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Recent Studies of the Anomeric Effect

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Contents

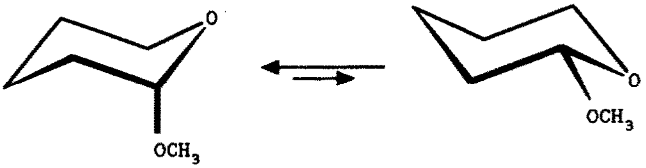
1. Introduction.

Since its discovery[1] and first enunciation,[2] the anomeric effect has continued to exercise the experimental and theoretical skills of a generation of chemists. In this regard, the appearance of two review articles in the early seventies,[3,4] and then three influential monographs in the early eighties,[5-7] has provided stimulus for the development of additional ingenious experiments as well as more rigorous theoretical calculations directed to the understanding of this conformational effect. This review actually attempts to present an organized discussion of those efforts described in the last decade. It will be clear, nevertheless, that a proper calibration of the anomeric effect in terms of calculated and observed properties is found to be not free from challenging complications.

2. Historical Aspects and Definitions.

2.1 The Edward-Lemieux Effect.

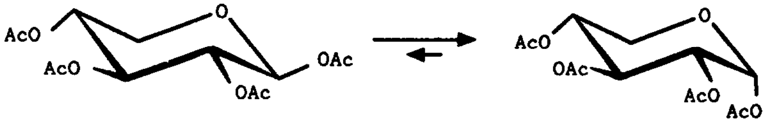
Various studies in the field of carbohydrate chemistry led J.T. Edward to propose, in 1955, that in the pyranose ring axial alkoxy groups at C(1) are in general more stable than equatorial ones, contrary to the usual order of conformational stabilities[1] (eq. 1).



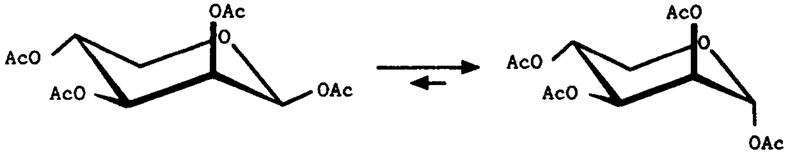
(1)

Edward's interpretation of this observation is based on the orientation of the unshared electrons of the ring oxygen (see Section 3) and is the first reference to the importance of lone electron pairs in determining conformational preferences. The area of stereoelectronic interactions is now, of course, very important in its contributions of conformational analysis to chemistry.

Nineteen fifty five is also the year when N.-J. (Paul) Chü and R.U. Lemieux began to study the anomerization equilibria of the fully acetylated derivatives of several aldohexopyranoses.[8] Their results confirmed the contribution of a stereoelectronic factor to these equilibria. For example, the $\beta \rightleftarrows \alpha$ equilibrium in the xylo-configurated pyranose favors the α anomer by 0.94 kcal/mol (eq 2). When the gauche non-bonded interaction between the acetoxy groups at C(1) and C(2) is removed (as in the β-lyxose → α-lyxose equilibrium, eq 3) the preference for the α form increases to 1.48 kcal/mol.



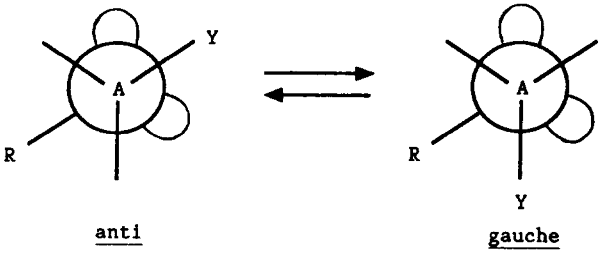
$\Delta G^{o} = -0.94$ kcal/mol (2)



$\Delta G^{o} = -1.48$ kcal/mol (3)

Although Chü's work was never published beyond his Ph.D. thesis,[9] the most salient results were presented at a meeting of the American Chemical Society.[2] It was at this time that the term "*anomeric effect*" was introduced: it refers to the tendency of an electronegative substituent at C(1) of a pyranoid ring to assume the axial rather than the equatorial orientation, in contrast to predictions based solely on steric grounds.

It soon became clear, however, that the phenomenon is not restricted to carbohydrates or for that matter six-membered heterocycles. Thus, the "*generalized anomeric effect*" is defined as the preference of the synclinal (*gauche*) position over the antiperiplanar (*anti*) in segments R-X-A-Y, where A is an element of intermediate electronegativity (e.g., C, P, S), Y denotes an atom more electronegative than A (e.g., O, N, or halogen), X denotes an element which possesses lone pairs, and R stands for H or C[10,11] (eq 4).



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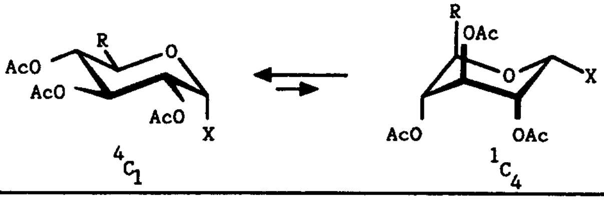
2.2 Some Consequences of the Anomeric Effect in Sugars.

While there are problems in the quantitative analysis of conformational equilibria for polyoxygenated structures,[8] many of the structural and chemical consequences of the anomeric effect are to be found in monosaccharides and their derivatives.[12,13]

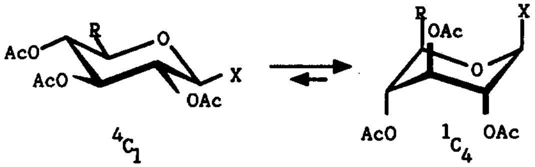
Thus, some of the most clear expressions of the anomeric effect are manifested in acylated aldopyranosyl halides, where the preference of halogen for axial orientation is so large that it is the dominant factor in determining conformations. For example, in the case of α-anomers with D-xylo or D-gluco configuration, e.g., 1α-6α, the tendency for axial orientation of the halogen ($^4C_1$) is so high that the alternate conformers with equatorial halogen ($^1C_4$) are detectable neither in solution nor in the crystal.[14] (Scheme 1).



Compd	X	R
1 α	F	H
2 α	Cl	H
3 α	Br	H
4 α	F	CH_2OAc
5 α	Cl	CH_2OAc
6 α	Br	CH_2OAc

Scheme 1

In the corresponding β-anomeric series, the tendency of the halogen to be axial is opposed by the preference of the other ring substituents to be equatorially oriented. One consequence of this is that bromides 3β and 6β have so far eluded synthetic efforts. The β-D-xylosyl halides 1β and 2β establish $^4C_1 \rightleftharpoons {}^1C_4$ equilibria with predominant participation (~80%) of the latter conformers, presenting an axially disposed halogen, despite the fact that now all the acetoxy substituents are also in axial positions.[14] (Scheme 2).



Compd	x	R
1 β	F	H
2 β	Cl	H
3 β	Br	H
4 β	F	CH_2OAc
5 β	Cl	CH_2OAc
6 β	Br	CH_2OAc

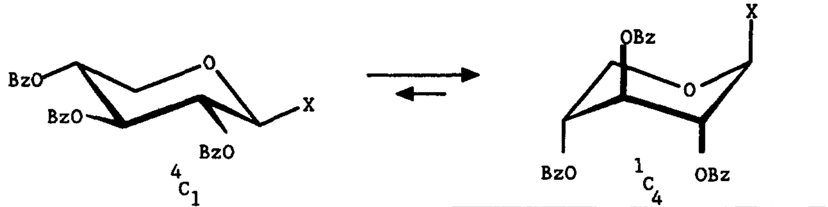
Scheme 2

Thus, the relative ratio of the axial and equatorial isomers at equilibrium depends mainly on the type of substituent (aglycon) on the anomeric center, on the other substituents on the ring, and on the solvent.

2.2.1 The Nature of the Aglycon.

The equilibrium composition of several tri-*O*-benzoyl-β-D-xylopyranose derivatives are summarized in Table 1.

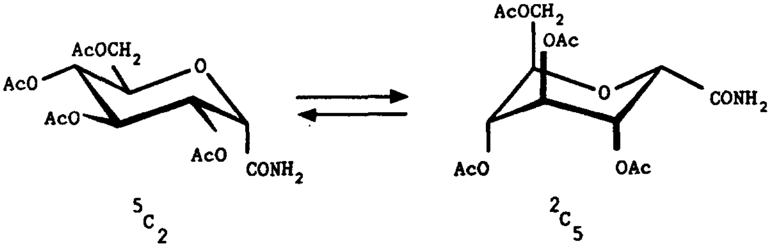
Table 1. Conformational Equilibria of Tri-*O*-benzoyl-β-D-xylopyranose Derivatives.[12]



Anomeric group	% $^1C_4$ conformer (in acetone)
H	19
MeO	26
AcO	47
BzO	50
F	90-100
Cl	98
Br	90-100

Inspection of these data shows that the preference for the axial position increases with the electron-withdrawing character of the anomeric substituent X; that is, F > O, and for the latter element, BzO > AcO > CH_3O.

On the other hand, carbon atom substituents at the anomeric center generally favor the equatorial position. For example, the carbamoyl-substituted derivative 7β displays a considerable proportion of the $^2C_5$ conformation (56% in $CDCl_3$), despite extensive 1,3- diaxial interactions of four bulky groups[15] (eq 5).

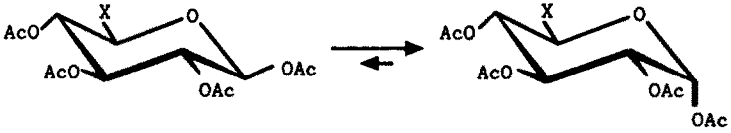


(5)

2.2.2 The Other Ring Substituents.

It is well known that the configuration of the hydroxyl group at C(2) in a pyranose ring substantially affects the anomeric equilibrium. Thus, in the case of D-mannopyranose, the axial hydroxyl group at C(2) increases the contribution of the α anomer relative to that for 2-deoxy-D-arabino-hexopyranose: 69% *vs* 47%, respectively. Conversely, if the hydroxy group at C(2) is in the equatorial position, as in D-glucopyranose, the proportion of the α anomer decreases to 36%[12] (see, also, eqs 2 and 3).[8]

On the other hand, the role of substituents at C(5) illustrated in Scheme 3, shows that an increase in the electronegativity of the substituent increases the axial preference of the acetyl group.[10]



Compound	X	Axial Anomer %
8	CH_2I	84
9	CH_2Cl	86
10	CH_2OAc	86
11	CH_2OTs	91

Scheme 3

2.2.3 The Effect of the Solvent.

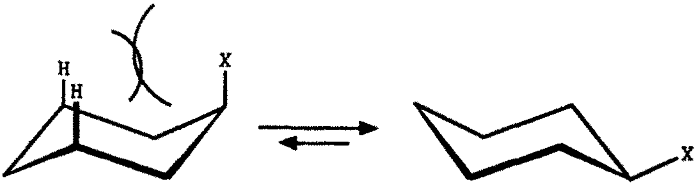
The variation of the axial preference depending on the nature of the ring substituents suggests that the anomeric effect is sensitive to solvation. Studies of acyclic and cyclic models are of invaluable assistance: results in this field will be extensively discussed in Chapter 3. With respect to specific solvent effects on carbohydrate stereochemistry, it has recently been suggested that variations in the hydrophilicity of pyranose sugars explain the features of the anomeric effect;[16] i.e., that it is the energy of interaction with the solvent which provides the driving force for glucopyranoses to adopt a given anomeric configuration. Indeed, hydrophilicity values for several model axial and equatorial were calculated by determining the volume around each molecule in which water molecules may hydrogen bond. A correlation between the difference in hydrophilic volume for each anomeric pair with the experimentally observed anomeric ratios in aqueous solution gave a good correlation coefficient of 0.974.

According to Walkinshaw,[16] this correlation indicates that the dominant factor in determining the anomeric equilibrium is the relative hydrophilicity of the two anomeric isomers -the energy gain in forming sugar- - -water hydrogen bonds outweighs intramolecular steric and electronic effects. The observation that the anomeric effect increases with decreasing dielectric constant (see

Chapter 3) would then be explained as caused by the reduction of the importance of sugar- - -solvent interactions and an increase in the relevance of van der Waals and electrostatic terms. This reasoning seems simplistic, however, in view of the fact that the anomeric effect exists in simple tetrahydropyrans (see, for example, Table 2 below). Hydrogen bonding can be only one of several contributions -it should always favor the equatorial conformation.

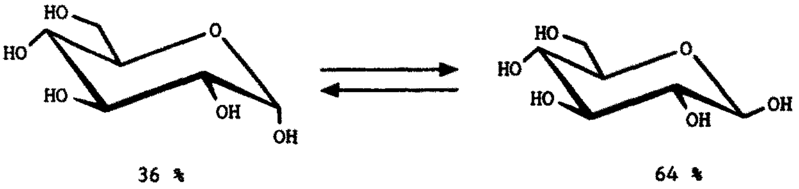
2.3 Quantitation of the Anomeric Effect.

The energy differences between the equatorial and axial conformations of monosubstituted cyclohexanes (*A* values) are of great interest to organic chemists since they serve as models for more complicated molecules.[17] Most groups prefer equatorial over axial positions, largely in order to avoid the repulsive steric interactions with the axial hydrogens of the 3- and 5-positions: thus, usually, the bulkier the substituent the larger the preference for the equatorial form[18] (eq 6).



(6)

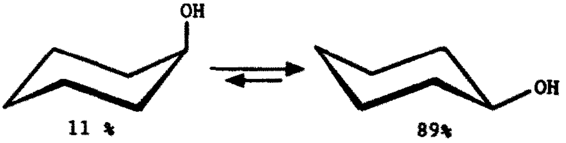
For example, D-glucose, the most abundant of the hexoses, exists in aqueous solution as 64% of the β-anomer and 36% of the α anomer (eq 7).



(7)

$$\Delta G^{o}_{25\,^{o}C} = -0.34 \text{ kcal/mol}$$

At first sight, the greater conformational stability of the isomer with all its substituents equatorial seems to be in accord with the conformational behavior of substituted cyclohexanes. However, the *A* value of the hydroxyl group *in aqueous solution* has been determined as -1.25 kcal/mol[19] (eq 8), so that a 89:11 ratio might have been anticipated for the β⇌α equilibrium in D-glucose.



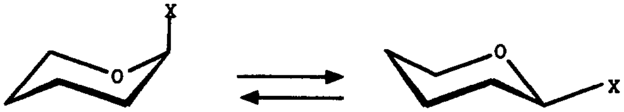
$$\Delta G^{o}_{25\,^{o}C} = -1.24 \text{ kcal/mol} \quad (8)$$

The magnitude of the anomeric effect is usually defined as the difference of the free energy difference ($\Delta\Delta G^\circ$) for the equilibrium studied and the conformational energy for the same substituent in cyclohexane.[20] In the system at hand, the difference between the free energies of the equilibria in eqs. 6 and 7 affords $\Delta\Delta G^\circ_{25^\circ C} = -0.34 - (-1.24) = 0.90$ kcal/mol, which quantifies the anomeric effect; that is, the *tendency* of the electronegative substituent at the anomeric carbon to assume the axial rather than the equatorial configuration (see Section 2.1).

In order to avoid the complications originating from the presence of several hydroxyl groups in sugars, the anomeric effect has subsequently been studied mostly in simpler analogues such as tetrahydropyrans,[21] 1,3-dioxanes,[22] 1,3-dithianes,[23] and so on.

Table 2 presents some pertinent values for anomeric effects estimated in this fashion for several 2-substituted tetrahydropyrans.[12,21]

Table 2. Evaluation of the Anomeric Effect (AE, kcal/mol) in 2-Substituted Oxanes, According to AE = ΔG°(oxane) -ΔG°(cyclohexane).[12]



X	ΔG° (oxane)	$-\Delta G^\circ$ (cyclohexane)	A E[a]
Cl	1.8	0.6	2.4
Br	1.8	0.5	2.3
OMe	0.9	0.8	1.7
OEt	0.8	0.8	1.6
SMe	0.5	1.0	1.5
OH	-0.1	0.9	0.8
NHMe	-0.9	1.3	0.4
CO_2Me	-1.4	1.3	-0.1

[a] kcal/mol

These results establish that the anomeric effect decreases as the electron-withdrawing ability of the substituent dwindles: halogen > RO > RS > HO > NH_2.

There is, however, a well-recognized difficulty with evaluation of the anomeric effect in this manner: the steric requirements of a group in the anomeric position of the heterocycle are different than those encountered in a cyclohexane. For example, a C-O bond is significantly shorter than a C-C bond (1.43 *vs.* 1.54 Å, respectively) and steric congestion of an axial 2-substituent should be greater to that of the same substituent in cyclohexane;[24] therefore, the magnitude of the anomeric effect tends to be underestimated.

In this regard, Franck[25] has suggested that the correction factor for the steric effect of an axial substituent in a heterocycle can be approximated by constructing a plot of *A*-values for substituents incapable of displaying an anomeric effect *vs* the conformational preferences of these groups in the heterocycle. In this fashion, a correction factor α is applied (equation 9), and the magnitude of the anomeric effect is then calculated according to equation 10.

$$\Delta G^{\circ}_{\text{steric}} = \alpha \bullet \Delta G^{\circ}(\text{cyclohexane}) \tag{9}$$

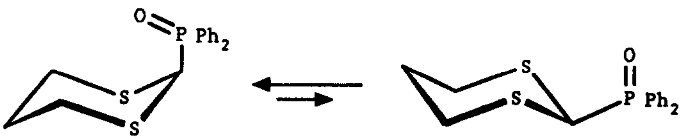
$$\text{AE} = \Delta G^{\circ}(\text{heterocycle}) - \Delta G^{\circ}_{\text{steric}} \tag{10}$$

In the system at hand, the accepted *A*-value as 0.8 kcal/mol for a -OMe can be interpolated to give $\Delta G^{\circ}_{\text{steric}} = 1.2$ kcal/mol for the substituent at C(1) in tetrahydropyran ($\alpha = 1.53$). Now, adding the observed axial preference for methoxytetrahydropyran of 0.9 kcal/mol (Table 2), a -OMe anomeric effect of 2.1 kcal/mol is derived; substantially larger than originally estimated.

Even a qualitative decision about the presence or absence of the anomeric effect may depend on whether the *A* values are corrected. For example, from the equatorial preference of the carbomethoxy group in tetrahydropyran (Table 2) it could be concluded that this group does not exhibit the anomeric effect. However, a correction of the *A* value (1.4 → 2.0 kcal/mol)[25] according to equation 10, suggests the existence of a moderate normal anomeric effect of 0.6 kcal/mol.[26]

Because of the unavoidable structural and electrostatic differences between the model groups used for the correlation and those giving rise to the anomeric effect, Franck's method is only approximate though quite useful.

Another definition used for estimating the anomeric effect is based on the comparison of the Gibbs free energy difference, ΔG°(heterocycle), with the energy $\Delta G^{\circ}_{\text{steric}}$ obtained from theoretical calculations using atom-potential functions such as the Hill equation.[27] When the entropic characteristics of a group are also known, then their contributions to $\Delta G^{\circ}_{\text{steric}}$ can be properly evaluated. For example, from the free energy $\Delta G^{\circ}_{25^{\circ}\text{C}} = 1.0$ kcal/mol for equilibrium 11, an anomeric effect amounting to 3.0 kcal/mol was estimated.[28] Here, $\Delta H^{\circ}_{\text{steric}} = 1.25$ kcal/mol (estimated by means of the Hill equation) and $T\Delta S^{\circ}_{25^{\circ}\text{C}} = 298\ \text{K} \bullet 2.6\ \text{cal/K} \bullet \text{mol} = 0.78$ kcal/mol;[28] therefore, $\Delta G^{\circ}_{\text{steric}} = 2.0$ kcal/mol.



$\Delta G^{\circ} = 1.0$ kcal/mol (11)

Obviously, the magnitude of the anomeric effect will depend on the correctness of the method used for calculating ΔG°_{steric}, which may be evaluated by molecular mechanics or molecular orbital methods (see Chapter 3). Furthermore, experimental ΔG°(heterocycle) usually apply to an equilibrium in a given solvent; therefore, a proper estimation of the anomeric effect should include the contribution of the solvent effect, i.e., this has to be represented in ΔG°_{steric}.

3. Origin and Consequences of the Anomeric Effect.

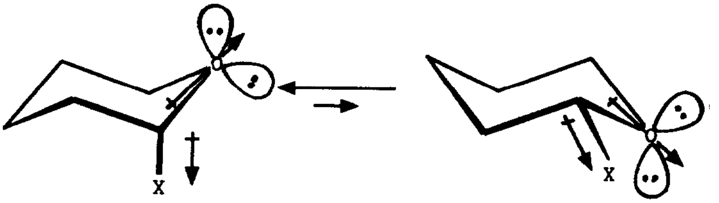
Several explanations have been advanced to account for the origin of the anomeric effect, and over the years, this aspect has been the cause of much debate. The following sections summarize recent evidence pertinent to the two most accepted rationalizations: (1) an unfavorable dipole-dipole interaction between the carbon-heteroatom bonds on the ring and the bond from C(1) to the equatorial, electronegative substituent,[1] and (2) interaction of the ring-heteroatom lone pairs with an antibonding σ^*-orbital of the ligand bond stabilizes the axial orientation of the anomeric substituent.[29]

From the accumulated results it is pretty evident that *both* factors contribute to the anomeric effect -a V_1 potential (dipole) as well as a V_2 potential (electronic interaction) on top of the usual V_3 (Pitzer) potential.

In addition, the recent discussions in terms of the principle of least nuclear motion,[30] or the lone pair interaction model[13,31] will be discussed.

3.1 The Electrostatic Model.

The increased stability of axial polar groups at the anomeric position of pyranose rings (Section 2.1) was attributed by Edwards[1] to the repulsive interaction between the ring dipole, generated by the unshared electrons of the endocyclic oxygen, and the nearly parallel polar bond in the equatorial conformer (eq 12).



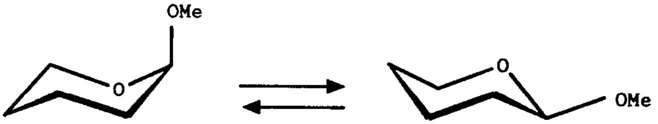
(12)

This is quite a plausible rationalization of the effect in view of the well-established importance of dipole-dipole interactions in conformational analysis: there is a preference for the conformation with the smallest resultant dipole moment. In the gas phase, it is generally found that the rotamer with the larger dipole moment has the larger electrostatic energy, and an increased overall energy.[32] This effect will be reduced on going to a medium with a higher dielectric constant, and as a result, the populations of the conformers will change with solvent.

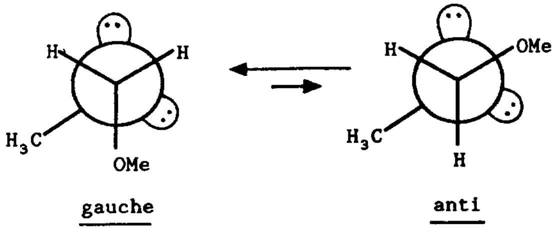
3.1.1 Solvent Effects.

As anticipated from the difference in dipole-dipole interactions between the axial and equatorial conformers depicted in equation 12, polar solvents generally stabilize the more polar (equatorial) conformation; i.e., axial preference decreases with increasing solvent dielectric constant.[21] Table 3 shows data for the anomeric effect for 2-methoxytetrahydropyrans in solvents of increasing polarity. It is apparent that the anomeric effect is higher in less polar media, and this kind of observation provides strong experimental support for the electrostatic rationalization of the anomeric effect. The lessening of the anomeric effect in more polar solvents is also reproduced by quantum mechanical calculations.[34] In addition, the analysis of the individual terms in the intramolecular energy of dimethoxymethane shows that the predominance of the *gauche* conformer (model for axial 2-methoxy THP) originates in the electrostatic repulsion present in the *anti* conformer[35] (eq 13; see also Section 3.5).

Table 3.Solvent Dependence of the Conformational Equilibrium of 2-Methoxytetrahydropyran.[33]



Solvent	ε	% axial conformer
CCl_4	2.2	83
benzene	2.3	82
CS_2	2.6	80
$CHCl_3$	4.7	71
acetone	20.7	72
methanol	32.6	69
acetonitrile	37.5	68
water	78.5	52

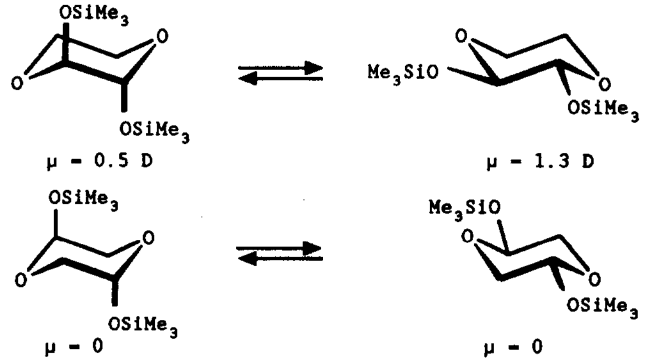


(13)

On the other hand, the electrostatic concept by itself is unable to rationalize variations of the bond lengths and angles that are characteristically associated with the anomeric effect (see Section 3.2). Furthermore, several recent reports disclose examples of preferential stabilization of the axial isomer in the more polar solvents.[36-38] Indeed, *trans*-2,3- (**12**) and *trans*-2,5-bis(trimethylsiloxy)-1,4-dioxanes (**13**) exhibit the conformational behavior summarized in Scheme 4, which also includes the corresponding dipole moments for each conformer as evaluated by molecular mechanics.[36] While increased solvent polarity stabilizes the diequatorial conformations in **12**, the opposite is true in **13**.

12:

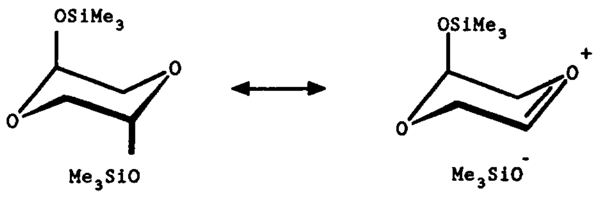
13:



Solvent	% of diaxial conformers 12	13
CCl_4	63	25
$CDCl_3$	53	32
$(CD_3)_2CO$	60	41
CD_3CN	60	46
CD_3OD	50	

Scheme 4.

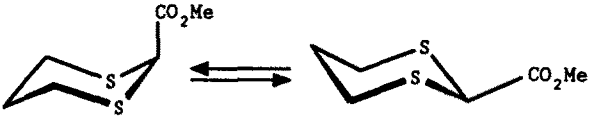
The unexpected enhancement of the anomeric effect in **13**, where μ(diequatorial) = μ(diaxial), in spite of the local group moments, was explained by Fuchs, et al.[36] in terms of stabilization of resonance structures originating from n-σ* hyperconjugative electron delocalization (eq 14; see Section 3.2).[39,40]



(14)

Similarly striking results were observed by Juaristi, et al.[37] during the conformational study of 2-carbomethoxy-1,3-dithiane. Whereas solvent effects *at room temperature* are as anticipated, a stronger anomeric effect in the less polar media, the *low-temperature* ΔG° measurements summarized in Table 4 show an opposite trend: the **14-ax/14-eq** ratio increases with increasing solvent polarity.

Table 4. Low-temperature Conformational Equilibria of 2-Carbomethoxy-1,3-dithiane (14).[37]

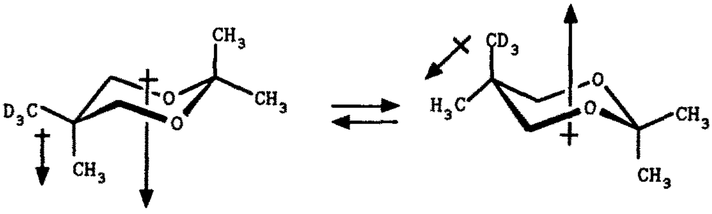


Solvent (ϵ)[a]	Temperature (°C)	K	ΔG°(kcal/mol)
CD_2Cl_2 (8.9)	-100	11.1	0.83
$(CD_3)_2CO$ (20.7)	- 90	12.6	0.92
CD_3OD (32.6)	- 90	22.3	1.13

[a] Dielectric constant

The marked contrast between ambient- and low temperature behavior was suggested as originating from a solvent compression effect. According to this proposal,[37] the population of the conformer with the smaller molar volume (the axial conformer) should increase with the more polar solvent owing to higher internal pressure by the solvent at low temperatures.

In this context, the conformational equilibrium isotope effect (CEIE) observed in **15-ax**$\rightleftharpoons$**15-eq** was found by Robinson, et al.[41] to be solvent dependent: there is a linear correlation between the CEIE and the polarity of the solvent. This observation is consistent with an equilibrium between species differing in the orientation of two electric dipoles. In the system at hand, one dipole is the resultant of the two C-O-C groups in the ring, and the other must arise from the difference in polarity between the C-H and C-D bonds, which are nearly parallel to the ring dipole in one conformer and approximately antiparallel in the other (eq 15).



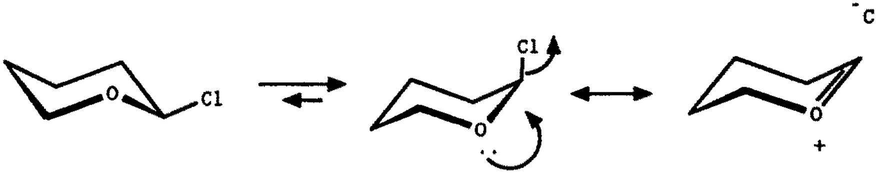
(15)

15-eq 15-ax

The increased predominance of **15**-ax in less polar solvents is in agreement with H in C-H being more negative than D in C-D, as expected from the inductive isotope effects observed on the pK_as of carboxylic acids.[42]

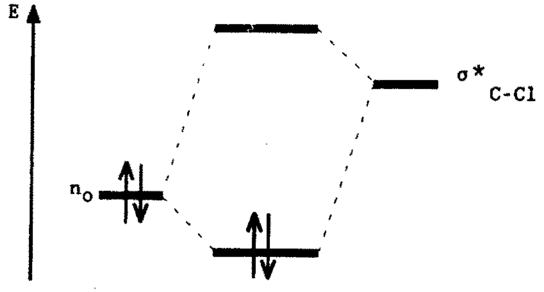
3.2 The Double-bond/No-bond Model.

The rationalization of the anomeric effect solely in terms of dipole-dipole interactions[1] fails to account quantitatively for observed axial preferences, and, most importantly, does not predict the bond-length and bond-angle changes which are characteristic of anomeric segments (see Section 3.2.2). In this regard, a second or additional, well accepted rationalization arose from investigations on α-halogenoethers. In these compounds, preference for the *gauche* (axial) orientation is associated with a significant lengthening of the carbon-halogen bond, and a concomitant shortening of the adjacent C-O bond.[29] The stereoelectronic explanation that was proposed is illustrated for 2-chlorooxane in equation 16. The stabilization of the axial conformer is attributed to delocalization of the antiperiplanar lone-pair orbital on oxygen to the antibonding orbital of the carbon-halogen bond. This interaction produces the lengthening of the C-Cl bond by electron transfer to its σ antibonding orbital, the contraction of the C-O bond by increasing its double-bond character, and an opening of the O-C-Cl bond-angle relative to the normal tetrahedral value because of the partial sp^2 character of the anomeric carbon. This effect seems absolutely certain for Cl or Br, which are more electronegative than oxygen.



(16)

According to this hyperconjugation model, electron delocalization within axial 2- chlorooxane is expressed as two resonance structures in the language of valence-bond theory (double bond-no bond resonance).[43] In the language of molecular orbital theory, the axial form is energetically preferred because it benefits from a two-electron interaction (n ⟶ σ*) between an occupied, high energy donor orbital and an empty, low energy acceptor orbital (Scheme 5).



Scheme 5

Since this stabilizing orbital interaction is inversely proportional to the energy difference between the interacting orbitals,[44] the strongest stabilising interactions will be between the most effective donors and the most effective acceptors. Or, in Kirby's words:[45] *there is a stereoelectronic preference for conformations in which the best donor lone pair or bond is antiperiplanar to the best acceptor bond.*

In this regard, the most effective donor orbital is a carbanion's lone pair (n_{C^-}) followed by unshared electron pairs in heteroatoms, and then sigma bonds:

$$n_{C^-} > n_N > n_S > n_O > \sigma_{C\text{-}S} > \sigma_{C\text{-}H}, \sigma_{C\text{-}C} > \sigma_{C\text{-}O} > \sigma_{C\text{-}F}$$

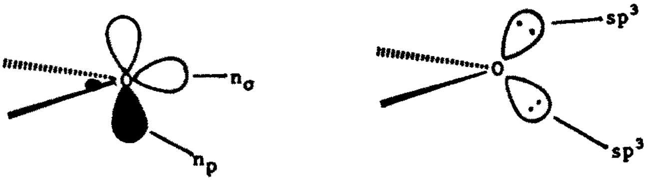
On the other hand, the most effective acceptor orbital is the empty p orbital in a carbonium ion, followed by the sequence:

$$\sigma^*_{C\text{-}Cl} > \sigma^*_{C\text{-}S} > \sigma^*_{C\text{-}F} > \sigma^*_{C\text{-}O} > \sigma^*_{C\text{-}C}, \sigma^*_{C\text{-}H}$$

As a consequence, $n \rightarrow \sigma^*$ interactions will always be stronger than $\sigma \rightarrow \sigma^*$ effects. Among these latter effects, the strongest are between $\sigma_{C\text{-}H}$ and $\sigma^*_{C\text{-}F}$, as in the *gauche* effect (see Section 3.6.1).

3.2.1 The Nature of the Lone Pairs.

It is clear at this point that the explanations of the anomeric effect, either according to the electrostatic model or to the negative hyperconjugation model, involve the non-bonding electron pairs of the heteroatom involved. Thus a correct understanding of those electron pairs is crucial here. In this respect, Kirby[46] has presented a most valuable discussion on whether the non-bonding electrons of bicovalent oxygen (the most common donor heteroatom in anomeric interactions) should be depicted as cannonical n_σ and n_p orbitals (Scheme 6a), or rather as localized sp^3 hybrid orbitals on tetrahedral centers (Scheme 6b).

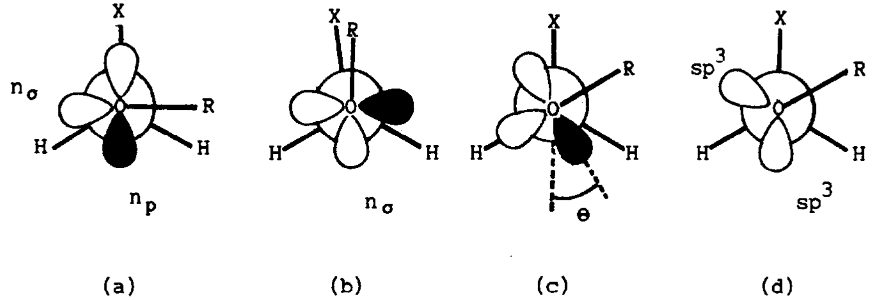


(a) (b)

Scheme 6

In this discussion,[46] Kirby considered a system RO-CH_2-X in terms of canonical (n_p and n_σ) as well as sp^3-hybrid lone pair orbitals. Of the former, the stereoelectronic effect is expected to be strongest in the R-O/C-X orthogonal conformation, in which the p-type lone pair and the $\sigma^*_{C\text{-}X}$ orbital are eclipsed (Scheme 7a). Conformation (b) in Scheme 7 can be disregarded because of unfavorable bond eclipsing, and because n_σ is substantially lower in energy than n_p, affording a weaker stabilization. Nevertheless, steric hindrance in (a) is proposed to lead in practice to a gauche conformation (c), which allows for some $n_\sigma \rightarrow \sigma^*_{C-X}$ stabilization while still keeping the stronger $n_p \rightarrow \sigma^*_{C-X}$ overlap.

The alternative description in terms of hybrid lone pairs (Scheme 7d) shows $n \rightarrow \sigma^*_{C-X}$ overlap with the antiperiplanar sp^3-hybrid lone pair, which is made up from one part s-orbital (σ symmetry) and three parts of p-orbitals (π symmetry) - closely similar to description (c).

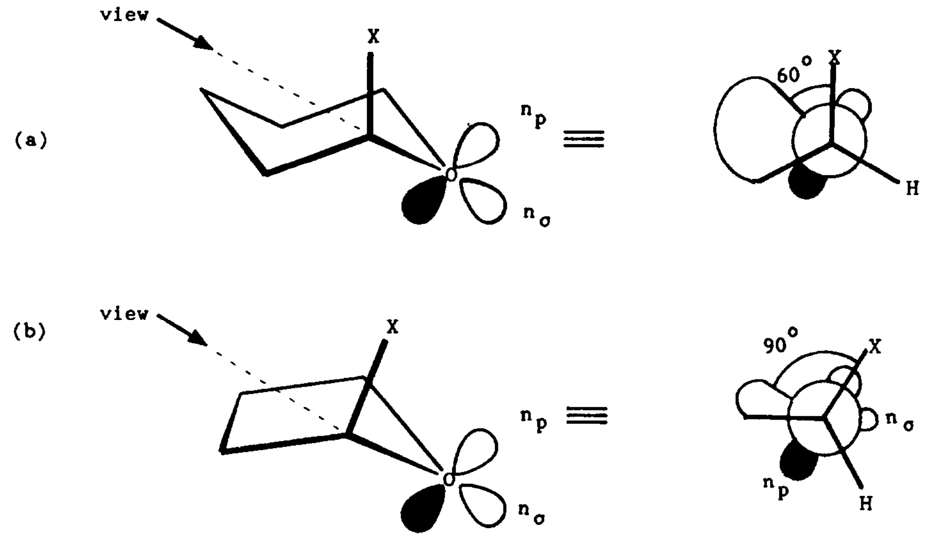


Scheme 7

Inspite of these arguments,[46] and inspite of the fact that most organic chemists usually prefer to use the description in terms of two equivalent sp^3-hybridized lone pairs, there is theoretical[47] and experimental[48] evidence that the lone pairs are directionally nonequivalent, one occupying a higher energy orbital with considerable p-character, and the other a lower energy s-type orbital. Some pertinent data are summarized by Laing,[49] who points out that the photoelectron spectrum for water affords *four* well-defined ionization bands at 12.6, 13.7, 17.2 and ca. 32 eV, which were assigned to the p-type lone pair, the two O-H bonding molecular orbitals, and the s-type lone pair, respectively.[50] By contrast, the sp^3 hybrid model of water indicates only *two* types of electrons, the bond pairs and the lone pairs.

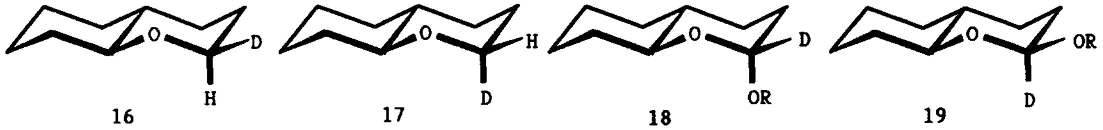
In this context, it has been shown[51] that the five-membered furanose ring orients polar substituents at the anomeric center in axial or pseudoaxial position much more strongly (95%) than the six-membered pyranose ring (56%). That this stronger anomeric effect is the result of the better ability of endocyclic oxygen to participate in stabilizing conjugation in five-rather than six-membered rings was convincingly argued by Dubois, et al.[52] by comparison with related hydrocarbons. Furthermore, structural comparison of furanoses *vs* pyranoses (Scheme 8) compelled these authors to suggest that the observed enhancement of the *endo* (see Section 4) anomeric effect in furanoses establishes the sp^2 hybridization of the endocyclic oxygen.

According to this reasoning,[52] in furanoses (Scheme 8b) and unlike pyranoses (Scheme 8a), the torsion angle, naturally close to 90°, favors a good $n_p \rightarrow \sigma^*_{C-X}$ overlap *for the* sp^2 *hybrid endocyclic oxygen.* By contrast, in the hypothesis of an sp^3 hybridization, the torsion angle allowing for $n_{sp^3} \rightarrow \sigma^*_{C-X}$ overlap is close to 60°, which is the natural structural angle in pyranoses but not in furanoses. In the sp^3 model the stabilizing conjugation would then be better assured in the six-membered heterocycles, contrary to observation.



Scheme 8

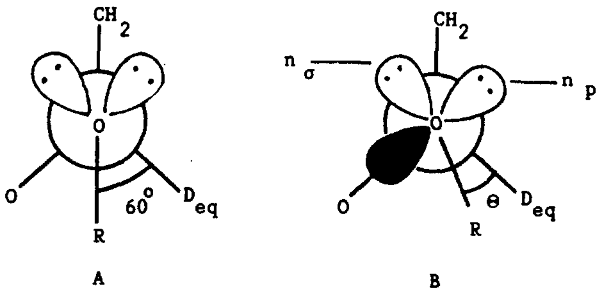
Further experimental support for the n_p/n_σ dissection of the lone-pair electrons in bivalent oxygen comes from the infrared studies of Touboul and Dana in tetrahydropyrans **16-19**.[53] (Scheme 9).



R = CH_3, $C(CH_3)_3$, $CH_2C_6H_5$, C_6H_5

Scheme 9

The C-D stretching bands of isomers **16** and **17** are centered at 2185 cm^{-1} (equatorial deuterium) and at 2103 cm^{-1} (axial deuterium). Derivatives **18** show, for an equatorial deuterium, a significant lowering of the $\nu_{C\text{-}D}$ frequency, which depends on the bulkiness of the R group: $\Delta\nu \sim -20$ cm^{-1} for phenyl or *t*-butyl, $\Delta\nu \sim -50$ cm^{-1} for methyl or benzyl. These frequency shifts were ascribed to conjugation of an exocyclic oxygen lone pair with $\sigma^*_{C\text{-}D}$, which should be facilitated when R is a small group. According to the sp^3-hybridized model, simultaneous stabilizing $n_O \rightarrow \sigma^*_{C\text{-}O}$ and $n_O \rightarrow \sigma^*_{C\text{-}D}$ interactions (conformer A, Scheme 10) are not expected to be very sensitive to the steric hindrance of R -contrary to the experimental result.



Scheme 10

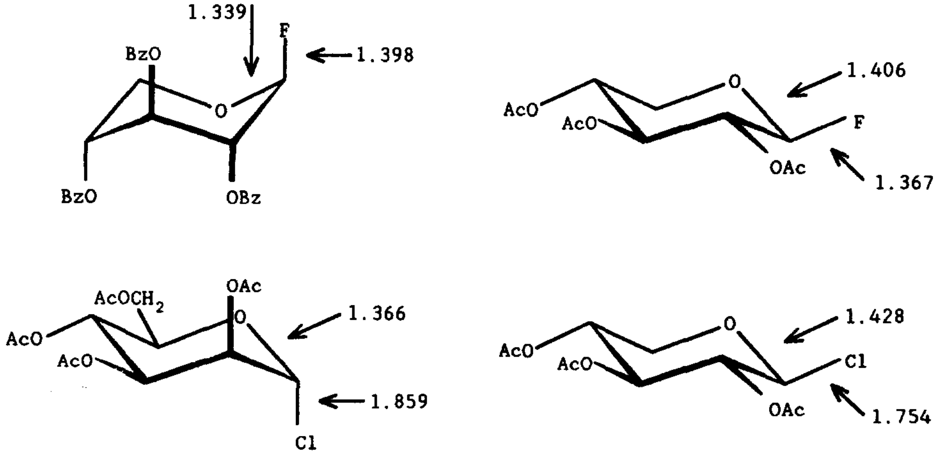
In conformation B (Scheme 10), the exocyclic oxygen is sp^2/p hybridized and presents both $n_p \rightarrow \sigma^*_{C\text{-}O}$ and $n_\sigma \rightarrow \sigma^*_{C\text{-}D}$ stabilizing interactions. With this model, bulky R groups may cause $\theta > 30°$, which reduces orbital overlap and thus the $\Delta\nu$ value -as experimentally observed. The infrared data from molecules **19** can be similarly interpreted, and seem to give credence to the hypothesis of sp^2 and p-type lone-pair orbitals at the exocyclic oxygen.

While the evidence presented here favors nonequivalent lone pairs, many theoreticians advise that partitioning of the lone pair density is difficult, and conclude that the two pictures are "equivalent".

3.2.2 Precise Structural Data and the Double-bond/No-bond Model for the Anomeric Effect.

As was already mentioned, detailed examination of the geometries about RO-C-X systems frequently show characteristic patterns of bond lengths and angles associated with particular conformations. These findings led to the proposal of a hyperconjugative mechanism used to rationalize the anomeric and other interesting stereochemical trends.

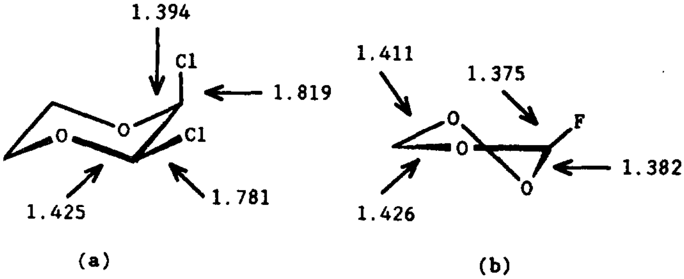
Scheme 11 shows several bond lengths at anomeric segments which are of particular interest in connection with the presumed $n \rightarrow \sigma^*$ orbital interaction.[54]



Scheme 11

Very interesting are the two fluoro compounds, where the benzoate crystallized in the all-axial conformation, whereas the acetate is all-equatorial. The shortening of the O-C(1) bond in the former (1.34 Å), relative to the one observed in the latter (1.41 Å) is quite substantial. This trend is confirmed in the chloro derivatives (Scheme 11). There is a corresponding lengthening of the carbon-halogen bonds in the axial anomers.

These patterns of behavior are reproduced in many other heterocycles such as *trans*- 2,3-dichloro-1,4-dioxane[29] (Scheme 12a) and fluoroethylene ozonide[55,56] (Scheme 12b), where the stronger interaction takes place with the peroxy oxygen atom (lone pair-lone pair repulsion within the O-O moiety is expected to enhance the n → σ* donation).

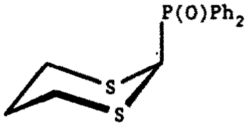


Scheme 12

Of particular interest are also the X-ray crystallographic data of orthocarbonates, $C(OR)_4$, which contain the maximum possible number (six) of anomeric O-C-O pairs at a single carbon center. Very recently, crystal structures of three tetrakis-(aryloxy)methanes have been determined,[57] and the observed bond lengths and angles support the presence of multiple anomeric interactions: by comparison with the average inner and outer C-O bond lengths obtained from 212 crystal structures of anisoles, a combination of the electronegativity effect due to multiple oxygen substitution and the anomeric effect provokes a substantial shortening of the inner C-O bonds. The lengthening of the outer C-O bonds was interpreted as indicating that the n_p lone pair on each of the oxygen atoms is used for negative hyperconjugation with adjacent σ^*_{C-O} orbitals rather than for conjugation with the phenyl ring.[57]

A remarkable exception to this structural trend was reported by Juaristi, et al.[58] following the discovery of a substantial anomeric effect in 2-(diphenylphosphinoyl)-1,3-dithiane, **20**.[59] Comparison of X-ray analyses of **20**-axial, and *r*-2-(diphenylphosphinoyl)- *c*-4,*c*-6-dimethyl-1,3-dithiane (**21**) was made in order to examine the possible importance of $n_S \rightarrow \sigma^*_{C-P}$ interactions which, if significant, would be manifested in shortened C-S and elongated C-P distances in the axial *vs* equatorial form. Selected bond lengths for **20**-axial together with corresponding values for **21**-equatorial are in Table 5.

Table 5. Selected Interatomic Distances (Å) in 20 and 21,[58] with Standard Deviations in Parentheses.



	20	21
S-C(2)	1.809 (3)	1.810 (4)
C(2)-P	1.825 (3)	1.840 (4)
P-O	1.486 (2)	1.481 (3)

Comparison of these values reveals that the C-P distance in **21** is quite similar but, if anything, slightly longer than that in **20**-axial. This observation, as well as the lack of any significant difference in the mean S-C(2) lengths, is contrary to expectations if an $n_S \rightarrow \sigma^*_{C\text{-}P}$ interaction makes an important contribution to the preferred axial conformation in **20**. Alternative rationalizations of the effect(s) responsible for the conformational behavior of **20** are discussed in Chapter 5.

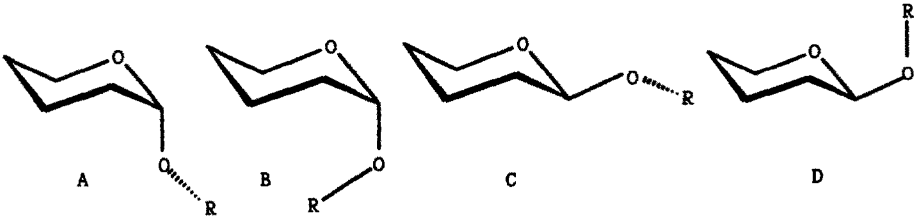
Concerning the manifestation of the structural criterion for the anomeric effect in carbohydrates, the C-O-C-O-C segments of 111 derivatives retrieved from the Cambridge Crystallographic Database were scrutinized by Fuchs, et al.[60] Statistical treatment of the ring- and *exo*-C(1)-O bond lengths and C(1)-O-C bond angles afforded the main following principal conclusions:

(1) Axial α-glycosides are almost twice as common as equatorial ones, which provides support for the enhanced stability (hence more frequent occurrence) of the former.

(2) Conformations in which the exocyclic anomeric oxygen lacks lone pairs antiperiplanar to the C(1)-O bond are totally absent, which confirms the importance of the *exo* anomeric effect (see Chapter 4).

(3) The axial α-glycosides with a R-inside conformation (Structure B, Scheme 13) are absent, due to overwhelming steric strain.

(4) The population of the β-glycosides shows a 3:1 distribution in the C and D forms (Scheme 13); the latter rotamer had been usually disregarded by other authors. (See, however, below).



Scheme 13

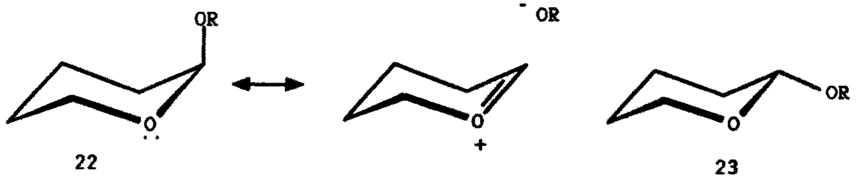
(5) The *endo-* and *exo-*C(1)-O bond lengths in the equatorial β-glycosides differ appreciably: the ring C(1)-O bonds approach the standard value (1.43 Å) while the exocyclic C(1)-O bonds are much shorter. At the same time, the internal C-O-C(1) bond angles have almost standard values (109°) as opposed to the larger external C-O-C(1) angles (114-5°). These data are again consistent with the importance of the *exo* anomeric effect (see Chapter 4).

(6) In both axial and equatorial glycosides, the dihedral O-C-O-R angles are appreciably larger than 60°. While in rotamer A (Scheme 13) this could be attributed to steric hindrance, in D (Scheme 13) a smaller than 60° dihedral angle was anticipated on steric grounds. The authors suggest that this finding constitutes experimental evidence for the non-equivalence of the oxygen lone pairs since the observed dihedral angles favor optimal $n_P \rightarrow \sigma^*_{C(1)-O}$ overlap. (See, however, below).

While the above statistical study has been questioned by Box[61] in view of the fact that the evaluation involves comparison of bond lengths obtained with different degrees of accuracy, a more recent report by Fuchs, et al.[62] describes the rigorous analysis of a larger set of 529 carbohydrate structures that contain O-C-O units. Indeed, for equatorial glycosides, contrary to the previous hypothesis[60] advanced in item (6) above, no correlation was found between bond lengths and bond angles with the magnitude of the O-C-O-R dihedral angles in conformer D (Scheme 13). Thus, the originally proposed dependence of the strength of the *exo*-anomeric effect on the orientation of the n_P lone pair was abandoned. In addition, the previous assertion[60] that conformer D (Scheme 13) contributes significantly to the conformational populations of equatorial glycosides was found to be erroneous, due to insufficient database in the original study.

In a related study, Cossé-Barbi and Dubois analyzed the X-ray data of 546, C_1-O_2-C_3-O_4-C_5 molecular fragments extracted from the Cambridge Crystallographic Database.[51] These authors argue that the $n \rightarrow \sigma^*$ model of the anomeric effect, accounting for the shortening of the internal O_2-C_3 bond, the lengthening of the C_3-O_4 bond, and the modification of the hybridization of O_2 and C_3 (which acquire a more pronounced s character) refers only to very simple structures with weak steric interactions: in a large population of structures, a remarkable dispersion of the values of bond lengths, bond angles, and torsion angles is actually observed.[51,60]

In this regard, Kirby, et al.[63-66] have found that the length of the C-O bond of ethers and esters varies in a systematic way depending on the steric and electronic interactions involved. In particular, the lengths of the C-O bonds at the acetal centers of a series of tetrahydropyranyl acetals **22** and **23** (Scheme 14) deviate significantly from the standard r = 1.43 Å.



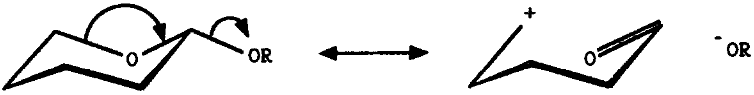
22 23

Scheme 14

More significantly, this variation is systematic and depends on the effective electronegativity of the exocyclic OR group: the more electronegative the group, the longer is the C-OR bond and the shorter the endocyclic O-C(OR) bond. For compounds **22**, these bond length changes are, of course, interpreted in terms of an stabilizing $n_O \rightarrow \sigma^*_{C\text{-}OR}$ interaction (Scheme 14).

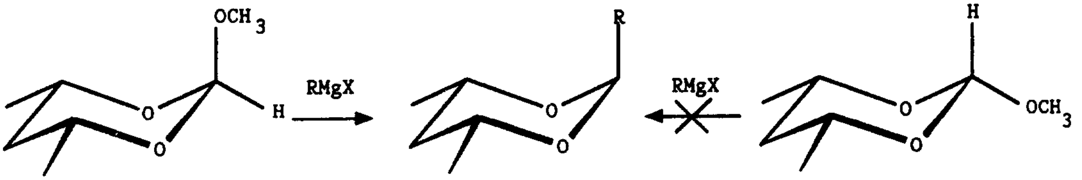
Most interestingly, similar (actually ca. 32% smaller) effects on bond lengths were found in equatorial acetals **23**, despite the fact that $n \rightarrow \sigma^*$ overlap is unfavorable here. This result was explained[64] in terms of $\sigma \rightarrow \sigma^*$ interaction, between the σ-bonding orbital of the endocyclic, remote C-O bond and the antiperiplanar $\sigma^*_{C\text{-}OR}$ orbital (eq. 17).

23:



(17)

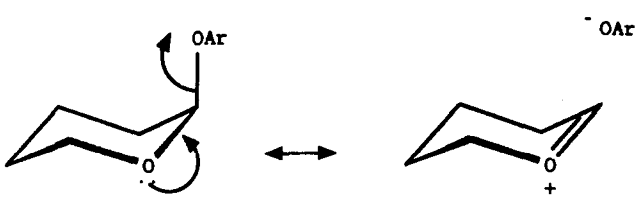
The stereoelectronic effects described above were related to reactivity. The pioneering work in this area was done by Eliel and Nader[67] who investigated the stereochemistry of the reaction of axial and equatorial 2-alkoxy-1,3-dioxanes with Grignard reagents, and concluded that it is governed by powerful stereoelectronic effects. Indeed, reaction of the axial diastereomer proceeded smoothly at room temperature to give the corresponding 2-alkyl derivative having the 2-alkyl group axially oriented. In contrast, the equatorial orthoester failed to react under similar conditions. (Scheme 15). In the axial isomer, the dioxane oxygens have each an electron pair properly disposed (antiperiplanar) to assist the ejection of the leaving group. Then the Grignard reagent attacks from the same side to afford the observed product.



Scheme 15

Specifically, C-O cleavage occurs readily only when a nonbonding electron pair on the remaining oxygen atom of the O-C-O segment is antiperiplanar to the bond being broken.[64,67] (See Chapter 7). Furthermore, with aryl acetals **24**, linear correlations are apparent between the pK_a of the conjugate acids (ArOH) of the leaving group (ArO^-; eq 18), and the length of the bond being broken.[68] This effect was also observed in the equatorial isomers (cf. eq 17).

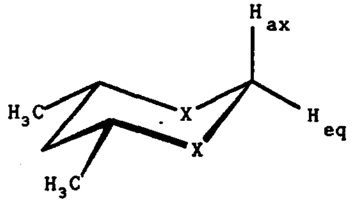
24:



(18)

3.2.3 Stereoelectronic Effects upon C-H Coupling Constants.

That the magnitude of the one-bond ^{13}C-^{1}H coupling constant for an axial C-H bond adjacent to N or O in a six-membered ring is invariably smaller by a significant amount (8-10 Hz) than ^{1}J for an equatorial bond, has been viewed as a manifestation of the generalized anomeric effect.[69,70] For example, the smaller ^{1}J for the C(2)-H_{ax} bond (157.4 Hz) relative to ^{1}J for the C(2)-H_{eq} bond (167.5 Hz) in *cis*-4,6-dimethyl-1,3-dioxane (25, Scheme 16) has been rationalized in terms of an n → σ* interaction between the antiperiplanar pair of non-bonded electrons on oxygen and the axial C-H bond on the adjacent carbon.



25: X = O
26: X = S

Scheme 16

While it has been noted that this correlation between the magnitude of ^{1}J and C-H bond orientation does not apply to C-H bonds adjacent to sulfur in thio-D-glycosides,[71] Bailey, et al.[72] have reported a 9.21 Hz difference in the magnitude of the ^{1}J couplings between C(2) and the axial and equatorial H(2) protons in *cis*-4,6-dimethyl-1,3-dithiane (26, Scheme 16). Nevertheless, assignment of the one-bond C(2)-H couplings revealed that the axial H(2) proton of 26 has the larger ^{1}J (154.1 Hz for H_{ax}; 144.9 Hz for H_{eq}). This result is, of course, opposite to the correlation noted in 25.

Considering that hydrogen-bond formation between solvent and the initially non-bonded electrons on the heteroatom would be expected to lower the energy of the (initially) n-electrons and thereby decrease the effectiveness of the n → $\sigma^*_{C\text{-}Hax}$ interaction,[22] the formation of hydrogen bonds should lead to an attenuation of the $|\Delta J|$ value. This was indeed the trend observed experimentally for 25,[72] and is consistent with the stereoelectronic interpretation discussed above. In contrast to the behavior of 25, the value of $|\Delta J|$ in the dithiane 26 is unaffected by hydrogen-bonding solvents, and the authors suggest that factors other than those originating from n → σ* interactions may be responsible for the differences in magnitude of $^{1}J_{C\text{-}Hax}$ and $^{1}J_{C\text{-}Heq}$ in the dithiane.[72]

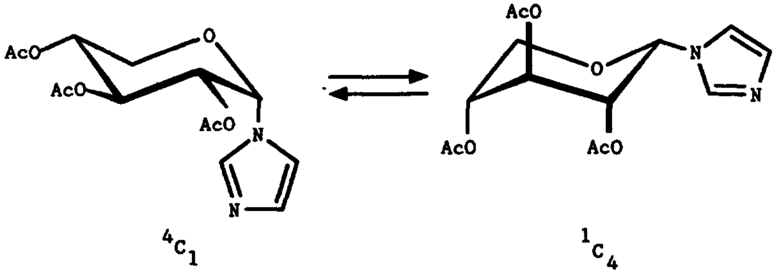
In this context, Wolfe, et al.[73] have recently proposed that stereoelectronic effects upon one-bond C-H coupling constants be termed "Perlin Effects". Furthermore, their analysis of experimental data confirmed that the effect reverses for C-H bonds adjacent to two heteroatoms from below the first row. More importantly, it was concluded that longer (weaker) C-H bonds have the smaller coupling constant.

With regard to the observations of Bailey, et al.[72] concerning the reversal of the relative magnitudes of the coupling constants (see above), it was concluded that the anomaly resides in the reversal of the bond lengths as a result of dominant $\sigma_{C\text{-}S} \rightarrow \sigma^*_{C\text{-}Heq}$ (rather than $n_S \rightarrow \sigma^*_{C\text{-}Hax}$) interactions.[73,74] An interesting possibility is that this effect is also responsible for the relative chemical shifts in the two series: δ_{ax} upfield of δ_{eq} in **25**, downfield in **26**.[75]

3.2.4 The Reverse Anomeric Effect.

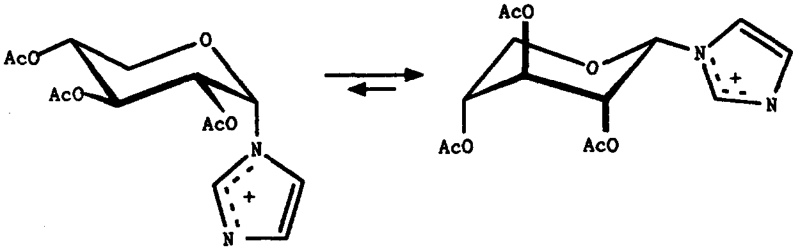
Negative hyperconjugation is not universally accepted as the explanation for the energetic and conformational consequences of the anomeric effect.[13,30,43,76,77] A major failure concerns the so-called "reverse anomeric effect",[78,79] whose best evidence comes from systems where the 2-substituent is the N^+ atom of a heterocycle. In particular, while the conformational equilibrium of α-D-xylo-compound **27** contains (in CCl_4) 35% of the $^1C_4$ form (eq 19), the protonated species **28** (eq 20) exists exclusively with the imidazolium group equatorial.

27:



(19)

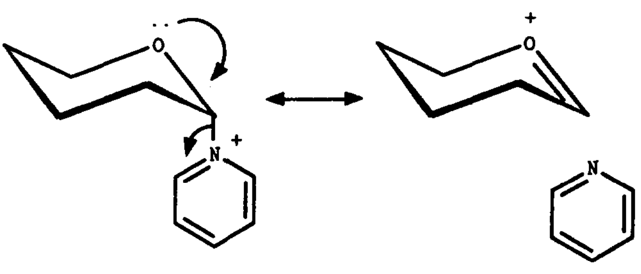
28:



(20)

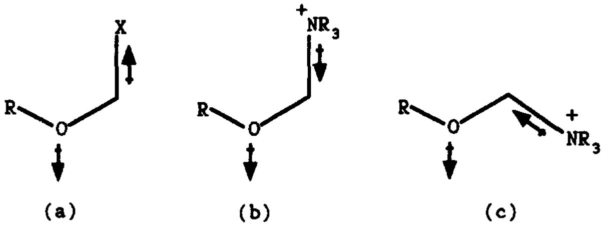
Clearly the steric requirements of the imidazole ring have not changed on going from **27** to **28**, but the evidence suggests that the preference for the equatorial conformation is stronger than the normal steric preference found in cyclohexane (*A*-value). This is the reverse anomeric effect.

According to the frontier orbital picture of the anomeric effect the overlap of the p-type lone pair on oxygen with the σ^* orbital of the axial carbon-quaternary nitrogen (Scheme 17) should occur in exactly the same way as with a carbon-oxygen or carbon-halogen bond. Therefore, the reverse anomeric effect should not exist based on the molecular orbital picture.



Scheme 17

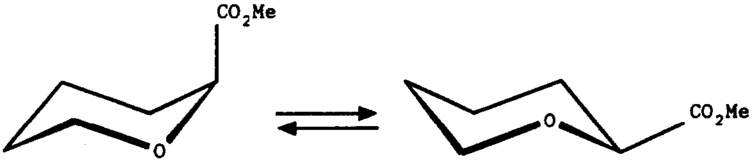
The reverse anomeric effect was initially attributed to a favorable through-space interaction of the positive charge (in equatorial N^+) with the unshared electrons present in the ring oxygen; however, this hypothesis has not been widely accepted.[78] An alternative explanation is that the anomeric effect is reversed because dipole-dipole interactions no longer reinforce the stereoelectronic preference. This picture is illustrated in Scheme 18, where the dipole moment associated with fragment C-O-C opposes that of C-X in the normal anomeric (*gauche*) arrangement (Scheme 18a). In the corresponding conformation of $ROCH_2{}^+NR_3$ (Scheme 18b) the C-X dipole is reversed, and the resultant moment is now a minimum in the antiperiplanar conformation (Scheme 18c). This interpretation assumes that dipolar effects are dominant in this system.



Scheme 18

Finally, Lemieux has proposed that when the aglycon is strongly electronegative and unable to stabilize the glycosidic bond due to lack of lone pair electrons, then the axial C-N$^+$ bond is so extremely weak as to make such an isomer energetically unlikely.[78]

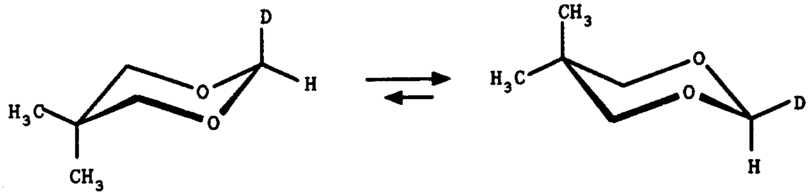
Be that as it may, there is only scarce experimental evidence about the reverse anomeric effect, and the evidence available is sometimes misleading due to improper evaluation of the reference steric term. For example, contrary to literature suggestion for the existence of a reverse anomeric effect in 2-carbomethoxytetrahydropyran[80] (eq 21) the predicted[25] $\Delta G^{\circ}_{steric}$ = -1.98 kcal/mol compared with the experimental[24] ΔG° = -1.38 kcal/mol indicates, in fact, a normal anomeric effect of 0.6 kcal/mol. Recently, Kleinpeter et al.[81] have estimated a substantial 0.9 kcal/mol value for the anomeric stabilization in the O-C-CO_2Et segment.



(21)

A substituent that clearly prefers the equatorial orientation to a greater extent when in the anomeric position than in cyclohexane is deuterium.[82,83] Indeed, whereas the deuterium in a CHD group in cyclohexane-d_1 prefers the equatorial over the axial position by 6.3 cal/mol,[84] Anet and Kopelevich have found that the deuterium in 5,5-dimethyl-1,3-dioxane-2-d_1 (29; eq 22) prefers the equatorial position by about 50 cal/mol.[82]

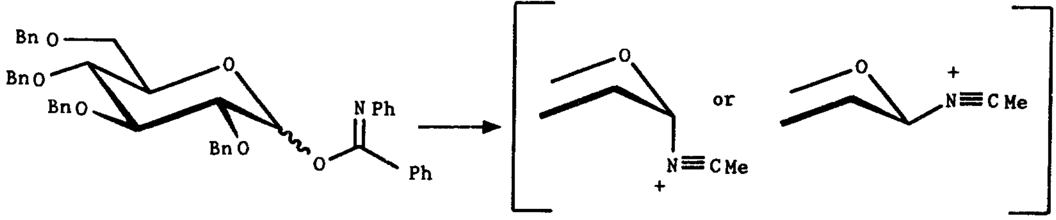
29:



(22)

This remarkable equilibrium isotope effect was rationalized[82] in terms of n → σ* hyperconjugation, according to which the bond to the axial substituent is weakened and lengthened. Differences in zero point energy contributions associated with the C-H stretching frequencies account for the observed isotope effect: it is easier to break an axial C-H bond relative to a similarly disposed C-D bond. (This is not, of course, an example of a reverse anomeric effect).

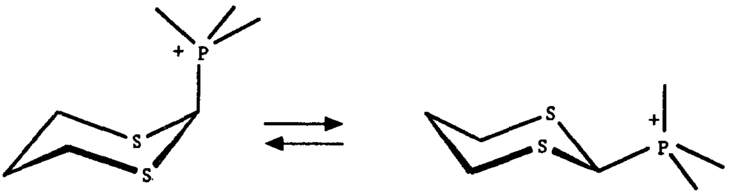
In the context of the reverse anomeric effect, an interesting exception has been described by Ratcliffe and Fraser-Reid,[85] in connection with work on glycosylacetonitrilium ions (30). That these intermediates can form from imidates 31 has been proposed by several workers; however, whereas Pavia, et al.[86] favoured the α-isomers, Schmidt and Michel[87] have proposed the β-counterpart (30β) because of the reverse anomeric effect. (Scheme 19). The results of Fraser-Reid show that the kinetic product of the reaction is the α-acetonitrilium ion.



31 30-α 30-β

Scheme 19

Quite striking also are the reports of substantial anomeric effects in 2-(triphenylphosphonio)[88] and 2-(diphenylphosphinyl)borane-1,3-dithiane,[89] where the phosphorus atom formally bears a positive charge. (Scheme 20). Evidently, in contrast to ammonium-substituted six-membered heterocycles, **32** and **33** do not present the reverse anomeric effect. (See also Chapter 5).



32, P^+ - PPh_3
33, P^+ - $P(BH_3)Ph_2$

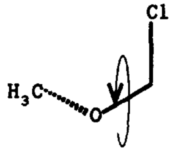
Scheme 20

3.2.5 Does an Anomeric Effect raise the Barrier to Conformational Change?

As we have seen, the hyperconjugative (double-bond/no-bond) picture of the anomeric effect confers a double-bond character to the C-O bonds; accordingly, Deslongchamps[90] has predicted that the energy barrier for C-O bond rotation should be higher than that observed in simple alkanes.

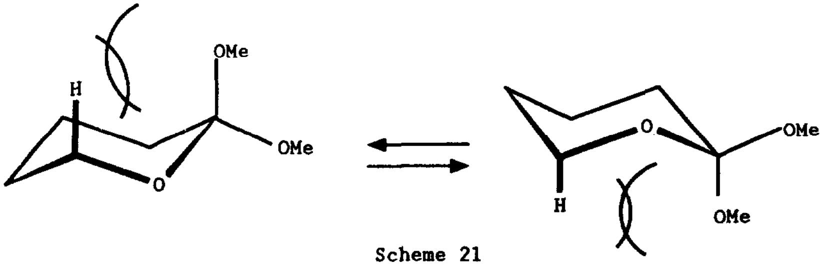
In line with this prediction, Anet and Yavari[91] determined that chloromethyl methyl ether exists in the *gauche* conformation **34**, and that the barrier for the rotation of the O-CH_2Cl bond amounts to 4.2 kcal/mol -ca. 2 kcal/mol higher than anticipated.

34:



In contrast with the previous results, Perrin and Núnez[92] found no evidence for such an increase but rather a slight decrease. Indeed, line-shape analysis of the variable-temperature ^1H NMR spectra of 2,2-dimethoxyoxane (**35**; Scheme 21) afforded a $\Delta G^{\ne}$ for ring inversion worth 8.7 kcal/mol for ring inversion, which is significantly lower than that for oxane (10.3 kcal/mol).[93] Perrin and Núñez conclude that the anomeric effect does not raise the barrier to conformational change in **35**, relative to other six-membered rings. Instead, they suggest a reduction in the barrier by 1.4-2.1 kcal/mol, which could be ascribed to better $n_p \rightarrow \sigma^*_{C\text{-}O}$ overlap in the eclipsed half-chair transition state conformation for ring inversion, or simply to a bad steric interaction in the ground state.

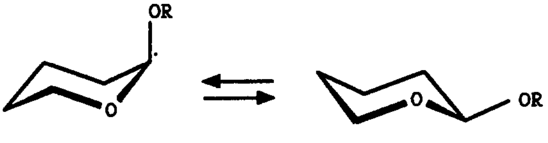
35:



Scheme 21

More recently, the barriers to ring inversion of 2-isopropoxy- (36), 2-(4-methoxyphenoxy)- (37), and 2-phenoxytetrahydropyran (38) were studied in order to see if the barrier is influenced by the anomeric effect.[94] The observed activation energies are reported in Table 6.

Table 6. Free Energies of Activation (kcal/mol) to Ring Inversion in 2-Oxytetrahydropyrans in CF_2Br_2.[94]



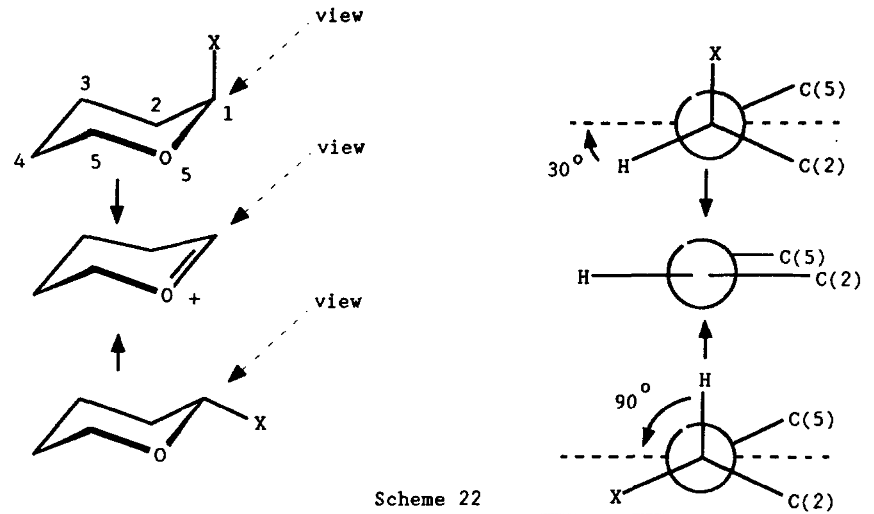
Compd	OR	% axial	$\Delta G^{\neq}_{ax\rightarrow eq}$	$\Delta G^{\neq}_{eq\rightarrow ax}$
36	$OCH(CH_3)_2$	62	8.9	8.7
37	OC_6H_5	86	8.8	8.2
38	$OC_6H_4OCH_3$	79	8.6	8.2

Comparison with the inversion barrier in tetrahydropyran (10.3 kcal/mol)[93] indicated again that the anomeric effect does *lower* the barrier to ring inversion. Ouedraogo and Lessard[94] suggest that this is due to the fact that the $n_{exo} \rightarrow \sigma^*_{C\text{-}O}$ orbital overlap can be maintained throughout the inversion process and thus impart some sp^2 character to the anomeric carbon, which would lower the inversion barrier (in analogy with, for example, methylenecyclohexane).

3.3 The Principle of Least Nuclear Motion as an Interpretation of the Kinetic Anomeric Effect.

One powerful opponent of the frontier orbital explanation of the anomeric effect, Sinnott[95] has recently summarized the difficulties, both of inadequate agreement with experiment and of conceptual confusion. The alternative rationalization that Sinnott offers is based on the "principle of least molecular deformation"; i.e., the commonsense, intuitive idea that those reactions are favored where the change in geometry is minimal.

The equivalence of the predictions of double-bond/no-bond resonance (or "antiperiplanar lone pair hypothesis"; see Chapter 7) and of the principle of least nuclear motion (PLNM) are illustrated by analysis of the reactions of axial and equatorial tetrahydropyranyl models (Scheme 22). The preferred conformation of the ionized form is assumed to be the half-chair, and the nature of the atomic motions is seen by taking as a plane of reference the plane defined by C(1), C(2), O(5) and C(5) of the oxocarbonium ion, and considering motions about the C(1)-O(5) bond, depicted in Newman projections in Scheme 22.



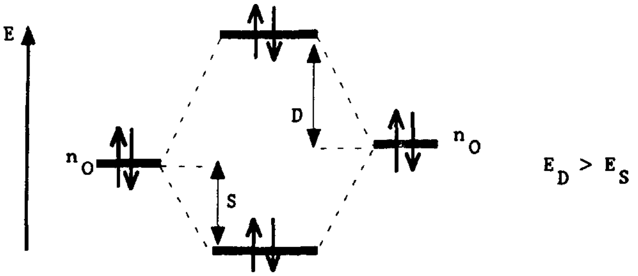
Scheme 22

For both isomers, the motions of C(2) and of C(5) can be described as a 30° rotation of the C(1)-C(2) and O(5)-C(5) bonds, respectively, about the C(1)-O(5) bond. By contrast, the motions of the hydrogen at C(1) in the two cases are quite different: in the axial isomer, the C(1)-H(1) bond rotates only 30°, whereas in the equatorial isomer it must rotate a full 90°. Clearly, more nuclear movement is involved in the (disfavoured) equatorial case.

3.4 The Lone Pair Interaction Model. (Eliel's Rabbit Ear Effect Revisited).

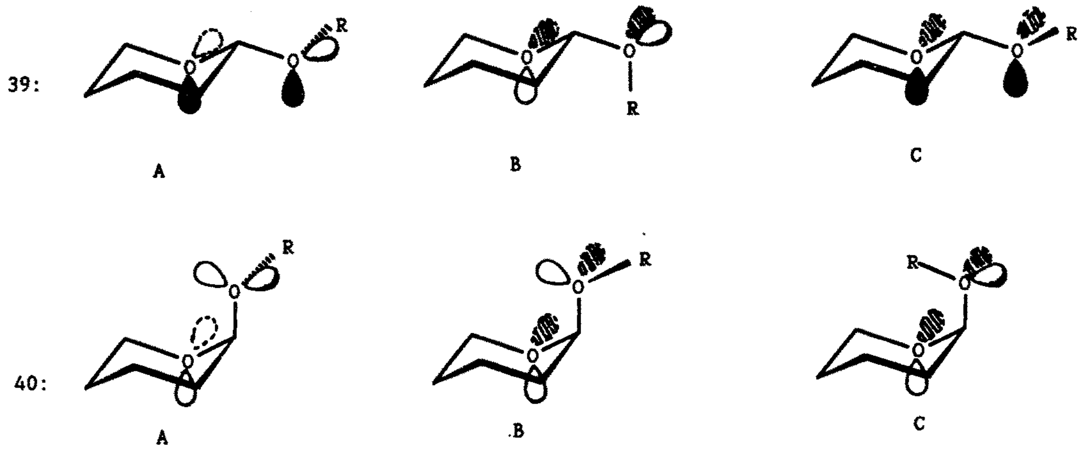
Recently, Box[13] has reviewed cases of molecules whose data do not support the n → σ* hypothesis of the anomeric effect, and concludes that this model is not useful for rationalizing the anomeric effects. Furthermore, Box proposes a hypothesis based on dominant n-n interactions,[31] with a minor contribution from the n → σ* interactions, as a better model to explain both the anomeric effects and the chemistry of acetals.

The n-n interaction hypothesis is based on the concept that when two occupied orbitals of similar energy interact through space, then they interact to produce two new orbitals. This two-orbitals/four-electrons interaction will be destabilizing as depicted in Scheme 23; i.e., the destabilization provoked by the new highest-energy orbital is greater than the stabilization gained by the formation of the low-energy orbital.



Scheme 23

Scheme 24 shows that all chair conformations available to the equatorial anomer in a 2-alkoxytetrahydropyran present at least one n-n interaction. On the other hand, the predominant conformations of the α-anomer have either one or none (**40C** is discarded due to steric crowding). A stereochemical consequence is that the anomer with the smaller number of unfavorable interactions will be more stable. Furthermore, for a given configuration, the rotamer presenting the smallest number of n-n interactions (**40A** in Scheme 24) should be the most stable.



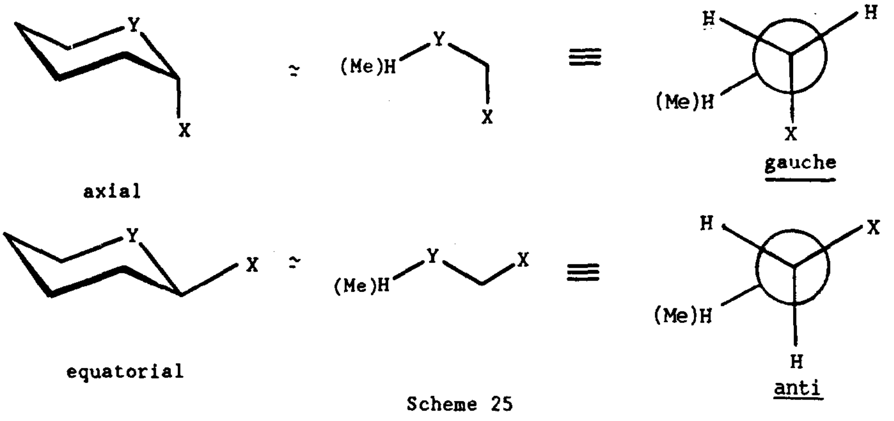
Scheme 24

Support for this lone pair interaction model comes from the photoelectron spectroscopy work of Jorgensen:[50] whereas the energy separation of the (interacting, presumably through-space) n orbitals in *trans*-1,8-dioxadecalin (model for equatorial anomers) is a remarkable 0.85 eV, the energy separation of the α-anomeric model was only 0.2 eV, suggesting that the β-anomeric arrangements are less stable because of the substantial through-space destabilization in these isomers.

3.5 Theoretical Studies of the Anomeric Effect.

As expected from the definition of the generalized anomeric effect (see Section 2.1), theoretical calculations carried out in simple molecules with the general formula X-CH_2-Y are sufficiently general to reproduce the behavior of larger systems (e.g., six-membered heterocycles) incorporating anomeric segments. Of course, high-level calculations (e.g., *ab initio*) are still prohibitively expensive if performed in medium- or large-sized rings.

Indeed, it has been shown that the axial preference found in 2-substituted tetrahydropyrans and tetrahydrothianes is reproduced by *ab initio* calculations in the preferred *gauche* arrangements of truncated segments over the *anti* conformation (Scheme 25).[96,97] This section will summarize the large number of theoretical studies, at various levels, reported in the last decade on molecules with the general formula XCH_2Y.



Scheme 25

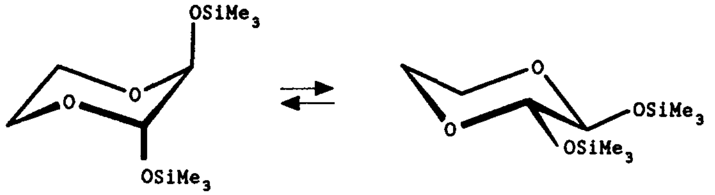
3.5.1 Molecular Mechanics.

The molecular mechanics or empirical force field method has been widely used for determining molecular structures and energies.[98] Concerning the C-O-C-O-C pattern characteristic of anomeric segments, the original version of Allinger's MM2 program (MM2'77) was already parametrized to reproduce the anticipated resonance form ($C\text{-}O^{+}{=}C$ + $^{-}O\text{-}C$) which involves donation of a in-plane lone pair of electrons on one oxygen into the antiperiplanar adjacent carbon oxygen bond. In addition, the MM2(77) program also "understood" the dipole-dipole interactions in the molecule, which will try to orient so as to minimize the electrostatic repulsion of the system (see Section 2.1). Thus reasonable dihedral angles and energies could be calculated with MM2. There were, however, some unsatisfactory results from these calculations involving the central C-O-C angle and the bond lengths.

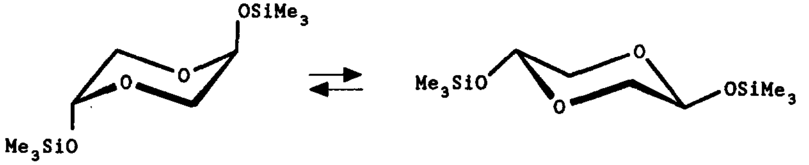
The tendency of C-O bond lengths to change as a function of the torsional angle at an acetal carbon was therefore included in a new version of the molecular mechanics program, MM2(82), based on the observed behavior of molecules incorporating anomeric segments, C-O-C-O-C, as indicated by ab initio calculations and experimental structural data. Experimental geometries and energies are reasonably well reproduced by the new program.[99]

Indeed, Anderson, et al.[100] report that the complex experimental conformational behavior of the methyl, ethyl and isopropyl acetals of formaldehyde, acetaldehyde, propionaldehyde, isobutyraldehyde, and pivalaldehyde is defined with the assistance of the molecular mechanics program parametrized for the C-O-C-O-C anomeric effect.[99]

In this context, Fuchs, et al.[101] have also parametrized MM2 for the anomeric effect. This program reproduced the conformational preferences of the mono, 2,3-di-, and 2,5-di-*tert*-butoxy-1,4-dioxanes. In addition, calculations with this modified force field helped explain the reasons for the alleviation of the anomeric effect in *trans*-2,3- and *trans*-2,5-di(trimethylsilyloxy)-1,4-dioxanes (eqs 23 and 24), a matter of some controversy.[102]



(23)



(24)

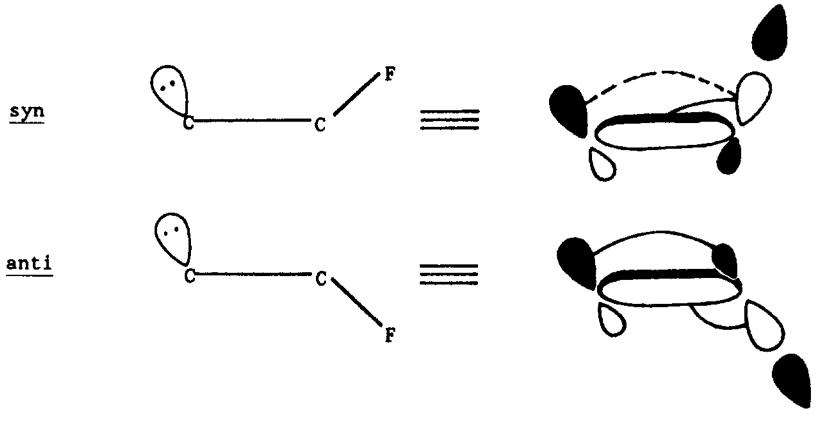
More recently, molecular mechanics have been carried out for twelve derivatives of 2-alkoxy-tetrahydropyrans with the alkoxy group in the axial and equatorial conformations.[103] Comparisons were made carrying out calculations with three different versions of the Allinger MM2 programs: (a) version 1977, (b) the Osawa and Jaime version (1981-1984),[104] and the MM2(85) version.[105] It was concluded[103] that force field calculations are good for describing the anomeric effect; in particular, the more stable conformer was in all cases the one with the anomeric substituent in axial position, giving axial/equatorial energy differences between 1 and 1.5 kcal/mol. These energy differences were predicted (in accord with experiment) to decrease when the dielectric constant of the medium is increased.

On the other hand, geometries are not described properly with the early versions of MM2: all bonds at the acetalic center remain constant in length and do not change upon passing from the equatorial to the axial conformation. By contrast, the MM2(85) program yielded geometries in very good agreement with experiment.[103]

The MM2(85) program was recently modified for application to linear and cyclic compounds including N-C-O units.[106] The force field is reported to permit the determination of the stability and geometry of the different conformers of pertinent compounds with high accuracy; i.e., the results were consistent with experimental data (NMR, X-ray, IR spectra and dipole moments).[107] Parametrization of MM2 for N-C-N fragments has been also performed.[108]

3.5.2 Extended Hückel Calculations.

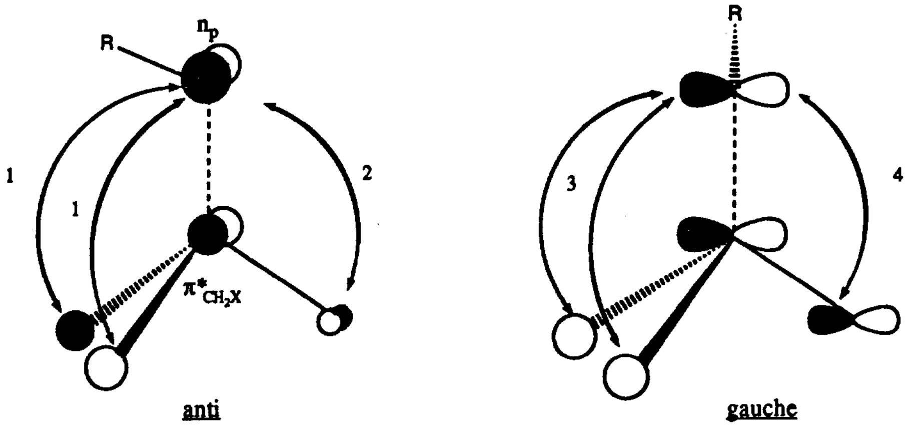
The preferred *gauche, gauche* conformation of dimethoxymethane is not predicted by the extended Hückel method.[109] Nevertheless, Inagaki, et al.[110] have recently proposed a new theory for the anomeric effect, which was based on extended Hückel calculations on the four bond orbitals (n_C, $\sigma_{C\text{-}C}$, $\sigma^*_{C\text{-}C}$ and $\sigma^*_{C\text{-}F}$) of interest in *syn*- and *anti*-β-fluoroethyl carbanion. The orbital interaction for transition $n_C \rightarrow \sigma^*_{C\text{-}F}$ was found to be the most favorable energetically, and rationalized so in view of the fact that it does not involve three-orbital phase discontinuity (Scheme 26).[110]



Scheme 26

3.5.3 Quantitative PMO Analysis.

In this context, Scheme 27 illustrates the application of the perburbation molecular orbital procedure to C-Y torsion in XCH_2YR, with the interaction taken as RY- - - -CH_2X.[111] In each conformation shown, the double occupied orbital is n_P (the p-type non-bonding orbital on Y), and the acceptor orbital is the unoccupied orbital of CH_2X that has the proper symmetry for overlap with n_P. In the antiperiplanar conformation, the acceptor orbital is $\pi^*_{CH_2X}$, but in the *gauche* conformation the acceptor orbital is $\sigma^*_{CH_2X}$.



Scheme 27

The primary (- - - - -) orbital interactions indicate that since the σ* orbital lies lower than the π* orbital, there is greater stabilization in the n → σ* interaction than in the n → π* interaction, accounting for the greater stability of the *gauche* conformation. This analysis also predicts a longer

C-X bond in the *gauche* conformation because of greater charge transfer to the antibonding C-X region in this case. Moreover, examination of the secondary (↔) orbital overlap in the *gauche* and *anti* conformations explain the systematic variations in XCY bond angles:[111] these are out-of-phase and repulsive in the latter. Because the hydrogen atoms of $\pi^*_{CH_2X}$ have larger coefficients than X, interaction 1 is more repulsive than 2: the YCH angles increase, and the YCX angle decreases. Maximum overlap between RY and CH_2X is attained by a *decrease* in the XCY angle. This decrease minimizes the secondary overlap 1 at the expense of a minor increase in the secondary overlap 2.

Pinto, et al.[111] point out that in the *gauche* conformation, the secondary interactions 3 and 4 are both negative, but 4 is more repulsive than 3. These authors suggest that maximum overlap between RY and CH_2X can now be achieved by reducing overlap 4 at the cost of increasing 3, which leads to an *increase* in the XCY angle. The authors conclude that, whereas the hyperconjugative model can rationalize the larger than tetrahedral X-C-Y angle found in 1-axially substituted pyranoses in terms of the greater trigonal character of the central carbon atom, such an argument does not account for the decrease in the X-C-Y bond angle that is observed in 1-equatorially substituted pyranoses. The PMO argument, on the other hand, appears to anticipate both effects.

3.5.4 Semiempirical MO Methods.

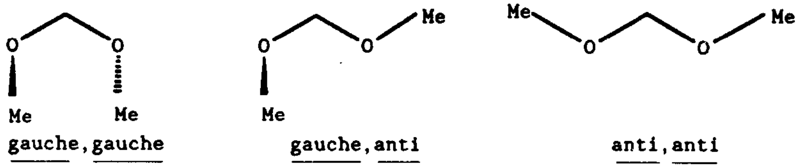
Semiempirical molecular orbital methods, CNDO and MNDO (Complete Neglect, and Modified Neglect, of Differential Overlap, respectively), and PCILO (Perturbative Configurational Interaction using Localized Orbitals) are capable of describing the electron distribution in molecules, as well as the changes produced by internal rotation. They provide, in principle, the total potential energy of individual conformers, without need to correct for "conformational effects". Thus, quantum chemical calculations offer insight into the orbital interactions in a molecule, and may reveal the factors responsible for the stabilization of a particular conformation.

Recently, Tvaroska[112] has pointed out that although there exists an inclination to consider *ab initio* results (see Section 3.5.4) as automatically superior to those of semiempirical methods, several calculations in molecules exhibiting the anomeric effect show the deceptiveness of this claim.

In this regard, a comparison of relative energies of dimethoxymethane conformations calculated by different methods with experimental values is shown in Table 7. It is seen that *gauche, gauche* conformations are predicted as preferred by both *ab initio* and semi-empirical MO calculations, and the calculated energies are generally consistent with experimental evidence (but hardly at the 4-21G level). From these, as well as additional results, Tvaroska concludes that the agreement of calculated results with the available experimental data seems to be better for selected semiempirical methods than for some *ab initio* calculations.[112,113]

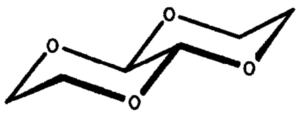
In contrast, several researchers find application of semiempirical methods thoroughly inadequate for the description of the anomeric effect. For example, Fuchs, et al.[114] have disclosed that simple CNDO calculations of **41** and **42** afford E(**42**) > E(**41**), in flagrant contrast to reality. Wiberg and Murcko[115] have also expressed their reservations concerning MINDO/2 studies for dimethoxymethane.

Table 7. Calculated Relative Energies (kcal/mol) of Stable Conformers of Dimethoxymethane with Respect to the *gauche, gauche* Rotamer Compared with Experimental Values.[112]



Method	gauche,anti	anti,anti
STO-3G	1.6	3.3
4-21G	4.5	5.3
CNDO/2	1.2	3.6
PCILO	1.2	2.6
MNDO	1.2	4.1
Experimental	1.5	3.0

Quite recently, Tvaroska and Carver described the results of a semiempirical all-valence-electron AM1 (Austin Model 1) theoretical conformational analysis of 16 oxane derivatives.[116] Comparison of the calculated anomeric equilibria with the experimental data revealed the failure of the AM1 method to reproduce experimental values, calculated energy differences between anomers being overestimated. Nevertheless, some evidence was presented that AM1 may be more useful in calculations of carbohydrate geometries than *ab initio* calculations with the STO-3G basis set.[116]



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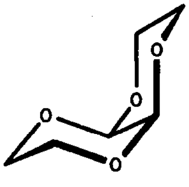


42

3.5.5 Nonempirical ab initio Calculations.

The best description of the conformational behavior of an isolated molecule is achieved by *ab initio* calculations with the sufficiently extended basis of the atomic orbitals, for example, 6-31G. In this regard, Wiberg and Murcko have calculated recently the conformational energy map for the rotamers of dimethoxymethane using both the 3-21G and 6-31G* basis sets with complete geometry optimization in each case.[115] Large changes in bond angles were found on C-O bond rotation, the 6-31G* results being more reasonable than those at the 3-21G level. An unusually large anomeric stabilization of *gauche, gauche* dimethoxymethane of 5.4 kcal/mol was estimated; nevertheless, calculations on equatorial and axial 2-methoxytetrahydropyran predicted the axial form to be favored by 1.33 kcal/mol, in fair agreement with experiment.

Prior to 1980 very few *ab initio* studies addressed the possible involvement of the second-row element sulfur in anomeric interactions.[96] In this regard, Vishveshwara and Rao[117] reported a comparison of STO-3G, 4-31G and 6-31G* studies of the anomeric effect for the O-C-O segment, with the finding that the STO-3G level was adequate. The anomeric effect in S-C-S and O-C-S systems was then studied at the STO-3G level, with limited studies made at the 4-31G level. The results for methanedithiol indicate that the *gauche, gauche* conformation is of lowest energy, being 1.0 and 1.2 kcal/mol more stable than the *gauche, anti* and *anti, anti* conformations, respectively. Thus a substantial anomeric effect is manifested for the S-C-S segment. Nevertheless, the authors note[117] that this anomeric effect is lower than that observed for O-C-O segments. Indeed, the energy differences between the *gauche, gauche* conformation in methanediol and the corresponding *gauche, anti* and *anti, anti* forms were estimated to be much larger: 2.6 and 3.9 kcal/mol, respectively. The results for thiolmethanol ($HOCH_2SH$) were intermediate between those for methanediol and methanedithiol. The lower anomeric effect in sulfur systems was attributed to a change in dipolar contributions to the total energy, as compared with the oxygen systems.

In contrast with these results, Schleyer, et al.[118] found no evidence for a significant S-C-S anomeric effect.[119] In fact, from the calculation (3-21G* level) of structures and energies for all possible first- and second-row disubstituted methanes, XCH_2Y (X,Y = F, O, NH_2, Cl, SH and PH_2) it was concluded that in contrast to very large anomeric stabilization energies in systems involving any combination of the first-row groups, F, OH, and NH_2, corresponding interactions are negligible when X and Y both involve second-row groups, Cl, SH, and PH_2. This result was attributed[118] to a inherently low π-donor ability of these groups and to the lower electronegativity of the second-row elements relative to their first-row counterparts. Nevertheless, it should be pointed out that Schleyer's evaluation is based on a different scheme than Vishveshawara's,[117] as discussed in ref. 73.

More recently, however, higher-level (MP4SDTQ/6-31G*//6-31G* and //HF6-31G*+ZPE) *ab initio* studies by the Schleyer group do predict substantial anomeric stabilization in S-C-S, S-C-P, and Se-C-Se segments,[120-122] worth between 1.0 and 2.0 kcal/mol.

An interesting study of the anomeric effect with central atoms other than carbon was reported also by Reed and Schleyer.[123] An*ab initio* for all normal valence polyfluorinated compounds F_nAH_m of the first-row elements Be through O and the second-row elements Mg through S was carried out at the HF/6-31G* level of theory. The stabilization energies were found to be quite large for elements A of intermediate electronegativity (P, C, S), weaker for the more electronegative elements (N, O), and much weaker or even destabilizing for the electropositive elements (Be, B, Mg, Al). The calculated trends in energetic stabilizations were attributed to $n_F \rightarrow \sigma^*_{A-F}$ negative hyperconjugation, which also accounts, in combination with electrostatic effects, to observed variations in F-A-F angles.

Along this line, *ab initio* calculations on $H_{4-n}Si(OH)_n$ (n = 0-4) species appear to show that significant anomeric stabilizations occur at silicon centers.[124] This result is in agreement with substantial evidence that negative hyperconjugation operates in silicon compounds.

In this context, Altona, et al.[11] have recently described their *ab initio* results on the study of the anomeric effect on molecules of the type $X\text{-}CH_2\text{-}OCH_3$, with X groups having relatively low electronegativity; e.g., $-CO_2H$, $-CO_2^-$, $-C\equiv N$ and $-C\equiv CH$. The energy difference between the *anti* and *gauche* conformers was found to decrease in the order $X = CO_2^- \gg CO_2H > C\equiv N > C\equiv CH$. Concerning predicted geometries, in all cases the anomeric C-O bond becomes shorter in going from the *anti* to the *gauche* conformer. Concomitantly, the C-X bond is elongated in this operation, although CO_2 is an exception. Incorporation of the methyl group in $HXCH(CH_3)Y$ has been described in the high level calculations of Wolfe, et al.[73]

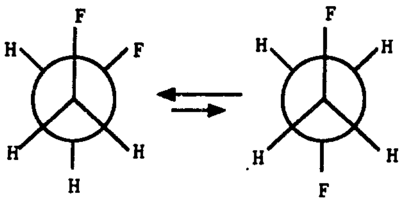
Concerning the N-C-N and N-C-O anomeric effects, Fuchs, et al.[108,125] have reported extensive *ab initio* studies of these segments at the 3-21G level of theory. Analysis of the results showed that the anomeric effect is operative in these systems, although this stereoelectronic effect seems to be reduced in methylenediamine or *N*-methylenediamine relative to dimethoxymethane. The experimental observation that 1-alkyl-1,3-diazanes exist predominantly in forms with axial N-H was reproduced by the calculations. With respect to O-C-N systems, results were consistent with the coexistence of two unequal anomeric effects: a strong $n_N \rightarrow \sigma^*_{C\text{-}O}$ anomeric interaction, and a weak $n_O \rightarrow \sigma^*_{C\text{-}N}$ one.

On the other hand, Dunitz, et al.[126] have reported high-level *ab initio* calculations made for fluoromethylamine. These authors posed a particularly interesting question: given that the usual interpretation of the anomeric effect involves an *anti* orientation of a lone-pair orbital with the acceptor bond, could there be any justification for invoking a *syn* anomeric effect, involving a *syn* orientation of the corresponding entities? Energy plots as function of the F-C-N-lp torsion angle show two minima, the lower corresponds to the *anti* orientation ($\tau = 180^\circ$; E set to zero), as expected; the other corresponds to the *syn*-planar one ($\tau = 0^\circ$; E = 5.08 kcal/mol). They are separated by a saddle point (E = 7.81 kcal/mol) at $\tau = 101.5^\circ$, where the donor (lone pair at nitrogen) and acceptor (C-F) orbitals are nearly orthogonal. While these results (energy criterion) appear to suggest that the *syn* anomeric effect provides ca. 5 kcal/mol less stabilization than the *anti* effect, structural expression of the anomeric effect in the calculations (e.g., C-F bond lengthening) suggests that the *syn* effect is quite comparable to the *anti* one.[126]

3.6 Further Manifestations of the Anomeric Effect.

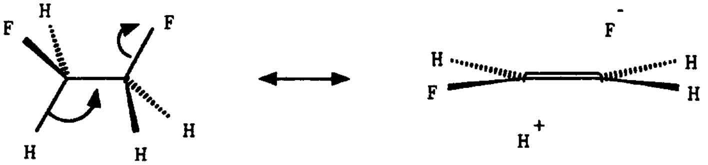
3.6.1 The gauche Effect.

The generalized anomeric effect describes the preference of compounds RX-C-Y for *gauche* conformations about the R-X bond (see Section 2.1). There exists a related effect, comparable in magnitude, in systems X-C-C-Y, where X and Y are electronegative groups.[127] For example, in the series XCH_2CH_2X (X = halogen) there is a gradual increase in the proportion of the *gauche* conformation in the direction I →F, so that *gauche*-1,2-difluoroethane clearly predominates in the gas phase[128] (eq 25).



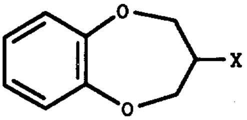
(25)

The origin of this gauche attractive effect, which overcomes unfavorable steric and/or dipolar interactions, was rationalized by Wolfe[127] in terms of a dominant attractive nuclear-electron attraction between X and Y, which dominates over nuclear-nuclear and electron-electron repulsive terms. However, stabilizing overlap between bond-anti-bond orbitals also provides a satisfying explanation of the gauche effect.[129,130] Thus in the *gauche* conformation of 1,2-difluoroethane, the C-H bonds serve as donors to the antiperiplanar C-F bonds (acceptors) (eq 26)



(26)

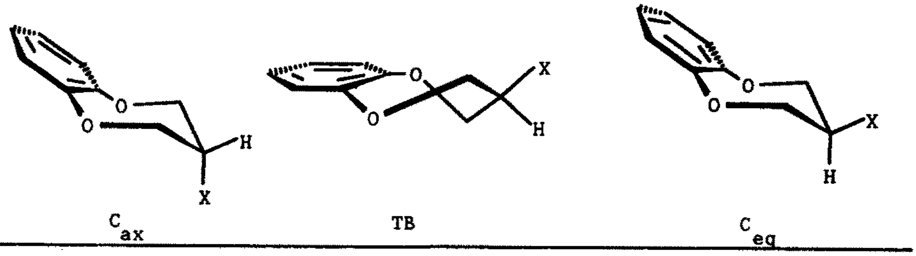
In this context, Dionne and St.-Jacques[131] studied the conformations of 3-halogenated derivatives of 1,5-benzodioxepins **43-47** in order to define the mechanism of the gauche effect.



43, X = OCH_3; **44**, X = F; **45**, X = Cl; **46**, X = Br; **47**, X = I

As summarized in Table 8, compounds **43-47** were found to exist as mixtures of chair (C) and twist-boat (TB) conformations, in ratios which vary depending on the nature of the polar substituent and on the solvent polarity. An attractive interaction is expected to operate in a O-C-C-X moiety when X = OCH_3 and F, whereas the gauche interaction might be negligible or repulsive for Cl, Br and I.[128,132] In agreement with this expectation, the percentage of the C_{ax} conformer, where the C-O and C-X bonds are *gauche*, increases in going from **47** to **44** (Table 8). This trend was interpreted by Dionne and St.-Jacques[131] in terms of stabilizing bond-antibond orbital interactions; in particular $\sigma \rightarrow \sigma^*$ interactions, which are proportional to $S^2/\Delta E$ where S is the orbital overlap and ΔE is the energy difference between the σ and the σ^* orbitals.

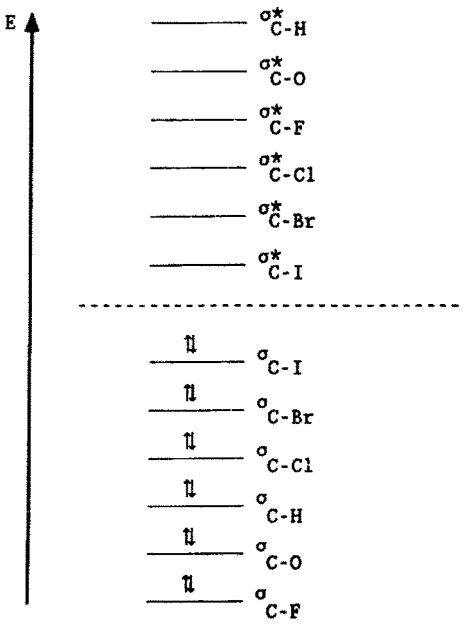
Table 8. Percentage of the Conformations of Compounds 43-47 at Low Temperature (-120 to 130°C).[a]



X	C_{ax}	TB	C_{eq}
OCH	33	67	
F	66	34	
Cl	21	63	16
Br	17	51	32
I	9	22	69

[a] In CHF_2Cl

The relevant orbitals and their relative energy levels are shown in Scheme 28. Stereoelectronic orbital interactions are anticipated to be more effective for *anti* arrangements of the donor (σ) and ac-



Scheme 28

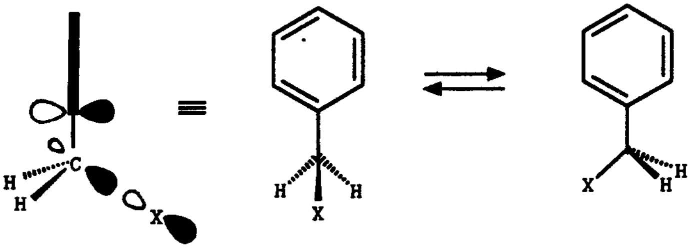
ceptor (σ^*) orbitals, and the stabilization should increase as the antibonding orbital σ^*_{C-X} energy decreases and the bonding orbital σ energy increases.

Because the C-O and C-X bonds are antiperiplanar in C_{eq}, the dominant interaction was proposed to be $\sigma_{C-X} \rightarrow \sigma^*_{C-O}$.[131] Scheme 28 indicates that the energy of the σ_{C-X} orbital decreases from I to F, which results in a less efficient interaction and reduced stability of the C_{eq} forms, in agreement with the data in Table 8.

On the other hand, C_{ax} is proposed to involve a dominant $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ interaction, in which an overriding overlap contribution affords the trend observed in Table 8. Finally, the trend noted for TB is opposite to that characterizing C_{eq}. The authors suggest that the $\sigma_{C-X} \rightarrow \sigma^*_{C-O}$ interaction is less important than $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$, which explains the similar upward trend noted for C_{ax} and TB.[131]

3.6.2 The Benzylic Anomeric Effect

Recently, Penner, et al.[133] determined the conformational preferences of benzyl-X compounds with the aim of establishing whether two-orbital two-electron stabilizing interactions ($\pi_{Ar} \rightarrow \sigma^*_{C-X}$) enhance the conformational preference for the perpendicular structure **48** (eq 27).

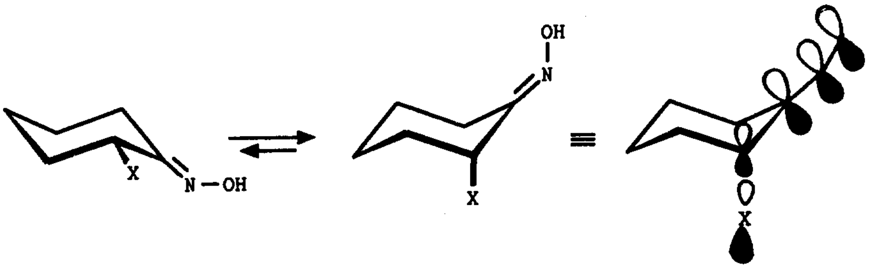


(27)

48 (perpendicular) (planar)

Except for X = F, all compounds studied (X = Cl, SH, SMe, S(O)Me and SO_2Me) adopt mainly the conformation in which the C-X bond is perpendicular to the plane of the benzene ring. The authors proposed therefore the existence of a benzylic anomeric effect, and that its magnitude, as a function of X, is SO_2Me, S(O) Me > Cl > SH, SMe > F.

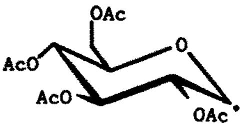
Pioneering work of Lessard[134] and Zefirov[135] has reported that the methoxy group of 2-methoxymethylenecyclohexane and 2-methoxycyclohexanone exists preferentially in the axial orientation. These observations have been explained by $\pi \rightarrow \sigma^*_{C-O}$ stabilization of the axial orientation of the methoxyl group. A related study by Denmark, et al.[136] has demonstrated a general preference for the axial conformation in α-chloro- and α-methoxycyclohexanone oximes (eq 28).



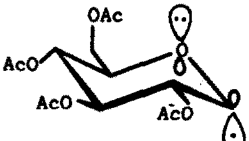
(28)

3.6.3 Anomeric Effect of Radicals.

Several research groups reported in 1983 that glucosyl radicals such as **49** react with different reagents to give the axially substituted products stereoselectively.[137-140] Further studies by Giese and Dupuis[141] give indication of an anomeric effect that stabilizes σ radical **50**.

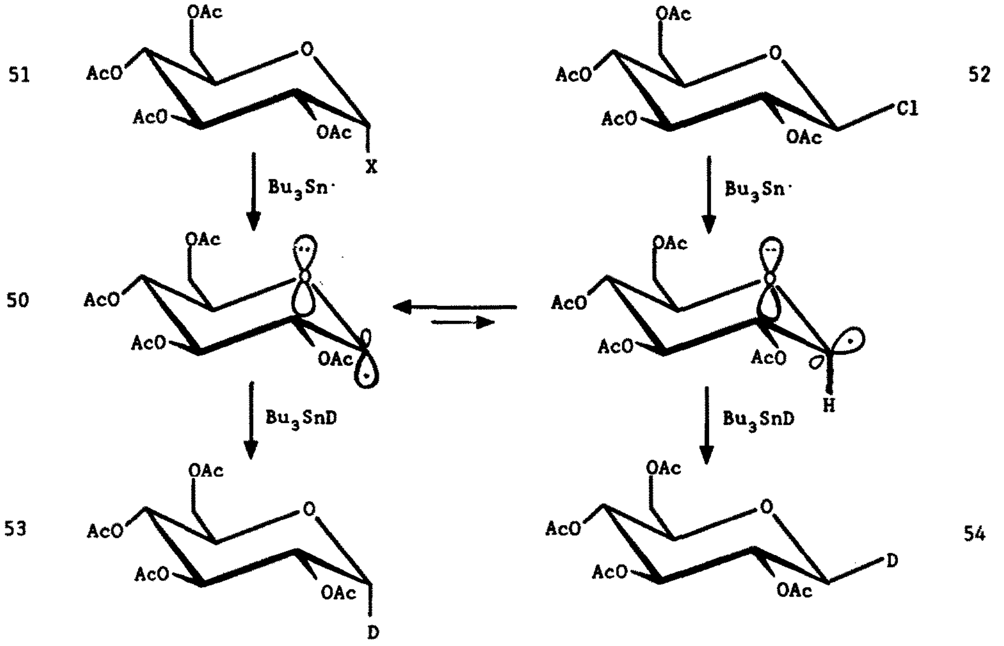


49



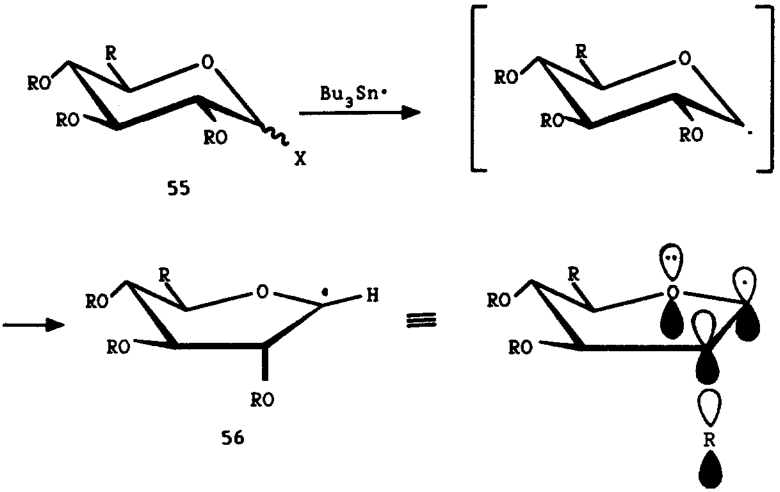
50

In particular, reduction of α-glucosyl halides **51** and β-glucosyl chloride **52** with Bu_3SnD afforded identical mixtures of deuterated products **53** and **54**. From the 98:2 (at -20°C) ratio of **53**:**54** the authors propose the manifestation of an anomeric effect that increases the participation of radical **50** in the equilibrium of the interconverting radicals (Scheme 29).



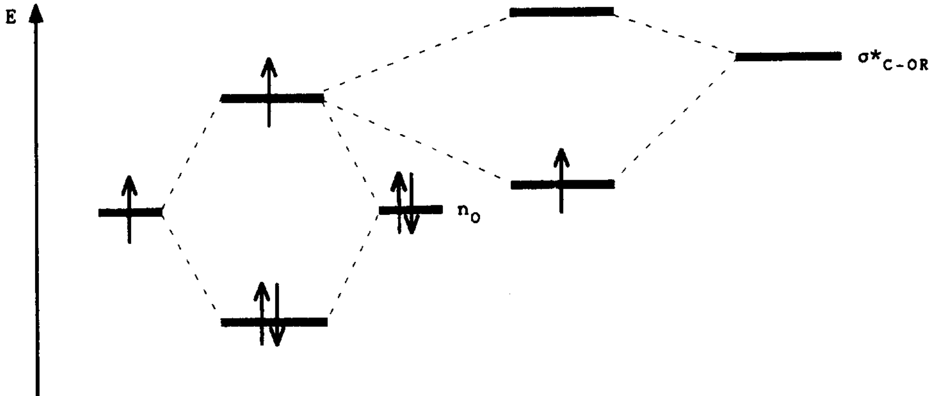
Scheme 29

More recently, Sustmann, Giese, et al.[142,143] have described the preparation of pyranosyl radicals from all-equatorially substituted precursors **55**. Interestingly, the radicals adopt a twisted "sofa" conformation **56** instead of retaining the $^4C_1$ conformation of the starting material (Scheme 30). This conformational effect was explained by what the authors call a "quasi-homo-anomeric" stabilization due to interaction of the radical's singly-occupied orbital with a σ* orbital of the adjacent β-CO bond in a coplanar arrangement..



Scheme 30

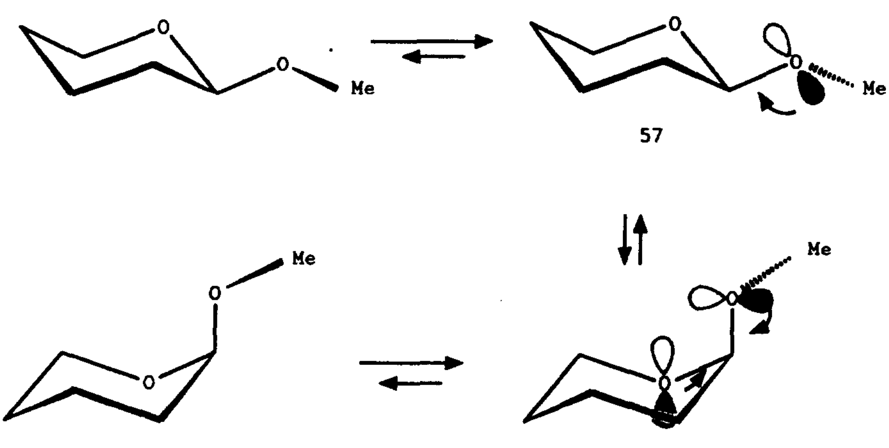
Scheme 31 presents a frontier-orbital rationalization for the "quasi-homo-anomeric" interaction,[144] which provides for the energy cost in the chair to twist-boat conformational change.



Scheme 31

4. Endo and Exo Anomeric Effects.

In 1969 Lemieux and coworkers discussed the possibility that, because the anomeric effect stabilizes the axial orientation of a methoxy group at the anomeric center of a glycoside, the same stereoelectronic effect should also influence the orientation of the aglycon.[145] Scheme 32 presents an illustration of this argument for 2-methoxytetrahydropyran, the *exo*-anomeric effect relates to the delocalization of electron density from the exocyclic oxygen, which is at a maximum when the p-type orbital for an unshared pair of electrons is antiperiplanar to the C(2)-ring oxygen, as indicated for 57 and 58. (Scheme 32).



57

58

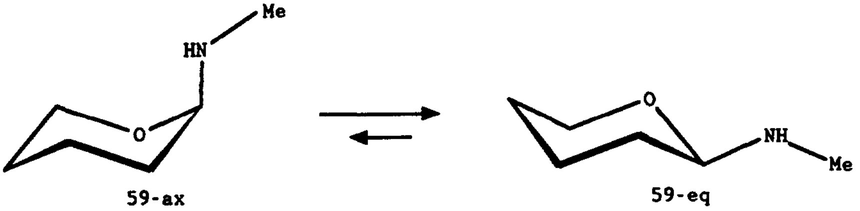
Scheme 32

It may be appreciated that the *endo* anomeric effect is the source of the driving force for a polar aglycon to adopt the axial orientation; i.e., 58 is the lower energy conformer. In the α-anomer 58 the two effects (*exo* and *endo*) compete for electron delocalization toward the anomeric carbon. Not surprisingly, structural data suggest that the *exo* anomeric effect is stronger for the β-anomer in which such competition is absent.[146,147]

In this context, Praly and Lemieux stress that an anomeric effect must be considered as the *difference* between the sum of the *endo*- and *exo*-anomeric effects in the equatorial conformer and the same sum for the axial conformer.[147] However, since the *endo* anomeric effect is absent in the equatorial isomer, it is stabilized exclusively by *exo* anomeric interactions (eq 29).

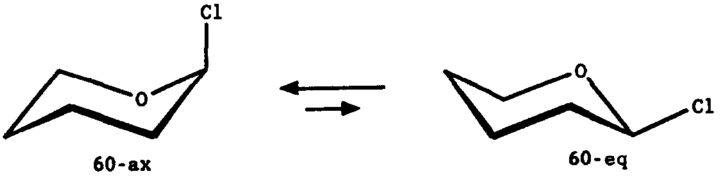
$$\text{Anomeric Effect} = (exo\text{-AE}_{eq}) - (exo\text{-AE}_{ax} + endo\text{-AE}_{ax}) \qquad (29)$$

According to equation 30, anomeric effects can have a wide range of values, including negative and positive values, depending on the relative magnitudes of the various *exo* and *endo* anomeric effects. Indeed, for the axial $\rightleftharpoons$ equatorial equilibrium in 2-methoxytetrahydropyran (Scheme 32) the axial conformer is strongly favored and, therefore, the term (*exo*-AE_{eq}) must be less stabilizing than (*exo*-AE_{ax} + *endo*-AE_{ax}); thus, the anomeric effect is positive. In contrast, in 2-methylaminotetrahydropyran (59) the basic nitrogen (good electron donor, poor acceptor) gives rise to strong *exo* anomeric effects. The contribution (*exo*-AE_{eq}) should thus be greater than (*exo*-AE_{ax}), and perhaps even greater than (*exo*-AE_{ax} + *endo*-AE_{ax}), so that equilibrium favors the equatorial conformer, in agreement with experiment[148] (eq 30).



(30)

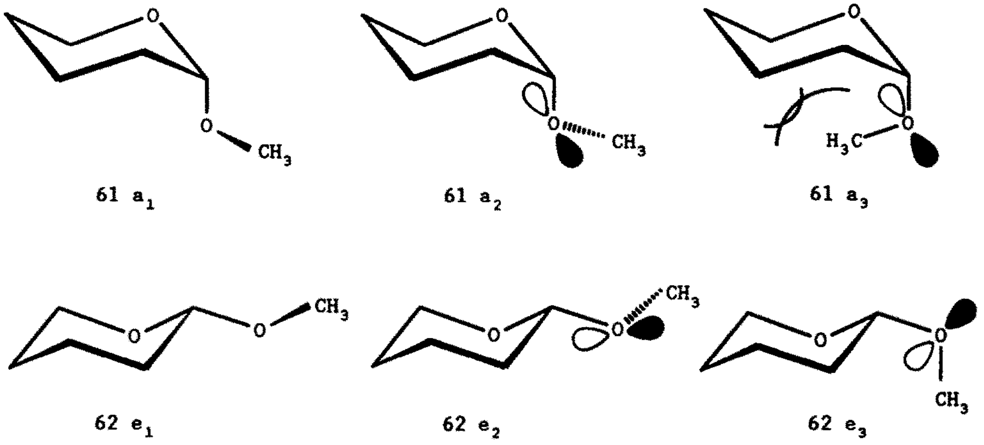
Booth and Khedhair have also interpreted the conformational behavior of 2-chlorotetrahydropyran (60) in terms of *endo* and *exo* anomeric effects.[149] *syn*-Axial steric interactions are relatively weak for axial chlorine, owing largely to the long C-Cl bond. In addition, the *exo*-anomeric effect for chlorine is expected to be weak. On the other hand, the authors notice the powerful acceptor properties of the C-Cl bond, which should ensure that the *endo*-anomeric effect is strong. Consequently, the equilibrium 59-ax $\rightleftharpoons$ 59-eq is heavily biased towards the conformation with axial chlorine (eq 31).



(31)

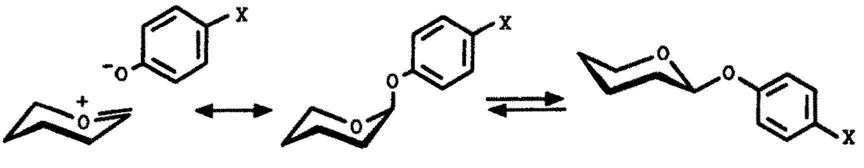
In this context, Booth, et al.[150] have recently reexamined the rotameric behavior of 2-methoxytetrahydropyran. Of the axial ($61a_1 \rightleftharpoons 61a_2 \rightleftharpoons 61a_3$) and equatorial ($62e_1 \rightleftharpoons 62e_2 \rightleftharpoons 62e_3$) staggered conformations three make important contributions (Scheme 33). The *exo* anomeric effect favors rotamers $61a_2$ and $62e_2$ in which the O-CH_3 bond lies antiperiplanar to the C(2) - C(3) bond (conformer $61a_3$ presents overwhelming steric repulsion). Indeed, convincing evidence for the dominance of conformations $61a_2$ and $62e_2$ in the crystalline state has been provided by X-ray crystallography (see Section 3.2.2). In addition, Booth, et al.[150] present evidence supporting the participation of rotamer $62e_3$ both in the crystalline state and in solution. The *exo* anomeric effect present in this conformation is proposed to overcome the concomitant steric hindrance arising from the *gauche* O-C(1)-O-CH_3 and C(2)-C(1)-O-CH_3 segments. (Scheme 33).

Further NMR studies by Booth, et al.[151] confirm the relevance of the *exo* anomeric effect for the conformational behavior of 2-methoxytetrahydropyran in solution; in particular, the predominance of conformers **61a$_2$** and **62e$_2$**, as well as the participation of rotamer **62e$_3$** was verified.



Scheme 33

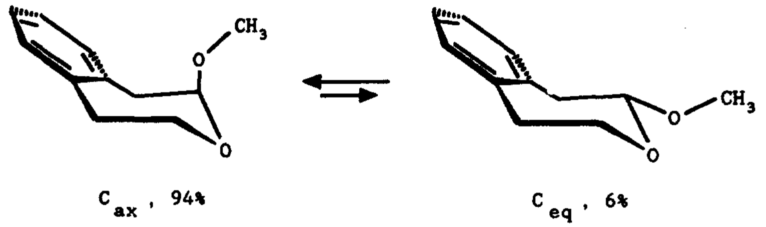
In this regard, Cook, et al.[39] and Ouedraogo and Lessard[94] have studied the conformational equilibria in 2-aryloxytetrahydropyrans, and found it to be sensitive to *para*-substituents on the aromatic ring. In particular, electron withdrawing groups (NO_2, CN) increase the population of **63-ax** (eq 32). This trend was explained in terms of an enhancement of the *endo* anomeric interaction in **63ax**, and a simultaneous weakening of the *exo* anomeric effect in **63eq**, because of the poorer donor capability of the ArO oxygen atom.



(32)

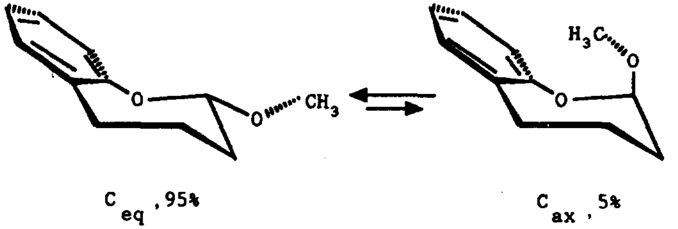
In another interesting study, Desilets and St.-Jacques[152] determined that the conformational equilibrium of 2-methoxy-3-benzoxepin (**64**) favors C_{ax} over C_{eq} in a 94:6 ratio (eq 33). In contrast, 2-methoxy-1-benzoxepin (**65**) favors C_{eq} to the extent of 95% (eq 34).

64:



(33)

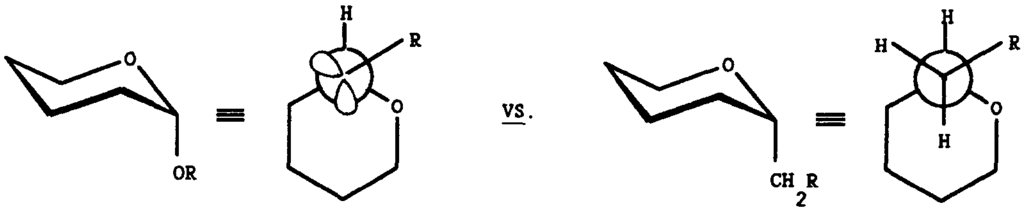
65:



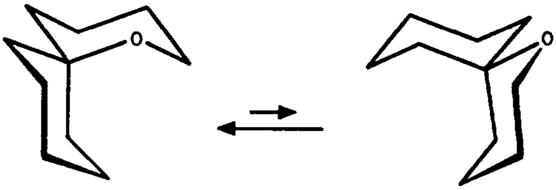
(34)

The opposite conformational preference for **64** and **65**, and the absence of twist-boat conformations in these compounds were explained[152] in terms of competing *endo* and *exo* anomeric effects; this in spite of the fact that it was tempting to invoke delocalization of the oxygen lone pair into the aromatic ring as responsible for the reduced participation of C_{ax} in the **65**-ax $\rightleftharpoons$ **65**-eq equilibrium. Indeed, it was estimated that the *l*p-O-C-OMe dihedral angle in **64**-ax is nearly 180°, which results in a strong *endo* anomeric interaction for this conformer. On the other hand, considerable departure from coplanarity was determined for **65**-ax, which ought to weaken the stabilizing *endo* $n_O \rightarrow \sigma^*_{C\text{-}O}$ interaction. Furthermore, it was suggested that the antiperiplanarity between a lone pair of electrons at the methoxy group and the ring C-O bond gives rise to an *exo* anomeric effect which stabilizes **65**-eq.

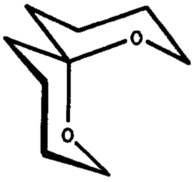
In this context, however, Kishi, et al. have recently questioned the real importance of the *exo* anomeric effect in the control of the relative population of rotamers in *O*-glycosides.[153-155] Indeed, comparison of the conformational preference of *O*-glycosides with that of C-glycosides shows a very good correspondence, which seems to suggest that the observed behavior is due to steric effects only.



In a reply from Deslongchamps and Pothier,[156] the different conformational behavior of spiro ether **66**, compared with that of spiro ketal **67** is pointed out. The former compound is conformationally heterogeneous at room temperature, whereas the latter was reported to exist in a single rigid conformation. The authors argue that this contrasting behavior demonstrates the importance of the *endo* and *exo* anomeric effects in the acetal function, so that the conformational preference exhibited by normal α- and β-O- glycosides must be a result of a combination of steric and stereoelectronic effect as previously proposed. To these reviewers, however, this proves the anomeric effect is important but does not seem to demonstrate the importance of the *exo*-anomeric effect.



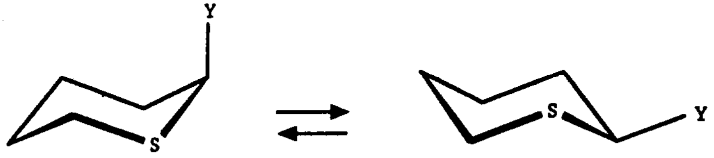
66 66'



67

5. Second- and Lower-Row Anomeric Interactions.

The evidence available by 1980, although scarce, gave clear indications for a substantial anomeric effect operating in 2-substituted thianes,[157] 1,3-dithianes,[158] and 1,3,5- trithianes[159] (eqs 35-37). The finding of a very strong S-C-P(O) anomeric effect in 1982[59] has provided a driving force for renewed efforts directed toward the understanding of the anomeric effect when involving second- and lower-row elements.



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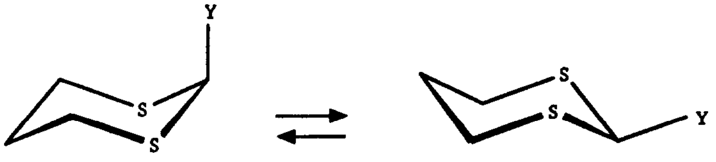

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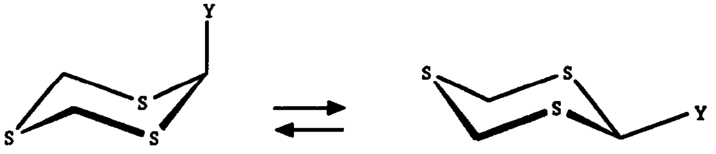


(37)

5.1 The S-C-X Anomeric Effect.

5.1.1 Study of the Anomeric Effect in 2-Substituted 1,3-Dithianes.

Juaristi and coworkers have described the conformational analysis of 2-substituted 1,3-dithianes [eq 36; Y = CO_2H, CO_2CH_3, SCH_3, SC_6H_5, $N(CH_3)_2$, and COC_6H_5], which reveals the interplay of steric, electrostatic and stereoelectronic effects.[37]

The low-temperature (-90° to -100°C) C-13 NMR spectra of these dithianes give rise to two sets of signals, which correspond to the axial and equatorial conformers. Integration of the peak areas for each of the conformers afforded the conformational free energy differences, which are summarized in Table 9. Sizable anomeric effects are apparent for (Y = SCH_3, SC_6H_5, COC_6H_5, CO_2CH_3 and CO_2H. By contrast, aminodithiane **68** (Y = $N(CH_3)_2$) exists in a highly predominant (>95%) equatorial orientation. The relative magnitude of the anomeric effects observed is (in order of decreasing importance): $CO_2H > COC_6H_5 > CO_2CH_3 > SC_6H_5 > SCH_3 >> N(CH_3)_2$.

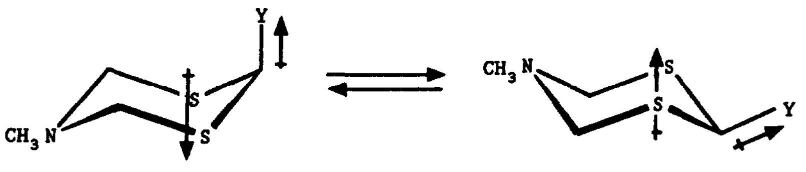
Table 9. Conformational Equilibria of 2-Substituted 1,3-Dithianes (Eq 36), in CD_2Cl_2.[37]

Substituent	Temperature (°C)	ΔG° (kcal/mol)
SCH_3	-100	0.64
SC_6H_5	-100	0.92
CO_2CH_3	-100	0.83
COC_6H_5[a]	-90	1.16
CO_2H	-90	>1.26

[a] In toluene d_8.

5.1.2 Study of the Anomeric Effect in 2-Substituted 5-Methyl-5-aza-1,3-dithiacyclohexanes.

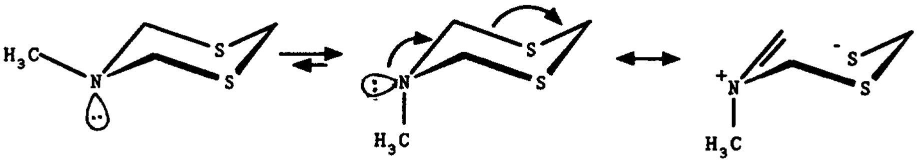
The relative order of the magnitude of the anomeric effect as a function of substituent is similar in the corresponding 1,3,5-dithiazines **69-73** (eq 38); however, the effects are smaller in magnitude.[160] There was observed a general tendency for a diminished axial preference in the more polar solvents, and this suggests the importance of dipole-dipole interactions in these systems: electrostatic repulsion disfavors the equatorial conformer.



(38)

69, Y = SCH_3; **70**, Y = SC_6H_5; **71**, Y = COC_6H_5; **72**, Y = $CO_2CH_2CH_3$; **73**, Y = $CO_2C_6H_5$

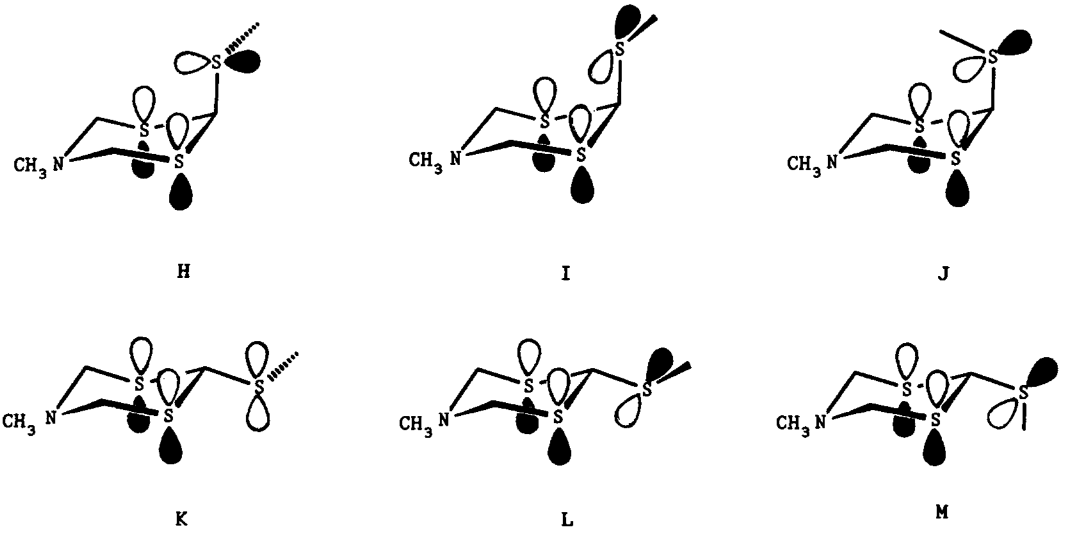
In this context, it is known that the methyl group at nitrogen in this system adopts the axial orientation in order to avoid the repulsion between lone pairs of electrons[161,162] and, possibly, to allow for favorable $n_N \rightarrow \sigma^*_{C\text{-}S}$ interactions[160,163] (eq 39).



(39)

The relative order in the magnitude of the anomeric effects observed in dithiazines 69-73, $CO_2C_6H_5 > CO_2CH_2CH_3 > COC_6H_5$, and $SC_6H_5 > SCH_3$,[160] which is also the trend observed in the 1,3-dithiane analogues[37] (see Section 5.1.1), is adequately explained in terms of *endo* and *exo* hyperconjugative interactions[147] (see Chapter 4).

Indeed, the antiperiplanar orientation of the p-type lone-pair orbital on the endocyclic sulfurs and the axial C(2)-SCH_3 bond allows for a significant *endo* anomeric interaction in conformations H and I (Scheme 34; conformer J is disfavored on steric grounds). Axial **69** is also stabilized by *exo* anomeric interactions in H and I. However, *exo* anomeric interactions also stabilize the equatorial conformers K-M (Scheme 34), and a relatively weak axial preference is therefore observed.



Scheme 34

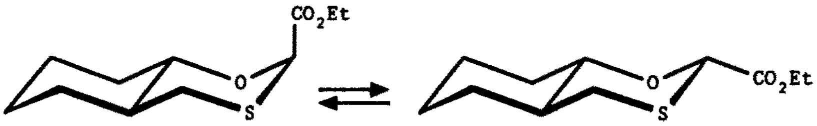
Substitution of the methyl group for a phenyl group in **70** ($SCH_3 \rightarrow SC_6H_5$) leads to an increased axial preference because the *endo* anomeric effect is stronger in axial **70** (lower energy of the $\sigma^*_{C\text{-}S}$ orbital; greater stabilization through the $n_S \rightarrow \sigma^*_{C\text{-}S}$ interaction), but the *exo* anomeric interactions are less important (lower energy of the donor n_S orbital).

In 71-73, the *endo* anomeric effect results from $n_S \rightarrow \sigma^*_{C\text{-}CO}$ interactions whereas torsion about the exocyclic C-CO bond can now turn on $\pi_{CO} \rightarrow \sigma^*_{C\text{-}S}$ interactions associated with an *exo* anomeric effect. However, $\pi_{CO} \rightarrow \sigma^*_{CX}$ interactions appear not to be dominant, probably because of the low energy of the π_{CO} orbital.[134] One can focus, therefore, on the unique *endo* anomeric interaction in the axial conformations.

5.1.3 Study of the Anomeric Effect in 2-Substituted *trans*-1,3-Diheterodecalins.

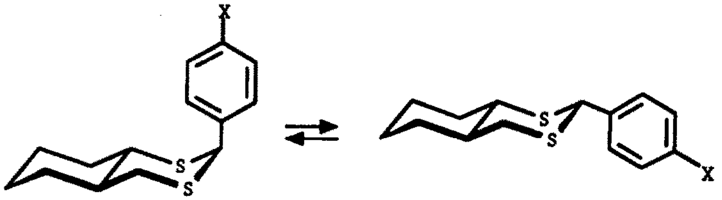
The axial $\rightleftharpoons$ equatorial equilibrium in 1,3-oxathiane derivative 74 favors neither isomer; i.e., $\Delta G^\circ = 0.0$ kcal/mol.[81] Consideration of the expected equatorial preference of the carboethoxy group in the absence of a conformational effect, led Tschierske, et al.[81] to suggest a S-C-CO_2Et anomeric interaction worth 1.1 kcal/mol in *n*-heptane (eq 40).

74:



(40)

On the other hand, in order to explore the possibility of the existence of an anomeric effect in 2-phenyl-1,3-dithiane, the conformational analysis of several *para*-substituted derivatives was studied by means of chemical equilibration of anancomeric 1,3-dithiadecalins 75-80[164] (eq 41).



(41)

75, X = OMe; 76, X = Et; 77, X = H; 78, X = Cl; 79, X = CN; 80, X = NO_2

As summarized in Table 10, the equilibria were sensitive to the *para*-substituent: the contribution of the axial isomer increases with growing electron-demand by the substituent. In fact, a linear dependence of ΔG° on the σ_p Hammett substituent constants supports the existence of a stabilizing hyperconjugative interaction between the lone pairs on sulfur and the antiperiplanar σ^* orbital on the axial C(2)-aryl bond.

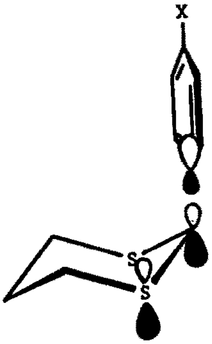
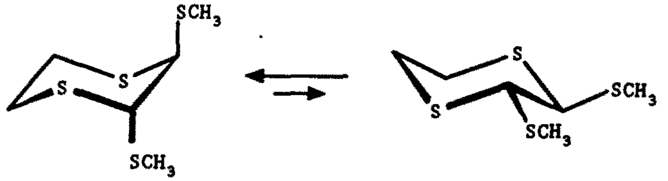


Table 10. Conformational Free Energies of 1,3-Dithiadecalins in 75-80 in CCl4.[164]

Compound	X	$-\Delta G^{o}$ (kcal/mol)	σ_p
75	OMe	2.6	-0.27
76	Et	2.5	-0.15
77	H	2.3	0
78	Cl	2.2	0.23
79	CN	1.8	0.66
80	NO_2	1.7	0.78

In a somewhat related study, Pericás, et al.[165] have determined the conformational equilibrium of *trans*-2,3-bis(methylthio)-1,4-dithiane (81) in $CDCl_3$ solution. The 83:17 mixture of diaxial and diequatorial conformers observed suggests that the S-C-S anomeric effect is strong enough to overcome repulsive gauche interactions[128] (eq 42).

81:

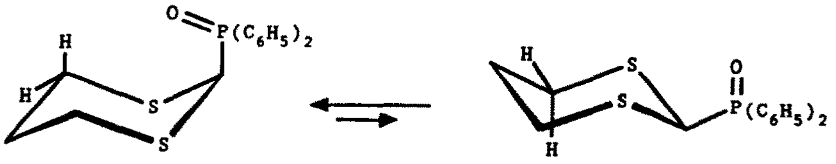


(42)

5.2 The S-C-P Anomeric Effect.[166]

2-[1,3]Dithianyldiphenylphosphine oxide (82) was prepared in our laboratory and studied as a precursor of ketene dithioketals.[167] It soon became obvious that the conformational behavior of 82 could provide useful information concerning the nature of the anomeric effect.

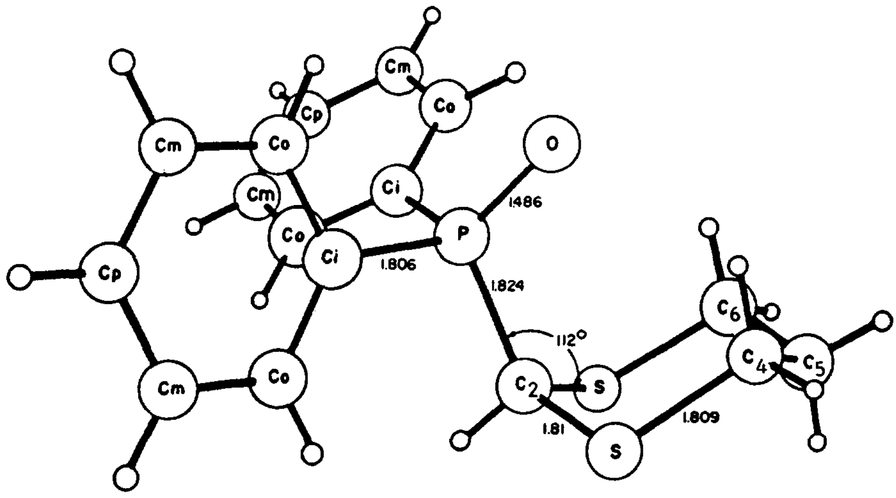
Assignment of the proton NMR spectrum of 82 indicated a very large (ca. 1.2 ppm) chemical shift difference between axial and equatorial protons at C(4,6).[59] This observation was taken as evidence for a deshielding effect of a *predominantly axial* phosphoryl group on the *syn*-axial H(4,6) (eq 43).



82-ax 82-eq

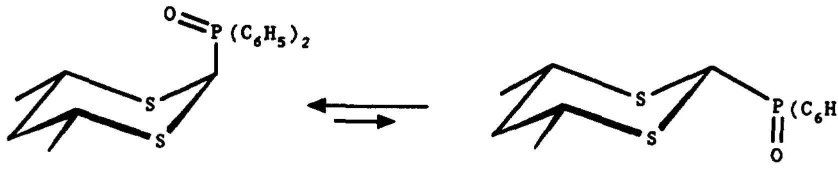
(43)

Definitive proof for the conformation of 82 in the solid state was obtained by single-crystal X-ray diffraction. A perspective view of the molecular structure in shown in Scheme 35. The heterocyclic six-membered ring exists in a chair conformation with the substituent being axial.[59]



Scheme 35

In order to quantitate the anomeric effect present in 82, chemical equilibration of anancomeric models 83 and 84 was successfully effected with basic catalysis (eq 44), and afforded a value of 1.0 kcal/mol for the conformational free energy difference favoring the axial isomer 83.[168]

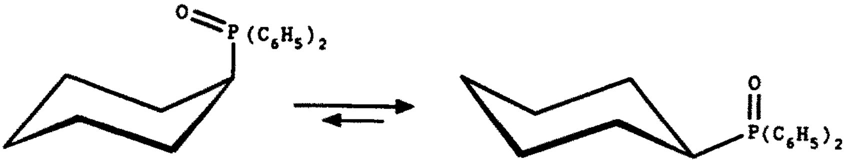


(44)

83

84

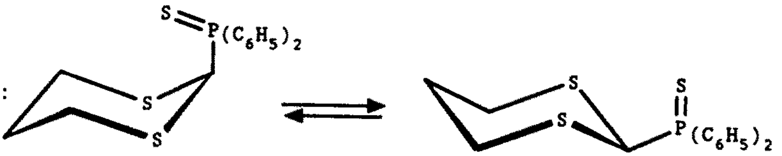
The conformational preference of the diphenylphosphinoyl group in cyclohexane (eq 45) has recently been determined:[28] $-\Delta G^\circ$ [P(O)Ph$_2$] = 2.74 kcal/mol; however, the steric requirement of this group at the C(2) position is smaller (because of the long C-S bonds) to the steric requirement in a cyclohexane. Indeed, ΔG°(2-*t*-butyl) in 1,3-dithianes is ca. 60% of ΔG°(*t*-butyl) in cyclohexane.[169] Thus, applying Franck's procedure[25] (see Section 2.3) the expected size of the diphenylphosphinoyl group in 82 is 60% of 2.74 kcal/mol, which affords an anomeric effect equal to 1.0 + (0.6 x 2.74) = 2.64 kcal/mol.



(45)

In a related study, the conformational equilibrium of 2-(diphenylthiophosphinoyl)-1,3-dithiane (85) was determined;[170] a value of $\Delta G^{\circ}[P(S)Ph_2] = 0.15$ kcal/mol was obtained at ambient temperature. Comparison with the *A*-value for the diphenylthiophosphinoyl group (3.6 kcal/mol),[170] and application of Franck's procedure for the correction of steric effects in dithiane, afforded a value of 2.2 kcal/mol for the anomeric effect originated from the S-C-P(S) segments in **85** (eq 46).

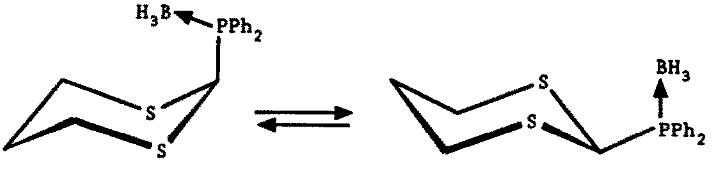
85:



(46)

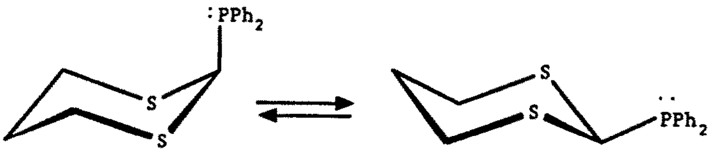
More recently, the conformational preferences of the (diphenylphosphinyl)borane and diphenylphosphinyl groups in the 1,3-dithian-2-yl ring were also determined by NMR analysis: -0.1 and -0.3 kcal/mol, respectively.[89] The slight predominance of the equatorial conformers nonetheless reflects the influence of substantial S-C-P(BH_3) and S-C-P: anomeric interactions, worth 1.8 and 1.0 kcal/mol, respectively (eqs 47 and 48).

86:



(47)

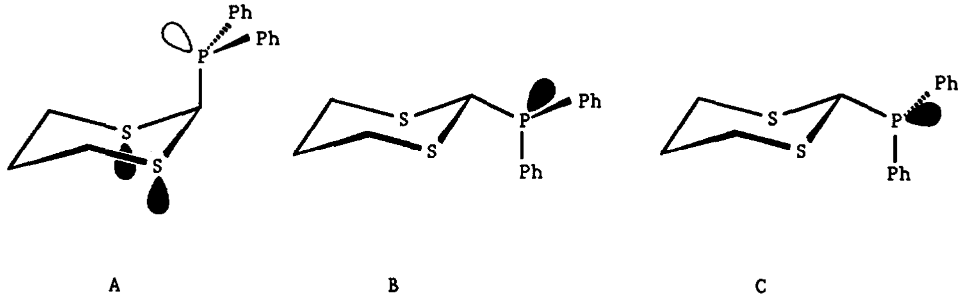
87:



(48)

The relative magnitude of the S-C-P anomeric effects in 2-*P*-substituted 1,3-dithianes **82**, **85**, **86**, and **87** increases in the same order as the electron-withdrawing properties of the organophosphorus groups studied; i.e., their σ_I values:[171] S-C-P(O) with σ_I 0.32, AE = 2.6 kcal/mol > S-C-P(S) with σ_I 0.23, AE = 2.2 kcal/mol > S-C-P(BH_3) with non-available σ_I, AE = 1.8 kcal/mol > S-C-P: with σ_I 0.10, AE = 1.0 kcal/mol.

This trend is adequately explained in terms of *endo* and *exo* hyperconjugative interactions.[147] Indeed, the antiperiplanar orientation of the p-type lone-pair orbital on the endocyclic sulfurs and the axial C(2)-P bond allows for a significant *endo* anomeric interaction in axial 87 (A, Scheme 36). However, *exo* anomeric interactions also stabilize the equatorial conformers B and C (Scheme 36), and a relatively weak anomeric effect is therefore observed.



Scheme 36

Coordination of the phosphorus atom to oxygen in 82 [$PPh_2 \rightarrow P(O)Ph_2$], to borane in 86 [$PPh_2 \rightarrow P(BH_3)Ph_2$] and to sulfur in 85 [$PPh_2 \rightarrow P(S)Ph_2$] leads to an increased axial preference because the *endo* anomeric effect is stronger in axial 82, 85 and 86 (lower energy of the $\sigma^*_{C\text{-}P}$ orbital; greater stabilization through the $n_S \rightarrow \sigma^*_{C\text{-}P}$ interaction), but *exo* anomeric interactions are not possible because of the unavailability of an antiperiplanar n_P orbital.

Nevertheless, through-space 3p-3d electron donation from sulfur to axial phosphorus[168] could also account for the results, especially since the precise structural data available[58] is not in line with the double bond-no bond picture expected from the $n_S \rightarrow \sigma^*_{C\text{-}P}$ hyperconjugation mechanism. (See Section 3.2.2).

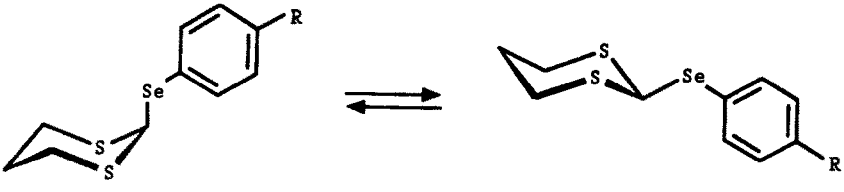
In this context, it is important to notice that electron transfer from sulfur to the axial phosphorus is supported by the observation of significant upfield ^{13}C chemical shifts for the ortho and para carbons in the axial phosphinoyl,[168] thiophosphinoyl,[170] phosphinyl-borane[89] and phosphinyl[89] groups.

Alternative rationalizations that have been considered to account for the strong S-C-P(O) anomeric effect, such as (a) electrostatic, attractive interaction between the phosphoryl oxygen and the *syn*-axial hydrogens,[168,172] and (b) repulsive interactions between the lone pairs on sulfur and on the equatorial phosphoryl oxygen,[173,174] appear, under this evidence, to play a minor role in the conformational equilibria of 82 and 85-87.

In this context, substantial anomeric effects (defined as the *tendency* of the electronegative substituent to assume an axial orientation) have been observed in 2-triphenylphosphonio-1,3-dithiane,[175] and in 2-diphenylphosphinoyl-1,3-dioxane and 2-diphenylphosphinoyl-1,3-oxathiane.[176,177]

5.3 The Se-C-X Anomeric Effect

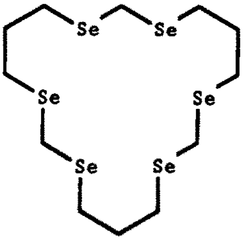
In 1985 Pinto, et al.[178,179] reported the axial conformational preference of the arylseleno moiety in 2-arylseleno-1,3-dithianes (eq 49). Furthermore, it was described that the anomeric effect in a series of 2-(4-substituted-phenylseleno)-1,3-dithianes (substituents, R = NO_2, CF_3, H, OMe, NMe_2) decreases as the electron-withdrawing ability in this series dwindles. This behavior was rationalized in terms of a dominant $n_S \rightarrow \sigma^*_{C\text{-}Se}$ orbital interaction, and the magnitude of the anomeric effect was estimated to vary from 1.6 to 2.2 kcal/mol in going from R = NMe_2 to R = NO_2.



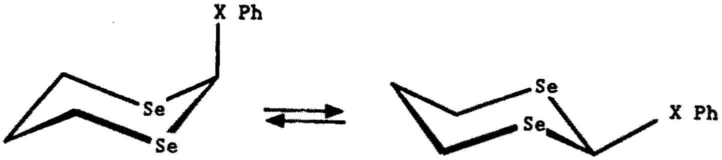
(49)

In this context, Pinto, et al. reported evidence for the existence of a Se *endo* anomeric effect, which produces an unusual solid-state conformation in selenium coronand 88.[180,181]

88:



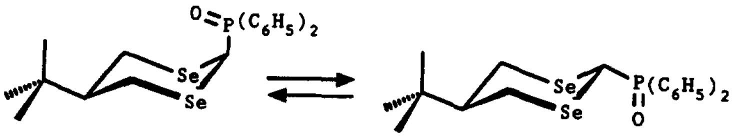
Additional evidence for the importance of *endo* $n_{Se} \rightarrow \sigma^*_{C\text{-}X}$ was adduced by the same Canadian group from the conformational study of 2-phenylthio- and 2-phenylseleno-1,3-diselenanes[182] (eq 50).



(50)

X = S, Se

In this regard, Mikolajczyk, et al.[183] have described the *cis* $\rightleftarrows$ *trans* equilibration of 2-(dimethoxyphosphoryl)-5-t-butyl-1,3-diselenanes 89. A substantial preference for the axial isomer (ΔG° = 1.2 kcal/mol) was observed, and the approximate magnitude of the anomeric effect in 89 was estimated as ca. 2.4 kcal/mol (eq 51).

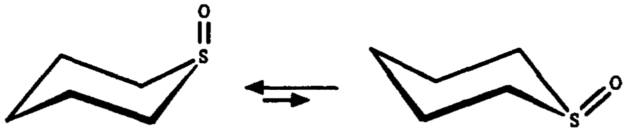


cis-89 trans-89

(51)

5.4 The S-S=O Anomeric Effect.

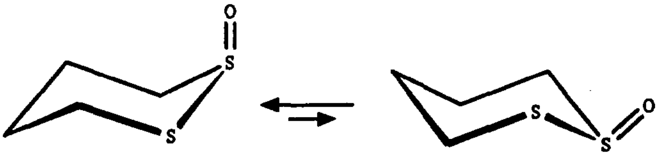
A quarter of a century ago, Johnson and McCants,[184] and Martin and Uebel[185] showed that the S=O group prefers an axial arrangement in thiane oxide 90 (eq 52). A quantitative determination of this equilibrium was accomplished by Lambert and Keske,[186] suggesting a conformational free energy difference of 0.2 kcal/mol.



90-ax 90-eq

(52)

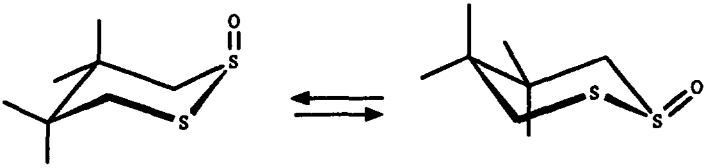
That substitution of an α-methylene by sulfur (90 → 91) results in a greater predominance of the axial conformer (eq 53) was first proposed by Harpp and Gleason,[187] and then confirmed by several groups in the early 1980s.[187-190]



91-ax 91-eq

(53)

In fact, the equilibrium 91-ax $\rightleftharpoons$ 91-eq is so much tilted to the left that the participation of the equatorial isomer is too small to permit quantitative measurement of the equilibrium constant. In this regard, Juaristi and Cruz-Sánchez[191] prepared 4,4,5,5-tetramethyl-1,2-dithiane mono-*S*-oxide (92), the rationale being that the *syn*-diaxial Me/S=O interaction in 92-ax would afford an equilibrium closer to unity in equation 54, thus allowing a more precise determination of the conformational preference of the S=O group.



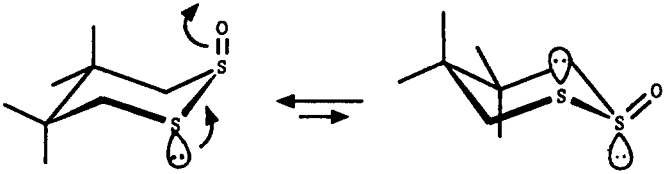
92-ax 92-eq

(54)

The NMR spectroscopic information on **92** indicates that the participation of **92-eq** in the equilibrium is not significant,[192] and suggested a conformational free energy difference in the equilibrium **91-ax** $\rightleftharpoons$ **91-eq** greater than 3.0 kcal/mol.

The unusually large stability of **91-ax** and **92-ax** relative to their equatorial conformations was suggested to be the result of stereoelectronic effects:[191,192] a $n_S \rightarrow \sigma^*_{S-O}$ hyperconjugative interaction[193] being responsible for the preferred antiperiplanar (diaxial) orientation of the S=O group and the lone pair of electrons at sulfur, and the *anti* arrangement of two lone pairs in **92-eq** destabilizing this conformer[194] (eq 55).

92:



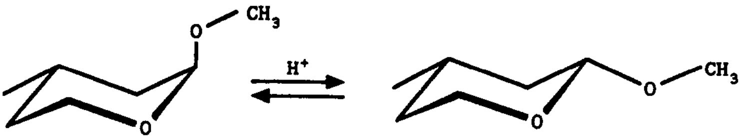
(55)

5.5 The O-P-X Anomeric Effect

Stereoelectronic manifestations in segments incorporating phosphorus as the central atom have been properly reviewed. For leading reports see refs. 195-198.

6. The Enthalpic Anomeric Effect

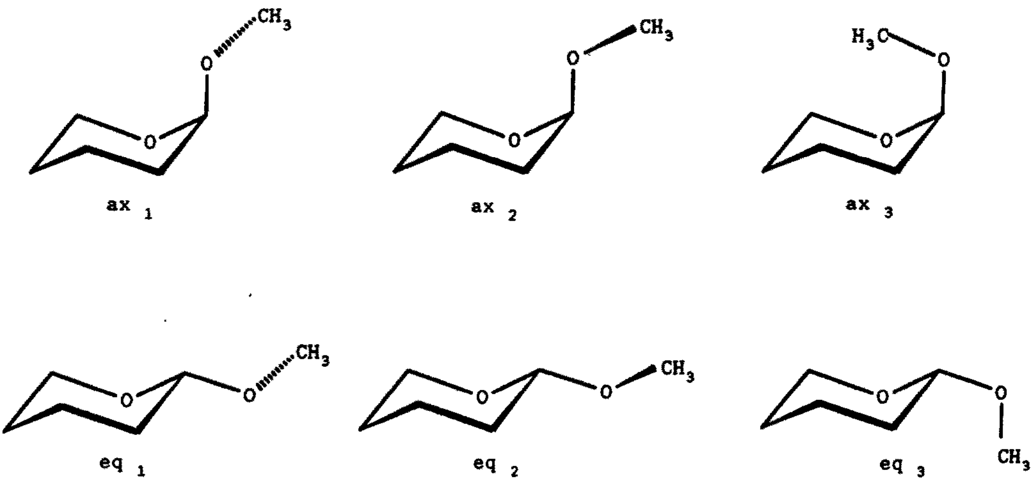
From a reexamination of the conformational preference of 2-methoxytetrahydropyran (eq 1), Booth, et al.[148] concluded that the axial $\rightleftharpoons$ equatorial equilibrium constants in the range 143 to 165 K are similar to those deduced from the chemical equilibration of *cis*- and *trans*-2-methoxy-4-methyltetrahydropyran at 245 and 273' K (eq 56). Analysis of the spectroscopic data gave $K = 0.26$, $\Delta H^\circ \sim 0.0$, and $\Delta S^\circ = -2.7$ cal/K•mol.



(56)

The implications of these thermodynamic data are quite dramatic: the axial preference of the methoxy group in tetrahydropyran, a prototype for the study of the anomeric effect, is determined by favorable entropy in this conformer. Of course, all other rationalizations of the anomeric effect have been advanced in terms of steric, electrostatic or stereoelectronic interactions that should be reflected in the enthalpy contribution to the free energy difference (see Chapter 3).

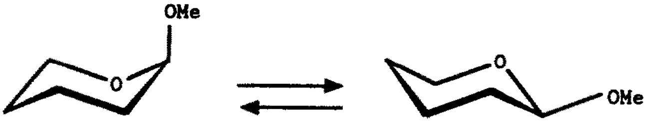
In order to account for the increased entropy in the axial isomer, Booth, et al.[148] surmised that the populations of both rotamers ax_3 and eq_3 are negligible (Scheme 37), and the proportion of the less stable rotamer ax_2 in ($ax_1 \rightleftharpoons ax_2$) is much greater than the proportion of the less stable rotamer eq_2 in ($eq_1 \rightleftharpoons eq_2$); this in turn would suggest that the *exo* anomeric effect is stronger in the equatorial anomer (see Chapter 4).



Scheme 37

The above conclusion, concerning a dominant change in entropy with little change in enthalpy, has been questioned by Lemieux,[199] who suspected Booth's findings reflected specific solvation effects. Indeed, Praly and Lemieux determined the solvent effect on thermodynamic parameters for 2-methoxytetrahydropyran (Table 11), and found ΔH° close to zero only in hydrogen-bonding solvents ($CDCl_3$, D_2O) or polar ones (CD_3CN). In contrast, the substantial enthalpy term in CCl_4-containing solvent mixtures is in agreement with earlier interpretations.

Table 11. Effect of Solvent on the Thermodynamic Parameters for the Axial⇌Equatorial Equilibrium in 2-Methoxy THP.[147]



Solvent	ΔH°(kcal/mol)	ΔS°(cal/K·mol)
CCl_4-C_6D_6 (10%)	0.8	-0.3
CCl_4-C_6F_6 (10%)	0.6	- 1
$CDCl_3$	-0.2	- 2
CD_3CN	0.1	-0.7

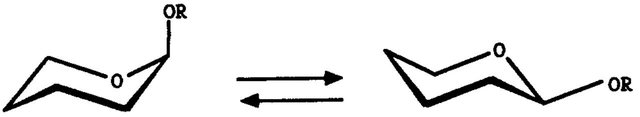
The decreased entropy in the equatorial conformer was then explained by Lemieux[199] in terms of a release of solvent when the equatorial conformer passes into the axial form. Indeed, since no *endo* anomeric effect is operative in the equatorial isomer, the endocyclic oxygen should be especially electron-rich and prone to solvation.

In this regard, *ab initio* MO calculations on 2-methoxytetrahydropyran (gas phase)[115] do not agree with the experimental (in $CDCl_3$-$CFCl_3$)[148] results, in particular, the calculated entropy difference was rather small, and the estimated ΔH°_{298} was 0.96 kcal/mol.[115]

Be this as it may, Booth has correctly stressed that since conformational entropy differences are usually quite significant, evaluations of the anomeric effect based on temperature-dependent ΔG° (rather than ΔH°) values are unsatisfactory.[149-150]

For example, in Scheme 38 the thermodynamic parameters for the conformational equilibria in several 2-substituted tetrahydropyrans are collected. Comparison with the corresponding parameters in the cyclohexane analogues revealed substantial *enthalpic* anomeric effects for the hydroxy, methoxy and chloro derivatives.[150] In the case of the methylamino group, $\Delta\Delta H^\circ \sim 0.0$ kcal/mol.[150] This result indicates an absence of a reverse anomeric effect, especially since the reference ΔH°_{steric} was not corrected for the more stringent steric requirements in an axial tetrahydropyran. (See Section 2.3).

More recently, Booth and Readshaw determined the equilibrium constants in 2-alkoxytetrahydropyrans **93-96** (eq 57). Plots of ln *K* against T^{-1} gave values for ΔH° (ax → eq) of -0.26, -0.12, -0.05 and 0.13 kcal/mol for OR = OEt, OCH_2CH_2F, OCH_2CHF_2 and OCH_2CF_3, respectively, in CD_2Cl_2. The corresponding ΔS° (ax → eq) values were -2.3, -2.2, -2.3 and -2.2 cal/K•mol.[200]

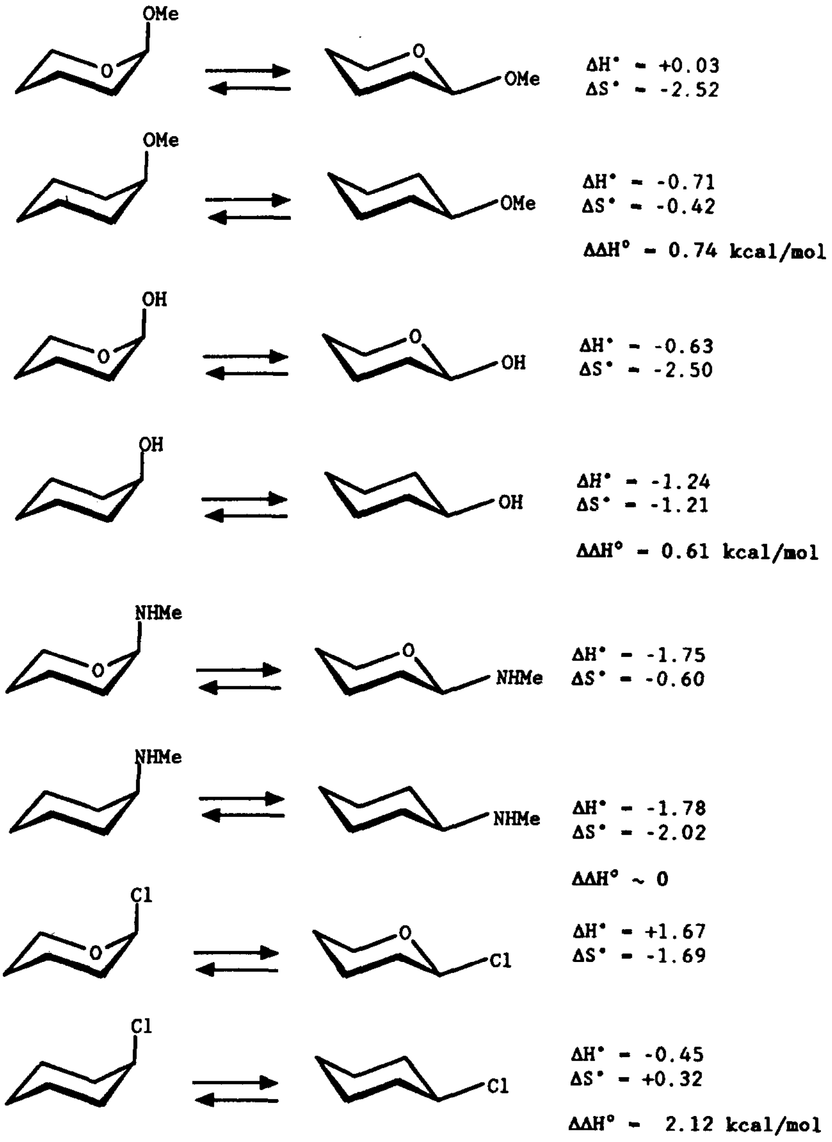


(57)

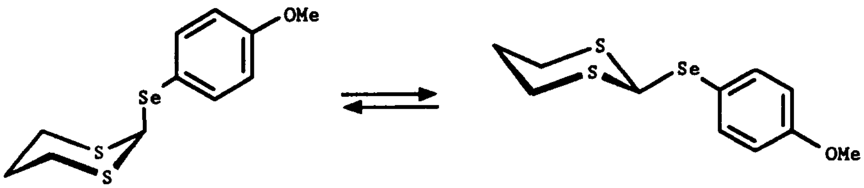
93, R = CH_2CH_3; **94**, R = CH_2CH_2F; **95**, R = CH_2CHF_2; **96**, R = CH_2CF_3

The trend in ΔH° values was attributed to the relative magnitudes of *endo* and *exo* anomeric $n_O \rightarrow \sigma^*_{C\text{-}O}$ interactions, which vary as the number of electronegative fluorine substituents increases (see Chapter 4). At temperatures higher than 120 K, the axial conformers predominate, but this is a consequence of the higher entropy. In fact, Booth and Readshaw emphasize,[200] for **93** and **94** it is the equatorial conformation which has the lower enthalpy.

In this context, Pinto, et al.[201] reported the temperature dependence of the anomeric effect in 2-[(4-methoxyphenyl)seleno]-1,3-dithiane (eq 58). Plots of ln *K* vs 1/T permitted evaluation of the enthalpic and entropic contributions to the S-C-Se anomeric effect in several solvents. ΔH° (ax → eq) values of +1.43, +0.98, and +1.59 kcal/mol, and ΔS° (ax → eq) values of +3.4, +2.1 and +4.8 cal/K•mol were obtained in toluene, methylene chloride, and acetone, respectively.


OMe
O
O
OMe
ΔH° = +0.03
ΔS° = -2.52
OMe
OMe
ΔH° = -0.71
ΔS° = -0.42
ΔΔH° = 0.74 kcal/mol
OH
O
O
OH
ΔH° = -0.63
ΔS° = -2.50
OH
OH
ΔH° = -1.24
ΔS° = -1.21
ΔΔH° = 0.61 kcal/mol
NHMe
O
O
NHMe
ΔH° = -1.75
ΔS° = -0.60
NHMe
NHMe
ΔH° = -1.78
ΔS° = -2.02
ΔΔH° ~ 0
Cl
O
O
Cl
ΔH° = +1.67
ΔS° = -1.69
Cl
Cl
ΔH° = -0.45
ΔS° = +0.32
ΔΔH° = 2.12 kcal/mol

Scheme 38



(58)

The observed stabilization of the axial conformer in terms of enthalpy, and its destabilization in terms of entropy was interpreted in terms of the dominance of $n_S \rightarrow \sigma^*_{C\text{-}Se}$ orbital interactions.[201]

Evidence for an enthalpic S-C-S anomeric effect was presented recently by Juaristi, et al.[160] Variable-temperature ^1H and ^{13}C NMR spectra of mobile dithiazines 70-73 (eq 38) permitted the evaluation of the thermodynamic parameters collected in Table 12.

Table 12. Thermodynamic Parameters for Equation 38.

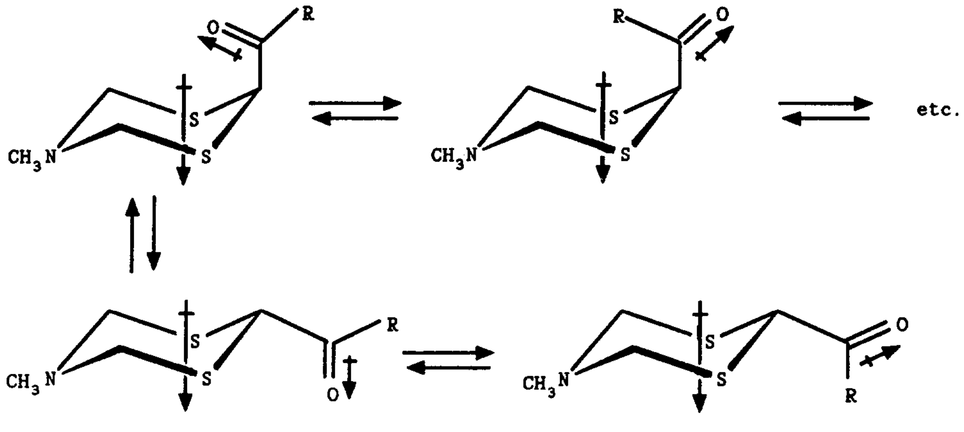
Compd	Y	Solvent	ΔH^o(kcal/mol)[a]	ΔS^o(cal/K · mol)[b]
70	SC_6H_5	$C_6D_5CD_3$	+0.44	+0.09
		$CD_2Cl_2/CFCl_3$(15:85)	+0.70	+0.56
		CD_2Cl_2	+0.59	+0.51
		CD_3COCD_3	+0.50	+1.40
		CD_3OD	+0.54	+1.29
71	COC_6H_5	$C_6D_5CD_3$	+0.10	-2.46
		CD_2Cl_2	-0.01	-0.80
		CD_3COCD_3	-0.25	-2.04
72	$CO_2CH_2CH_3$	$C_6D_5CD_3$	-0.35	-5.46
		CD_2Cl_2	-0.03	-1.70
		CD_3COCD_3	-0.04	-1.38
		CD_3OD	+0.27	-0.95
73	$CO_2C_6H_5$	$C_6D_5CD_3$	-0.06	-4.99
		CD_2Cl_2	-0.17	-3.90
		CD_3COCD_3	-0.05	-2.24
		CD_3OD	+0.29	-1.87

[a] Positive values indicate that the axial conformer is favored enthalpically.

[b] Positive values indicate that the equatorial conformer is favored entropically.

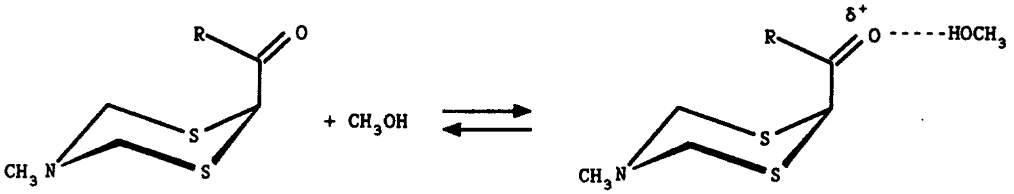
The thermodynamic data obtained for the **70**-ax$\rightleftharpoons$**70**-eq equilibrium definitively shows that the axial preference of the thiophenyl group is of enthalpic origin; the enthalpy term dominates over the entropy contribution, which actually favors **70**-equatorial. The sizeable ΔH° terms (0.5-0.7 kcal/mol; Table 12) must of course overcome the steric hindrance present in **70**-axial, so that the magnitude of the anomeric effect in this system may well exceed 1.0 kcal/mol.

In contrast to **70**, the thermodynamic data for the carbonyl derivatives **71**-**73** show that the ΔH° term in most solvents is close to zero. Of course, $\Delta H^\circ \sim 0$ in these systems may still be indicative of a significant anomeric effect owing to the countervailing steric effect. Inspection of Table 12 shows that the axial predominance of **71**-**73** is controlled by the entropy difference, the axial conformers being of higher entropy. A likely explanation for this phenomenon can be advanced in terms of the local dipole-dipole interactions present in the axial and equatorial conformers. (A significant solvent effect is found in the equilibria of **71**-**73**; the anomeric effect decreases as the polarity of the solvent increases). For axial **71**-**73**, the C=O dipole should always be aligned antiparallel to the ring dipole, independently of rotation around the C(2)-CO bond (Scheme 39), and all rotamers would then be favorable on electrostatic grounds. In equatorial **71**-**73**, however, a lower energy rotamer would only be obtained when the C=O bond dipole is pointing away from the ring dipole; this would restrict the conformational freedom of the equatorial conformer. (Scheme 39). Supporting evidence for this explanation comes from the observation that this entropy effect is more important in the less polar solvents, where the electrostatic interaction is more demanding. (Table 12).



Scheme 39

Interestingly, ΔH° is positive for **72** and **73** *in methanol*, but negative in all other solvents. A plausible interpretation of this effect is as follows: hydrogen bonding by the hydroxylic solvent methanol to the carbonyl group makes the *endo* anomeric effect more effective, by lowering the energy of the $\sigma^*_{\text{C-CO}}$ orbital (eq 59).



(59)

7. The Kinetic Effect.

Time limitations did not allow the present reviewers to prepare a suitable discussion of the extensive recent literature on this topic, which actually include both enthusiastic adherents, and skeptical opponents of the so-called Antiperiplanar Lone Pair Hypothesis (ALPH). Nevertheless, we would like to present a list of key studies in this area in refs. 30 and 202-213.

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