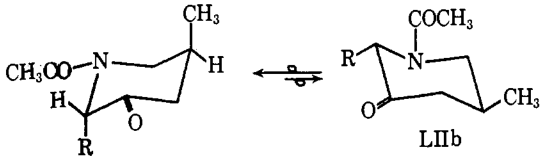
[101] T. Masamune, I. Yamazaki, and M. Takasugi, *Bull. Chem. Soc. Japan*, **39**, 1090 (1966).



LII

coworkers obtained similar results in that treatment of 23-dehydro-3,N-diacetylveratramine with alkali afforded a 1:10 equilibrium mixture of this compound and its C-22 epimer.

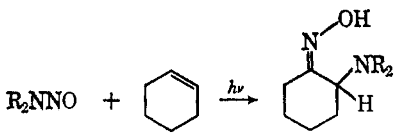
The nmr work by Johnson, *et al.*,[99] on N-benzoyl-5α,6-dihydroveratramine has shown that this compound exists in that conformation with all of the substituents in the piperidino ring axial. They conclude that the ketoamides studied by Augustine[100] and Masamune[101] also exist preferentially in this type of conformation (LIIa rather than LIIb). The isomerization of this system would be expected to give the C-22 diastereoisomer which would exist largely with the substituents at C-22 and at C-25, axially and equatorially oriented, respectively.



LIIa LIIb

The effect of the N-acyl group here is undoubtedly due to the fact that in the ground state overlap of the pair of electrons on nitrogen with the carbonyl group dominates the system. Thus it has all the makings of an exocyclic double bond and gives rise to a special case of $A^{(1,3)}$ strain.

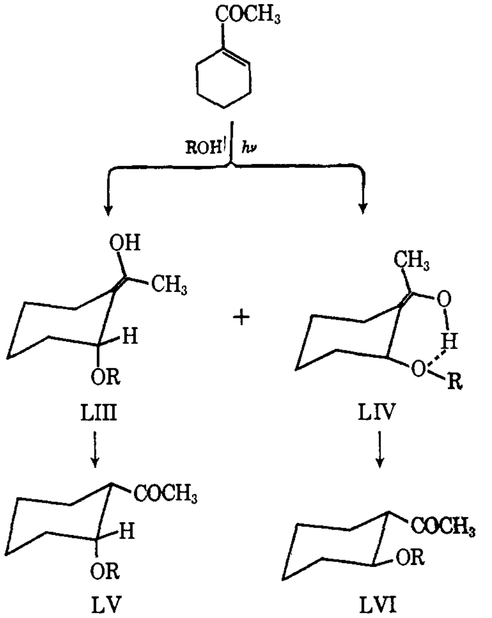
Related to this is some work recently reported by Chow.[102] He studied the conformations of a series of compounds LIIc derived from the photochemical addition of N-nitroso secondary amines to cyclohexene, and in which the oxime has the *syn* configuration. The C-2 hydrogen atom in these compounds did not give an nmr signal characteristic of an axial proton. The suggestion was made that the C–N bond in these compounds was bent down in order to make intramolecular hydrogen bonding possible. However, it seems much more likely in view of the nature of the system that the R_2N group in these compounds is axial and that the C-2 proton is equatorial. The half-height width of the nmr signal due to this proton is approximately 7 cps, in agreement with this point of view.



LIIc

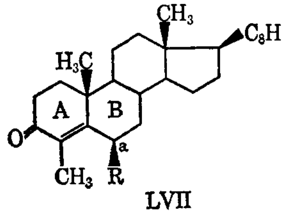
$R_2 = Bu_2$; $-(CH_2)_4-$; $-(CH_2)_5-$; $O(CH_2CH_2)_2-$

The recent work of Ramsey and Gardner[103] can be usefully compared with that of Chow. The former workers have found that the photochemical addition of an alcohol to 1-acetylcyclohexene occurs *via* the enolic intermediates LIII and LIV and gives rise to a mixture of the two possible isomers LV and LVI, in which the former predominates. The fact that some *trans* isomer (LVI) was produced was explained by invoking a hydrogen-bond stabilization of the enolic form which it was felt would compensate for the strain normally associated with such geometry. This enol was found to be longer-lived than LIII.



2. *Isomerizational Preference*

Some of the best examples of $A^{(1,3)}$ strain in this area involve bi- or polycyclic compounds in which ring B is regarded as the methylenecyclohexane moiety. Little is available that could be called quantitative information, however. Shoppee, *et al.*,[104] have examined a number of 6-substituted 4-methylcholest-4-enes (LVII).



LVII

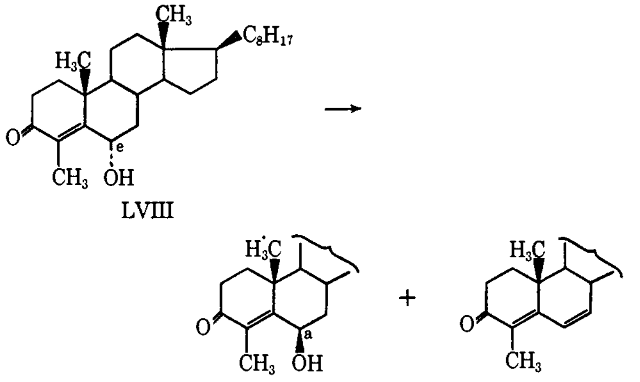
---

[102] Y. L. Chow, *Can. J. Chem.*, **43**, 2711 (1965).

[103] B. J. Ramsey and P. D. Gardner, *J. Am. Chem. Soc.*, **89**, 3949 (1967).

[104] C. W. Shoppee, F. P. Johnson, R. E. Lack, R. J. Rawson, and S. Sternhell, *J. Chem. Soc.*, 2476 (1965).

Attempts to epimerize LVII (R = Br or CH_2OAc) though hydrolysis of the derived enol acetates failed, only the 6β compounds being recovered. No better results were obtained by trying to isomerize LVII (R = Br) with hydrogen chloride in glacial acetic acid. The same workers were, however, able to prepare the highly unstable 6α-hydroxy compound LVIII, and this was completely isomerized to the quite stable 6β alcohol LIX when left in contact with Light's silica gel for 12 hr; some elimination also occurred to give the 3-keto-4,6-diene LX.



LVIII

LIX

LX

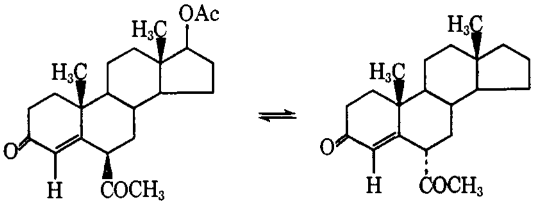
All of the structures were assigned on the basis of nmr evidence, and the instability of the 6α *vs.* 6β derivatives was diagnosed as being due to the severe nonbonded interaction between the methyl at C-4 and the 6α-R substituent.

A similar finding was reported by Petrov, *et al.*,[105] who observed that 4,6α-dimethyltestosterone acetate was very easily epimerized to the 6β isomer (LVII, R = CH_3). This represents a most important case since it is the only one involving only methyl groups where, in effect, $A^{(1,3)}$ strain is pitted against a 1,3-diaxial interaction. In this case the methyl group at the C-6 position has a choice of being involved in steric strain with either the C-4 methyl or the C-10 methyl group and apparently the latter involves less nonbonded interaction energy, giving credence to the opinion expressed earlier that all things being equal $A^{(1,3)}$ strain > 1,3-diaxial strain in six-membered ring systems. Undoubtedly the position of the methyl group in LVII (R = CH_3) is not purely axial but is at some equilibrium point where the $A^{(1,3)}$ and 1,3-diaxial steric interactions of the three methyl groups give a minimum for the internal strain in the molecule. As a result, it is very likely that ring B is distorted in the 6β isomer. By contrast, in the 6α isomer the B ring is probably severely skew- or boat-shaped as a result of the 4-Me–6α-Me interaction.[105]

Davies and Petrov[106] have also made an extensive study of R-band variations in the ultraviolet spectra of a series of 4,6-disubstituted 3-keto-4-ene steroids. The R bands in the case of the 6β-substituted compounds are well resolved and shift 7–20 mμ with respect to the parent 3-keto-4-ene steroid. For 6β-substituted compounds the R band is poorly resolved and does not shift relative to the parent compound. Substituents at C-4 have no effect on the R band. In the case of 4,6α-dimethyltestesterone propionate the R band, while poorly resolved, was shifted bathochromically, indicating a semiaxial substituent at C-6, in keeping with the expected boat-like character of ring B in this compound.

One troublesome feature is to be noted concerning the product of chlorination of 4-chlorotestosterone propionate. On the basis of R-band evidence (no shift with respect to starting material), this material was assigned the 6α-chloro configuration. Despite this, the compound has an ORD spectrum very similar to that of 4-chloro-6β-bromotestosterone propionate, whereas by comparison the 4,6α- and 4,6β-dimethyl analogs do show differences from one another in their ORD spectra. Nevertheless the ORD data are not given serious consideration, and the 6α orientation of the chlorine atom is asserted to be correct.

Gorodetsky and Mazur[88] have attempted to isomerize 6β-acetyl-4-methyltestosterone acetate (LVII, R = $COCH_3$) under acid conditions, but no conversion to the 6α isomer was noted. When the Δ^4 double bond was reduced, isomerization of the acetyl group from the 6β to the 6α position occurred with ease. However, in the case of 6β-acetyltestosterone acetate (LXI), acid-catalyzed equilibration afforded a 45:55 mixture of the 6β and 6α isomers (LXI and LXII, respectively). An almost identical ratio was found when the 3-deoxy compounds derived from LXI and LXII were equilibrated.[107] The relatively high proportion of the 6β isomer present at equilibrium merits some discussion since it is not likely that the nonbonded interaction between the hydrogen atom at C-4 and the 6α-acetyl group in LXII could alone account for this. It is well to compare this result with those of related 6α- and 6β-nitro steroids since the acetyl and nitro groups have been found to be approximately the same size.[19–21]



LXI

LXII

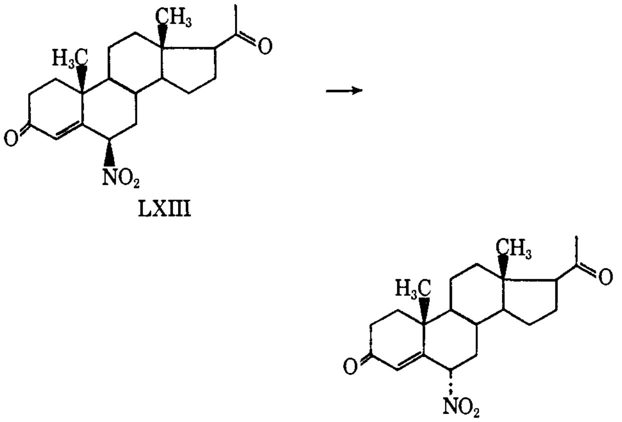
---

[105] D. Burn, G. Cooley, B. Ellis, A. R. Heal, and V. Petrov, *Tetrahedron*, **19**, 1757 (1963).

[106] M. T. Davies and V. Petrov, *ibid.*, **19**, 1771 (1963).

[107] M. Gorodetsky, D. Amar, and Y. Mazur, *J. Am. Chem. Soc.*, **86**, 5218 (1964).

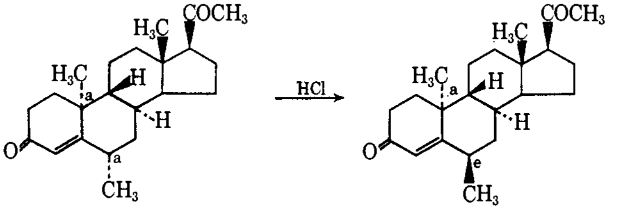
6β-Nitroprogesterone (LXIII), for example, is converted[108] by a trace of base to the 6α isomer (LXIV) in better than 90% yield.



LXIII

LXIV

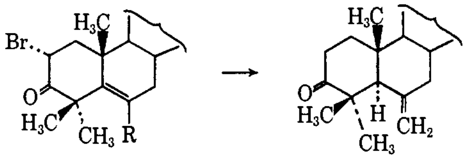
Again in the light of the former equilibrium, the isomerization[109] of LXV to LXVI (92% yield) would not be expected to be so complete, considering the small difference in size between acetyl and methyl. The answer, suggested by Mazur, *et al.*,[88] is that in the 6β-acetyl case homoallylic conjugation between the Δ⁴ double bond and the carbonyl of the 6β-acetyl group occurs to help stabilize this particular isomer. This presumably cannot occur in the case of the nitro group. In support of this argument circular dichroism measurements indicate that in the 6β isomer the acetyl group is so oriented that the carbonyl function points toward C-1 as would be required by such conjugation. In the 6α isomer the pertinent orbitals are orthogonal to each other. Despite this erudite suggestion cognizance must be taken of the fact that homoallylic conjugation is considered to be largely an excited-state phenomenon and whether it can make any contribution to ground-state stabilities is still a matter for conjecture.



LXV LXVI

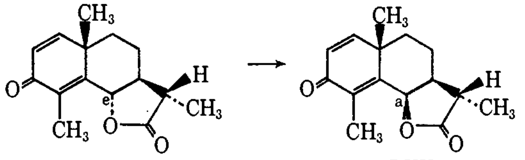
In the triterpenoid series, Holker, *et al.*,[110,111] have noted that in the lanosterol derivative LXVII (R = CH_3), the A ring has a classical boat shape (C-3–C-10, stem-to-stern). In this conformation the C-6 methyl group is approximately 2.9 Å from either of the methyl groups at C-4.

In the conformation where ring A is chair shaped, the 4α-methyl is only about 2.1 Å from the C-6 methyl group—an impossible situation. Nevertheless, exactly what contribution the latter interaction makes toward keeping ring A in the boat conformation is indeterminate since the corresponding dimethyl compound (LXVII, R = H) was also found to have a boat-shaped ring A. Probably it simply raises the ground-state energy level *vis-à-vis* LXVII (R = H). The interesting fact that emerges from this work,[112] however, is that the double bond in LXVII (R = CH_3) is very easily isomerized by acid to the exocyclic position to give LXVIII, a reversal of the normal *exo-endo* double-bond isomerization trend (*vide supra*). During this change some of the strain in the starting material is relieved in the product since the latter has a *trans*-A/B fusion and a chair-shaped ring A, a situation in which the methylene group at C-6 bisects the CH_3–C_4–CH_3 angle.

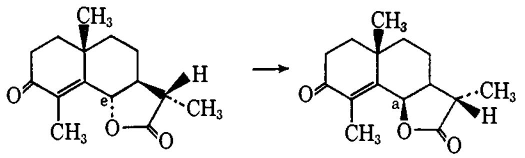


LXVII LXVIII

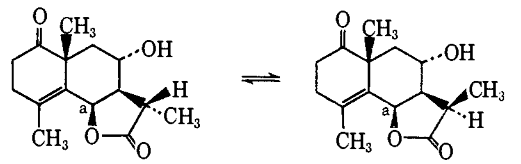
Other interesting examples of this type of $A^{(1,3)}$ strain exist in the santonin series of compounds. For instance, Ishikawa[113,114] found that hydrogen chloride or bromide in dimethylformamide smoothly isomerized (−)-α-santonin (LXIX) to santonin-C (LXX). Sim-



LXIX LXX



LXXI LXXII



LXXIII LXXIV

---

(108) A. Bowers, M. B. Sanchez, and H. J. Ringold, *J. Am. Chem. Soc.*, 81, 3702 (1959).

(109) H. Van Kamp and S. J. Halkes, *Rec. Trav. Chim.*, 84, 904 (1965).

(110) R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963).

(111) B. B. Dewhurst, J. S. E. Holker, A. Lablache-Conlier, M. R. G. Leeming, J. Levisalles, and J.-P. Pete, *Bull. Soc. Chim. France*, 3259 (1964).

(112) J. S. E. Holker, University of Liverpool, England, private communication.

(113) H. Ishikawa, *J. Pharm. Soc. Japan*, 76, 504 (1956).

(114) H. Ishikawa, *ibid.*, 76, 507 (1956).

ilar results were obtained with α-dihydrosantonin (LXXI), the product being LXXII. In a related series, Dauben, *et al.*,[115] noted that ψ-santonin (LXXIII) is stable to base at the C-6 position. Partial isomerization, however, does occur at the site adjacent to the carbonyl group to give an equilibrium mixture of starting material and LXXIV.

Although in the cases of LXIX and LXXI the conversion of the *trans*- to the *cis*-lactone is in itself an exothermic process, a large part of the driving force for isomerization must come from the $A^{(1,3)}$ strain between the C-4 methyl group and the C-6 oxygen atom since the products themselves contain a fairly strong 1,3-diaxial interaction between the C-6 oxygen atom and the C-10 methyl group.

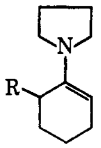
IV. SELECTED CASES

In the above sections, $A^{(1,2)}$ and $A^{(1,3)}$ strain were treated separately. However, in many, but not all, instances these strain effects occur together. Certain areas have been selected therefore to demonstrate the wide-ranging application of these factors and these are discussed below.

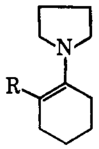
A. ENAMINES

Compounds of this class provide almost ideal examples of $A^{(1,2)}$- and $A^{(1,3)}$-strain effects. Although their generalized use as synthetic intermediates first had its advent in 1954,[116] organized studies on the stereochemistry of various systems have been carried out only of late, and much still remains to be done.

The contribution of importance in this area was made by Stork[116,117] who suggested that, to account for its almost exclusive alkylation at C-6, the pyrrolidine enamine of 2-methylcyclohexanone exists almost completely as the trisubstituted double bond form (LXXV, R = CH_3) rather than as the alternate possibility LXXVI (R = CH_3). Nmr analyses of this system by Berchtold[118] and especially by Gurowitz[119] have adequately confirmed this view. The reason cited by Stork[117] for this preference was steric inhibition of resonance. In LXXVI it was felt that the interaction of the methyl group with the *syn*-methylene adjacent to nitrogen would prevent coplanarity between the lone pair of electrons on nitrogen and the double bond, hence the preference for the alternate form (LXXV, R = CH_3) where it was presumed such steric difficulties did not exist. The conformational circumstances of LXXV (R = CH_3) were not discussed. However, Williamson,[35] in attempting to explain the known difficulty of alkylating an enamine such as LXXV (R = alkyl) *vis-á-vis* the case LXXV (R = H), advanced, without experimental proof, what is essentially the $A^{(1,2)}$-strain argument. He suggested that LXXV (R = alkyl) existed largely as the conformer with the alkyl group quasi-axially oriented ($A^{(1,2)}$ strain). As a consequence, axial approach by a reagent to the 2 position would suffer steric repulsion from the already present quasi-axial substituent at C-6. Axial approach is to be expected as the preferred reaction path, because of the stereoelectronic requirements of the system. Subsequent investigation has proved both aspects of this hypothesis to be correct. For instance, Malhotra and Johnson[34] studied the mechanism of hydrolysis of 1-(N-pyrrolidinyl)cyclohexene (LXXV, R = CH_3) in a mixture of deuterioacetic acid and deuterium oxide. It was found that hydrolysis was complete in 5 min and that the resulting 2-methylcyclohexanone contained 6.8 d_0, 57% d_1, 34% d_2, and 2.2% d_3 species (mass spectrometry). Its infrared spectrum showed principal C–D stretching bands at 2190 (s) (equatorial C–D) and 2220 (m) cm^{-1} (–CD_2–), indicating it to be a mixture of 6-*eq* deuterated (major) and 6,6-dideuterated (minor) products. The presence of a very weak band at 2120 cm^{-1} (axial C–D) showed the formation of a very small amount of 2-*ax*- or 6-*ax*-deuterated ketone.



LXXV



LXXVI

When 2-methylcyclohexanone and 1 equiv of pyrrolidine were allowed to stand in 1.5 equiv of deuterioacetic acid–deuterium oxide in diglyme for 1 hr, the recovered ketone contained 32.4% d_0, 35.8% d_1, and 34.5% d_2 species, and again infrared studies showed the latter two components to be 6-*eq*-deuterated and 6,6-dideuterated 2-methylcyclohexanone. A complete sequence of events in the formation and decomposition of this enamine which will accommodate the above data is illustrated in Chart I. The formation of enamine LXXV (R = CH_3) probably proceeds almost completely by way of the 2-*ax*-methyl conformer of the starting ketone which would also account for its slower rate of formation than in the case of 1-pyrrolidinocyclohexene. Certainly the pathway outlined seems the best explanation for the dominance of the 6-*eq*-deuterated component (LXXXII) in the product. *Via* this route the severe $A^{(1,3)}$ strain in an intermediate such as LXXVIII is avoided since in the crucial step, *i.e.*, the formation of the imminium salt LXXX, no such strain is involved. Direct dehydration of either of the aminocarbinols LXXVII or LXXIX to LXXV (R = CH_3) seems most improbable since the conditions

---

(115) W. G. Dauben, W. K. Hayes, J. S. P. Schwarz, and J. W. McFarland, *J. Am. Chem. Soc.*, **82**, 2232 (1960).

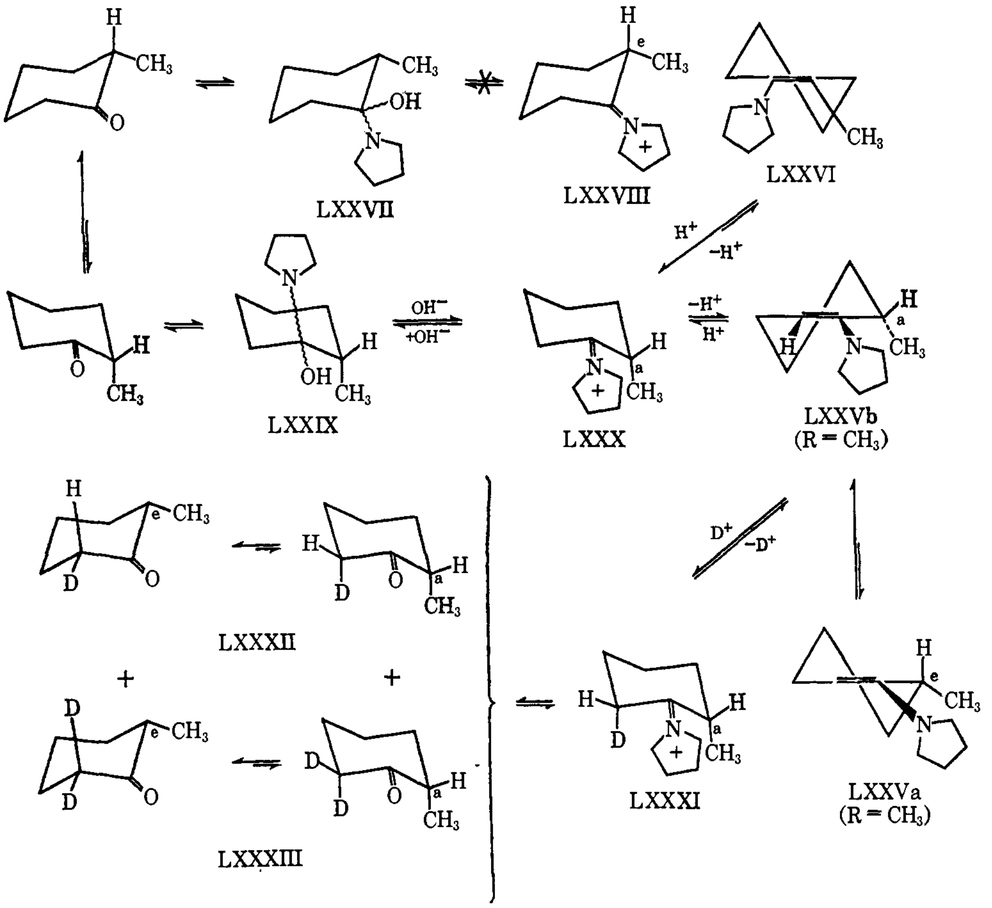
(116) G. Stork and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).

(117) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(118) G. Berchtold, quoted in footnote 8 by H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

(119) W. D. Gurowitz and M. A. Joseph, *Tetrahedron Letters*, 4433 (1965).

CHART I



of the experiments described above are scarcely severe enough to dehydrate a tertiary carbinol.

The other products of the reaction require explanation. The comparatively large amount of the 6,6-dideuterated component LXXXIII undoubtedly arises during the partial equilibration that is occurring because the 6-*ax*-deuterium atom in LXXXI now has approximately the same acidity (apparent rather than real) as the 6-*eq*-hydrogen atom by virtue of the deuterium isotope effect. Hence in the reverse step, *i.e.*, the deprotonation of LXXXI to give LXXV (R = CH_3), the probability of the loss of the deuterium atom is essentially the same as that for hydrogen loss at this center.

What of the small amount of the 6-*ax*- and/or 2-*ax*-deuterated component which is present in the final product? This with equal likelihood could come from either or both LXXVI (R = CH_3) and LXXVa (R = CH_3) since the former is known to be present in small amount from nmr studies, and there is no reason to believe that the latter does not exist, at least to a small extent, in conformational equilibrium with LXXVb (R = CH_3). An important but at the moment speculative point is that probably the formation of LXXVI arises by removal of the C-2 equatorial proton from LXXX despite the poor stereoelectronics of the process (the alternate route, by deprotonation of LXXVIII, seems unlikely because of the highly improbable formation of this imminium salt, as discussed above). This, however, does lead, by the principle of microreversibility, to the conclusion that an enamine with a tetrasubstituted double bond in a simple system such as LXXVI protonates equatorially. Normal enamine reactivity must be considerably depressed in systems such as LXXVI because of the poor ability of the lone pair of electrons on nitrogen to activate the C-2 position; *i.e.*, the polarization

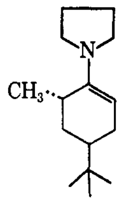
$$\overset{\curvearrowright}{\ddot{N}}\!-\!\overset{\curvearrowright}{C_1{=}C_2}\!-$$

cannot take place with ease. Experimental proof of these points is lacking for these systems, however.

That, in the main, protonation of LXXV is governed by the stereoelectronic principle[120] is *shown* by the fact that hydrolysis of the pyrrolidine enamine LXXXIV of 2-methyl-4-*t*-butylcyclohexanone, with deuterioacetic acid in deuterium oxide, leads largely to a mixture of 6-*ax*-deuterated and 6,6-dideuterated *trans*-2-methyl-4-*t*-butylcyclohexanone (LXXXV).

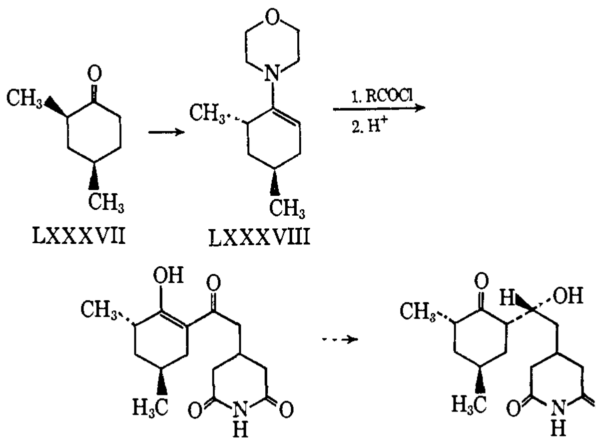
---

(120) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).



LXXXIV

Additional experimental justification of the major pathway outlined in Chart I is the fact that *cis*-2-methyl-4-*t*-butylcyclohexanone (LXXXVI) fails to undergo any significant incorporation of deuterium when allowed to stand in the presence of pyrrolidine and a deuterioacetic acid–deuterium oxide catalyst mixture—a consequence of its inability to flip to put the 2-methyl group in a position where it would not interfere with imminium salt formation. This experiment also demonstrates the difficulty of utilizing a pathway *via* an immonium salt such as LXXVIII by the latter in the chair or boat form. The formation of LXXXIV mentioned above starts, it would seem, from *cis*-2-methyl-4-*t*-butylcyclohexanone (LXXXVI) and proceeds, of necessity slowly, by way of the small amount (~7%) of *trans* isomer (LXXXV) inevitably present at equilibrium. This points out a most important application of *pyrrolidine* enamines: their utilization for the conversion of 2-substituted ketones to their less stable isomers, in effect, an example of the rather rare endergonic process. It is especially useful in the case of 2,4-disubstituted ketones, LXXXV being obtained in 70% yield by hydrolysis of LXXXIV while *cis*-2,4-dimethylcyclohexanone (LXXXVII) can be converted to its *trans* isomer in the same over-all yield. The morpholine enamine LXXXVIII of this latter ketone was used to great advantage by Johnson, *et al.*,[121,122] in the synthesis of the antibiotic cycloheximide XC *via* the diketone LXXXIX. This and related work by Schaeffer and Jain[123] demonstrated for the first time the correctness of Williamson's hypothesis concerning the axial orientation of the 2-substituent in such enamines.



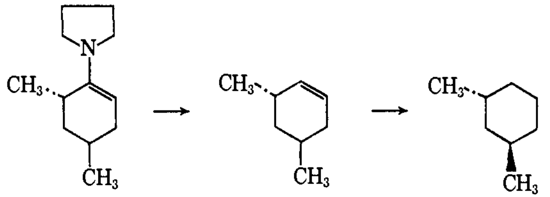
LXXXVII LXXXVIII

LXXXIX XC

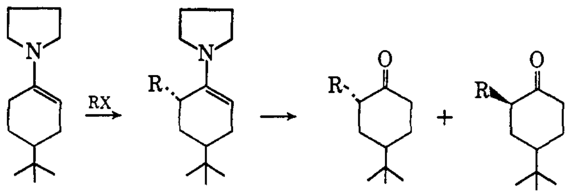
TABLE III

R	% yield (XCV + XCVI)	% XCV present
CH_3I	23	70
n-C_3H_7I	43	90
$CH_2{=}CH_2CH_2Br$	39	93
$BrCH_2CO_2Et$	31	>50
$C_6H_5CH_2Cl$	30	Undetermined

Not only this but Johnson and Whitehead[33] were able to demonstrate by an independent route that the methyl groups in compounds such as LXXXVIII were *trans* to one another and that this orientation was not just due to some effect of the subsequent hydrolysis step. The method employed involved $AlHCl_2$ reduction of XCI to XCII, which it must be assumed does not affect the stereochemistry of the methyl groups. Catalytic reduction of XCII then afforded *trans*-1,3-dimethylcyclohexane, thus reflecting the *trans* stereochemistry in XCI. Alternatively the synthesis of the less stable isomers of this type of ketone can be achieved directly by alkylation of the enamine of the appropriate 4-substituted cyclohexanone, according to Wolff, *et al.*[124] They examined the alkylation of XCIII with a series of halides and found that the ketones obtained after hydrolysis contained largely the *trans*-2,4-dialkylcyclohexanone. Their results are shown in Table III.



XCI XCII



XCIII XCIV XCV XCVI

They envisioned the alkylation as proceeding *via* the pathways shown in Chart II. Here it should be noted that the ratio of XCV to XCVI probably reflects the relative amounts of axial and equatorial attack that take place by RX on XCIII and is not necessarily related to the composition of the ketone that might be derived by decomposition of a thermodynamically

---

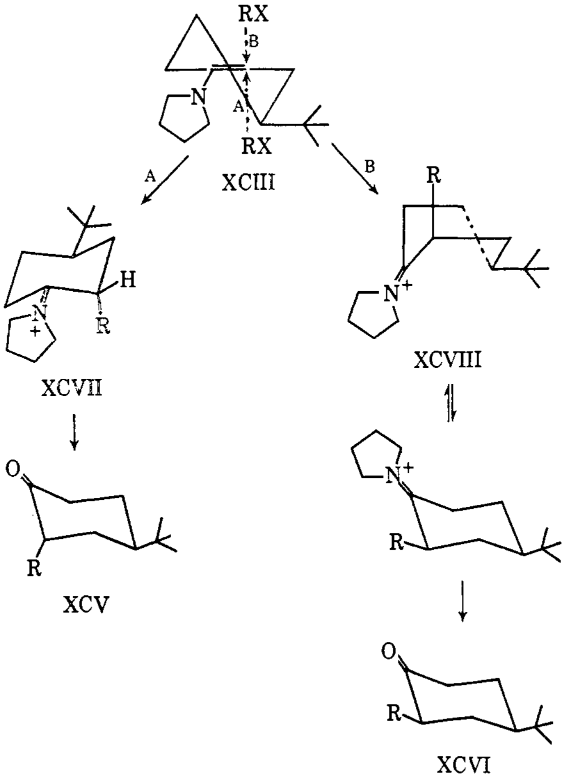
(121) F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Am. Chem. Soc.*, **86**, 118 (1964).

(122) F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *ibid.*, **88**, 149 (1966).

(123) H. J. Schaeffer and V. K. Jain, *J. Org. Chem.*, **29**, 2595 (1964).

(124) S. Karady, M. Lenfant, and R. E. Wolff, *Bull. Soc. Chim. France*, 2472 (1965).

CHART II



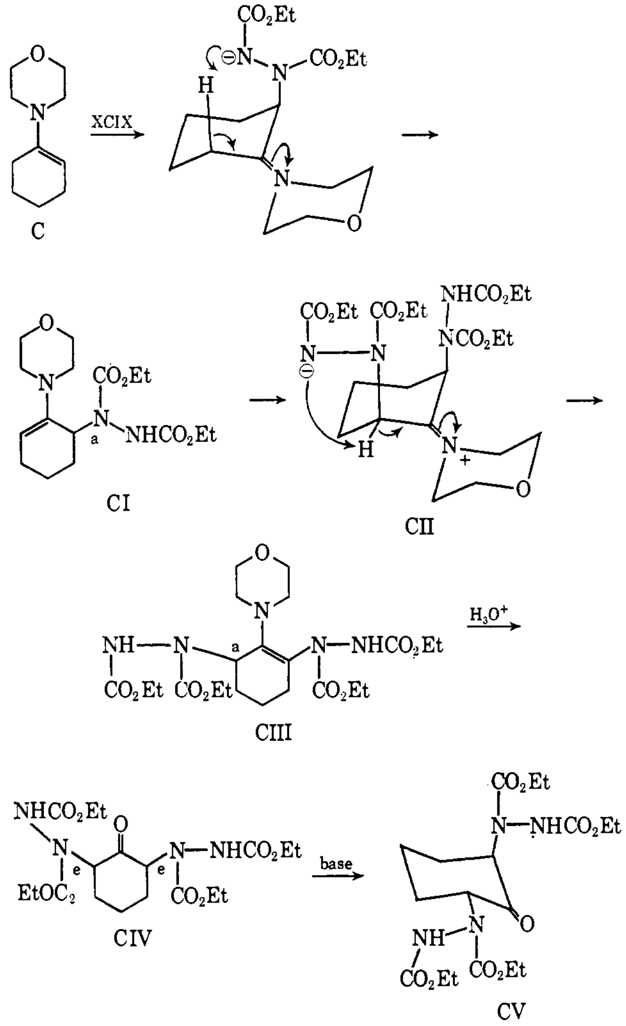
equilibrated sample of the corresponding enamine XCIV. In addition it seems likely that hydrolysis of XCVIII probably proceeds *via* the boat rather than the chair form for reasons cited previously.

While dealing with the alkylation of enamines of substituted ketones, it is important to mention the work of Risaliti, *et al.*,[125,126] who studied the reaction of diethyl azodicarboxylate (XCIX) with the morpholine enamine of cyclohexanone (C). The initial product was formulated as CI and the product of further substitution as XCIII. The complete mechanism was formulated as shown in Chart III.

The hydrolysis product CIV proved to be unstable, giving rise on acid treatment to a more stable isomer. The latter was formulated as the *trans* isomer CV, and CIV as the *cis* isomer, by analogy with the dibromination of C which proceeded to give ultimately the *cis*-2,6-dibromocyclohexanone. The latter compound is known to be unstable to acid giving the *trans* isomer CVIII when equilibrated (eq 2).

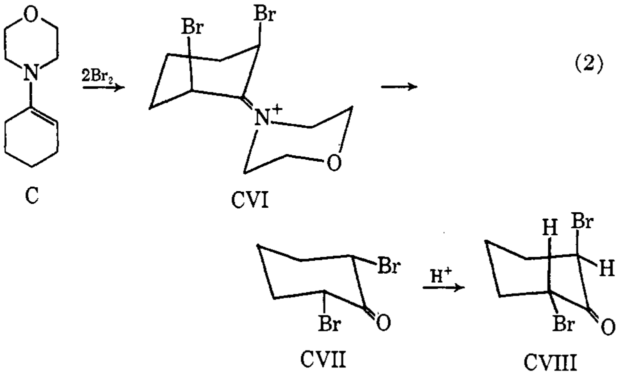
Parallel results[127] to those obtained in the sequence C → CV were obtained in the reaction of XCIX with CIX. The product CX on mild hydrolysis afforded the ketone CXI which when refluxed in an acid medium gave an isomeric product (eq 3).

CHART III



The instability of both CIV and CXI seems anomalous since *cis*-2,6-di-*t*-butylcyclohexanone is much more stable than its *trans* isomer. In addition it does not seem logical to equate the instability of CIV with that of CVII since that of the latter depends on a strong dipole interaction between the bromine atoms and the carbonyl group, and it would be surprising if this were true both of CIV and CXI.

An alternative argument is that the intermediate enamine XCI hydrolyzes *via* CXII by *axial protonation*



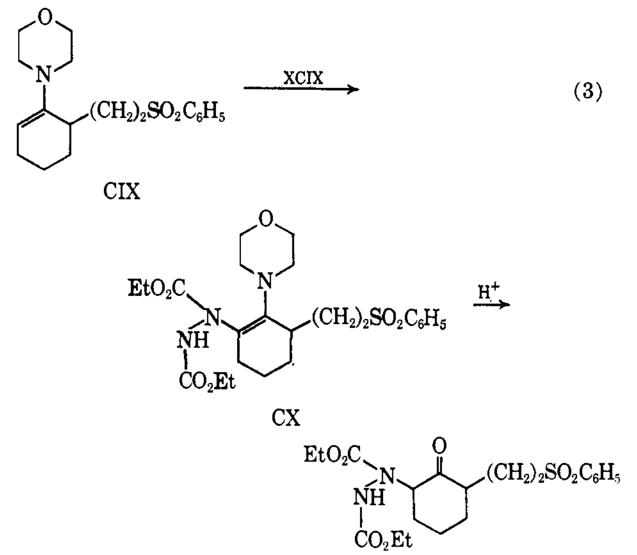
(2)

---

(125) A. Risaliti and L. Marchetti, *Ann. Chim.*, **53**, 718 (1963).

(126) A. Risaliti and L. Marchetti, *ibid.*, **55**, 635 (1965).

(127) A. Risaliti, S. Fatutta, M. Forchiassin, and E. Valentin, *Tetrahedron Letters*, 1821 (1966).

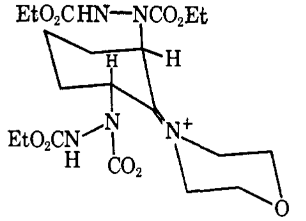


CIX (3)

CX

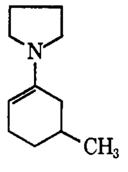
CXI

of the double bond, in accordance with stereoelectronic requirements. It also seems likely that in this particular case the 1,3-diaxial interaction between the diethyl hydrazodicarboxylate groups in XC is greater than the $A^{(1,3)}$ strain in C. Thus although equatorial protonation of XCI would be favored to some degree by the steric resistance afforded the proton donor by the axial hydrazodicarboxylate group at C-6, its deprotonation would probably be much more rapid than attack by water on the imminium salt. The ultimate conclusion is that the immediate hydrolysis product CIV is probably the *trans* isomer and its rearrangement product CV is the *cis* isomer, a reversal of the original assignments. Similarly CXI must be assigned *trans* stereochemistry if the above arguments are valid.

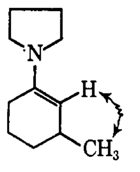


CXII

The question that is asked immediately is why then does the product CVII of dibromination of C have *cis* stereochemistry when on the basis of the above argument it should be *trans*-2,6-dibromocyclohexanone. The answer to this may lie in the fact that the imminium salt CVI in this instance was not converted to an enamine under the experimental conditions used but was hydrolyzed directly to the ketone in which case the *cis* isomer must be expected. Certainly further investigation is needed here.

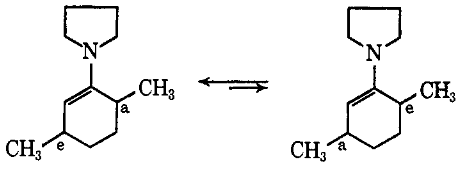


CXIII

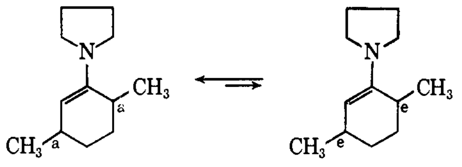


CXIV

Lastly it is interesting to examine the pyrrolidine enamine of 3-methylcyclohexanone. Nmr studies[128] indicate that this material exists as a 70:30 mixture of CXIII and CXIV. Since both compounds might be expected to exist predominantly as the conformers with equatorial methyl groups the relative ratios in which they occur could be explained roughly as being due to the $A^{(1,2)}$ strain in CXIV. On the basis of the 70:30 ratio, the strain would assume a value of 0.6 kcal/mole whereas 0.25 kcal/mole was the value obtained by calculation earlier in the article (section II). Nevertheless, if the former value is used to compute the equilibrium composition of the pyrrolidine enamines derived from 2,5-dimethylcyclohexanone, a ratio of 60:40 for CXV:CXVI can be predicted. This is derived by computing the difference in strain between CXV and CXVI and $\approx [2(1,3\text{-diaxial } CH_3\text{–H interactions}) - 1(1,3\text{-diaxial } CH_3\text{–H interaction} + 1(A^{(1,2)}\ CH_3\text{–H interaction})] = [2 \times 0.9 - (0.9 + 0.6)] = 0.3$ kcal/mole. Experimentally the reaction of 2,5-dimethylcyclohexanone with pyrrolidine under forcing conditions led to a mixture of enamines, the nmr spectrum of which showed two different vinylic protons at 244 cps ($J = 2$ cps) and 253 cps ($J = 4$ cps). The areas under these doublets indicate the two components CXV and CXVI to be present in a 62:38 (±2%) ratio, respectively. Mild hydrolysis of the product then gave a 3:2 mixture of the *cis* and *trans* isomers of 2,5-dimethylcyclohexanone, thus confirming the ratio assigned to the enamine mixture.



CXV



CXVI

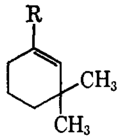
Whether this agreement between calculation and experiment is real or fortuitous remains to be seen. However, studies by Champagne, *et al.*,[129] have shown that the equilibrated enol acetates of 3,3-dimethylcyclohexanone exist as a 38:62 mixture of CXVII

---

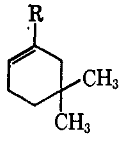
(128) S. K. Malhotra, D. F. Moakley, and F. Johnson, *Chem. Commun.*, 448 (1967).

(129) J. Champagne, H. Favre, D. Vocelle, and I. Zbikowski, *Can. J. Chem.*, **42**, 212 (1964).

(R = OAc) and CXVIII, respectively. The corresponding enamine of this ketone exists as a 20:80 mixture of CXVII (R = NC_4H_8) and CXVIII (R = NC_4H_8). Certainly further investigation is necessary before the 0.6-kcal/mole value for the $A^{(1,2)}$ strain between CH_3 and H can be accepted as realistic. An alternative, but less likely explanation for the distribution of isomers



CXVII



CXVIII

noted above is that such forms as CXIV and CXVII have less opportunity for double-bond hyperconjugation with hydrogen. This, it should be noted, is true for CXIV because it must exist to a considerable extent in the conformation with an axial methyl group (the 3-*eq*-H atom does not contribute). Double-bond equilibrations of this type also have been discussed recently by Staley[84] from yet another point of view, namely that of differences in the hybridization of the molecules concerned. Further work on other 3-substituted cyclohexanones is in progress.

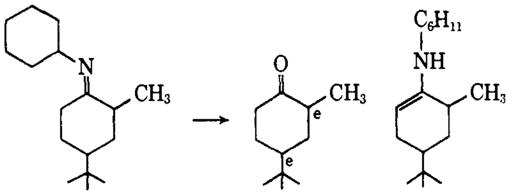
In closing this section a further comment is necessary. This concerns the use of pyrrolidine for the formation of enamines of cyclohexanones having a C-2 substituent. At least in this case, as the work of Gurowitz[119] has demonstrated, one can be sure that the resulting product largely has the double bond in the less substituted position. Why the situation should change so radically when other secondary amines are used is still not clear, and for this reason we have avoided discussion of the subject thus far. Gurowitz has shown that basicity of the amine is not a highly significant factor and has proposed that what is really important is the ability of the amine to form an exocyclic (partial) double bond, *i.e.*

$$>\overset{\curvearrowright}{\ddot{N}}—\overset{\curvearrowright}{C}=C$$

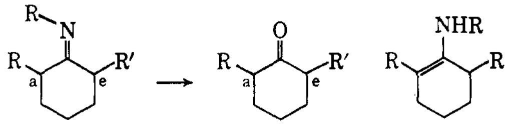
This is in reality a variation of Brown's rules[130,131] concerning the relative stabilities of exocyclic and endocyclic double bonds in five- and six-membered rings. However, while this offers a reasonable explanation, in a sense it also begs the question, since the basis for these rules is not well understood.[82] Certainly other factors such as the relative ability of the methylene groups adjacent to nitrogen in five- and six-membered rings to stabilize an exocyclic double bond (*i.e.*, hyperconjugation), and/or the effect of ring strain on the hybridization of the nitrogen atom, must be considered before any understanding of the whole situation can be achieved. This only serves to point up the major difficulty in the enamine field, namely the lack of good quantitative data about simple systems.

B. IMINES

Very little work has been done on the stereochemistry of cyclic ketimines or on the alkylation products of the derived anions. Johnson and Whitehead[33] found that methylation of the cyclohexylamine Schiff base of 4-methylcyclohexanone gives after mild hydrolysis largely *cis*-2,4-dimethylcyclohexanone in contrast to the enamine procedure. More recently Malhotra and Johnson have decomposed the cyclohexylamine Schiff base CXIX of 4-*t*-butyl-2-methylcyclohexanone under mildly acid conditions and obtained again largely the *cis* isomer of the ketone. This undoubtedly reflects the composition of CXIX in which the cyclohexyl ring on nitrogen is *anti* to the methyl group at C-2 so that A strain does not operate to any degree here. Hydrolysis to some extent does proceed *via* the enamine CXX since the use of D_2O-DOAC as the hydrolyzing agent leads to the incorporation of about 18% deuterium in the product. Only in such a case where the Schiff base has substituents both at C-2 and C-6, as in CXXI, could the less stable isomer (CXXII) of the resulting ketone be expected on hydrolysis, since the Schiff base itself, as a result of the operation of $A^{(1,3)}$ strain, undoubtedly has the stereochemistry depicted in CXXI (R′ ≠ H). There is of course the alternate possibility that such a Schiff base will exist as the tautomer CXXIII. Even so, the same product, CXXII, would be expected as in the case of the hydrolysis of the corresponding enamine provided the C-protonation occurred stereoelectronically. To a certain degree this speculation has been substantiated recently by the work of Conia and Briet[132] who found that the alkylation of CXXIV (R = CH_3) by isobutyl bromide or methallyl chloride led to greater proportions of the less stable isomer (undoubtedly the 2,6-*trans* form) of CXXV [R′ = $CH_2CH(CH_3)_2$ or $CH_2C(CH_3)=$



CXIX LXXXVI CXX



CXXI CXXII CXXIII

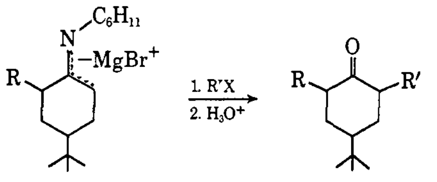
---

(130) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(131) H. C. Brown, J. H. Brewster, and H. Schechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

(132) J. M. Conia and P. Briet, *Bull. Soc. Chim. France*, 3888 (1966).

CH_2, respectively]. Surprisingly in the case of CXXIV ($R = CH_2C_6H_5$), alkylation with methyl iodide afforded a somewhat greater proportion of the more stable isomer of the product CXXV ($R = CH_2C_6H_5$; $R' = CH_3$).

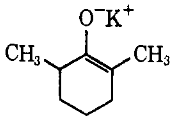


CXXIV CXXV

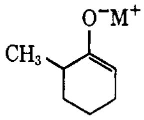
C. ANIONS AND CATIONS. KETONIZATION AND ENOLIZATION

An area of continuing interest to most organic chemists concerns the deprotonation of ketones and the reprotonation and alkylation of the resulting anions.

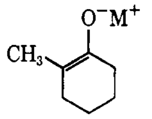
In an earlier section it was noted that $A^{(1,2)}$ strain was a controlling factor in the conformational composition of the potassium enolate anion XIII of 2,6-dimethylcyclohexanone. The nonbonded $A^{(1,2)}$ interaction here was considered as being between the methyl group at C-6 and the solvated O^-K^+ ion pair. (The size of the oxygen anion is commonly regarded as being greater than that of oxygen itself.)



XIII



CXXVI

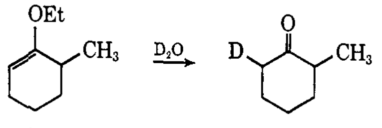


CXXVII

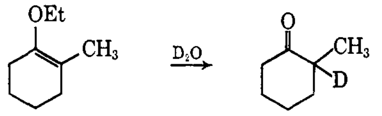
Malhotra and Johnson[36] have applied this result to the problem of the reactivities of the enolate anions CXXVI and CXXVII of 2-methylcyclohexanone. This revolves around the finding that methylation of the equilibrium mixture of CXXVI and CXXVII with methyl iodide gave the 2,2-dimethyl- and 2,6-dimethylcyclohexanones in a ratio of 4:1, whereas a 1:1 mixture of these materials would have been expected if the product composition reflected the starting enolate anion composition.[133] Certainly, however, as House and Kramar[133] have commented, the situation is not as clear-cut as this since higher alkylated products are obtained. These undoubtedly arise more from 2,6-dimethylcyclohexanone than from 2,2-dimethylcyclohexanone since it has been shown that this is the case in the Michael reaction of 2-methylcyclohexanone with methyl acrylate.[134] Certainly from the point of view of steric hindrance to approach of the reagent this is the expected result if cognizance is taken of stereoelectronic control.

Nevertheless, by analogy with the enamine case, Malhotra and Johnson[36] have pointed out that since it could be expected that part of CXXVI will be present as the conformer with the methyl group axial, stereoelectronic alkylation of the enolate would be inhibited sterically to some degree by the C-6 methyl group. Thus the rate of alkylation of CXXVII, wherein little or no steric hindrance exists, might be expected to be higher than that of CXXVI, hence the larger quantity of 2,2-dimethylcyclohexanone in the product.

Support for the proposed conformational state of CXXVI comes from the acid-catalyzed hydrolyses of the enol ethers CXXVIII and CXXIX in deuterium oxide–methanol-d_1.[133,135] In the latter case C–D infrared stretching frequencies of the ketone CXXXI suggest that the deuterium atom occupies an axial position as might be expected on the basis of stereoelectronic deuteration of CXXIX. However, in the case of CXXX the corresponding bands in the infrared spectrum indicate that it is a mixture of 6-*eq*-D and 6-*ax*-D isomers. This composition is best explained on the basis of CXXVIII containing a substantial proportion of the conformer with an axial methyl group, with of course the implicit assumption that the hydrolysis is again stereoelectronically controlled.



CXXVIII CXXX



CXXIX CXXXI

Recently Caine and Huff[136] studied the rates of alkylation of kinetic and equilibrium mixtures of lithium enolates of CXXVI and CXXVII and concluded that the latter alkylates about twice as fast as the former. They also pointed out that while CXXVI may be less reactive than CXXVII because of the steric factor cited by Malhotra and Johnson, alternatively CXXVII may be more reactive than CXXVI because of the enhancement of its nucleophilicity by the methyl group. They did mention, however, that the latter factor might be cancelled by the steric effect of the methyl group in this anion. To completely resolve this problem, a good comparison of the above alkylation rates with that of the enolate anion of cyclohexanone itself seems needed.

The stereochemistry of the protonation of *exocyclic enolate anions* in cyclic systems was investigated extensively by Zimmerman and his coworkers. The re-

---

[133] H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

[134] H. O. House, W. L. Roelofs, and B. M. Trost, *ibid.*, **31**, 646 (1966).

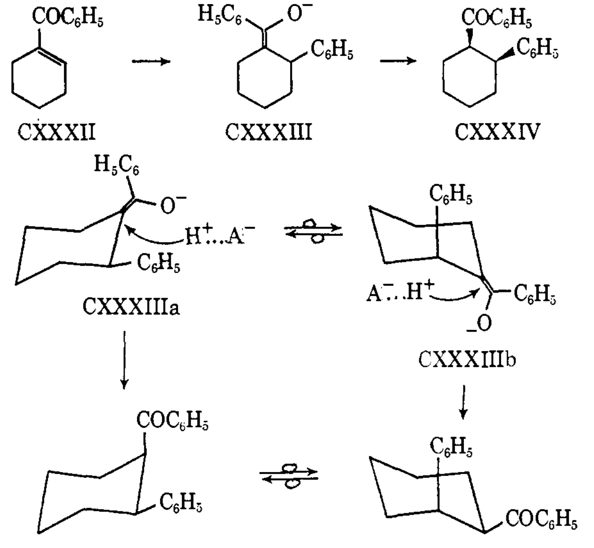
[135] H. O. House and B. M. Trost, *ibid.*, **30**, 1341 (1965).

[136] D. Caine and B. J. L. Huff, *Tetrahedron Letters*, 4695 (1966).

sults of their research have been summarized recently,[137] and the most important principle to emerge, and one which remains inviolate to date, is that protonation of these enolate anions with a nonbulky acid occurs largely from the least hindered side.[138] Despite this, in a considerable number of their cases, the reasoning involved would appear to be fallacious from the point of view of the conformation of the material that is being protonated.

The case of the enolate anion CXXXIII of 1-benzoyl-2-phenylcyclohexane is a good case in point.[138] The preparation of CXXXIII was achieved by the 1,4 addition of phenylmagnesium bromide to benzoylcyclohexene (CXXXII). C-Protonation then afforded largely *cis*-1-benzoyl-2-phenylcyclohexane (CXXXIV), the less stable of the two possible isomers.

In explaining this phenomenon Zimmerman regarded (a) protonation as occurring "equatorially" on conformer CXXXIIIa to give CXXXIVa and (b) that the transition state resembled the starting enol or enolate depending on which was accepted as being the more crucial in the C-protonation step. He cited as a reason for the former assumption the fact that "axial protonation" was seriously hindered by the axial C-3 and C-5 hydrogen atoms. However, predictions based on $A^{(1,3)}$ strain would lead to the conclusion that the more stable conformer of CXXXIII is CXXXIIIb rather than CXXXIIIa. In fact, considering the magnitude of the possible interactions involved (C_6H_5 and O^- or C_6H_5/C_6H_5), one might expect the former conformer to be the exclusive form of CXXXIII. Thus protonation of the enolate anion should occur from the lower face of the molecule in fact "axially," since attack on the upper face would be sterically inhibited by the C-2 phenyl ring.

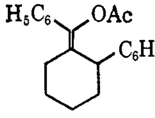


CXXXII CXXXIII CXXXIV

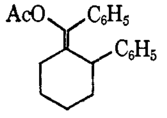
CXXXIIIa CXXXIIIb

CXXXIVa CXXXIVb

Evidence that the latter interpretation is the correct one was obtained by Malhotra and Johnson[139] who trapped the enolic forms of CXXXIII by quenching the enolate with acetic anhydride. The product consisted of approximately a 1:1 mixture of the two enol acetates CXXXV and CXXXVI. Each of these materials exhibited benzylic proton absorption in the nmr spectrum as a poorly resolved triplet ($J \sim 3$–5 cps) which had a half-height width of 7 cps. This is characteristic of an *equatorial* proton coupled to an adjacent methylene group. Thus the phenyl ring at C-2 in both CXXXV and CXXXVI must be axially oriented and, by inference, axial in CXXXIII also. In fact, the addition of phenylmagnesium bromide to CXXXII undoubtedly occurs stereoelectronically (*i.e.*, axial attack), and the product CXXXIIIb, being rigid, undergoes no sensible conformational change until after protonation when an equilibrium containing reasonable amounts of both CXXXIVa and CXXXIVb is established.



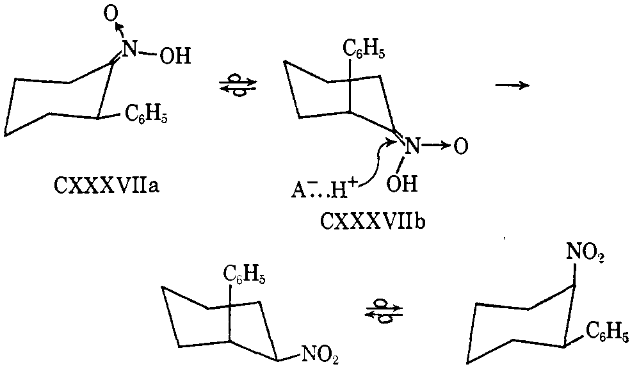
CXXXV



CXXXVI

That the C-3 and C-5 protons do not interfere markedly with "axial" protonation has been shown by House[140] who studied the ketonization of, among other compounds, the lithium enolate salt of 1-acetyl-4-*t*-butylcyclohexanone (enolized toward the ring). The product contained almost equal quantities of the *cis* and *trans* isomers of the ketone.

A case[141] which is very similar to that described above concerns the protonation of 1-*aci*-nitro-2-phenylcyclohexane (CXXXVII). The latter when C-protonated gives the less stable isomer CXXXVIII of



CXXXVIIa CXXXVIIb

CXXXVIIIa CXXXVIIIb

---

(137) H. E. Zimmerman, "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 345–406.

(138) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

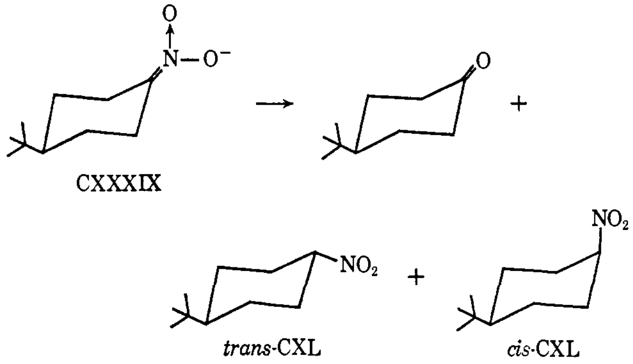
(139) Malhotra and F. Johnson, *J. Am. Chem. Soc.*, **87**, 5493 (1965).

(140) H. O. House, private communication.

(141) H. E. Zimmerman and T. E. Nevins, *J. Am. Chem. Soc.*, **79**, 6559 (1957).

2-nitro-1-phenylcyclohexane. Here, however, it was possible to examine the conformational state of CXXXVII directly by nmr spectroscopy. This revealed the presence of a benzylic proton absorption as a triplet ($J = 4.6$ cps) having a half-width height of ~9 cps, a reasonable value for an equatorial proton at such a location. Thus it seems inevitable that the same arguments that were used for CXXIII above apply here also; the most stable conformation of CXXXVII is CXXXVIIb and protonation must occur "axially" on this conformer, rather than "equatorially" on CXXXVIIa as suggested by Zimmerman.

A later paper by Bordwell and Vestling[142] discusses the C-1 deprotonation of, among other nitro compounds, the *cis* and *trans* isomers of 2-*p*-chloro- and 2-*o*-methoxyphenyl-1-nitrocyclohexanes. The *trans* isomer of each pair was converted to the nitronate ion at least 200 times more slowly than corresponding *cis* compound, in agreement with the above arguments. A second interesting feature of their work concerns the protonation of the nitronate salt (CXXXIX) derived from 4-*t*-butyl-1-nitrocyclohexane (CXL). Besides 4-*t*-butylcyclohexanone, this produced a 1:3 mixture of the *cis* and *trans* isomers of CXL, respectively. If protonation were influenced much by the axial hydrogen atoms at C-3 and C-5, then a higher proportion of *cis*-CXL than *trans*-CXL would be expected in the product provided the transition state for protonation is close to product. (This assumes that none of the 4-*t*-butylcyclohexanone comes from the nitro compounds once they are formed.) Some evidence for this type of transition state is provided by their C-1 deprotonation study on *cis*-CXL and *trans*-CXL. Here they found that the former was deprotonated five times faster than the latter. This disparity in rates would tend to favor a transition state having considerable sp^2 character and reflects the higher ground-state energy of *cis*-CXL.



CXXXIX

trans-CXL

cis-CXL

Application of these ideas to the decarboxylation of 2-phenylcyclohexane-1,1-dicarboxylic acid (CXLI) follows logically. This system was studied previously by Zimmerman and Giallombardo.[143] They had found that maximum specificity was observed in collidine at 60° where 72.5% of *cis*-2-phenylcyclohexanecarboxylic acid (CXLII) was obtained. When corrected for any isomerization of *cis* acid under the reaction conditions, this corresponds to 76% CXLIII. Since a substantial amount of the *trans* acid CXLIV is produced in this case, one can only conclude that, while the reaction mainly proceeds *via* CXLIIb, it must also occur to a smaller extent by way of CXLIIa. To how much smaller an extent is difficult to answer, because 4-phenylcyclohexane-1,1-dicarboxylic acid (CXLV) affords CXLVI and CXLVII in a 58:42 ratio under similar decarboxylation conditions.[144]

It does not seem likely that CXLIV arises by "equatorial" protonation of CXLIIb because acetic acid protonation of the *aci*-nitro compound CXXXVIIb gives the *cis* isomer CXXXVIII almost exclusively. One could not expect the 2-phenyl group to exert differing steric effects in these two molecules. On the other hand it is difficult to understand why $=C(OH)_2$ has a seemingly smaller steric effect than $=N(\rightarrow O)OH$. Related to this case is a study recently reported by Abell and Lennon.[145] They examined the stereochemistry of the decarboxylation of 1,1,2-tricarboxylic acids of the three-, four-, five- and six-membered carbocyclic rings in collidine, 5 *N* hydrochloric acid, and without a solvent. In collidine only the cyclopropyl compound yields any *trans* isomer of the 1,2-dicarboxylic acid. Decarboxylation without solvent gives largely *cis* isomers. On the other hand, in 5 *N* hydrochloric acid all four of the acids give mainly the *trans*-1,2-dicarboxylic acids under nonequilibrating conditions. It seems most anomalous that in the latter case such small amounts of the *cis* isomers are produced. Seemingly in the case of the six-membered ring only *trans* isomer is produced. This would suggest, contrary to all expectation, that the transition state closely resembles the product under these circumstances. In such a highly acidic medium where the corresponding anion is a very poor base (*i.e.*, Cl$^-$), a transition state resembling the enol would be anticipated.

An important point to mention here is that protonation in the above cases does not occur in an equatorial sense, because steric hindrance largely prevents it. As noted above in the decarboxylation of 4-phenylcyclohexane-1,1-dicarboxylic acid, approach from either side by a nonbulky acid can occur with almost equal ease (*i.e.*, there is little or no stereoelectronic effect). The scarcity of examples where protonation occurs largely in an equatorial sense is simply due to the fact that few systems have been examined where a suitably situated

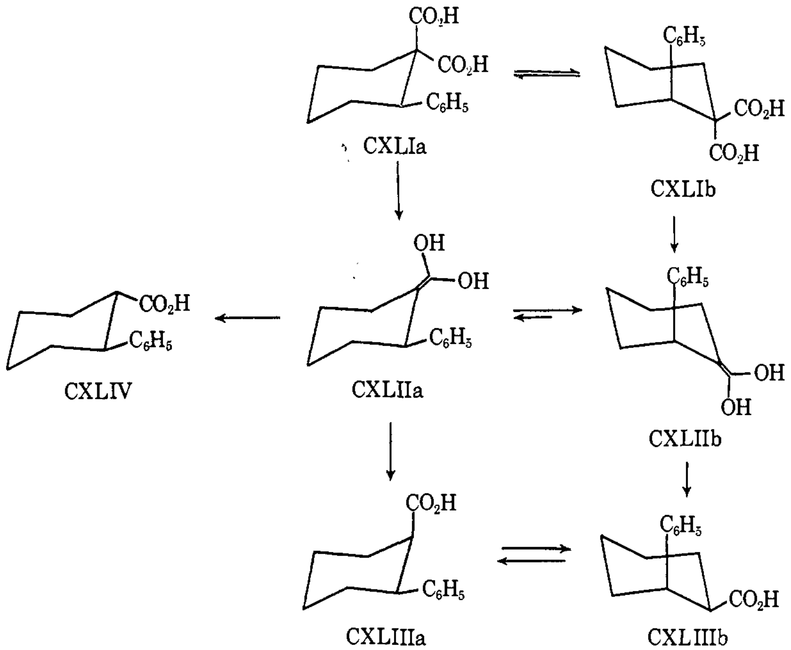
---

[142] F. G. Bordwell and M. M. Vestling, *J. Am. Chem. Soc.*, **89**, 3906 (1967).

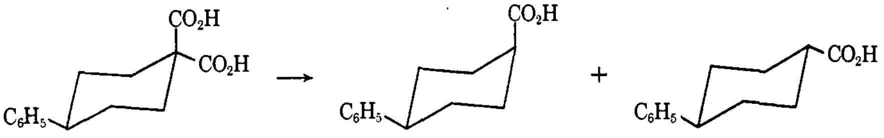
[143] H. E. Zimmerman and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956).

[144] H. E. Zimmerman and T. W. Cutshall, *ibid.*, **80**, 2893 (1958).

[145] P. I. Abell and D. J. J. Lennon, *J. Org. Chem.*, **30**, 1206 (1965).



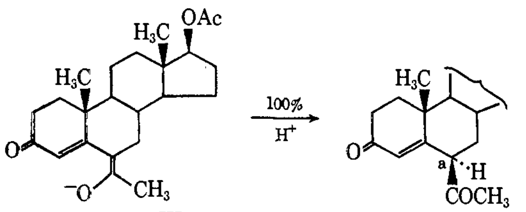
CXLIa CXLIb CXLIV CXLIIa CXLIIb CXLIIIa CXLIIIb



CXLV CXLVI CXLVII

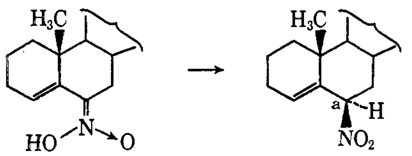
group might make this direction of protonation the dominant one.

A good example of this, however, is the kinetic protonation of the enolate anion CXLVIII[88] which affords CXLIX in 100% yield. The C-10 methyl group in this case provides the steric hindrance which prevents protonation on the β face of the molecule.



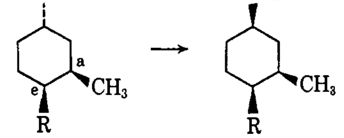
CXLVIII CXLIX

McKenna and his coworkers[146] have described a similar case, in the cholestene series, involving the *aci*-nitro compound CL which gives rise to CLI on protonation under kinetic conditions. Similar results have been obtained by Jones, *et al.*,[147,148] and by Bowers and his associates[108] with other steroidal systems.



CL CLI

Undoubtedly the process could be used with a high degree of specificity to convert the more stable isomer of compounds such as CLII to the less stable isomer (CLIII), provided R were large enough to make the molecule fairly rigid. Exceptions to this mode of protonation appear to exist. For example, it has been reported[149] that the mild acidification of the sodium salt of 9,10-dihydro-9,10-(*trans*-11-nitro-12-phenylethano)-anthracene regenerates the *trans* isomer where the *cis* isomer should be expected. No simple explanation suggests itself for this result.



CLII CLIII

Another unusual result reported[150] recently is the reduction of CLIV using lithium in liquid ammonia. The initial product undoubtedly possesses a 4β-methyl group since the intermediate Δ^3-enol for steric reasons must protonate largely on the lower face. The further

---

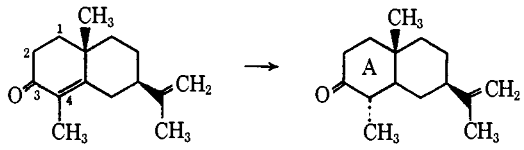
[146] J. McKenna, J. M. McKenna, and P. B. Smith, *Tetrahedron*, 21, 2983 (1965).

[147] J. R. Bull, E. R. H. Jones, G. D. Meakins, and P. A. Wilkinson, *J. Chem. Soc.*, 2601 (1965).

[148] W. A. Harrison, E. R. H. Jones, G. D. Meakins, and P. A. Wilkinson, *ibid.*, 3210 (1964).

[149] W. E. Noland, H. I. Freeman, and M. S. Baker, *J. Am. Chem. Soc.*, 78, 188 (1956).

[150] G. L. Chetty, S. K. Rao, S. Dev, and D. K. Banerjee, *Tetrahedron*, 22, 2311 (1966).



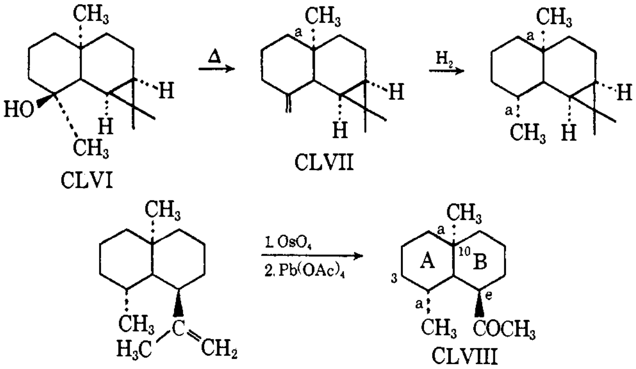
CLIV CLV

isomerization of this material to the 4-*eq*-methyl compound CLV probably occurs during isolation, because of the strain in the 4β-methyl isomer arising from either a 1,3-diaxial interaction between the methyl groups or possibly a boat form of ring A.

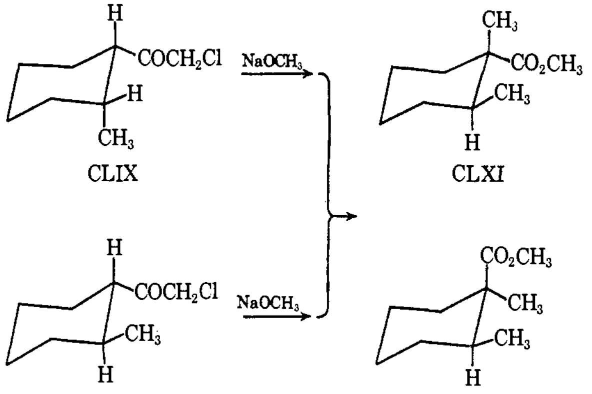
The ketonization processes discussed above lead naturally to a discussion of the complementary reaction, enolization. If in this type of reaction the transition state resembles the product (as discussed previously), then substituents β to the carbonyl group under certain circumstances would be expected to have a sterically hindering effect if equatorially oriented, but to have little or no effect if axially situated.

Gorodetsky and Mazur[88] have described an interesting pair of examples where steric inhibition of enolization obviously plays a part. The ultraviolet spectrum of CXLVIII mentioned above exhibits maximum absorption at 422 mμ (ϵ 22,300), whereas its 4-methyl homolog has a maximum at 410 mμ (ϵ 9100). They suggested that this disparity is due to incomplete enolization of the latter because of steric factors. Even in the former case one might expect some steric hindrance to enolization toward the ring by comparison, say, with a 3β-acetyl-Δ^4-steroid.

An interesting case is provided by the work of Büchi, *et al.*[151] They found that a maaliol (CLVI) derivative, of reputed structure CLVIII, prepared as shown below, would incorporate only three deuterium atoms when treated with boiling D$_2$O–NaOD. The deuterium atoms were all located on the methyl group, indicating an inability of the ketone to enolize easily toward the ring. The steric resistance to enolization here appears to be rather high since it would seem to arise only from the *peri*-CH of the adjacent ring. One possible explanation is that the A ring adopts a twisted boat shape (C-3–C-10, stem-to-stern) to avoid the 1,3-diaxial interaction between the methyl groups. The methyl group at C-4, now equatorial, would hinder enolization. A second possibility is that the C-4 methyl group in CLVIII has been assigned the wrong orientation and is in fact equatorially oriented. However, epoxidation of the olefin γ-maaliene (CLVII) occurs largely on the upper face, and, since one could expect hydrogenation to follow the same steric course, this lessens the possibility of a mistaken assignment. Another case in the same category has been reported by House and Richey.[152] They observed that while both ketones CLIX and CLX gave the same mixture of products, CLXI and CLXII, when treated with sodium methoxide, the former reacted 100 times faster than the latter. No conversion of CLIX to CLX was observed under the reaction conditions and the relative ease of enolization toward the ring using an A$^{(1,3)}$-strain argument was advanced to explain the disparity in the reaction rates.



CLVI CLVII CLVIII



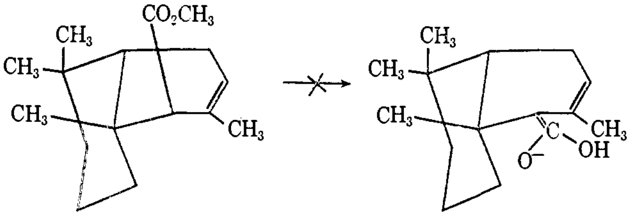
CLIX CLXI CLX CLXII

As mentioned earlier in the article the ester XVIII fails to undergo any conjugation of the double bond with the ester group even under very vigorous alkaline conditions.[41] This is readily understood on the basis of the A$^{(1,3)}$ strain involved *on both sides* of the potential enolate intermediate CLXIII. It would be interesting to determine if a very powerful base such as $(C_6H_5)_3C^-$ could effect this conjugation since the transition state in this instance might have considerably more sp^3 character. Thus isomerization would take place *via* a carbomethoxy carbanion rather than an enolic form. There can be no doubt of the greater stability of the double bond when situated α,β to the carboxylic group since formation of the α,β-unsaturated acid XXI does occur under acid conditions (formation of acid chloride, then hydrolysis). The latter undoubtedly involves a purely carbonium ion mechanism with little or no involvement of the carboxy function. The reason for the greater stability of the double bond

---

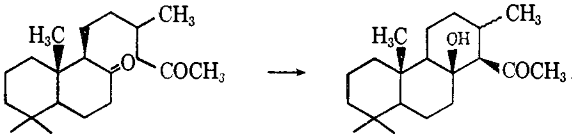
[151] G. Büchi, M. Schach von Wittenau, and D. M. White, *J. Am. Chem. Soc.*, **81**, 1968 (1959).

[152] H. O. House and F. A. Richey, *J. Org. Chem.*, **32**, 2151 (1967).

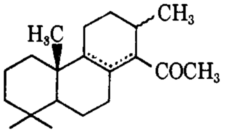


XVIII CLXIII

when in this position makes for interesting speculation. The carboxy group in XXI must be twisted to such an extent that little conjugation with the double bond is to be expected. This view is reinforced by some work recently reported by Overton and Renfrew.[153] They found that the cyclization of CLXIV afforded the hydroxy ketone CLXV which did not undergo spontaneous dehydration under the basic conditions of the reaction or on subsequent treatment with dimethylsulfinyl carbanion in boiling dimethyl sulfoxide. Dehydration could be accomplished by acid which first gave rise to CLXVIa but on prolonged treatment with perchloric acid to CLXIVb, a compound that shows only a slight conjugation between the double bond and the ketone as judged from its ultraviolet spectrum. Neither of the latter compounds showed vinylic hydrogen absorption in the nmr spectrum.



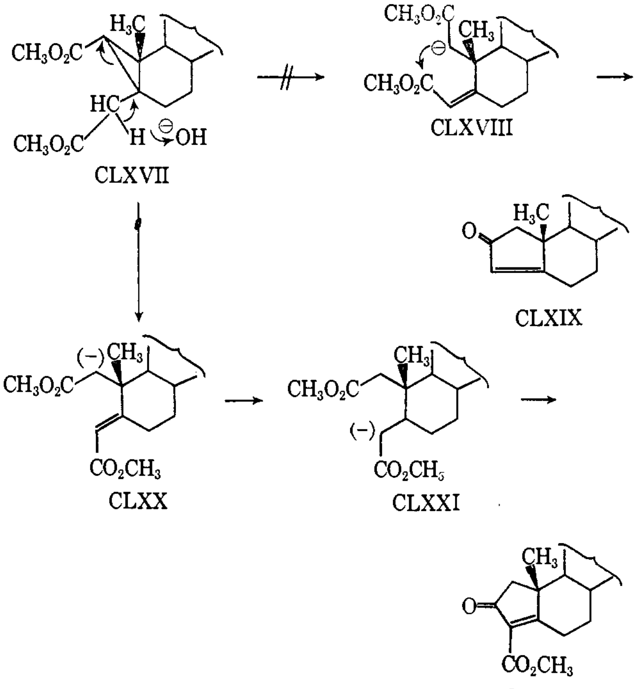
CLXIV CLXV



CLXVIa, $\Delta^{8,9}$
CLXVIb, $\Delta^{8,14}$

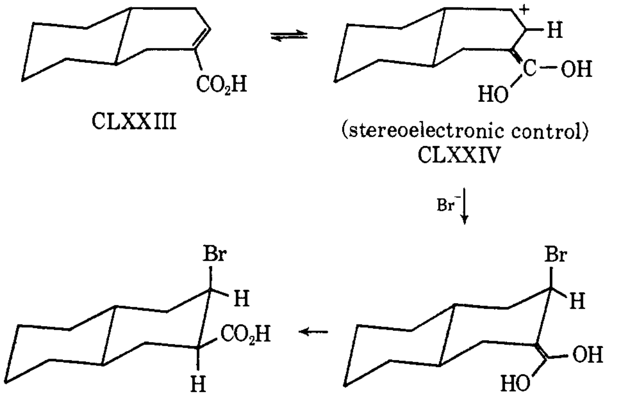
An interesting example where the expected reaction course did not take place because of $A^{(1,3)}$ strain is due to Shoulders, *et al.*[154] They treated CLXVII with base and expected to get CLXIX *via* the intermediate CLXVIII. However, the product turned out to be CLXXII. Undoubtedly the strain in the transition state leading to CLXVIII is too high and the alternate path *via* the relatively unstrained CLXX and CLXXI is followed.

Caple and Vaughan[155] have drawn attention to another application of $A^{(1,3)}$ strain. They had previously established[156] that kinetically controlled hydrobromination in toluene of *trans*-Δ^2-octalin-2-carboxylic acid (CLXXIII) led to *trans*-3-*ax*-bromodecalin-2-*eq*-carboxylic acid (CLXXVI) and postulated the mechanism shown. No evidence could be obtained for the presence of the diaxial isomer CLXXVII, and this originally had led them to believe that this case was an exception to Zimmerman's ideas concerning "equatorial" protonation.

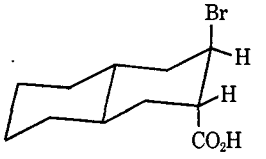


CLXVII CLXVIII CLXIX CLXX CLXXI CLXXII

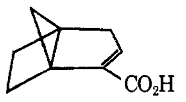
The intermediate bromo acid–enol CLXXV, they now have pointed out, corresponds to the preferred conformation in $A^{(1,3)}$-strain theory and leads predictably to CLXXVI. Identical behavior was observed in the addition of hydrogen bromide to the bicyclic compound CLXXVIII.



CLXXIII (stereoelectronic control) CLXXIV CLXXVI CLXXV



CLXXVII



CLXXVIII

---

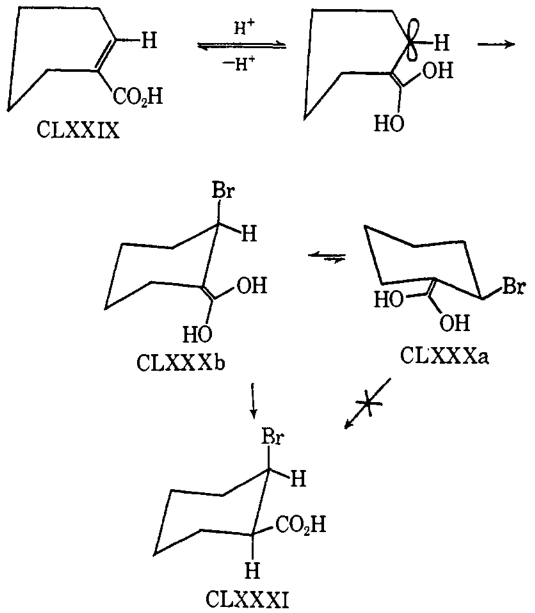
(153) K. H. Overton and A. J. Renfrew, *J. Chem. Soc.*, *C*, 931 (1967).

(154) B. A. Shoulders, W. W. Kwie, W. Klyne, and P. D. Gardner, *Tetrahedron*, 21, 2973 (1965).

(155) R. Caple and W. R. Vaughan, *Tetrahedron Letters*, 4067 (1966).

(156) W. R. Vaughan and R. Caple, *J. Am. Chem. Soc.*, **86**, 4928 (1964).

Vaughan and Caple also now consider that the hydrobromination of cyclohexene-1-carboxylic acid (CLXXIX) proceeds *via* a sterically controlled ketonization of the intermediate bromo acid–enol CLXXXb with an axial bromine atom. Originally they had felt that CLXXXI was derived from conformation CLXXXa based on the arguments proposed by Zimmerman.

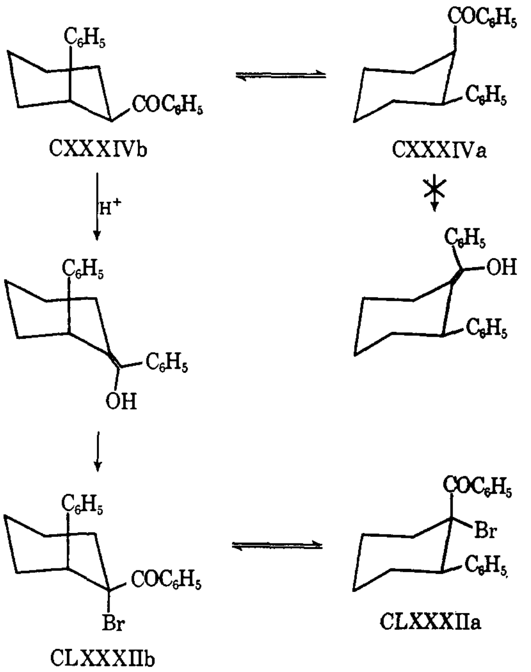


Similar steric control was also observed[157] in the ketonization process involved in the addition of hydrogen bromide to cyclopentene-1-carboxylic acid in toluene. However, the application of A strain to five-membered rings is discussed in more detail later.

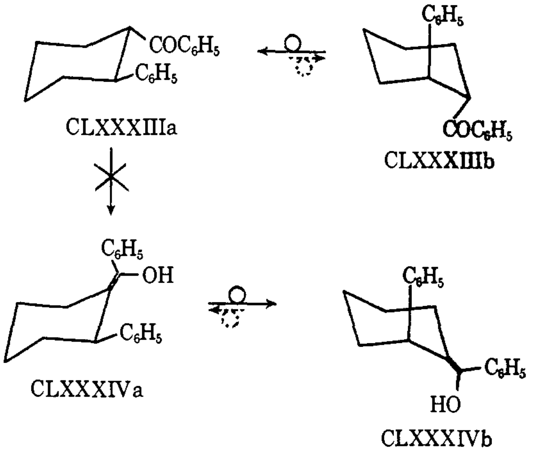
A set of reactions which is closely related to the work of Caple and Vaughan concerns the acid-catalyzed bromination of the isomers of 1-acetyl- and 1-benzoyl-2-phenylcyclohexane.

In the case of the *cis* isomer CXXXIV of the latter compound, bromination[138] occurs with relative ease and leads to 1-benzoyl-1-bromo-2-phenylcyclohexane (CLXXXII), whereas the *trans* isomer CLXXXIII is essentially resistant to bromination under the conditions used. This is easily understood in terms of a transition state for enolization which looks like product (a situation complementary to the nature of the transition state in the protonation of enolic forms).

The enolization, hence bromination, can proceed in the case of CXXXIV *via* the conformer CXXXIVb since no severe nonbonded interactions are encountered in the transition state. However, the acid-catalyzed enolization of CXXXIVa must necessarily be a much more energetic process because of the $A^{(1,3)}$ strain in the developing transition state. Thus, this pathway is forbidden to a high degree.



The same reasoning applies to the enolization of the *trans* isomer CLXXXIII. The difference in this case is of course that while $A^{(1,3)}$ strain inhibits the enolization of conformer CLXXXIIIa, conformer CLXXXIIIb is essentially forbidden, because of the large disparity in energy between it and its conformational isomer CLXXXIIIa. Attainment of the enolic form CLXXXIVb from CLXXXIIIb would of course be fairly easy since $A^{(1,3)}$ strain is not involved. Neither pathway is available, however, because the conditions used for bromination seem incapable of mustering the necessary energy to make one of them feasible. A more powerful reagent, however, might cause bromination to occur in the desired sense especially if the transition state for enolization could be moved closer to the starting material (*i.e.*, CLXXXIII). This point concerning transition states is discussed again below.

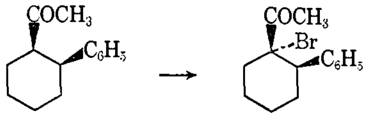


Without pursuing the argument *ad nauseam*, the explanation used above also applied to the *cis*

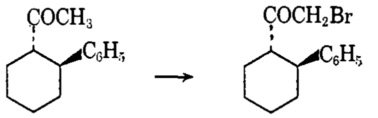
---

[157] W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *J. Am. Chem. Soc.*, 87, 2204 (1965).

and *trans* isomers of 1-acetyl-2-phenylcyclohexane (CLXXXV and CLXXXVI, respectively). The former undergoes bromination[158] to the ring on give CLXXXVII since enolization in this direction can utilize an unstrained transition state. The *trans* isomer, however, can enolize much more easily in the direction of the methyl group and hence leads to CLXXXIX. This is then directly comparable with the base-catalyzed enolization of CLVIII cited earlier.

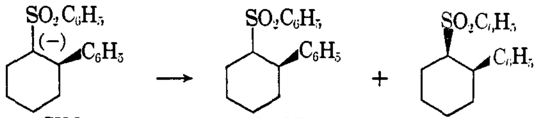


CLXXXV CLXXXVII



CLXXXVI CLXXXIX

So far we have dealt with transition states and enolate or enolic intermediates that are considered essentially planar (sp^2 hybridized). Cases where the anion is largely sp^3 hybridized are thus all the more interesting. Such a case is the anion CXC of 1-benzenesulfonyl-2-phenylcyclohexane. Protonation experiments by Zimmerman and Thyagarajan[159] on CXC have demonstrated that largely the *trans* isomer CXCI is produced together with smaller amounts of the *cis* isomer CXCII. In fact, this evidence was used as proof of the sp^3 nature at the C-1 carbon atom of CLXVI. Confirmatory evidence that such carbon atoms are largely tetrahedral has been forthcoming from the work of Corey, *et al.*,[160,161] and Breslow and Mohacsi.[162]

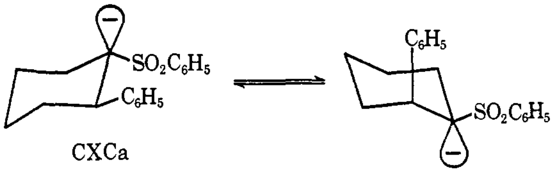


CXC CXCI CXCII

The most interesting results obtained by Zimmerman with this system, from our point of view, concern the isomer ratios of CXCI and CXCII obtained under different protonating conditions. With increasing proton-donor size greater amounts of CXCII were produced, thus demonstrating in this case the slightly greater steric effects of the C-3 and C-5 axial hydrogen atoms over the equatorial C-2, phenyl group, and C-6 hydrogen atom. A similar trend was noticed with increasing acidity of the protonating agent or conversely decreasing basicity of the conjugate anion. This was interpreted as being due to a change in the transition state toward sp^2 character and, as a consequence, a decreased importance of the bulk of the benzenesulfonyl group and increased importance of the requirements of the proton donor.

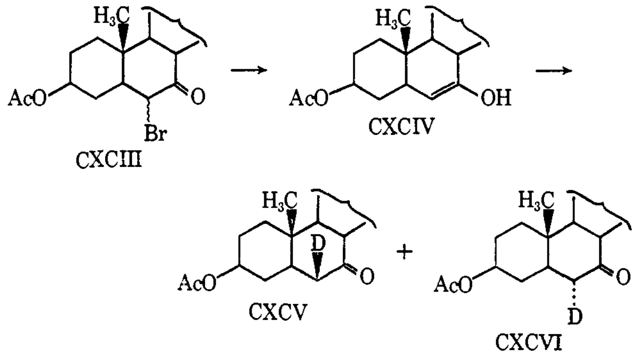
In view of previous discussion it seems much more likely that $A^{(1,3)}$ strain is again involved and that the conformer CXCb assumes greater importance, *vis-à-vis* CXCa, as the transition state changes in the direction of the sp^2 state. Unfortunately the 4-phenyl isomer which would cast light on this situation has not been studied.

An example of the complementary case, *i.e.*, increasing sp^3 character of the transition state with increasing basicity of the protonating medium, has recently been described by Tchoubar and her associates.[163] These workers studied the isomer product ratio obtained when the enolate anion CXXXIII was quenched kinetically in an increasingly basic medium. They concluded that the proportion of the *trans* ketone (CLXXXIII) in the product rose as the strength or concentration of the base increased, in accordance with the hypothesis that in basic media the transition state for protonation should resemble more closely a keto-carbanion than an enolate anion.[164]



CXCa CXCb

Corey[120] reported a similar situation where the possibility exists that increasing acidity of the medium leads to greater sp^2 character in the transition state for enol protonation. This concerns the ketonization of the enol CXCIV obtained from the reduction of 3β-acetoxy-6β-bromocholestanone-7 (CXCIII) by zinc in an acid medium. Using DOAc the product ratio of CXCV to CXCVI was 90:10, whereas with DBr/



CXCIII CXCIV CXCV CXCVI

---

(158) H. E. Zimmerman, *J. Am. Chem. Soc.*, **79**, 5554 (1957).

(159) H. E. Zimmerman and B. S. Thyagarajan, *ibid.*, **80**, 3060 (1958).

(160) E. J. Corey and E. T. Kaiser, *ibid.*, **83**, 490 (1961).

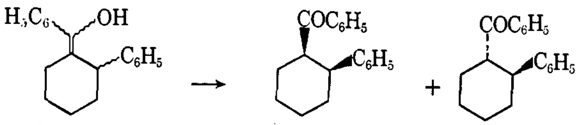
(161) E. J. Corey, H. Koenig, and T. H. Lowry, *Tetrahedron Letters*, 515 (1962).

(162) R. Breslow and E. Mohacsi, *J. Am. Chem. Soc.*, **83**, 4100 (1961); **84**, 684 (1962).

(163) P. Angibeaud, H. Riviere, and B. Tchoubar, *Compt. Rend.*, **263C**, 160 (1966).

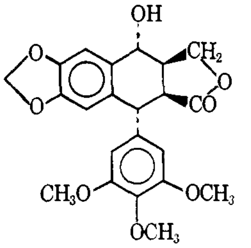
(164) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

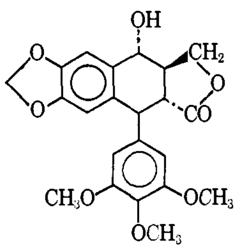
CHCL$_3$ it became 60:40. These results are in agreement with the idea that strong acids decrease the importance of the stereoelectronic factor in processes such as the protonation of enols.

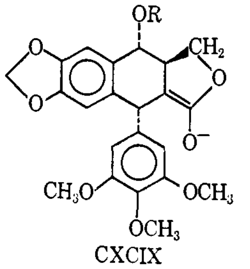

CXXXIII CXXXIV CLXXXIII

This work has a bearing on the mechanism of isomerization of CXXXIV to CLXXXIII which occurs quite easily in a hydroxylic medium containing a little strong base. There is a choice. Either CLXXXIII is produced from CXXXIV *via* an anionic intermediate which has considerable sp^3 character at C-1 (*i.e.*, looks somewhat like a ketocarbanion) or else it is produced *via* one of the higher energy intermediates associated with the sp^2 state of CXXXIII, *i.e.*, by "equatorial" protonation of CXXXIIIb or "axial" protonation of CXXXIIIa. *It appears that the acidity (or basicity) of the medium may be the controlling factor in determining which mechanism is involved in the isomerization.* Further investigation in this area, however, seems necessary.

A considerably more complicated situation exists in a case discussed recently by Gensler and Gatsonis.[165] This concerns the conversion of picropodophyllin (CXCVII) to podophyllotoxin (CXCVIII) *via* the

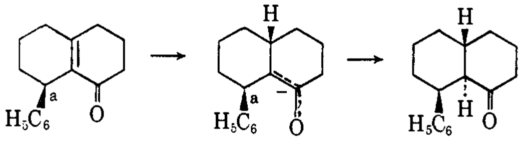

CXCVII


CXCVIII


CXCIX

enolate anion CXCIX (R = tetrahydropyranyl). The quenching of this enolate anion with acetic acid afforded a 45:55 mixture of CXCVII and CXCVIII, respectively. It was anticipated that protonation would occur largely from the topside of CXCIX since it was thought that the conformation of CXCIX with a quasi-axial trimethoxyphenyl ring would be the more stable. The alternate form with a quasi-equatorial aryl group is ruled out because of the allylic strain between the trimethoxyphenyl ring and the oxygen of the enolate. The rationale put forward by Gensler and Gatsonis is that the transition state, in this particular case, shows considerable sp^3 character in the direction of CXCVII since the latter is thermodynamically more stable than CXCVIII. Thus protonation occurs from both sides of the molecule, because such a change in geometry makes the rearside of the molecule reasonably accessible to a proton donor. There seems little reason, however, to assume that the transition state differs much from the starting anion. It appears more probable that the latter itself resembles a ketocarbanion, perhaps as a result of the greater strain associated with the enolate form.

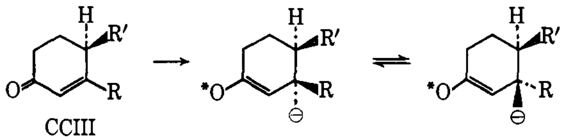
An interesting case[166] for comparison is the protonation of the lithium–liquid ammonia reduction product CCI of CC. This gives rise exclusively to CCII. The reason for higher selectivity here may be the lack of strain associated with the enolate form of CCI.


CC CCI CCII

D. STEREOCHEMISTRY OF LITHIUM–LIQUID AMMONIA REDUCTIONS

One other type of reaction which lies within the compass of this section is the metal–ammonia reduction of cyclic α,β-unsaturated ketones (CCIII). The following recapitulation constitutes what is known concerning the mechanism of this process.

Originally it was stated[167] that such reductions always lead to the more or most stable isomer of the resulting saturated ketone. The reason given was that the intermediate carbanion CCIV could rapidly equilibrate between two forms CCIVa and CCIVb. Since under normal circumstances CCIVb could conformationally


CCIII CCIVa CCIVb

be expected to be the stabler of the two, subsequent protonation should give largely the ketone derived from CCIVb. There were, however, exceptions to the rule and the thesis was further modified by Stork and Dar-

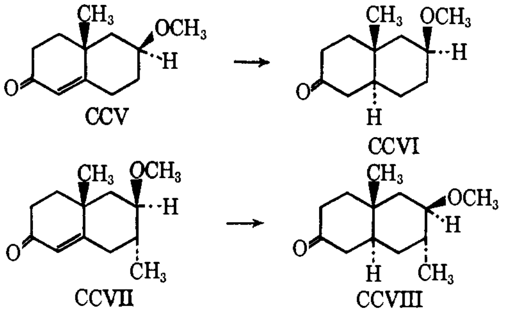
---

[165] W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 4004 (1966).

[166] H. O. House and R. W. Bashe, II, *ibid.*, **30**, 2942 (1965).

[167] D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

ling[168] who pointed out that what perhaps is really important in such reductions is that the carbanion at the β position in the intermediate CCIV should be in that orientation which maximizes its overlap with the double bond of the enoxy group. They demonstrated this by showing that reduction of both CCV and CCVII afforded only the *trans*-decalones CCVI and CCVIII, respectively.

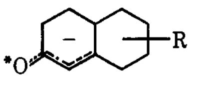


CCV → CCVI

CCVII → CCVIII

In the first of these cases it was pointed out that the *cis*-decalone should be somewhat more stable than the *trans* by about 0.4 kcal/mole whereas in the second case the *cis*-decalone should be favored by about 2 kcal/mole. Yet in both cases only the *trans* isomer was formed.

Both of these investigations were predicated completely on the basis of the protonation transition state resembling the enolic product (*i.e.*, the β-carbon atom being largely tetrahedral), a view which has been argued for by Zimmerman.[137] In a very elegant paper Robinson[169] has discussed this point at length in examining the sodium–ammonia–methanol reduction products of a series of $\Delta^{1(9)}$-2-octalones. These reductions all proceeded with very high selectivity to give the *trans*-2-decalones together with only minute amounts of the *cis* isomers. He concluded that the product ratios could be accounted for qualitatively if the transition states were similar to the conformation of a highly basic intermediate anion CCIX, in which the C-9 carbon atom (*i.e.*, β-carbon) is trigonal, rather than to the products in which the C-9 carbon atom is tetrahedral.



CCIX

In essence Stork and Darling's view was refuted because strain energy calculations for the two forms CCIVa and CCIVb, in the decalone series, in no case revealed energy differences large enough to account for the very high selectivity of the reaction. On the other hand, rough estimates for the energy differences between the three possible conformations of CCIX and between those of their possible protonation products seemed great enough to account for the observed results.

The difficulty in analyzing Stork and Darling's interpretation accurately, as Robinson has pointed out, is that the thermodynamic relationship between the Δ^1-*cis*- and Δ^1-*trans*-decalones is unknown. On the other hand, it is difficult to see why protonation of CCIX occurs only on the α face of the molecule if indeed the system is as flat and delocalized as Robinson suggests. It does not seem logical that the stereoelectronic effect could be so demanding in such a case. In fact, quite the reverse argument can be put forward in that since high selectivity is the rule with these systems the orientation of the charge at the β-carbon must be quite specific, especially since 1,3-diaxial steric effects such as those seen in CCVII do not appear to be a hindrance to protonation. Even in such a case as CC in which the phenyl ring appears from available nmr evidence[166] to be axially oriented in the starting material (the 2-alkyl ketone effect once again), protonation takes place on the upper or β face of the molecule.

Zimmerman[137] has commented that intuitively one might expect that there should only be weak interaction between the negative charge on the β-carbon atom and the already electron-rich enolate system (assuming the system being protonated to be a dianion). This being the case, since the preferred hybridization of a carbanion not stabilized by electron delocalization is sp^3, the tendency to this state at the β-carbon in CCIV should not be surprising.

This argument is of course subject to some question since it is not known whether protonation of a dianion or a radical anion is taking place. The second reduction potentials of simple α,β-unsaturated ketones do not appear to be known. Whether the medium M–NH$_3$–EtOH is capable of adding two electrons to such a system is a matter for conjecture. Perhaps polarography could help resolve this point.

Apart from Zimmerman's comments it seems only logical from the point of view of transition state ideas[164] that protonation should be occurring on a largely tetrahedral carbanion since the medium in which the protonation is taking place is very highly basic.

In a further examination of this reaction, the authors recently undertook a reduction study of some monocyclic α,β-unsaturated ketones of the type CCIII (R and R′ = variety of substituents) with the objective of investigating the nature of the protonation transition state at the β-carbon atom.[170] The argument is simple. If the transition state at the β-carbon atom is trigonal during protonation, the products should reflect the conformational composition of the starting material.

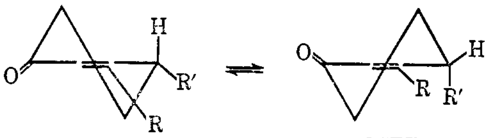
---

[168] G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).

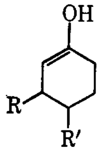
[169] M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

[170] S. K. Malhotra, D. F. Moakley, and F. Johnson, *Tetrahedron Letters*, 1089 (1967).

In conformer CCCIIIa the $A^{(1,2)}$ strain between R and R′ must be quite high since from models the dihedral angle R-C-3-C-4-R′ is now $<30°$. Therefore it could be anticipated that the conformer CCIIIb would be most favored even in such cases where $R = R' = CH_3$. In accordance with Hammond's principle,[164] the product of reduction should contain a high proportion of the 3,4-*cis* isomer provided, of course, that protonation occurs as selectively as in other cases. Conversely if the protonation transition state at the β-carbon were tetrahedral, then the composition of the products as mentioned before should reflect the thermodynamic equilibrium relationship of the *cis* and *trans* forms of the enol CCX or more precisely the forms CCIVa and CCIVb. The energy difference in question can be estimated as ~0.9–1.3 kcal/mole for the case where $R = R' = CH_3$. This implies that the product in this case should contain ~88–93% of *trans*-3,4-dimethylcyclohexanone. Table IV contains the results obtained with a series of 3,4-disubstituted 2-cyclohexenones. The investigation as it stands is not adequate to explain the detailed mechanism of the metal–ammonia reduction. However, several comments can be made. With purely alkyl substituents at the C-3 position the protonation transition state of this center appears to be largely tetrahedral. The results for the 3,4-diethyl-Δ^2-cyclohexenone seem somewhat out of line. Whether this is due to a change in the transition state in the direction of a more trigonal β-carbon atom or perhaps more likely to the greater nonbonded interactions in form CCIVb than in CCIVa is not known. It is under further investigation, however.



CCIIIa CCIIIb

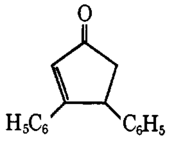


CCX

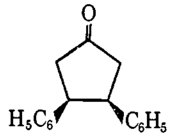
TABLE IV

Starting material		Product	
R	R′	% *trans*	% *cis*
CH_3	CH_3	84	16
CH_3	C_2H_5	84.5	16.5
C_2H_5	C_2H_5	43.5	56.5
C_6H_5	CH_3	6	94
C_6H_5	C_6H_5	2	98

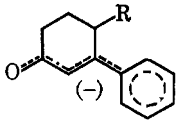
The case where CCIII carries a substituent at the β-carbon, itself capable of overlap with a developing *p* orbital at that center in the transition state for protonation, has been considered by Stork and Darling.[171] They noted that under such circumstances it seemed likely that form CCIVa would achieve importance because the proper orientation of R to allow its overlap with the carbanionic center on the β-carbon may force R′ to become axial in the transition state to minimize interference between R and R′ (a complete anticipation of the general case of $A^{(1,2)}$ strain). This explanation was applied to the case of the reduction of CCXI which gives, it seems, only CCXII, the less stable isomer of 3,4-diphenylcyclopentanone. Nmr evidence is now available[172] which shows that CCXI does indeed have a pseudo-axial C-4 phenyl group. The final two results of Table IV must, of course, be placed in the same category. Since delocalization of the β carbanion by the phenyl ring is considered to occur, the transition state for protonation must be much closer to trigonal than to tetrahedral geometry. There is then a partial double bond between C-4 and the phenyl ring (*viz.*, form CCXIII) so that around C-4 and C-5 all the elements of $A^{(1,3)}$ strain exist, thus accounting for the high proportion of the *cis* isomer in the product. One may speculate whether the protonation of hot carbanions, such as those encountered in the reduction of CC, CCVII, and other $\Delta^{(1,9)}$-2-octalones, may not be subject to steric approach control whereas the cooler varieties, such as CCXIII, are. Again a much more detailed investigation appears necessary.



CCXI



CCXII



CCXIII

Despite all research so far, the problem concerning the very high product selectivity observed in the reduction of $\Delta^{(1,9)}$-2-octalones remains unsolved.

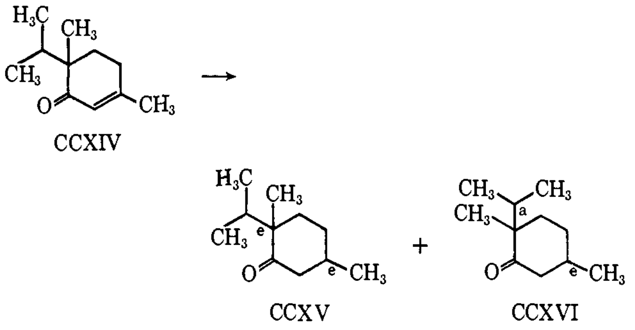
Before closing this section one other case deserves consideration, the reduction of CCXIV. Catalytic hydrogenation yields 70% CCXV and 30% CCXVI. As Djerassi[173] pointed out, this result is consistent with CCXIVa being the predominant conformer and that absorption on the catalyst surface and entry of hydrogen occur on the upper face.

---

[171] N. N. White, private communication, cited by G. Stork and S. D. Darling in footnote 23 of ref 168.

[172] P. Bladon, S. McVey, P. L. Pauson, G. D. Broadhead, and W. M. Horspool, *J. Chem. Soc., C*, 306 (1966).

[173] C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 4433 (1961).

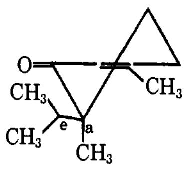


CCXIV

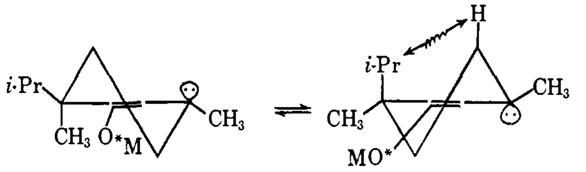
CCXV

CCXVI

On the other hand, the lithium-ammonia reduction of CCXIV led to a product containing 75% CCXVI and only 25% CCXV, a result for which no ready explanation was at hand.



CCXIVa



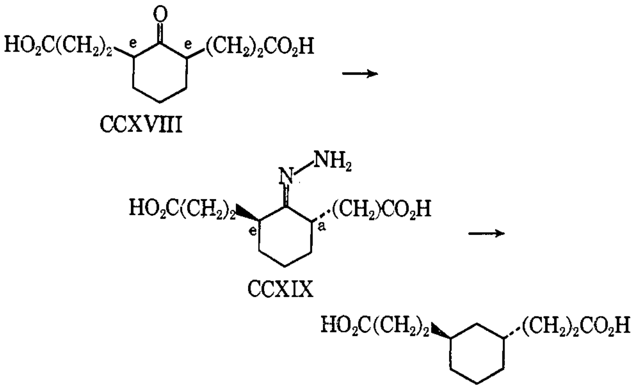
CCXVIIa

CCXVIIb

It would appear that this is another case where $A^{(1,2)}$ strain is the controlling factor. Seemingly the nonbonded interaction between the solvated O^-M^+ ion pair and the isopropyl group in CCXVIIa is greater than the 1,3-diaxial interaction shown in CCXVIIb so that the latter form predominates prior to protonation of the C-3 carbanionic center. Thus in this reduction CCXVI is the dominating product. We have depicted the reaction as involving an enolic carbanion in the protonation step; nevertheless, the same argument can be applied even if the transition state for protonation is planar.

E. MISCELLANEOUS CASES

A number of other examples where A strain seems to be the controlling factor are worthy of note. One of the most interesting is the Wolff–Kishner reduction of 2,6-bis(carboxyethyl)cyclohexanone (CCXVIII) which gives rise to *trans*-1,3-bis(carboxyethyl)cyclohexane (CCXX) the *cis* isomer being isolated in only small amounts.[174] This is obviously a case of $A^{(1,3)}$ strain involving a pseudo-allylic system. Whether or not the hydrazone CCXIX is formed selectively from the *trans* isomer of CCXVIII by base-catalyzed isomerization of CCXVIII or whether CCXVIII forms a hydrazone which is then isomerized by base to CCXIX is a matter for conjecture, but the author inclines to the former view. Certainly the postulated mechanism[40,175] of the Wolff–Kishner reduction would allow no change in the orientation of the substituents once reaction was initiated.

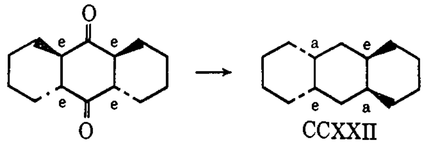


CCXVIII

CCXIX

CCXX

In the same category as the above example is a case described by Clarke[176] and others.[177,178] They were able to prepare in reasonable yield the perhydroanthracene CCXII together with smaller amounts of other isomers by the double Wolff–Kishner reduction of the perhydroanthraquinone CCXXI, but offered little in the way of an explanation for the latter's formation.



CCXXI

CCXXII

Prior to this, CCXXII had proved extremely elusive from a preparative viewpoint and represented the only stereoisomer of perhydroanthracene still unprepared. $A^{(1,3)}$ strain furnishes an excellent reason for the course of the reaction and this example represents a very powerful demonstration of the ability of this type of strain to control stereochemistry. Even in the Wolff–Kishner reduction of CCXXIII a disproportionate amount of the *cis* isomer of CCXXIV is produced,[179] based on the thermodynamic equilibrium ratio expected for the products. A more complicated case, related

CCXXIII

CCXXIV

---

[174] T. L. Westman, R. Parades, and W. S. Brey Jr., *J. Org. Chem.*, **28**, 3512 (1963).

[175] D. Todd, *J. Am. Chem. Soc.*, **71**, 1356 (1949); see also D. H. R. Barton, W. Klyne, and N. J. Holness, *J. Chem. Soc.*, 3456 (1949).

[176] R. L. Clarke, *J. Am. Chem. Soc.*, **83**, 964 (1961).

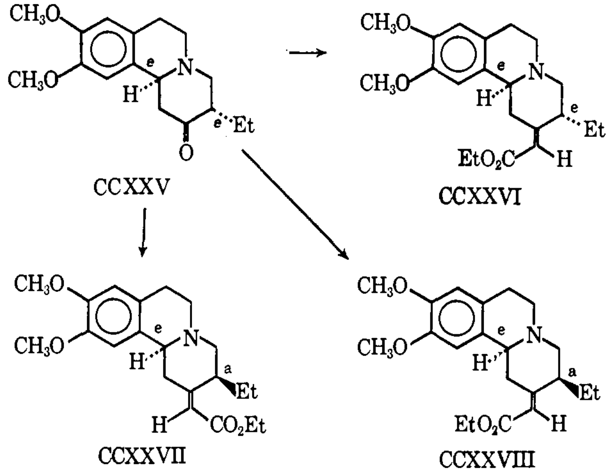
[177] N. S. Crossley and H. B. Henbest, *J. Chem. Soc.*, 4413 (1960).

[178] R. K. Hill, J. G. Martin, and W. H. Stouch, *J. Am. Chem. Soc.*, **83**, 4006 (1961).

[179] H. Peters, R. A. Archer, and H. S. Mosher, *J. Org. Chem.*, **32**, 1382 (1967).

perhaps to XLIV described earlier, concerns the reaction of the sodium salt of $(EtO)_2POCH_2CO_2Et$ with CCXXV.[180] In the absence of excess base this leads to CCXXVI which can be regarded as the normal product, together with smaller amounts of CCXXVII. However, in the presence of excess base the main product is CCXXVIII. The course of the reaction in the absence of excess base seems reasonable. However, the production of a large amount of CCXXVIII in the presence of base appears strange since such a compound with an axial ethyl group would not be expected to be the most thermodynamically stable isomer.

The presence of CCXXIX could not be detected in line with A-strain ideas. The severe steric strain to be anticipated in such a molecule was pointed out by the authors.[180]

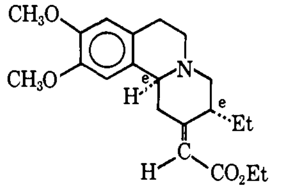


CCXXV

CCXXVI

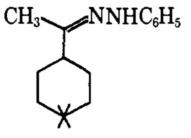
CCXXVII

CCXXVIII

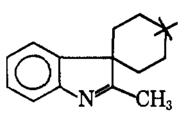


CCXXIX

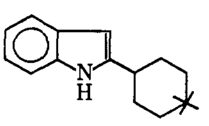
Lastly A strain has been invoked by Lyle[181] to explain the different reaction paths taken when CCXXX is cyclized by acids of varying bulk. In the case of a nonbulky acid such as phosphoric acid, the product is CCXXXII, contrary to what would be expected. On the other hand, the bulky acid zinc chloride leads to CCXXXI. These results are rationalized by considering the rotational conformers of the intermediate. If R is a bulky acid (*i.e.*, more bulky than -NH-), then conformer CCXXXIIIa will prevail because it displays the lesser $A^{(1,3)}$ strain so that approach of the phenyl ring to the double bond can take place with reasonable probability with the resulting formation of CCXXXI. However, if R is simply a proton, CCXXXIIIb will be, because of A strain, the preferred conformer. Since under these circumstances the probability of the phenyl ring being in the vicinity of the double bond is low, an alternate reaction involving the intermediate CCXXXIV takes precedence despite the fact that the latter has the double bond in the less favorable thermodynamic position. Thus in this case the product is CCXXXII. It should be noted that acetic acid cyclization also yields CCXXXI, but here acetylation is considered to precede cyclization so that in this case R = acetyl, and the same explanation holds as for the zinc chloride cyclization.



CCXXX

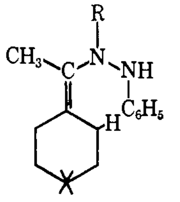


CCXXXI

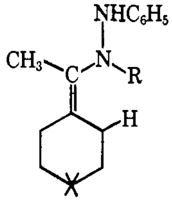


CCXXXII

X= >CH_2 or >NCH_3

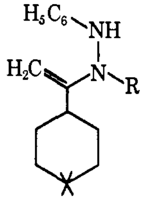


CCXXXIIIa



CCXXXIIIb

X = CH_2 or NCH_3



CCXXXIV

X = CH_2 or NCH_3

V. FIVE-MEMBERED RINGS

The applicability of A strain to five-membered rings is on much shakier ground. Theoretically, with a little modification the concepts should apply, but experimental evidence is lacking to support this premise.

In five-membered rings the transannular 1,3-diaxial interaction does not seem to be associated with as much energy as in the case of six-membered rings.[182-184] Therefore, in a system such as CCXXXV, even though ideally the dihedral angle in the grouping R′-C-C-R may be greater than 40-43° (a six-membered ring case), the interaction between R′ and R could be great enough

---

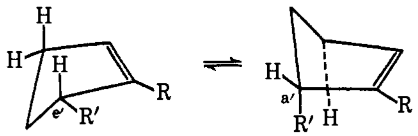
[180] C. Szantay, L. Toke, and P. Kolonits, *J. Org. Chem.*, **31**, 1447 (1966).

[181] R. E. Lyle and L. Skarlos, *Chem. Commun.*, 644 (1966).

[182] J.-C. Richer and C. Gilardeau, *Can. J. Chem.*, **43**, 3419 (1965).

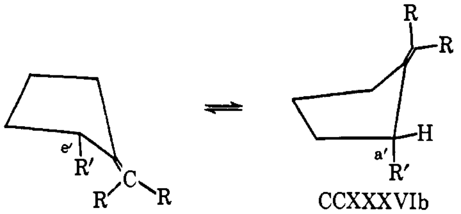
[183] B. Fuchs and R. G. Haber, *Bull. Res. Council Israel*, **A11**, 30 (1962).

[184] B. Fuchs and R. G. Haber, *Tetrahedron Letters*, 1323 (1966).



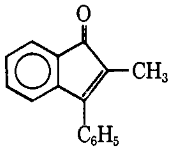
CCXXXVa CCXXXVb

to ensure that the compound exists largely as conformation CCXXXVb rather than CCXXXVa. Exactly the same reasoning can be applied to the pair of conformers CCXXXVIa and CCXXXVIb, the latter

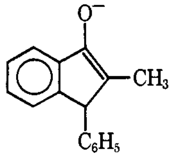


CCXXXVIa CCXXXVIb

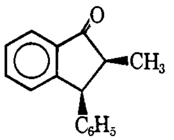
predominating if R and R′ have any reasonable steric size. On the experimental side it has already been mentioned that the metal–ammonia reduction of 3,4-diphenyl-2-cyclopentenone (CCXI) gives *cis*-3,4-diphenylcyclopentanone[171] in complete analogy with the corresponding six-membered ring case. Related to this is the reduction of CCXXXVII discussed by Zimmerman.[185] The enolic product CCXXXVIII on careful quenching yields largely CCXXXIX. Insofar as



CCXXXVII



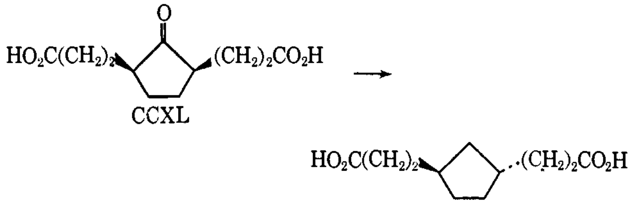
CCXXXVIII



CCXXXIX

$A^{(1,3)}$ strain is concerned, the hydrobromination of 1-cyclopentenecarboxylic acid described by Vaughan and Caple[157] fits in admirably. This affords the *cis* isomer of 2-bromocyclopentanecarboxylic acid as the primary product.

Another case in this category is the Wolff–Kishner reduction of CCXL described by Westman and Kober.[185a] This leads to pure CCXLI in 80% yield. The selectivity of reaction *surpasses* that in the corresponding six-membered ring case mentioned earlier, since little of the *cis* isomer of CCXLI could be found in the mother liquors.



CCXL

CCXLI

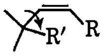
These examples represent the sum of available knowledge and without further experimentation a complete generalization cannot be made for five-membered ring systems.

The situation with respect to other rings is perhaps worse. Such stereochemical work as has been done is of very limited scope and affords little evidence pro or con for the operation of A strain in three-, four-, seven-, or higher membered rings.

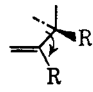
It is worth noting that the decarboxylation of the 1,1,2-tricarboxylic acids in the cyclopropane, cyclobutane, and cyclopentane series gives the *cis*-1,2-dicarboxylic acid in each case when the reaction is carried out in collidine.[145] However, as in the six-membered ring case, decarboxylation in 5 *N* HCl yields preponderantly the *trans*-dicarboxylic acids.

VI. Epilogue

Although A strain has been discussed very largely in the context of six-membered rings in this article, the phenomenon of allylic strain seems to be a universal property of the systems CCXLII and CCXLIII.



CCXLII



CCXLIII

When either of these groups appears in a molecular structure, a nonbonded interaction between R and R′ will occur, the magnitude of which will depend on (a) the size of R and R′ and (b) the dihedral angle that the bond C–R makes with the C–R′ bond. If the R and R′ are large and the dihedral angle is small, the interaction energy will be high, and *vice versa*. Thus certain highly substituted aliphatic compounds might be expected to exhibit A strain.

A good case in point concerns α-methylstyrene. Its ultraviolet spectrum by comparison with that of styrene suggests steric inhibition of resonance.[186–188] The latter in terms of A strain would be due to interference of the phenyl ring with the hydrogen atoms of the methyl group. Other molecules which display a break in coplanarity of their unsaturated groups due to this type of hindrance are 1,1,3-trimethylbutadiene[189] and 2,4,7-trimethylocta-2,4-dien-7-ol,[190–192] where the interfering groups can be considered to be two methyl

---

[185] H. E. Zimmerman, *J. Am. Chem. Soc.*, **78**, 1168 (1956).

[185a] T. L. Westman and A. E. Kober, *J. Org. Chem.*, **29**, 2448 (1964).

[186] C. G. Overberger and D. Tanner, *J. Am. Chem. Soc.*, **77**, 369 (1955).

[187] H. P. Koch, *J. Chem. Soc.*, 123 (1948).

[188] A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, pp 97–100.

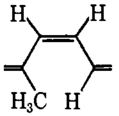
[189] J. C. Lunt and F. Sondheimer, *J. Chem. Soc.*, 2957 (1950).

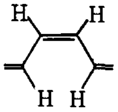
[190] A. E. Braude, *ibid.*, 1890 (1949).

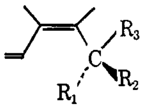
[191] W. F. Forbes, "Steric Effects in Conjugated Systems," G. W. Gray, Ed., Academic Press Inc., New York, N. Y., 1958, Chapter 6.

[192] E. S. Wright and R. L. Erskine in ref 191, Chapter 7.

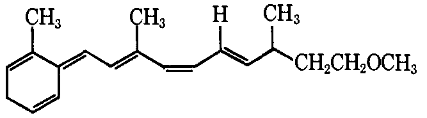
groups or a hydrogen atom and the -$C(CH_3){=}CH$- moiety. Such inhibition of resonance was first noted by Braude for β-ionone.[191] However, he did not advance the idea that the phenomenon was contingent upon the appropriate substitution in the three-carbon allylic skeleton. Before leaving this particular area, it is well to notice that Pauling's rules,[193] used in the study of carotenoids, fall into this classification also. These rules state that structures of type I having a *cis* double bond will show pronounced steric hindrance, and thus the *cis* configuration will be assumed only by those double bonds which are of type II.


type I


type II

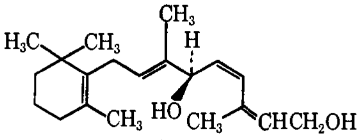

type Ia

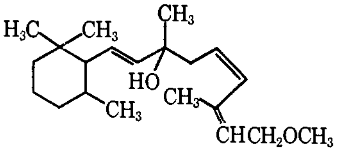
The synthesis of such systems as type I did, however, prove feasible, but their ultraviolet spectra are indicative of a break in conjugation in this area of the polyene. In particular Oroshnik and Mebane[194] have examined the electronic spectrum of CCXLIV and found that it shows an ill-defined peak of low intensity, λ_{max} 270–380 mμ (ε 21,200), whereas the *trans* isomer gives a well-defined trio of peaks at λ_{max} 325 mμ (ε 46,000), 340 (62,500), and 358 (54,400). These workers extended Pauling's ideas to another system which they considered would always show steric inhibition of resonance, namely type Ia shown above. This grew out of a reexamination of the tetraene CCXLV which Isler, *et al.*,[195,196] had described as showing only end absorption. Oroshnik and Mebane confirmed this observation, then synthesized the corresponding *trans* isomer, and demonstrated that it possessed normal diene characteristics.

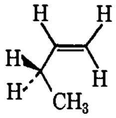

CCXLIV

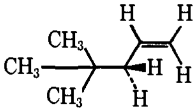
It is most interesting that even in CCXLVI the intensity of the spectrum is reduced by comparison with the related *trans* isomer, and much more closely approximates the compound having a triple bond in place of the *cis*-ethylenic group. Absorption by the other diene in CCXLVI prevented a quantitative comparison, however.

A much more recent piece of work involving aliphatic compounds where A strain exhibits an effect is due to Bothner-By, Naar-Colin, and Gunther.[77] These workers examined the conformational preferences of several 1-butenes by nmr spectroscopy. In the case of 1-butene itself, the planar arrangement shown in CCXLVII was found to be preferred. However, progressive substitution of the terminal methyl group by methyl groups led to molecules in which conformations with the staggered arrangement contributed more and more to the equilibrium picture. In the fully substituted compound, 4,4-dimethylpentene-1, this latter conformation, *viz.* CCXLVIII, is essentially the only one present at equilibrium. The situation can be analyzed possibly as a case of hyperconjugation *vs.* $A^{(1,3)}$ strain, the former dominating in CCXLVII, the latter in CCXLVIII.


CCXLV


CCXLVI


CCXLVII


CCXLVIII

Another nmr study which also can be included here is that due to Hayashi, *et al.*,[197] who recently have studied the equilibrium isomerizational preferences of a series of substituted alkylidenecyanoacetic esters of the type $R(CH_3)C{=}C(CH)CO_2R'$, where R = alkyl group larger than methyl. They concluded (a) that the isomer with the β-methyl group *cis* to the alkoxycarbonyl group always predominates at equilibrium and (b) that the *cis–trans* ratio of isomers directly parallels the steric requirements of the alkyl group R.

Finally it should be noted that compounds in which the double bond of the allylic system is part of an aromatic ring also fall within the compass of A strain. Thus many *ortho*-substituted benzenes can be regarded as allylic or pseudo-allylic systems. However, other than drawing attention to the relationship, no further discussion of this aspect of allylic strain seems merited since in this area the phenomenon appears to be well understood.

---

(193) L. Pauling, *Fortschr. Chem. Org. Naturstoffe*, **3**, 203 (1939).

(194) W. Oroshnik and A. D. Mebane, *J. Am. Chem. Soc.*, **76**, 5719 (1954).

(195) O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

(196) O. Isler, W. Huber, A. Ronco, and M. Kofler, *ibid.*, **32**, 489 (1949).

(197) T. Hayashi, M. Igarashi, S. Hayashi, and H. Midorikawa, *Bull. Chem. Soc. Japan*, **38**, 2063 (1965).

ACKNOWLEDGMENT.—The author thanks The University of Oxford and, in particular, Professor Sir E. R. H. Jones for the hospitality of The Dyson Perrins Laboratory during the writing of this article. Special thanks are due also to Drs. S. K. Malhotra and M. J. T. Robinson for the many fruitful conversations that helped to clarify certain aspects of the discussion.