A Review on the Conformational Aspects
in the 1,3-Dioxane System.

Marc J.O. Anteunis, Dirk Tavernier and Frans Borremans

State University of GENT, Department of Organic Chemistry
Laboratory for NMR spectroscopy
Krijgslaan 271 (S-4bis)
Gent, B-9000
Belgium.

Table of Contents

Conformational Aspects of the 1,3-dioxane System.

I. Introduction.

The interest in the conformational behaviour of heterocyclic
systems, of which 1,3-dioxane is a simple representative, can
be judged from the rapid expansion this field has undergone
since the first reviews have appeared (Riddell, 1967; Eliel,
1972a; Bogatskii et al., 1968; Eliel, 1970a; Eliel, 1969a;
Eliel, 1970b; Eliel, 1971a;   Romers et al., 1969; Eliel et
al., 1964). One can also realize the present situation from
the ever growing number of contributions in several annual
surveys, such as "Progress in Nuclear Magnetic Resonance", J.
W. Emsley, J. Feeney and L.H. Sutcliffe Eds., Pergamon Press,
Oxford (since 1965) and "Annual Reports on the Progress of
Chemistry, The Chemical Society", Arrowsmith, Bristol.

The early investigations on the conformation of 1,3-di-
oxane used classical methods such as dipole moment measure-
ments (Otto, 1937; Arbuzov, 1960) and IR spectroscopy (Laurent,
1958). Other investigations followed rapidly; NMR techniques
(^{1}H-NMR: Friebolin et al., 1962;   Samitov et al. , 1964;
Barbier et al., 1964a; Barbier et al., 1964b; Delmau, Barbier,
1964; Ramey, Messick, 1965; Anteunis et al., 1966a; Delmau et
al., 1966; Anderson, 1967; Booth, Thurnborrow, 1968; Pihlaja,
Äyräs, 1970; Maroni et al., 1972; Eliel et al., 1972; Maroni

et al., 1972; Tavernier, Anteunis, 1974; and also ^{13}C-NMR: Riddell, 1970; Kellie, Riddell, 1971), X-ray data (de Kok, Romers, 1970; Kellie et al., 1972; Collins et al., 1974), chiroptical properties (Tocanne, 1970), thermochemical methods (Snelson et al., 1961; Pihlaja, Heikkilä, 1967; Pihlaja, Luoma, 1968), acoustic relaxation phenomena (Hamblin et al., 1968; Eccleston, Wyn-Jones, 1969; Hamblin et al., 1969), microwave spectroscopy (Pickett, Strauss, 1970; Kewley, 1972), electron diffraction (Schultz, Hargittai, 1974) and appearance potentials in mass spectroscopy (Pihlaja, Jalonen, 1971). These applications have finally enlarged to a great extent our knowledge about heterocyclic systems in general.

Different research teams all over the world have been interested in conformational studies of heterocyclic systems, especially the 1,3-dioxanes: E.L. Eliel in the United States, J. Anderson, F. Riddell, M. Robinson and E. Wyn-Jones in the United Kingdom, J. Delmau, P. Maroni, L. Cazaux and J. Tocanne in France, H. Friebolin in Germany, the Leyden group in the Netherlands and among the Russian authors Y. Samitov, A. Bogatskii and A. Vereshchagin must be mentioned. Since somewhat more than a decade we are ourselves involved in the conformational description of the 1,3-dioxane system, mainly relying on ^{1}H-NMR spectroscopy. The large number of recent developments has prompted us to compile a survey in which the spatial behaviour will receive our prime attention.

II. The Ring Shape of 1,3-dioxane.

The basic conformation of 1,3-dioxane is the chair form. Otto (1937) and Arbuzov (1960) reached this conclusion from a comparison of the experimental dipole moment with calculated ones for the planar, the chair and a boat form.

A. X-ray data.

The complete X-ray analysis of five 1,3-dioxane derivatives has until now been reported. The atomic coordinates of 2-(p-Cl-phenyl)-1,3-dioxane (1) are shown in FIG.1 (de Kok, 1970). On the basis of ^{1}H-NMR data (see later) it is believed that the ring shape in 1 does not significantly differ from the ring shape in 1,3-dioxane itself. The aliphatic part C_4-C_5-C_6 is as flattened in 1,3-dioxane as in cyclohexane [ring torsion angles of 56-55°; Buys, Geise, 1970a; Geise et al., 1971; Bastiansen et al., 1973). On the other hand, the acetal part, O_1-C_2-O_3, is clearly puckered with a ring torsion angle of 63°.
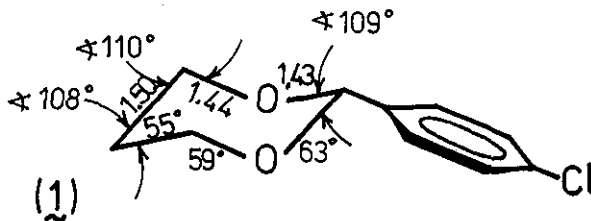

Fig. 1

This same puckering is also found for the 1,3-dioxane ring incorporated into the more complex structure 2,10-diphenyl-1,3,6,9,11,13-hexaoxodispiro[4.1.5.2]tetradecane (2) (Collins et al., 1974).
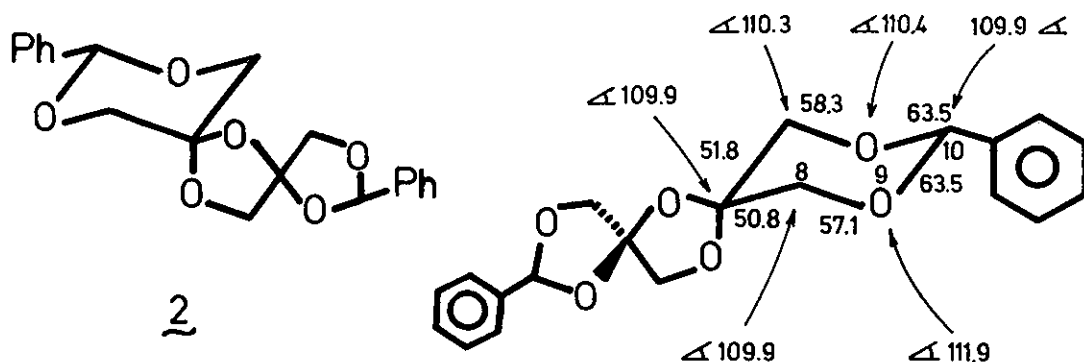
Fig. 2

The aliphatic part in 2 is more flattened than it is in 1 (FIG.2). The heavily substituted 2-(4-bromophenyl)-r-2,4,4-cis-6-tetramethyl-1,3-dioxane (3) was examined (Kellie et al., 1972) in order to obtain data on deformed rings (FIG.3).

Bond angles

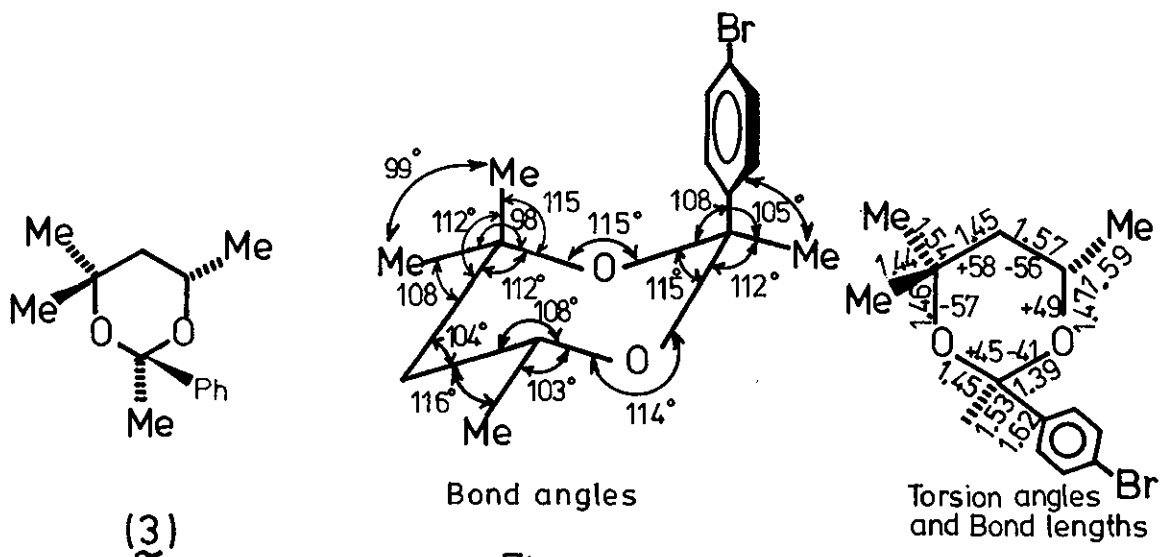Torsion angles and Bond lengths

(3)

Fig. 3

The molecule still exists in a chair form, but suffers much
flattening in the acetal part of the ring; the interbond angle
between the geminal methyl groups has decreased to a value of
99°. These two deformations reduce the repulsions between
axial phenyl and axial methyl.

The structure of r-2-(p-bromophenyl)-cis-4,cis-6-dimethyl-
1,3-dioxane (4) was recently reported (Nader, 1975; FIG.4).
The equatorial 4,6-methyl groups cause a slight flattening
of the entire ring in comparison to 1 , and the C-C-Me bond
angles open 4° at the cost of the O-C-Me angles.

The X-ray analysis of r-2-(p-trifluoromethyl-phenyl)-trans-
4,trans-6-dimethyl-1,3-dioxane (5) (Nader, 1975; FIG.5) con-
firms that an axial 2-aryl substituent substantially distorts
the 1,3-dioxane ring geometry. The O-C-O region is flattened
while the torsional angles remain virtually unaffected in the
C-C-C moiety. The phenyl group is bent outward to decrease
its syn-axial interactions with the axial hydrogen atoms at
C-4 and C-6.

Fig. 4

Fig. 5
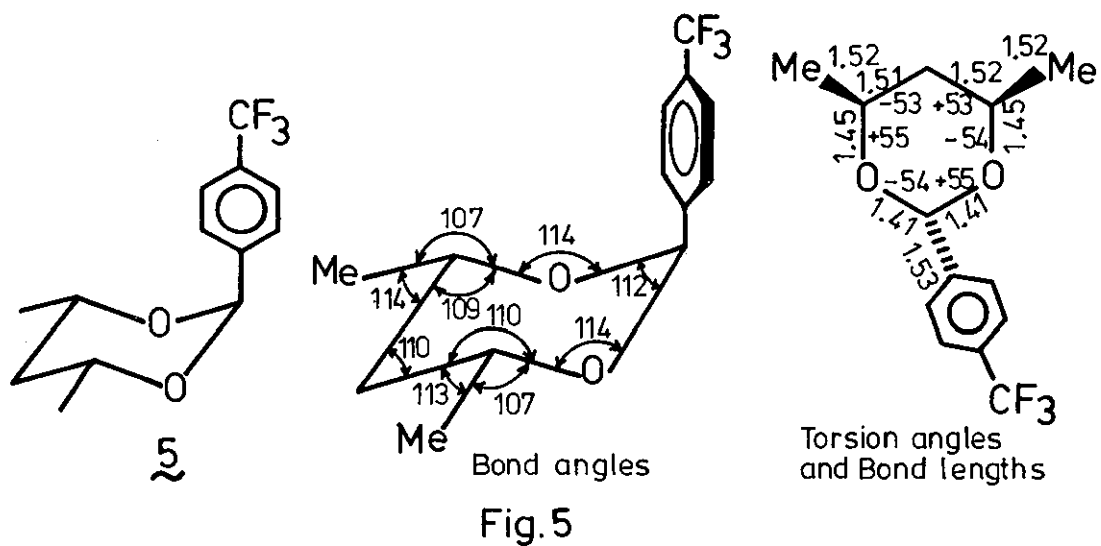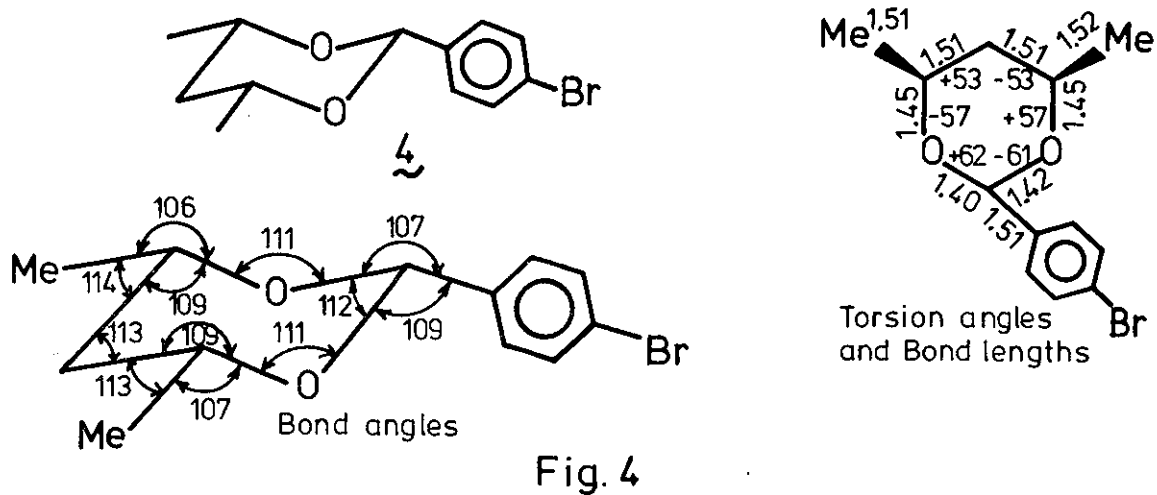
B. Coupling Constants.

In principle, the J(H,H) coupling constants in 1,3-dioxane itself can be extracted from a slow exchange spectrum; in practice, due to the relative complexity of the spin system at conventional field strengths this task is not so simple (Eliel, 1972a). We have run a slow exchange ^{1}H-NMR spectrum of 1,3-dioxane at 300 Mhz (T $\sim$ -90°C), FIG.6. The experimental and calculated spectrum (LAOCOON program) compare well. The NMR parameters are given in TABLE I.

TABLE I. Coupling constants in 1,3-Dioxane (CS_2; -90°C), 2-(p-Cl-phenyl)-1,3-Dioxane (1) (CCl_4, room temperature) and cyclohexane.

	$J_{2e,2a}$	$J_{4e,4a}$	$J_{5e,5a}$	$J_{4e,5e}$	$J_{4a,5e}$	$J_{4e,5a}$	$J_{4a,5a}$
1,3-dioxane	-6.2	-11.8	-13.0	1.2	2.3	4.9	12.4
1 [a]		-11.5	-13.2	1.3	2.6	4.9	12.3
cyclo-hexane [b]	$^2J=-13.05$			2.96		3.65	13.12

a) Buys, Eliel, 1970b;
b) Garbisch, Griffith, 1968.

For purposes of comparison, the coupling constants of 2-(p-Cl-phenyl)-1,3-dioxane (1) (Buys, Eliel, 1970) and of cyclohexane (Garbisch, Griffith, 1968) are included in TABLE 1. The important fact is that the coupling constants in 1 and in 1,3-dioxane are nearly identical. This is compelling evidence for
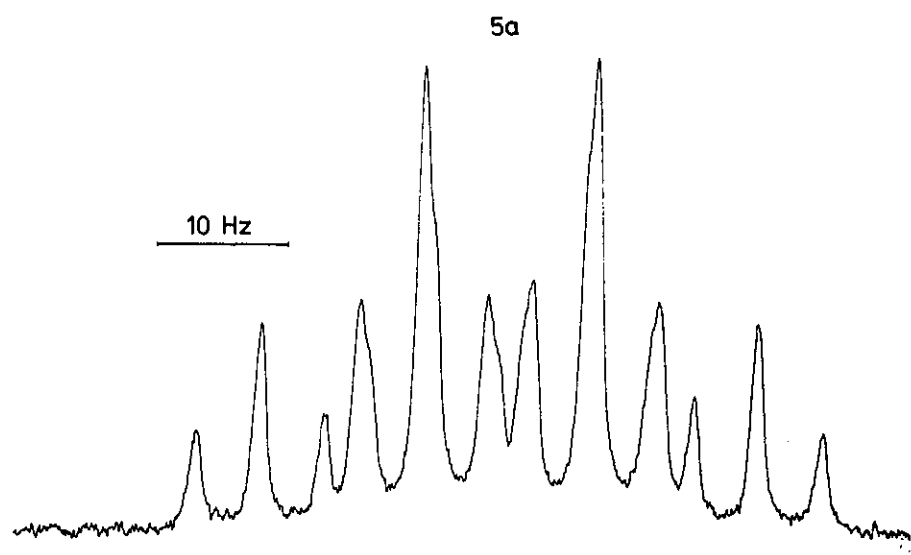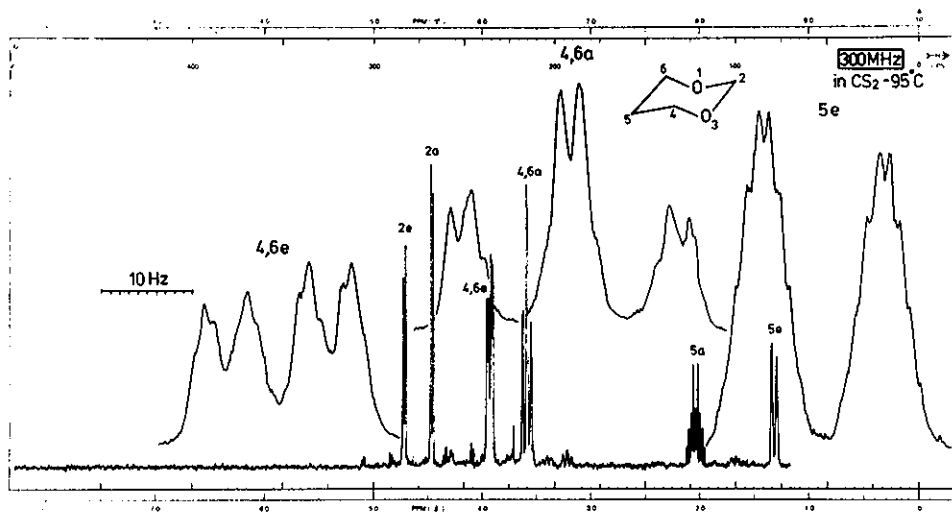
Figure 6

the statement that 2-substitution does not alter the ring sha-
pe of 1,3-dioxane. More indirectly, this had been concluded
(Buys, Eliel, 1970) from the invariantness of the coupling
constants in a series of 2-substituted-1,3-dioxanes (2-Me, 2-
i.Pr, 2-t.Bu, 2-Ph, 2-p-Cl-Ph).

1. Vicinal coupling constants.

We compare first the coupling constants in 1,3-dioxane and cy-
clohexane. The vicinal coupling constants involving H5e are
smaller than would be expected on the basis of the Karplus re-
lation. It has been proposed that these low values originate
from the planar M-mode arrangement of the C5-H5e bond and the
equatorial p-O electron lobe (Anteunis et al., 1966a). This
orientation includes the geometric requirements for the maxi-
mal lowering effect on ^3J by an electronegative substituent X
in a H-C-C-X fragment (Booth, 1965; Williams, Bhacca, 1964;
Karplus, 1963; Bystrov, 1972).
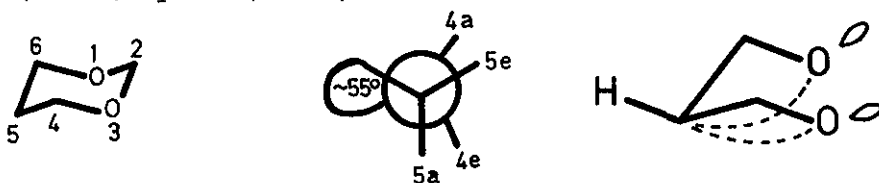
The vicinal coupling constant J(4e,5a) is rather large and
this observation was at the basis of an early suggestion (An-
teunis et al., 1966a) that the ring torsion angle in the ali-
phatic part of 1,3-dioxane was smaller than 60°. It is dif-
ficult to estimate the torsion angle from the vicinal coupling
constants, because their magnitude is influenced by several

factors. It has been attempted rather successfully to eliminate the influence of the electronegative oxygen atom by relating the ratio R of J^{tr}/J^{cis} (Lambert, 1967; Buys, 1969) to the ring torsion angle τ. One obtains the relation:

$$R = (3 - 2\cos^2\tau + 0.1\cos\tau)/(4\cos^2\tau - 0.2\cos\tau)$$

Applied to $\underset{\sim}{1}$, one computes a torsion angle of 55°, in excellent agreement with the X-ray result (Buys and Eliel, 1970).

2. Geminal coupling constants.

The geminal coupling constants increase algebraically in the series $^2J5$, $^2J4$ and $^2J2$. This reflects the influence of the electronegative oxygen atom. It is now well recognized that a main factor, controlling the magnitude of the nuclear spin-spin coupling within a $X-CH_2-Y$ moiety, is the spatial arrangement of the p-electron pairs present in the X and/or Y fragments (Bothner-By, 1965; Anteunis, 1966; Anteunis et al., 1971a; Anteunis et al., 1971b; Cookson, Crabb, 1972). This has been called the "parallelity effect" (Anteunis et al., 1971b). A series of 1,3-dioxanes has been synthesized having various ring shapes, and accordingly different orientations of the oxygen p lobes with respect to the $2-CH_2$ fragment. The values of $^2J2$ in this series span on interval as large as -2.8 to -6.5 Hz (Anteunis et al., 1971b). An empirical relation between ^2J and τ_i (the torsion angles of the line bisecting the H-C-H valence angle and each of the four adjacent p-orbitals) has been derived (Anteunis et al., 1971b):

$$^2J = -14.75 + 4.86 \sum_{i=1}^{4} \sin^2 \tau_i \quad \ast$$

By way of illustration, one can consider the values of $^2J2$ in 1,3-dioxolanes [+1.0 to -1.5 Hz, depending on the flatness of the system (Anteunis et al., 1971c)] in 1,3-dioxanes possessing a 2,5-TB (twist-boat; both ^4_3T or ^3_4T) conformation [-2.8 Hz], those in the chair form [-6.2 Hz], in tetrahydropyranes [-10.5 to -11.5 Hz, O-CH_2 fragment] and finally in cyclohexane [-13.0 Hz]. It might be mentioned that for the obtention of the above given relation, idealized conformational features (e.g. torsion angles of 60°) of the chair forms and idealized (calculated) geometries of non-chair forms of cyclohexane (Bucourt, 1974) were assumed. The empirical relation between $^2J2$ and the orientation of adjacent p-electron lobes could be extended to other heteroatoms such as S, Se. In that case additional parameters, such as electronegativity E_i and bond distances d_i, must be included (Anteunis et al., 1971b).

We turn now to a discussion of the effect of alkyl and aryl substitution on the coupling constants in 1,3-dioxane. Alkyl substitution in the 4 and 5-position has a marked lowering effect on $^3J(a,a)$ up to 1 Hz (Booth, Thurnborrow, 1968; Pihlaja, Äyräs, 1970b), but the effect on the other vicinal coupling constants is small. The $^2J2$ coupling is easily measured because the O-CH_2-O group is well isolated from the

_____

$\ast$ In the original paper (Anteunis et al., 1971b), p.1923, the value of -6.54 instead of -14.57 has erroneously been given.

aliphatic part of the ring, as well with respect to chemical
shift as with respect to spin-spin interproton coupling.
Small but real long-range effects of alkyl (aryl) substitu-
tion in the aliphatic part on ^2J can then conveniently be
obtained. In a series of 4-(p-X-phenyl)-1,3-dioxanes (X =
$N(Me)_2$, H, F, NO_2) a small algebraic decrease of ^2J (-6.2 to
-6.5 Hz) with increasing electronegativity of the substitu-
ent was observed (Swaelens et al., 1970). The effect of
equatorial alkyl groups on ^2J is small. In symmetrical cis-
4,6-dialkyl-1,3-dioxanes (R = Me, Et, i.Pr, t.Bu) the rela-
tion

$$^2J = -6.18 + 0.05 \ \Sigma C_{no}$$

holds, where C_{no} is the total number of C-atoms in the 4,6-
alkyl side chains (Tavernier, 1971). A rather similar ef-
fect is induced by 4,6-axial alkyl groups, and a positive
increment of 0.1 Hz to ^2J for each αC-atom in the alkyl side
chain has been observed (Swaelens et al., 1970). The effect
of axial alkyl groups on $^2J2$ is however more difficult to
isolate than the effect of equatorial groups, due to the oc-
curence of minor amounts of boat form when 4-axial alkyl
groups are present (Anteunis, Swaelens, 1970). Somewhat
puzzling is the rather low value of ^2J (-5.6 to -5.8 Hz) which
is found in 5,5-dialkyl-1,3-dioxanes, especially when one of
the 5-alkylgroups is secondary (Coene, Anteunis, 1970a).

3. Long-range coupling constants.

A host of long-range coupling constants have been uncovered in 1,3-dioxanes (Ramey, Messick, 1965; Delmau, Duplan, 1966; Anteunis et al., 1966a, Anderson, 1967). Some characteristic values are given in TABLE II.

TABLE II. Long-range Couplings in 1,3-Dioxanes (in Hz).

$^4J(2e,4e) \sim 1.5$	$^4J(2e,6a) \sim 0.5$
$^4J(4e,6e) \sim 2.5$	$^4J(2a,6a) < 0.5$
$^5J(2e,5e) \sim 0.9$	$^4J(2a,4e) < 0.4$
	$^4J(4a,6e) \sim 0.5$
	$^4J(4a,6a) \sim 0.5$

The sign of these couplings are not all known. Their values are sensitive to the substitution pattern in the 1,3-dioxane nucleus in a way that is not completely understood. Thus, in 2-methyl-spiro(1,3-dioxane-5,7'-norborn-2'-ene) the 4a,6a coupling is zero but J(4e,6e) is 3.25 Hz, one of the largest values ever encountered (Bernaert et al., 1973). An axial 4-methyl reduces (in absolute value) the coupling J(2e,6e) and J(2e,6a) (Delmau et al., 1968).

4. Vicinal exo-Coupling Constants.

It is known that the greater the strain a group undergoes, the more efficient the vicinal coupling is involving the protons on that group (Jackman, Sternhell, 1969; Samek, 1971;

Anteunis 1971). In olefins and other more sophisticated

structures this strain-enhanced vicinal coupling, although

often small, is extremely useful for structural assignments,

especially when the different isomers are available and the

choice can be made by comparison.

In six membered rings, this phenomenon causes an axial me-

thyl to possess the largest exo-coupling. CHART 1 lists

some data obtained in 1,3-dioxanes and related heterocycles

(Anteunis, 1971; Tavernier, Anteunis, 1971b; Shoppee et al,

1966; Geens et al., 1972). The magnitude of ΔJ, the diffe-

rence of the exo-couplings eq-Me versus ax-Me, is not con-

stant. The difference as expected is small for the 5-Me in

1,3-dioxanes, but sizeable in the 4 position. The same

phenomenon is also known for trifluoromethyl groups; but here

ΔJ is quite large and may be treated quantitatively with res-

pect to conformational descriptions. For 4-trifluoromethyl-

1,3-dioxanes. ΔJ ∿ 3 Hz is observed (Dirinck, Anteunis, 1972).

CHART 1
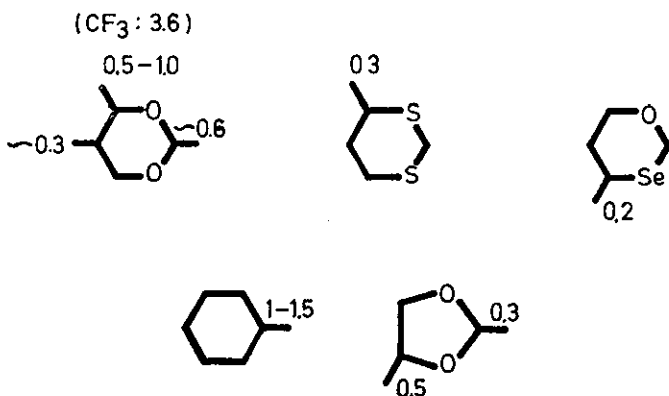
C. Chemical Shifts in 1,3-Dioxane.

The chemical shifts of the ring hydrogen atoms of 1,3-dioxane,
obtained from a low temperature spectrum (CS_2 solution) are :

$$H2e = 4.72\delta \quad H2a = 4.46\delta$$
$$H4e = 3.92\delta \quad H4a = 3.58\delta$$
$$H5e = 1.31\delta \quad H5a = 2.03\delta$$

The remarkable feature is the low field position of H5a com-
pared to its equatorial counterpart (Anteunis et al., 1966a).
The chemical shifts of a large number of alkyl substituted
1,3-dioxanes have been reported (Pihlaya, Äyräs, 1970a; Maroni
et al., 1973; Tavernier, Anteunis, 1974a). The shift effects
on the ring hydrogen atoms which occur on introduction of a
methyl group are given in TABLE III.

TABLE III. Shift Increments in ppm due to a Methyl Group

|	α	βeq	βax	γeq [b]	γax [b]
2 Me eq	$\sim$0	–	–	$\sim$0	$\sim$0
4 Me eq	$\sim$0	$\sim$0	−0.40	$\sim$0	$\sim$0
5 Me eq	$\sim$0	−0.1	−0.40	–	–
2 Me ax	+0.30	–	–		+0.4
4 Me ax	±0.15	−0.1	0.2	−0.2	+0.25
5 Me ax	±0.2[a]	−0.3		–	–

The notation $\sim$0 means that the increments are less than 0.1 ppm, a positive
sign indicates a downfield shift.
(a) Very sensitive to secondary effects
(b) The γ effect of 4-Me on the C-6 and C-2 hydrogen atoms is essentially
    identical, and have been lumped together in a single γ effect.

The shift increments associated with methyl substitution in
1,3-dioxane parallel closely those found in cyclohexane. An
exception though is the negligible α (geminal) effect of equa-
torial methyl. In cyclohexane, the α-effect of an equatorial
methyl is a downfield one, by +0.15 ppm (Danneels, Anteunis,
1975).

The effect of alkyl groups other than methyl has also been
studied, especially in the case of 4-substitution. An amu-
sing linear regression was calculated between $\delta(2e \rightarrow 2a)$ (the
chemical shift difference between H2e and H2a) and ΣC_{no} (Ta-
vernier, Anteunis, 1966) e.g., $\delta(2e \rightarrow 2a) = 17.9 + 1.17 \ \Sigma C_{no}$
(in Hz at 56.4 Mhz). The α-effect of alkyl groups depends
strongly on the conformation that the alkyl group itself can
assume. These gross-effects, with the conformational beha-
viour in mind, may be predicted with reasonable accuracy, as
a summation of effects caused by the first and the further
removed elements in the side chain (Anteunis, Danneels, 1975).
A reasonable approximation of the conformations of the alkyl
group with respect to the 1,3-dioxane nucleus can be obtained
from the exo coupling constants (Tavernier, Anteunis 1971b).
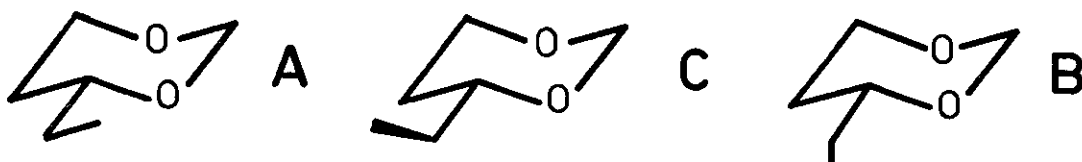
Thus, an anti C-C bond orientation produces a downfield shift

(B) but a gauche orientation (A and C) an upfield shift. (Ta-
vernier, Anteunis, 1974).

D. Microwave Spectra and Electron Diffraction.

The electron diffraction curve of gaseous 1,3-dioxane (Schultz,
Hargittai, 1974) does not lead to a unique determination of
its molecular geometry. However, in conjunction with initial
parameters used in the study of the microwave spectra of 1,3-
dioxane (Pickett, Strauss, 1970; Kewley, 1972) the following
parameters were obtained using a least-squares treatment (chair
form):

r(O1-C2)Å	1.393	O-C-O	115.0°
r(O1-C6)Å	1.439	C-O-C	110.9°
r(C-C) Å	1.528	O-C-C	109.2°
r(C-H) Å	1.095	C-C-C	107.7°

III. Conformational energies of substituents in 1,3-dioxane.

A. Methodology.

Two approaches have mainly been used for the determination of
the conformational preferences of substituents in 1,3-dioxane.

In the chemical approach, a diastereomer equilibrium,
supposed to reflect exactly a conformer equilibrium, is esta-
blished and analyzed. This method demands an epimerizable
center. As 1,3-dioxanes are acetals, a configurational equi-

librium at C-2 is easily established at moderate temperatures
by (Lewis)acids.
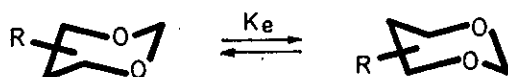
B1 = some blocking or anancomerizing group
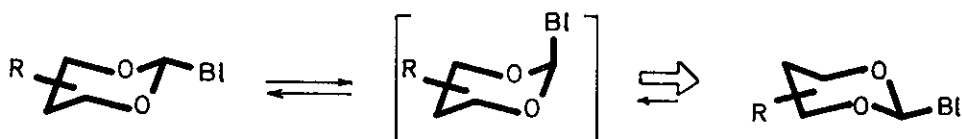
A modification is the study of a 4-component equilibrium (Eli-
el et al., 1974).

In the NMR-method, the conformational equilibrium is as-
sayed using shift and coupling parameters, often with recour-
se to slow exchange spectra where a direct integration is pos-
sible of appropriate signals originating from the different
conformers.

Other methods (acoustic relaxation, calorimetry etc.)
have also been used succesfully, but it must be said that the
two first mentioned methods are the most commonly employed.
The chemical approach and the NMR methods both have their ad-
vantages and draw-backs.

In the chemical approach, the two diastereomers must be
synthesized. The equilibrium should be approached from both
sides, making sure that not too many concomitant side pro-

ducts are formed. The analysis of the equilibrium mixture is usually done by G.C.. Reproducibility and accuracy are difficult to achieve. Even "on-column" injections of samples can result in misleading determinations, and it was found at these laboratories (Swaelens, 1970; Bhatti, 1973) that injection of standard mixtures of isomers fails to reproduce their relative composition. One of the reasons might be a residual and preferential adsorption of isomers, as denounced after steam-washing the used columns. Still, the "on-column" injection technique using capillary (open) columns is the best one. It remains however a precarious task to extract $\Delta H°$ and $\Delta S°$ values from a study of the equilibrium at different temperatures.

The NMR methods give a rapid access to equilibrium data at different temperatures. The best procedure undoubtedly makes use of wisely chosen model compounds in order to obtain the temperature dependence of the selected NMR parameters (Jensen, Beck, 1968; Borremans, Anteunis, 1975). If slow exchange spectra of the conformational mixture are available, equilibrium data obtained from spectra under rapid exchange conditions should at least be extrapolated and checked against the composition, determined by direct integration. Again, the determination of $\Delta H°$ and $\Delta S°$ remains a risky task. $\Delta H°$ and $\Delta S°$ values reported in the literature should in general be considered with the greatest care. Often the best one can do in comparing different cases, is to discuss $\Delta G°$ values obtained at comparable temperatures.

Conformational equilibria are most accurately obtained
on compounds for which the ratio of the conformer concentra-
tion is about unity. Therefore, as a rule, we used di- or
polysubstituted derivatives, and conformational preferences
of the different substituents are weighed against each other.
We call this the "counterpoise" technique, where a substitu-
ent is pitted against an other one, e.g. methyl.
The problem of "additivity" then arises, that is: in how far
is the stability of a polysubstituted derivative really des-
cribed by an exact summation of the individual contributions
to strain? Additivity must certainly be violated in the ca-
ses of geminal and vicinal substitution. More secured are
the cases of structure with remote substitution, as e.g. 2,4-,
or 4,6-disubstituted derivatives. On the other hand, devia-
tions from additivity may disclose mutual interaction effects,
or changes in molecular shape.

B. Results.

1. Alkyl and Aryl substitution.

In TABLE IV the A-values reported in the literature are col-
lected. The conformational preference of a substituent de-
pends on the site of substitution. For methyl, the order of
equatorial preference is C-5 < C-4 < C-2, a logical result of
increasing 1,3-diaxial strain, taking into consideration the
shorter bond length of C-O (1.45 Å) as compared with C-C
(1.54 Å). It is striking that naive ideas sometimes work very

well. Thus the A-value of 4-methyl would be expected to be
half the strain of 2-methyl (4/2 kcal.mole^{-1}) augmented with
an additional Φ_1-butane strain (0.8 kcal.mole^{-1}) resulting
in exactly the experimental value of 2.8 kcal.mole^{-1}. Simi-
larly, the A-value (0.8 kcal.mole^{-1}) of 5-methyl was predic-
ted from the A value of methoxyl(0.6 kcal.mole^{-1}) in cyclo-
hexane (Anteunis et al., 1966b; Riddell, Robinson, 1967). A
lot of A-values for 2-substituents were determined by equili-
bration of the isomeric 2-substituted-cis-4,6-dimethyl-1,3-
dioxanes. It has been demonstrated (Eliel et al., 1974) that
the equatorial 4,6-dimethyl groups buttress the outwards ben-
ding of the 4,6-axial hydrogen atoms under the strain caused
by the 2-axial substituent. It follows that these A-values
may be somewhat overestimated.

The A-values of simple alkyl groups are not seriously in-
fluenced by the solvent, and the slight dependence actually
observed is presumably a result of steric hindrance to solva-
tion (Eliel, Raileanu, 1970).

The relative order of the A-values of methyl and phenyl
is interesting. In 5-position, the A-value of phenyl is lar-
ger, ($\Delta A = -0.3$), in 2-position it is smaller than for methyl
($\Delta A = 1.0$), and for the 4-position an in-between situation is
met ($\Delta A = -0.1$ kcal.mole^{-1}) (Feeney et al., 1968; Anteunis et
al., 1973).

TABLE IV. ΔG°-values in alkyl- and aryl-substituted 1,3-Dioxanes (kcal.mole^{-1}). Positive value means equatorial preference for the substituent.

Group 5-Substitution. Substituent	ΔG° kcal.mole^{-1}	METHOD	TEMP (K)	SOLVENT or STATE	REFERENCES
5-Me	0.89 0.87	Eqb.	303	CHCl$_3$ 5CF$_3$COOH)	c
	0.81	Eqb.	—	—	a
	0.80	Eqb.	298	ether BF$_3$O(Et)$_2$	b
	0.83	NMR-4 NMR-6	298	CCl$_4$	e
	0.80	NMR-6	298	CCl$_3$F	d
5-Et	0.81 0.75	Eqb.	303	CHCl$_3$	c
	0.67	Eqb.	298	ether	b
5-i.Pr	1.10 1.05	Eqb.	303	CHCl$_3$	c
	0.98	Eqb.	298	ether	b
5-t.Bu	1.7	Eqb.	303	CHCl$_3$	c
	1.36	Eqb.	298	ether	b
	1.37	Eqb.	298	c.hexane	
	1.53	Eqb.	"	CCl$_4$	
	1.52	"	"	ØH	
	1.47	"	"	ether	
	1.57	"	"	DME	
	1.66	"	"	NO$_2$B	f
	1.73	"	"	acetonitrile	
	1.78	"	"	CHCl$_3$	
	1.62	"	"	MeOH	
	1.59	"	"	t.BuOH	
	∿1.85	"	"	Ac OH	
	∿1.97	"	"	formic acid	
5-Ph	1.03	Eqb.		ether	b

Table IV (Continued).

4-Substitution..

4-Me	2.9	Eqb.	298	ether	b
	2.8(ΔH)	Thermo			g
	2.52(ΔH)	Acoustic	RT		h
	3.4(ΔH)	Appearance Potential in MS		gas	j
	2.97	Inferred from eqb.in bicyclic systems	RT		k
	2.95	Ind. Eqb.	303	BuLi/ N(Et)$_3$	i
4-Et	A(Me) + 0.1	NMR-4	303	CS$_2$	i
4-n.Pr	A(Me) + 0.05	"	"	"	i
4-i.Bu	A(Me) + 0.05	"	"	"	i
4-neoPe	A(Me)	"	"	"	i
4-i.Pr	A(Me) + 0.65	"	"	"	i
	A(Me) + 0.5	"	RT	CCl$_4$	l
4-c.Hex	A(Me) + 0.55	"	303	CS$_2$	i
4-Ph	2.85	Ind. Eqb.	RT	BuLi/ N(ET)$_3$	i
	5.3(ΔH)	Acoustic	RT		h
4-vinyl	A(Me)-0.7	Eqb.	303		m

2-Substitution.

2-Me	4.07(ΔH)	Thermo			g
	3.98	Eqb.	298	ether	n
	3.8 (ΔH)	App. potential in MS		gas	j
2-Et	4.04	Eqb.	298	ether	n
2-i.Pr	4.17	eqb.	298	ether	n
2-Ph	3.12	Eqb.	298	ether	n

a. Pihlaja, 1967; b. Eliel, Knoeber, 1968; c. Riddell, Robinson ,1967;
d. Pihlaja, Ayräs, 1969; e. Delmau et al., 1968; f. Eliel, Raileanu;
g. Pihlaja, Luoma; h. Hamblin et al., 1969; i. Anteunis et al., 1973a;
j. Pihlaja, Jalonen, 1971; k. Anteunis, 1970; l. Maroni et al., 1972 ;
m. Anteunis, Coryn, 1973; n. Nader, Eliel, 1970.

Methods as indicated in TABLE IV.

Eqb.	Equilibrium method
Ind. Eqb.	Indirect equilibrium method
NMR-1	Proton chemical shift using reference substances
NMR-2	Chemical shift method using slow exchange spectrum as reference
NMR-3	Proton measurements utilizing areas under peaks measured at low temperatures
NMR-4	Average coupling constants using reference compounds
NMR-5	Chemical shift, extrapolated without reference substance
NMR-6	Average coupling constants using low temperature method
NMR-9	Low temperature parameters with correction for temperature dependency of these parameters obtained from reference compounds
Thermo	Thermochemical method
Acoustic	Acoustic method

As in cyclohexane, the A-values of 2-ethyl and 4-ethyl are somewhat larger than the A-value of methyl, but in the 5-position ethyl has a smaller conformational preference than methyl. The reasons for these peculiarities are not quite clear. In 4-position, the order of A-values $\underline{i}$.Pr > Et > $\underline{n}$.Pr ∿ $\underline{i}$.Bu ∿ $\underline{neo}$Pe ∿ Me was found by an NMR counterpoise technique. The neopentyl group represents a special case, in that there is net tendency for this group to bend outwards, with a concomitant opening of the C_4-CH_2-$\underline{t}$.Bu angle (Tavernier, Anteunis, 1971b).

The conformational equilibria in 2,2-geminal substituted 1,3-dioxanes were investigated by the equilibration method (using a 4-methyl substituent as a holding group) and by an NMR method (using also 4-methyl-substituted derivatives as a

model)(Pihlaja, Äyräs, 1970c; Bailey, Eliel, 1974). The data are collected in TABLE V.
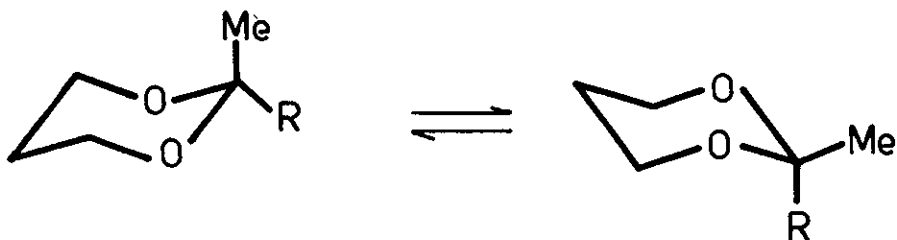
The free energy differences for these equilibria were calculated from the individual A-values of the alkyl groups, and from gauche interactions.

TABLE V. Conformational Preferences in 2-methyl, -2-R-1,3-dioxanes (kcal.mole^{-1}). Positive sign means preference of R group for the equatorial position.

R	ΔG°_{303} [a]	ΔG°_{300}		ΔG°calc. [a,b]
Et	0.41	0.29[b]	0.32[c]	0.41
n.Pr	0.30			
Bu	0.44			
i.Bu	0.40	0.47[a]		
i.Pr	0.61	0.56[a]	0.63[c]	0.96
sec. Bu	0.48			
Ph			2.42[c]	~0.86

a. Pihlaja, Äyräs, 1970c; NMR-1 CCl$_4$.
b. Pihlaja, Äyräs, 1970c; dir. Eqb.
c. Bailey, Eliel, 1974.

The experimental and calculated free energy differences are
in reasonably good agreement for methyl, ethyl and methyl,
isopropyl. However, 2-phenyl prefers the axial position by
a much larger amount than would be expected assuming additi-
vity of A-values. Similar conclusions are reached from a
study of 2,2,5-trialkyl-1,3-dioxanes (Gren et al., 1973).

Conformational equilibria in 5,5-dialkyl-1,3-dioxanes
were studied using an NMR technique (Coene, Anteunis, 1970a;
Anteunis et al., 1974a) and by the equilibration approach
(Eliel, Enanoza, 1972).

The A-values for 5-mono substitution are not known for every
substituent that has been built into the 5,5-gem. grouping.
However, in those instances where these A-values are known it
appears that by geminal substitution the larger substituent
is less favoured than would be expected from the additivity
principle and a consideration of additional non-bonded strain.
An additivity of some sort is seen in the case of 5-methyl-
5-ethyl-1,3-dioxane: ethyl prefers somewhat the axial posi-
tion over methyl, as is the case for 5-monosubstitution. This
same trend is also observed in going from 5-methyl - 5-phenyl-
to 5-ethyl - 5-phenyl-1,3-dioxane (the result from the NMR me-

thod is in this case not in agreement with the equilibration
result; Eliel, Enanoza, 1972; Tavernier, Anteunis, 1975).
The 5,5-gem. grouping methyl,phenyl shows a preference of
phenyl for the axial position - additivity is qualitatively
followed -, but we saw that for 2,2-substitution the phenyl
group markedly prefers the axial position (or the situation
opposite to the one expected). It is surprising that in 5-
methyl,5-vinyl-, and 5-methyl,5-ethynyl-1,3-dioxane the .unsa-
turated groups $-CH=CH_2$ and $-C\equiv CH$ prefer the equatorial posi-
tion over methyl (Anteunis et al., 1974a) in carbon disul-
phide (apolar) and acetone (polar) solution, whereas in the
slightly polar solvent dichloromonofluoromethane both unsa-
turated groups prefer the axial position. Special solvent
effects are possibly responsible for these observations.

There are also equilibrium data on record for tri-, and
tetra-substituted-1,3-dioxanes.
In 4,4,5-trimethyl-1,3-dioxane (6) the conformer with equato-
rial 5-methyl is favoured ($\Delta G^{\circ}_{300} = 1.5$ kcal.mole^{-1} CCl_4, NMR-4,

Delmau et al., 1968; $\Delta G^{\circ}_{298} = 1.45$ kcal.mole^{-1} from equilibra-
tion, Pihlaja, Äyräs, 1969). One would naively have expected
a free energy difference of zero, because the conformer with
equatorial methyl is strained by two ϕ_1-butane interactions

(2 x 0.8 kcal.mole^{-1}). It was proposed that the destabiliza-
tion of axial methyl results from a "reflex effect" associa-
ted with the presence of an axial 4-methyl (Delmau et al.,
1968). The free energy difference of the conformers of trans-
4,5,6-trimethyl-1,3-dioxane (7) is 0.6 kcal.mole^{-1} (Pihlaja,
Äyräs, 1969) from equilibrium and NMR-data, the conformer with
equatorial 5-methyl being again the more stable one. The re-
luctance for the axial position is however much less than in 6.
Probably the outward bending of the axial 4-methyl is more re-
sisted to by the gem.Me in 6 than by the gem.hydrogen in 7.
This entails a greater destabilization of axial 5-methyl in
the former.

There are few data for 4,5-disubstituted 1,3-dioxanes.
The NMR spectrum of cis-4,5-dimethyl-1,3-dioxane does not dis-
close an undue preference for the conformer with equatorial
5-Me. Anteunis, Coryn (1973) investigated the equilibrium in
cis-4-vinyl,5-methyl-1,3-dioxane (NMR) and found ΔG^{o}_{298} = 1.50
kcal.mole^{-1}. The A-values of 4-vinyl and 5-methyl are 2.2$_5$
and 0.8 respectively, and there is then in this case no depar-
ture from additivity.

A number of trans-4,5,5-trimethyl-6-alkyl-1,3-dioxanes
(alkyl = etyl, n.propyl, isobutyl, neopentyl, isopropyl, phe-
nyl) were examined by ^{1}H-NMR spectroscopy under slow exchange
conditions. (Tavernier, Anteunis, 1973). The data are given
in TABLE VI.

TABLE VI: ΔG°_{186} in $\underline{trans}$-4,5,5-trimethyl-6-R-1,3-Dioxanes (CS_2 sol) in kcal.mole^{-1}.

R	Et	$\underline{n}$.Pr	$\underline{i}$.Pr	$\underline{i}$.Bu	$\underline{neo}$Pe	Ph
ΔG°_{186}	0.07	0.08	0.67	0.0	0.51	>1

ΔG° positive if R prefers the equatorial position.

ΔG° obtained either by integration of appropriate resonances in the slow exchange spectrum or by extrapolation of fast exchange parameters to low temperatures.

In general, the ΔG°-values are not very different from what would be expected from the earlier data of "isolated" alkyl groups (TABLE IV), despite possible changes in molecular shape or neighbourhood interactions that must be involved. Serious departures are neopentyl and, as expected, phenyl. The neopentyl group is "heavier" in the present environment, because the tendency to relieve strain by an "outward-backward" bonding is hindered by the additional 5-substitution. Phenyl substitution deserves further attention. The electronic spectrum of $\underline{trans}$- and $\underline{cis}$-4,5,5-trimethyl-6-phenyl-1,3-dioxane is almost identical (λ_{max} at 262, 255, 249 nm) but discloses changes with respect to $\underline{cis}$ 4-methyl, 6-phenyl-1,3-dioxane (λ_{max} 220-270, 233 nm).
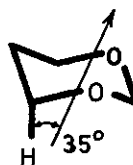
2. Polar substitution.

1,3-dioxane has a dipole moment of 2.13 D in benzene (Walker, Davidson, 1959). The dipole moment of polar substituted derivatives can yield conformational information (comparison of experimental and calculated dipole moments). It is therefore of interest to know the direction of the dipole moment in 1,3-dioxane itself. Two approaches leading to almost equivalent results are feasible:

(i) neglecting the C-H contributions and adopting a value of 1.22 (Exner e.a., 1968) or 1.32 D (Bailey, Eliel, 1974) for the C-O bond;

(ii) taking a C-H contribution of 0.3 D and a C-O contribution of 0.9 D (Danneels, Anteunis, 1975), that is, the accepted value for open chain ethers (Smyth, 1937). This gives a calculated dipole moment of 2.1 D. The dipole moment lies in the symmetry plane and makes an angle of 35° with the axial protons on C4,6. When dealing with idealized hexanoïd chair forms, a simplified calculation method has recently been published (Borremans, Anteunis, 1975).

TABLE VII gathers the data reported for polar substituted 1,3-dioxanes.

TABLE VII ΔG° values (kcal.mole^{-1}) in Polar Substituted 1,3-Dioxanes. Positive ΔG-value means equatorial preference for polar substituent.

SUBSTITUENT	ΔG°-value kcal/mole	METHOD	TEMP (°C)	SOLVENT OR STATE	REFERENCES
5-F	-0.36	Eqb.	25	CCl$_4$	a
	-0.605	Eqb.	25	MeOH	b
	-0.62	Eqb.	25	Ether	b
	-0.78	NMR-F-1	RT(?)	CCl$_3$F	c
	-0.83	Eqb.	25	ΦH	b
	-0.87	Eqb.	25	CHCl$_3$	a
	-1.22	Eqb.	25	MeCN	b
5-Cl	+1.40	Eqb.	25	CCl$_4$	a
	+1.20	Eqb.	25	Ether	b
	+0.89	Eqb.	25	ΦH	a
	+0.94	Eqb.	25	CHCl$_3$	a
	+0.25	Eqb.	25	MeCN	a
	+1.1	DM	25	CCl$_4$	d
	+1.3	NMR	RT(?)	CCl$_4$(J)	d
5-Cl-5-Me	+0.05	NMR-9	-28	CHFCl$_2$	e
	-0.50	NMR-3	-88	CHFCl$_2$	e
5-Br	+1.71	Eqb.	25	CCl$_4$	a
	+1.45	Eqb.	25	Ether	a
	+1.17	Eqb.	25	ΦH	a
	+1.35	Eqb.	25	CHCl$_3$	a
	+0.68	Eqb.	25	MeCN	a
5-Br-5-Me	+0.18	NMR-9	-28	CHFCl$_2$	e
	-0.32	NMR-3	-88	CHFCl$_2$	e
5-I-5-Me	+0.25	NMR-9	-28	CHFCl$_2$	e
	-0.10	NMR-3	-88	CHFCl$_2$	e
5-OH	-0.86	Eqb.	80	c.Hex 0.1 M	f
	-0.91	Eqb.	25	CHCl$_3$	f
	+0.41	Eqb.	25	Ether	f
	+0.71	Eqb.	25	i-BrOH	f
5-OH-5-Me	-0.41	Eqb.	25	Ether	g
	-1.74	Eqb.	25	CHCl$_3$	g
	+0.09	Eqb.	25	i-PrOH	g
	-0.60	Eqb.	25	MeCN	g
	-0.18	Eqb.	25	DME.	g
5-OCH$_3$	+1.06	Eqb.	25(?)	Hex	h
	+0.59	Eqb.	25(?)	ΦH	h,i
	+0.83	Eqb.	25(?)	Ether	h,i
	+0.16	Eqb.	25(?)	CHCl$_3$	h,i
	+0.01	Eqb.	25(?)	MeCN	h,i

5-OCH$_2$CH$_3$	+1.24	Eqb.	25(?)	Hex	h,i
	+0.82	Eqb.	25(?)	ΦH	h,i
	+1.05	Eqb.	25(?)	Ether	h,i
	0.51	Eqb.	25(?)	CHCl$_3$	h,i
	0.19	Eqb.	25(?)	MeCN	h,i
5-OCH$_3$-5-Me	0.34	Eqb.	25	Ether	g
	~0.10	Eqb.	25	CHCl$_3$	g
	-0.39	Eqb.	25	MeOH	g
	-0.12	Eqb.	25	MeCN	g
5-OAc	0	Eqb.	25	Ether	b
5-NH$_2$-5-Me	-0.16	NMR-5	extrapolat. to 25	aceton	j
5-N(Me)$_2$-	+0.75 ± 0.07	NMR-9	~6	CHFCl$_2$	k
	+0.64 ± 0.01	NMR-9	-40	CHFCl$_2$	k
5-NH$_3^\oplus$	-3.14	Eqb.	RT	CHCl$_3$-TFA	l
5-NH(CH$_3$)$_2^\oplus$	<~2	Eqb.	RT	ΦCN-TFA	l
5-N(CH$_3$)$_3^\oplus$	~2.01	Eqb.	RT	CHCl$_2$COOH	l
5-NO$_2$	-0.38	Eqb.	30	CCl$_4$	b
	-0.63	Eqb.	30	CHCl$_3$	b
	-0.81	Eqb.	30	CH$_2$Cl$_2$	b
	-0.89	Eqb.	30	CDCl$_3$	b
5-NO$_2$-5-Me	-0.43	Eqb.	25	CCl$_4$	g
	-0.62	Eqb.	25	Ether	g
	~0.89	Eqb.	25	CHCl$_3$	g
	-1.17	Eqb.	25	CH$_2$Cl$_2$	g
5-SMe	1.82 ± 0.01	Eqb.	26.5	c.Hex	m
	1.74 ± 0.02	Eqb.	26.5	CCl$_4$	m
	1.73 ± 0.02	Eqb.	26.5	Ether	m
	1.55 ± 0.01	Eqb.	26.5	ΦH	m
	1.13 ± 0.02	Eqb.	26.5	MeCN	m
5-S(CH$_3$)$_2^\oplus$	1.20	Eqb.	RT	CHCl$_2$COOH	b
	0.90	Eqb.	RT	CF$_3$COOH	b
	< -2.0	Eqb.	RT	CHCl$_2$COOH-CF$_3$COOH	b
5-SOMe	~ca. 0.60	Eqb.	54	CCl$_4$	m
	-0.82 ± 0.11	Eqb.	54	CHCl$_3$	m
	-0.74 ± 0.07	Eqb.	54	ΦH	m
	-0.86 ± 0.09	Eqb.	54	MeCN	m
5-SO$_2$Me	-1.16 ± 0.10	Eqb.	50	c.Hex	m
	-1.19 ± 0.10	Eqb.	50	CHCl$_3$	m
	-1.07 ± 0.09	Eqb.	50	ΦH	m
	~ca. 0.90	Eqb.	50	MeCN	m
5-CH$_2$OH	+0.03 ± 0.04	Eqb.	25	Ether (0.2 M)	g
	~0.27	Eqb.	27	CCl$_4$ (")	b
	-0.16 ± 0.04	Eqb.	25	CHCl$_3$ (")	g
	+0.11 ± 0.04	Eqb.	25	DME (")	g
	+0.03 ± 0.04	Eqb.	25	MeOH (")	g
	+0.12 ± 0.04	Eqb.	25	MeCN (")	g

5-CH$_2$OH-5-Me	-1.03 ± 0.04	Eqb.	25	CCl$_4$	g
	-0.68 ± 0.03	"	25	Ether	g
	-0.98 ± 0.03	"	25	CHCl$_3$	g
	-0.55 ± 0.02	"	25	DME	g
	-0.57 ± 0.02	"	25	MeOH	g
	-0.62 ± 0.02	"	25	MeCN	g
5-CH$_2$OCH$_3$	+0.05	"	30	Ether	b
5-CH$_2$OCH$_3$-5-Me	-0.73 ± 0.03	"	25	CCl$_4$	g
	-0.63 ± 0.03	"	25	Ether	g
	-0.61 ± 0.03	"	25	DME	g
	-0.69 ± 0.03	"	25	CHCl$_3$	g
	-0.66 ± 0.02	"	25	MeOH	g
5-CH$_2$F	-0.20 ± 0.01	NMR-9	-40	CHFCl$_2$	n
	-0.23 ± 0.04	NMR-F	RT	CS$_2$	n
	-0.12 ± 0.04	NMR-F	RT	CDCl$_3$	n
	-0.09 ± 0.04	NMR-F	RT	Acet.-d$_6$	n
	-0.0 ± 0.04	NMR-F	RT	CD$_3$CN	n
	+0.05 ± 0.04	NMR-F	RT	DMSO-d$_6$	n
	+0.06 ± 0.04	NMR-F	RT	D$_2$O	n
5-CH$_2$F-5-Me	-1.20 ± 0.05	NMR-3	-95	CHFCl$_2$	o
	-1.00 ± 0.05	NMR-5	-40	CHFCl$_2$	o
5-CH$_2$Cl	-0.18 ± 0.005	NMR-9	-40	CHFCl$_2$	n
5-CH$_2$Cl-5-Me	-1.20 ± 0.05	NMR-3	-95	CHFCl$_2$	o
	-1.20 ± 0.10	NMR-3	-95	CS$_2$	o
	-1.09 ± 0.03	NMR-9	-40	CHFCl$_2$	o
	-1.11 ± 0.03	NMR-9	-40	CS$_2$	o
5-CH$_2$Br	-0.085 ± 0.012	NMR-9	-40	CHFCl$_2$	n
5-CH$_2$Br-5-Me	-1.00 ± 0.05	NMR-3	-95	CHFCl$_2$	o
	-1.00 ± 0.05	NMR-3	-95	CS$_2$	o
	-0.99 ± 0.04	NMR-5	-40	CHFCl$_2$	o
	-0.99 ± 0.04	NMR-5	-40	CS$_2$	o
5-CH$_2$I	+0.11 ± 0.01	NMR-9	-40	CHFCl$_2$	n
5-CH$_2$I-5-Me	-0.85 ± 0.05	NMR-3	-95	CHFCl$_2$	o
	-0.85 ± 0.05	NMR-3	-95	CS$_2$	o
	-0.85 ± 0.04	NMR-5	-40	CHFCl$_2$	o
	-0.85 ± 0.04	NMR-5	-40	CS$_2$	o
5-CH$_2$F-5-CH$_2$Cl	-0.07 ± 0.01	NMR-9	-40	CHFCl$_2$	n
5-CH$_2$F-5-CH$_2$Br	-0.19 ± 0.01	NMR-9	-40	CHFCl$_2$	n
5-CH$_2$F-5-CH$_2$I	-0.375 ± 0.005	NMR-9	-40	CHFCl$_2$	n
5-CH$_2$Cl-5-CH$_2$Br	-0.110 ± 0.005	NMR-9	-40	CHFCl$_2$	n
	-0.115 ± 0.005	NMR-9	-40	CS$_2$	n
5-CH$_2$Cl-5-CH$_2$I	-0.33 ± 0.01	NMR-9	-40	CHFCl$_2$	n
	-0.35 ± 0.01	NMR-9	-40	CS$_2$	n
5-CH$_2$Br-5-CH$_2$I	-0.22 ± 0.015	NMR-9	-40	CHFCl$_2$	n

$5-CHF_2-5-Me$	1.87	NMR-1	RT	$CHFCl_2$	p
	1.69	NMR-1	RT	CS_2	n
$5-CF_3$	0.23 ± 0.05	NMR-3	-105	$CHFCl_2$	o
	0.44 ± 0.03	NMR-2	-60	$CHFCl_2$	o
	0.60 ± 0.03	NMR-2	-20	$CHFCl_2$	o
$5-Ac-5-Me$	-1.1	NMR-5	27	CS_2	q
$5-Ac$	0.53	Eqb.	25	Ether	r
	0.28	Eqb.	25	MeCN	r
$5-COOMe$	0.82	Eqb.	30	Ether	r
	0.22	Eqb.	27	MeCN	r
$5-COOMe-5-Me$	-0.09 ± 0.05	Eqb.	25	Ether	g
	-0.63 ± 0.03	Eqb.	25	MeCN	g
$5-CN$	$+0.21$	Eqb.	30	Ether	b
	-0.55	Eqb.	30	MeCN	b

6-Me-trans

$4-CF_3$	-0.60	Eqb.	20	CS_2	p
$4-CHF_2$	-0.204	Eqb.	-33	CS_2	p
	-0.254	Eqb.	+2	CS_2	p
	-0.290	Eqb.	+33	CS_2	p
	-0.320	Eqb.	+53	CS_2	p
$4-CH_2F$	-0.023	Eqb.	-33	CS_2	p
	-0.058	Eqb.	+2	CS_2	p
	-0.094	Eqb.	+33	CS_2	p
	-0.114	Eqb.	+53	CS_2	p

4,6-diMe

$2-OCH_3$	-0.4	Eqb.	RT(?)	Ether?	r
$2-C_6H_5$	2.86 ± 0.02	Eqb.	25	Hex	s
	3.08 ± 0.02	Eqb.	25	ΦH	s
	3.12 ± 0.02	Eqb.	25	Ether	s
	3.40 ± 0.04	Eqb.	25	MeCN	s
$2-\emptyset-CF_3C_6H_4$	3.08 ± 0.02	Eqb.	25	Hex	s
	3.14 ± 0.04	Eqb.	25	CCl_4	s
	3.16 ± 0.02	Eqb.	25	Ether	t
	3.29 ± 0.03	Eqb.	25	MeCN	u
$2-C\equiv CH$	-0.21 ± 0.02	Eqb.	25	CCl_4	u
	-0.06 ± 0.03	Eqb.	25	Ether	u
	$+0.94 \pm 0.03$	Eqb.	25	MeCN	u
$2-vinyl$					
$2-C\equiv C-C_6H_5$	-0.315 ± 0.03	Eqb.	25	CCl_4	u
	0.00 ± 0.02	Eqb.	25	Ether	u
	$+0.59 \pm 0.01$	Eqb.	25	MeCN	u
$2-CH_2Cl$	-4.19 ± 0.06	Eqb.	25	Ether	u

2-CH$_2$Cl-2-Me	+0.009 ± 0.004	Eqb.	25	c.Hex	u
	-0.058 ± 0.006	Eqb.	25	Ether	u
	-0.108 ± 0.007	Eqb.	25	MeCN	u
	-0.17 ± 0.03	Eqb.	25	MeOH	u
2-CH$_2$Br-2-Me	-0.111 ± 0.004	Eqb.	25	c.Hex	u
	-0.159 ± 0.004	Eqb.	25	Ether	u
	-0.22 ± 0.01	Eqb.	25	Me CN	u
2-COOMe-2-Me	-3.16 ± 0.04	Eqb.	25	c.Hex	u
	-3.0 ± 0.2	Eqb.	25	Ether	u
	-3.94 ± 0.06	Eqb.	25	MeCN	u
5-CH=CH$_2$-5-Me	0.26	NMR-3	-73	CS$_2$	v
	0.22	NMR-3	-73	Acet-d-$_6$	v
	-0.04	NMR-3	-73	CHFCl$_2$	v
5-C≡CH-5-Me	0.23	NMR-3	-73	Acet-d-$_6$	v
	-0.55	NMR-3	-73	CHFCl$_2$	v

4-Me

a. Abraham et.al., 1972; b. Eliel, Kaloustian, 1970; c. Mager, Eliel, 1973;

d. Verhit, et.al., 1973; e. Borremans, 1975; f. Eliel, (PAC), 1971;

g. Eliel, Enanoza, 1972; h,i. Eliel, Hofer, 1973; j. Coene, Anteunis, 1970b;

k. Borremans, 1973, unpublished; 1. Eliel, Alcudia; m. Eliel, Eraus, 1972;

n. Borremans, Anteunis, 1975; o. Borremans, 1975; p. Dirinck, Anteunis, 1972/73;

q. Coene, Anteunis, 1970; r. Eliel, Rev. 1970; s. Bailey, Eliel, 1974;

t. Nader, Eliel, 1970; u. Bailey, Eliel, 1974; v. Anteunis, Camerlynck, Dewaele, 1974.

The situation for polar substituents may be complex, not
only as a result of the mutual interactions of the dipoles
(respectively of the substituent and the ring; μ(1,3-dioxane)
= 2.14 D; (Walker, Davidson, 1959), but also because of a
differential stabilization of the conformers by the medium.
The 1,3-dioxane system, with its well defined structure, should
be an ideal case for such investigations. Polar effects (e.g.
the anomeric effect) have also been efficiently studied in
simpler models, such as tetrahydropyranes (Eliel, Giza, 1968;
Pierson, Runquist, 1968; Anderson, Sepp, 1968).

In the absence of specific solute-solvent association ef-
fects, the solvent can be treated as a continuum surrounding
the solute molecule. Such a model, based on Onsager's reac-
tion field theory and including dipole- as well as quadrupole
moment contributions to the energy content of a special confor-
mer in solution, has been developed (Abraham, 1967). Although
the model suffers from gross simplifications, the calculated
effect of the variation of the solvent dielectric on the equi-
libria of a variety of 5-heterosubstituted 1,3-dioxanes is in
"good" agreement with experiment (Abraham, 1972). In this con-
text equilibrium data in the gas phase, which are lacking,
would be of definite interest.

Specific solvent effects can be operative in determining
the conformational behaviour of heterosubstituted 1,3-dioxanes
and it has been observed in some cases for some solvents that
the change in conformational preference does not parallel f.i.

the dielectric constant of the medium. The moderate dependency on solvent of the equilibrium in 5-methyl-5-vinyl- and 5-methyl-5-ethynyl-1,3-dioxane (Anteunis et al., 1974a), parallels the "anomalous" behaviour observed in 5-methoxy and 5-ethoxy-1,3-dioxane derivatives (Eliel, Hofer, 1973) for aromatic and polyhalogenohydrocarbons as the solvents. These solvents behave as more polar than their dielectric constants suggest. In the aromatic solvents this is possibly caused by the (anisotropic) polarisability by the polar solute. In the polyhalocarbons H-bonding is not necessarily involved (Eliel, Hofer, 1973).

The axial preference of fluorine in 5-position has been discussed in several papers (Hall, Johnson, 1972; Mager, Eliel, 1973; Binsch et al., 1973) and an attractive F/O gauche interaction was postulated (Abraham et al., 1972). The axial preference of the 5-hydroxyl group in apolar aprotic solvents imposed by intramolecular hydrogen bonding (Baggett et al., 1963; Barker et al., 1963), is destroyed or partially offset in hydrogen-donating or hydrogen-accepting solvents (Eliel, Kaloustian, 1970). Also the 5-amino group prefers the axial position over Me (by 0.16 kcal.mole^{-1}) in 5-methyl-5-amino-1,3-dioxane in acetone at room temperature (Coene, Anteunis, 1970b).

The behaviour of 5-CF$_{3-n}$H$_n$-substituted 1,3-dioxanes (n = 1,2) is remarkable. On grounds of steric and gross dipole moment considerations one would expect an equatorial preference,

whereas in fact the conformers with axial difluoromethyl- and
monofluoromethyl groups are favoured in dichloromonofluorome-
thane by 1.9 kcal.mole^{-1} in 5-methyl-5-difluoromethyl-1,3-di-
oxane and 1.1 kcal.mole^{-1} in 5-methyl-5-fluoromethyl-1,3-di-
oxane respectively (Anteunis, Dirinck, 1972; Anteunis, Borre-
mans, 1973). In 5-trifluoromethyl-1,3-dioxane there is no pre-
ference at all when the 5-trifluoromethyl-group is compared
against a 5-methyl group (ΔG°_{273}(5-trifluoromethyl) in Freon-21
= ΔG°_{300}(5-methyl)). This feature is imposed by solvent effects,
since at lower temperatures or in more polar solvents this e-
quilibrium shifts readily towards the axial conformer (Borre-
mans, 1975). It is clear, that the presence of H-atoms in the
fluoromethylated substituent, could play a preponderent role
in this behaviour, and that considerations of mutual orientations
of group dipole moments lead to wrong conclusions, especially
if the dipoles are not directly connected with each other as in
the case of these 5-substituted derivatives (Anteunis, Borre-
mans, 1973). A series of 5-halomethyl-substituted-1,3-dioxanes
has therefore been investigated, in order to disclose the na-
ture of this behaviour (Borremans, Anteunis, 1975) and it was
concluded that localized polar effects are indeed decisive.
Thus the positive charge on the carbon and/or the induced frac-
tional charge in the C-H bond of the 5-CH$_2$X group interact fa-
vourably with the ring oxygen atoms, sta-
bilizing the axial position. This is pre-
sumably a manifestation of a general at-
tractive interaction of a C-X bond (X =
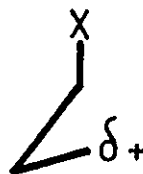
electronegative element) and a positivated γ-carbon in ϕ_1-conformation.

Probable manifestations of this same effect are the axial pre-
ference of 5-hydroxymethyl, despite of the lack of an intra-
molecular H-bond (Dratler, Laszlo, 1970; Eliel, Banks, 1972),
and the observation that the 5-methoxymethyl group has almost
no conformational preference (Eliel, Kaloustian, 1970). Other
comparable situations have been uncovered. Although 5-SMe
prefers the equatorial position, the dimethylsulfonium, methyl-
sulfinyl and methylsulfonyl substituents all prefer the axial
position (Eliel, Evans, 1972). Even trimethylammonium, posses-
sing an effective volume comparable to tert.butyl, strongly
prefers the axial position at C-5 in 1,3-dioxane (Van Cauwen-
berghe et al., 1974; Eliel Alcudia, 1974).

The "internal solvation" hypothesized (Eliel, 1972a) to
explain the stability of the axial 5-nitro group by the 1,3-
dioxane ring oxygens, parallels the close approach between the
nitro-group and the oxygen in the second five-membered ring in
2-O-(p-bromobenzene sulphonyl)-1,4:3,6-dianhydro-D-glucitol-5-
nitrate as revealed by X-ray analysis (Camerman, 1965).

The situation in 4-polar substituted 1,3-dioxanes seems
rather clear-cut. The preference of $CF_{3-n}H_n$ - over CH_3 - for
the axial position (Dirinck, Anteunis, 1972; Dirinck, Anteunis,
1972/1973) can simply be pictured as the result of an electro-
static contribution, the larger the dipole of the fluoromethy-

lated group is, the more it can compensate the ring dipole mo-
ment in the essentially opposite (axial) direction (μ(trifluoro-
methyl) = 2.03 D; μ(1,3-dioxane) = 2.14 D).

The axial preference of the 2-methoxy-group, amounting to
0.4 kcal.mole^{-1} (Eliel, 1970b), is a manifestation of the well
documented anomeric effect (Lemieux, 1964). Contributions of
the latter effect have also been ascribed to 2-ethynyl-, and
2-phenyl-ethynyl-1,3-dioxanes which assume the axial position
in apolar, but prefer to stand equatorially in polar solvents
(Eliel, 1970b). The increased tendency for the axial position
for groupings bearing a partial positive charge on the atom
bound to the anomeric carbon, e.g. 2-p.-trifluoromethyl-phenyl-,
2-chloromethyl-, 2-bromomethyl and 2-ethoxycarbonyl, has been
discussed (Bailey, Eliel, 1974) in terms of a reverse anomeric
effect (Coxon, 1966).

3. Rotameric behaviour of side chains.

   a) Alkyl and Aryl groups:

   Riddell and Robinson (1971) studied the rotamer popula-
tion of the alkyl groups in 2-ethyl-, and 2-isopropyl-1,3-di-
oxane (8) and (9) by measuring the vicinal coupling constant
^{3}J(H2a,αH) as a function of temperature. By means of a suita-
ble computer program and from the reasonable assumption that
the gauche and anti coupling constants for the ethyl and iso-
propyl groups can be related to the coupling constant in 2-

methyl-1,3-dioxane by comparison with ethane, propane and isobutane, they obtained the results given in TABLE VIII.

TABLE VIII: Vicinal Coupling Constants and Thermodynamic Parameters for the Rotamers in 2-Et and 2-$\underline{i}$.Pr-1,3-Dioxane (8) and (9).

	J_g	J_a	ΔH[a]	ΔS[b]
8	2.1 ± 1	9.4 ± 2.5	-0.7 ± 0.4	-1.2 ± 1.0
9	3.1 ± 0.7	6.8 ± 1.6	-0.8 ± 0.4	-1.5 ± 0.7

[a] The conformer with twice a gauche O-C-C-C interaction is the least stable one (kcal.mole^{-1}).

[b] In cal.K^{-1}.mol^{-1}; including entropy of mixing due to the presence of enantiomers.

Tavernier and Anteunis (1971b) have examined the conformational equilibrium within the alkyl groups ethyl, isobutyl, neopentyl and isopropyl in the 4-position of 1,3-dioxane, as well for the equatorial as for the axial position. The populations of the different rotamers of these alkyl groups were estimated from the magnitude of the exo coupling constants. It was concluded that the anti orientation in a (R)O-CH$_2$-CH$_2$-unit is somewhat more stable ($\sim$200 cal.mole^{-1}) than the gauche orientation (see also Dale, 1974). A comparative shift study of several phenyl-substituted 1,3-dioxanes has revealed that the rotameric behaviour of phenyl, and thus also

its conformational preference, depends on the direct envi-
ronment of this plane-symmetric group. Two selected geome-
trical orientations may be pictured: a(n) (ortho)gonal and
a bisectional (parallel) position (CHART 2).
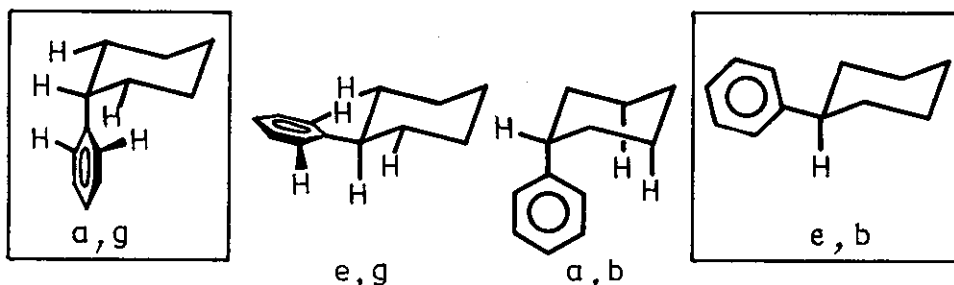
CHART 2

The problem in phenyl cyclohexane has been treated theoreti-
cally by Allinger and Tribble (1971). The a,g and e,b forms
were calculated to be the preferred rotamers. In the a,b
forms non-bonded 1,3-syn axial strain is too high, in e,g
the vicinal equatorial C-H bonds hinder the ortho H atoms
appreciably more than in the a,g form. As a result the ob-
served rotameric preferences for phenyl in some substituted
1,3-dioxanes, as pictured in CHART 3, are logical (Bernaert
et al., 1974).

From the above statements, it is logical that the conforma-
tional energy term of 4-phenyl amounts to 1.0 kcal.mole^{-1} or
more in _trans_-4,5,5-trimethyl-6-phenyl-1,3-dioxane, because
the preference for the gonal orientation is counteracted by
the presence of the 5 equatorial methyl group (see above).
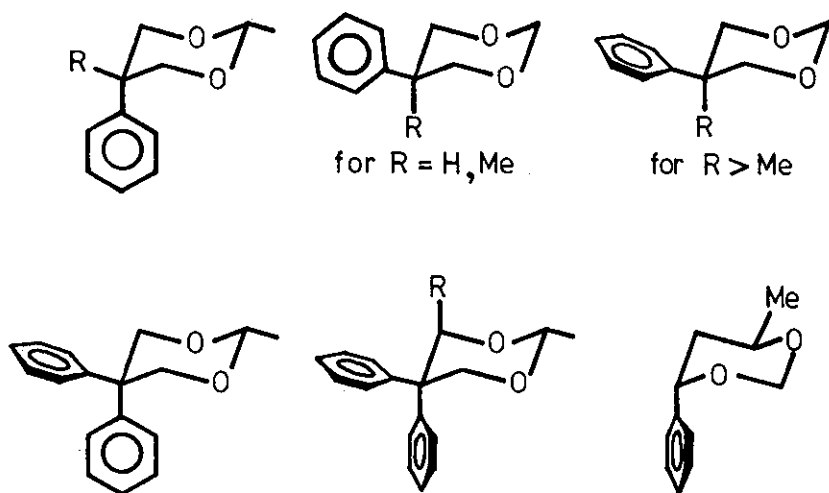
CHART 3

Probably for the same reason, the normal equilibrium state
A⇌B of the dioxadecalane system (favoured axial R) is less
extreme (Swaelens, Anteunis, 1969) if R = Ph (to be compared
with R = Me), although for the isolated case ΔG^o(Ph) < ΔG^o(Me)).
The rotameric behaviour of the aryl group in 2-position is
well known from X-ray data. The equatorial 2-phenyl group
in 2,10-diphenyl-1,3,6,9,11,13-hexa-oxo-dispiro[4,1,5,2]te-
tradecane (2) (Collins et al., 1974) assumes a bisectional (or
parallel) position, whereas in 2-(p-chlorophenyl)-1,3-dioxane
(1) (de Kok, 1970) the aryl group is gonal (or perpendicular).
In r-2-(p-bromophenyl)-cis-4,cis-6-dimethyl-1,3-dioxane (4)
(Nader, 1975) the disposition is again close-to-bisecting.
This suggests that the energy difference between both orien-

tations is small, and determined mainly by packing forces in
the solid state (Nader, 1975) and this supports the proposal
that an equatorial phenyl at C-2 rotates quite freely in so-
lution (Bailey, 1973).

The axial 2-aryl groups in 2-(p-bromophenyl)-r-2,4,4-cis-6-
tetramethyl-1,3-dioxane (3)(Kellie et al., 1972) and in r-2-
(p-trifluoromethylphenyl)-trans-4-trans-6-dimethyl-1,3-dioxa-
ne (5) prefer the gonal conformations thus decreasing syn-
axial repulsions.
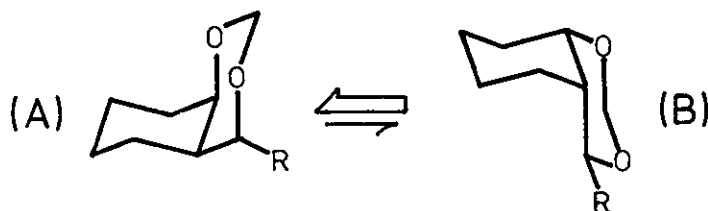
(extra destabilization of A with $\sim$0.4 kcal.mole^{-1} if R = Ph).

Phenyl orientations have also been studied in other hetero-
cyclanes, e.g. β-aryl-succinic anhydrides where the bisectio-
nal orientation is the preferred one, but presumably not if
an additional geminal methyl is introduced (Koer, Altona, 1974).
This statement lies in the line of the previous behaviour in
1,3-dioxanes: the occurence of a (heavy) geminal substituent
tends to prevent the bisectional position.

b) Side chains containing Polar Moieties.

The CH_2-N^+ bonds in the equatorial trimethylammonium-

methyl grouping in 4-trimethylammoniummethyl-, cis-2-methyl-4-trimethylammoniummethyl-, and cis-4-trimethylammoniummethyl-6-methyl-1,3-dioxanes stay skew with respect to the O3-C4 bond, e.g. in a quasi 1,3-syn-axial interaction with the "equatorial" oxygen p orbital, whereas in the equatorial 2-trimethylammoniummethyl-grouping all possible rotameric positions are almost equally populated (Van Cauwenberghe et al., 1974).

The side chain orientation in 4-bromomethyl-1,3-dioxane is identical (Van Cauwenberghe, 1974) to that one observed in 4 — halomethyl-1,3-dioxolanes (Borremans, et al., 1973), e.g. the C-Cl bond and O3-C4 stay antiperiplanar.

It has been claimed that in 2-chloromethyl-1,3-dioxane the rotamer which places the C-Cl bond gauche with respect to both C2-O1 and C2-O3 is stabilized enthalpically by 0.55 kcal.mole^{-1} (Eccleston, et.al., 1971) in spite of the estimated (Bailey, Eliel, 1974) 1.5 kcal.mole^{-1} repulsive interaction with the lone pair orbitals on oxygen.

The halogens in 5-axial halomethyl grouping point outward the 1,3-dioxane ring, whereas in the 5-equatorial conformers fluorine prefers slightly the 1,3-synaxial position with respect to the axial H-4,6 atoms, in contrast to the other halogens (Borremans, Anteunis, 1975).

4. Polycyclic 1,3-dioxane derivatives.

The 1,3-dioxadecalane system has been studied in some detail
(Swaelens, Anteunis, 1969a; Swaelens, Anteunis, 1970).

"O - in"   "C-in"("O-out")
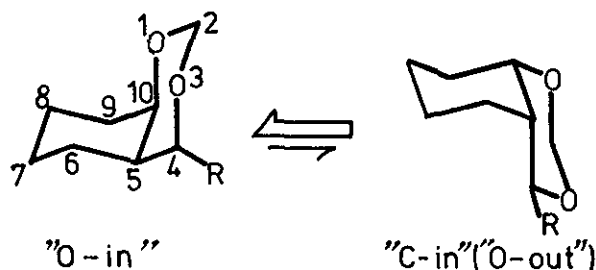
There are two different all-chair conformations of the <u>cis</u>-
isomer. These are called the O-in/O-out (or resp. C-out/C-in)
forms. The energy difference is ~2.2 kcal.mole^{-1}, O-in being
the more stable conformer[*]. This value was obtained from an
equilibration of the isomeric 2,7-dimethyl-1,3-dioxadecalanes
in the temperature range 273-373 K . The unknown $\Delta G°$(O-in/O-
out) was pitted against the known A-value of methyl in cyclo-
hexane. The equilibrium favours O-in by 1.29 kcal.mole^{-1} at
298 K . $\Delta H°$ was found to be 0.5 kcal.mole^{-1} (again in favour
of O-in).
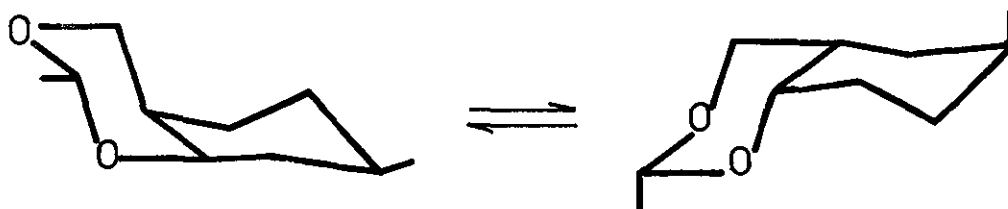
[*] The naïve approach let us to estimate in 1,3:2,4-di-O-methylene-L-thre-
itol a different $\Delta G°$(O-in,O-out) = 3.5 kcal.mole^{-1} (from the data of Swae-
lens, Anteunis, 1969a).

The equilibrium in the cis-2,4-dimethyl-1,3-dioxadeca-
lane (FIG.7) was investigated by a slow exchange NMR method
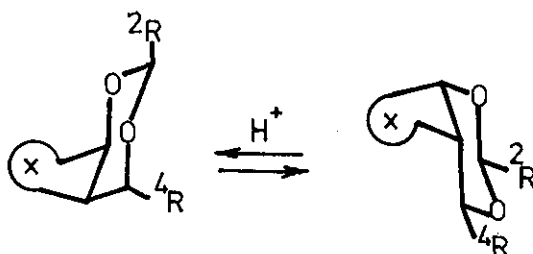
Fig. 7

^4R = Me;   X = 6

$\Delta G^{\circ}{}_{191}{}^{a}$ 0.65   (CS_2, NMR, R = H)

$\Delta G^{\circ}{}_{298}{}^{b}$ 0.51   (CCl_4, D. Eqb., R = Me)

$\Delta G^{\circ}{}_{293}{}^{c}$ 0.69   (CCl_4, D. Eqb., R = Me)

a. Swaelens, Anteunis, 1969;
b. Swaelens, Anteunis, 1970;
c. Bhatti, Anteunis, 1973.

(Swaelens, Anteunis, 1969a), and by the equilibrium approach
(Swaelens, Anteunis, 1970; Bhatti, Anteunis, 1973). The equi-
librium mixture was analyzed in both investigations by GC.
In the experiments carried out by Swaelens a capillary column
with splitter was used, but Bhatti used on-column injections
of the samples. The obtained results for the free energy dif-
ferences are slightly different (0.51 and 0.69 kcal.mole^{-1}
respectively). This illustrates that much care and attention
should be given to the analytical problems encountered when
determining the composition of a mixture using G.C.(see § III.A).
In the opinion of the present authors there has been a tendency
to overemphasize the certainly real difficulties to be taken
into account when using NMR as the analytical technique, but
we are convinced that somehow the reliability of G.C.analysis
has been taken for granted too easily. Swaelens and Anteunis
(1970) have deduced that the A-value of 4-methyl is 3.0 kcal.
mole^{-1}, from the following data: (i) the energy difference of

O-in/O-out in cis-1,3-dioxadecalane; (ii) the energy of cis-
4-methyl-1,3-dioxadecalane (FIG. 7); (iii) the ϕ_1-butane-in-
teraction.

Swaelens and Anteunis (1969a) measured (slow exchange NMR)
the equilibrium state in a series of 4-R-cis-1,3-dioxadeca-
lanes (FIG. 7; x = 6 & TABLE IX).

TABLE IX. $\Delta G°$(C-in/O-in) in kcal.mole^{-1} for 4-substituted-cis-1,3-dioxa-
decalanes (in CS_2 at 191 K).

^{4}R	Me	Et	n.Pr	i.Bu	i.Pr	sec.Bu	Ph	CF_3
$\Delta G°$	0.65	0.94	0.92	0.86	0.88	0.88	0.25	(a)

(a) strongly displaced towards axial CF_3, K_e > 20.

The phenyl case has been discussed above (§ III.B.3). In
this series the O-in conformation is more favoured for ^{4}R = Et
than for ^{4}R = Me, that is ethyl stays in this environment more
easily in the axial position than methyl. We mentioned earlier
(§ III.B.1) that for isolated 4-alkyl groups the A-value of
ethyl is slightly larger than for methyl. This reverse obser-
vation in the dioxadecalane system was subsequently corrobora-
ted by equilibrium data (Bhatti, Anteunis, 1973). The study of
the cis-1,3-dioxabicycloalkanes (Bhatti, Anteunis, 1973), see
FIG. 7 (x = 5-8) and TABLE X.

Thus for x = 5, and 6, the "O-in" form having 4-methyl-axial is the preferred one, but the "C-in" form becomes on the contrary less favoured for x = 7, and x = 8. This may point to the fact that the methyl-gauche interaction, which remains in the "C-in" forms (4-methyl equatorial), is less strained in the higher homologues than in the dioxadecalane case (x = 6).

The 2,4-dioxabicyclo[3.3.1]-nonane system has been investigated (Marvell, Provant, 1964; Swaelens, Anteunis, 1969b), but only a qualitative description has been reached from the ^{1}H-NMR studies.

It has been proposed that both rings are substantially flattened, (10, R = H) and this was corroborated by a similar study on the even more strained derivative 10, R = Me.

(Anteunis et al., 1974b).
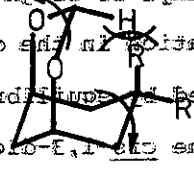
These results parallel the observed flattening in the corres-
ponding carbocyclic analogue (Brown et al., 1964). Some un-
saturated bicyclic derivatives, prepared by a Prins conden-
sation of cyclic polyolefins and formaldehyde (Coryn, Anteu-
nis, 1974) have also been investigated. A surprising obser-
vation is that cis-bicyclo[6.4.0]-10,12-dioxa-3-dodecene (11)
exists predominantly in the "O-out" form (Anteunis, Coryn,
1974), in spite of the fact that a 4-vinyl group in dioxane
has a larger A-value than a 5-alkyl group (Anteunis, Coryn,
1973).

"O-out"   "O-in"
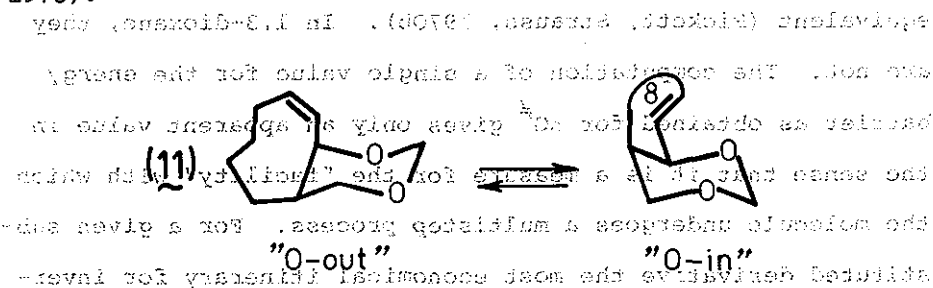
The reversed situation in the present case is clearly the
result of the cyclic nature of the C_4-C_5 substitution in the
1,3-dioxanic part, and inspection of models and considera-
tions of conformational features of cyclooctene, reveal that
the above mentioned conformational behaviour is the result
of a conformational-transmission effect (cf. Bucourt, 1974)
imposed by the cyclooctene ring.

IV. Barrier for Ring Reversal.

A. General Considerations.

There is a **sixfold** degeneracy for ring reversal in cyclohexane, but only a threefold one in 1,3-dioxane. It is now recognized that midway the inversion path the flexible forms are mutually in rapid equilibrium by libration (Kellie, Riddell, 1974). The energy fluctuations during the pseudorotation are degenerate in cyclohexane, in a way that the small barriers separating the energy minimum conformations are all equivalent (Pickett, Strauss, 1970b). In 1,3-dioxane, they are not. The computation of a single value for the energy barrier as obtained for $\Delta G^{\neq}$ gives only an apparent value in the sense that it is a measure for the "facility" with which the molecule undergoes a multistep process. For a given substituted derivative the most economical itinerary for inversion can be a composite phenomenon: after the molecule has reached flexible forms along a (set of) favoured route(s) these forms become involved in a pseudorotation until pseudorotational partners are obtained from which further evolution leads to complete inversion. The last part of the process is not necessarily enantiomeric to the first part. Thus the apparent barrier height is not only influenced by the number of possible itineraries (affecting $\Delta S^{\neq}$) but also by the chosen itinerary. The introduction of a strain along one of the a priori possible itineraries will in principle result in a by-

pass along a (set of) more favoured route(s). It is then dif-
ficult to relate the observed changes in $\Delta G^{\neq}$ quantitatively
with structural alterations of the ground state or of the
transition state. It is presumably also the reason why, even
for dramatic changes in the basic structure of the cyclic com-
pounds, $\Delta G^{\neq}$ remains strikingly similar (TABLE XI).

TABLE XI. Barriers for Ring Reversal $\Delta G^{\neq}$ of some six-membered Rings
(kcal.mol^{-1} at T_c).

cyclohexane	10.5	(a)
tetrahydropyraan	10.3	(a)
thiane	9.4	(a)
selenane	8.2	(a)
tellurane	7.3	(a)
piperidine	10.4	(b)
1,3-dioxane	9.9	(c)
1,3-dithiane	10.3	(c)
1,3-diselenane	8.2	(d)
1,4-dioxane-d$_7$	10.0	(e)
3,3,6,6-tetraMe- 1,2-dioxane	14.3	(f)
1,2-dithiane-4,5-d$_4$	11.6	(g)
1,2,3-trithiane	13.2	(h)

(a) Lambert et al. (1973)

(b) Lambert et al. (1967b)

(c) Friebolin et al. (1969)

(d) Geens et al. (1969)

(e) Jensen and Neese (1971)

(f) Schmid et al. (1966)

(g) Claison et al. (1960)

(h) Kabuss et al. (1966).

Of course, in the entire process of reversal, each torsion angle has to change sign and each structural feature resulting in a change in the rotational barrier around one of the ring bonds, must effect somehow the total apparent barrier. It will however depend on the nature of the dips (the energy minima along the itinerary in how far quantitatively such a structural alteration will have its impact and become perceived (FIG.8A). Thus the introduction of two vicinal heteroatoms possessing lone pair orbitals raises sharply the barrier (FIG.8B and TABLE XI).
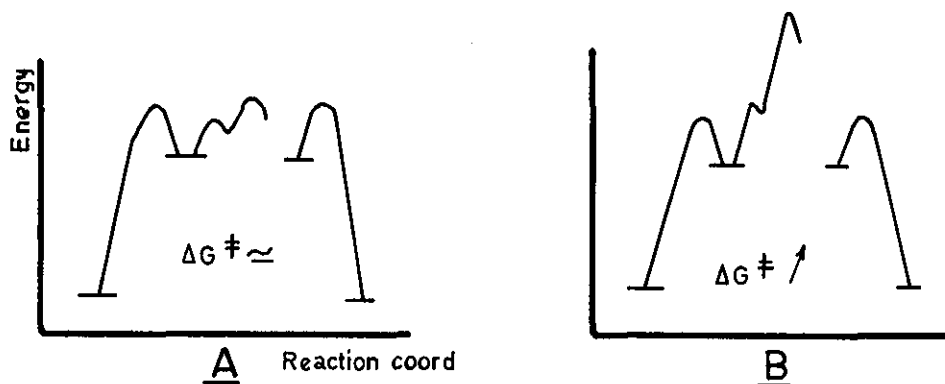
Fig. 8

More than half of the barrier to ring reversal in 1,3-dioxanes may come from torsional strain. Taking the rotational barriers in dimethyl ether and n.propane as reference points the relative energy contents of the three half-chair (mono-planar) forms have been estimated (Harris, Spragg, 1968) and are shown in Chart 4.

0.0   0.3   0.7₇   kcal . mole^{-1}
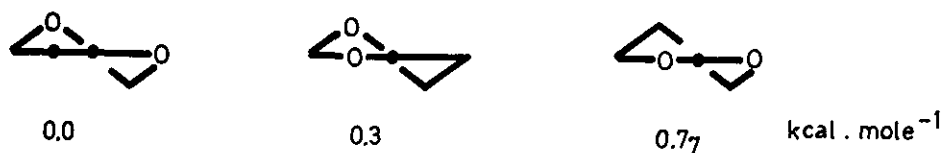
CHART 4

Depending on the site of substitution one or another of
these forms may become the preferred intermediate during
the ring reversal. It is therefore of interest to have
a quantitative idea on the preferred substitution pattern
in these flexible forms, a problem on which we will come
back later (see flexible forms).

B. Results.

The barrier to inversion in 1,3-dioxane is $\Delta G^{\neq}$ = 9.7 kcal.
mole^{-1}. The occurrence of a geminal dimethylation can have
two opposite effects on the rate of ring reversal because
(a) the axial methyl group can strain the ground state,
to result in a lower barrier and/or (b) the rotational bar-
rier next to a quaternary center can be different from the
one in ethane. In 5,5-dimethyl-1,3-dioxane, which has a
higher barrier than the parent compound, effect (b) must
be predominant (Friebolin et al., 1969; Coene, Anteunis, 1970c),
as the conformational free energy of 5-methyl is small (yet,
the rather low absolute value of ^2J in 5,5-dimethyl-1,3-di-
oxane, which can be measured directly in the slow exchange,

NMR spectrum, discloses a change in ring shape with respect
to 1,3-dioxane itself). The much higher A-value for 2-methyl
and 4-methyl on the contrary results in a dominating effect
of the enhanced strain in the ground state. Gem-2,2-dimethyl-
substitution lowers the barrier to ring reversal by 0.5-1.0
kcal.mole^{-1}. The barrier in 5,5-diethyl-1,3-dioxane is slight-
ly lower than in the 5,5-dimethyl compound. An explanation
has not yet been offered. The same trend is also noted in cy-
clohexane and 1,2,3-trithiane derivatives (Goor, Anteunis, 1975;
De Beule, Anteunis, 1974) and presumably the lower barrier in
5,5-diethyl-1,3-dioxane is not directly a consequence of the
heterocyclic ring. The lower barrier in 5,7-dioxa-spiro[2,5]-
octane can be ascribed to ring flattening caused by the three-
membered ring to be compared with the Thorpe-Ingold effect
(Coene, Anteunis, 1970c; Anderson, 1970). Geminal di-isopro-
pyl substitution presents some interesting aspects, especially
by comparison with (a) geminal dimethyl substitution   (b) spi-
ro adamantylene substitution (compounds 12, 13, 14), where
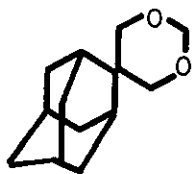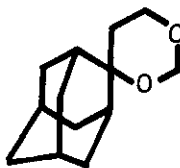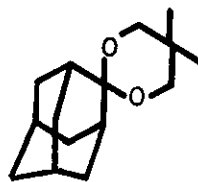
(12)   (13)   (14)

there are also two tertiary C atoms bonded to the 1,3-dioxane
nucleus. In 5,5-diisopropyl-1,3-dioxane, the barrier is lower

by 3 kcal.mole^{-1} than in 5,5-dimethyl-1,3-dioxane, but the 5-adamantylene derivative (12) has a barrier only slightly lower than in the latter compound.

4,4-diisopropyl-1,3-dioxane and the 4-adamantylene derivative (13) topomerize at the same rate, and both have a barrier lower than 4,4-dimethyl-1,3-dioxane. Finally, the inversion rates of 2,2-dimethyl and 2,2-diisopropyl-1,3-dioxanes are about equal, but both invert somewhat slower than the 2-adamantylene derivative. An explanation has been offered for the exceptionnally low barrier in 5,5-diisopropyl-1,3-dioxane (Tavernier et al., 1974). A characteristic feature of the 5-position is that "methyl-inside" rotamers (fig.9) of axial alkyl groups have a large, but not a forbiddingly large energy content. The methyl-inside strain is estimated to be 3.1 kcal.mole^{-1} (Eliel, Enanoza, 1972). On the other hand, a 1,3-di-
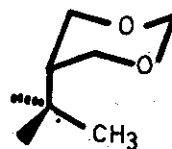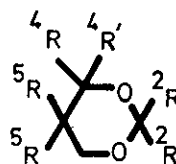
Fig.9

oxane ring featuring a methyl-inside conformation would be expected to have a low barrier to inversion (the methyl-inside ... oxygen distance must be much larger in the transition state than in the ground state). However, the axial isopropyl group in the anancomeric 2-methyl-5,5-diisopropyl-1,3-dioxane has not a methyl-inside conformation as the ground state. This was concluded from chemical shift data, from the chemical shift changes in function of added lanthanide shift reagent, and from the fact that there is only a very small long range coupling of the methine hydrogen of axial isopropyl with H-4/6a.

TABLE XII.

TABLE XII. Barriers to Ring Reversal in 1,3-Dioxanes (in kcal.mole^{-1} at T_c).

4R	4R	2R	2R'	5R	5R'	ΔG‡		
H	H	H	H	H	H	9.7 (a)	9.9 (c)	10.0 (g)
H	H	H	H	Me	Me	10.5 (a)	10.9 (c)	11.0 (g)
H	H	H	H	Et	Et	10.1 (a)		
H	H	H	H	$(CH_2)_2$		9.6 (a)		
H	H	H	H	$(CH_2)_3$		10.2 (a)		
H	H	H	H	$(CH_2)_4$		10.7 (a)		
H	H	H	H	$(CH_2)_5$		10.1 (a)	10.9 (g)	
H	H	H	H	_i_.Pr	_i_.Pr	7.3 (b)		
H	H	H	H	cyclo Pr	cyclo Pr	9.8 (b)		
H	H	H	H	Ø	Ø	10.7 (b)		
H	H	Me	Me	H	H	8.4 (c)	7.8 (e)	
H	H	$(CH_2)_4$		Me	Me	9.5 (a)		
H	H	$(CH_2)_5$		Me	Me	8.9 (a)		
H	H	_i_.Pr	_i_.Pr	Me	Me	9.9 (a)		
H	H	Me	Me	Me	Me	8.9 (c)		
Me	Me	H	H	H	H	9.1 (c)		
_i_.Pr	_i_.Pr	H	H	H	H	8.1 (b)		
Ø	Ø	H	H	H	H	9.5 (b)		

	ΔG‡
12	10.0 (b)
13	8.2 (b)
14	9.0 (a)
15	10.8 (b)
16	10.7 (f)
17	~7.5 (f)
18	11.4 (d)
19	10.0 (d)

(a) Coene, Anteunis, 1970c; (b) Tavernier et al., 1974; (c) Friebolin et al., 1969; (d) Tavernier et al., 1973; (e) Anderson, Brand, 1966; (f) Tavernier et al., 1975; (g) Greenberg, Laszlo, 1970.

A multistep process was therefore proposed. First, the re-
lative stable "outside" axial isopropyl is transformed by
rotation into the relatively unstable methyl-inside form,
which topomerizes readily, and a second isopropyl rotation
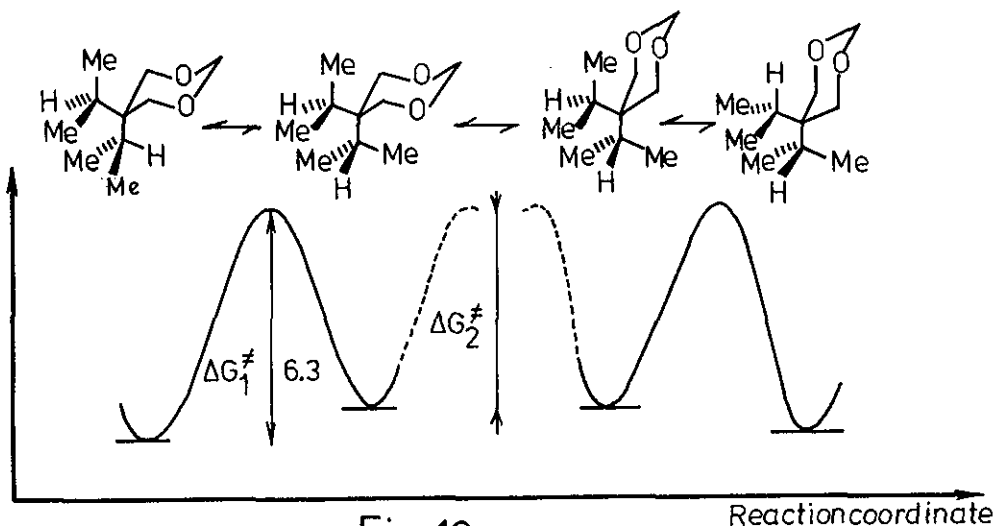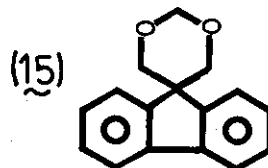produces the starting form (Fig.10).

Fig. 10

Reaction coordinate

This "Van 't Hoff-type" profile, characterized by three es-
timated barriers of about 7 kcal.mole^{-1}, and by two minima
with an energy level comparable to the starting and final
chair form, explains the over-all value of 7.3 kcal.mole^{-1}.
Essential to this picture is the fact the axial isopropyl
group must be able to escape into a methyl-inside conforma-
tion, which is relatively easy in the 5-position. This si-
tuation is less clearly or not at all met in the 4,4-diiso-
propyl and 2,2-diisopropyl derivatives, respectively. No
analogous itinerary with the in-between dips in the energy

profile can be found in these compounds.

It is interesting that 5,5-dicyclopropyl-1,3-dioxane has the more usual barrier of 9.8 kcal.mole^{-1}. Small rehybridization effects of the branched 5-geminal groups apparently change the picture dramatically. It may seem surprizing that 5,5-diphenyl-1,3-dioxane and the fluorene derivative (15) have the normal barrier of 10.7 kcal.mole^{-1}. However, we saw above that 5-phenyl, which has a low conformational preference of 1.0 kcal.mole^{-1}, assumes the bisectional position when axial. The ground state of 5,5-diphenyl-1,3-dioxane and of 15 is then presumably not unduly strained, in accordance with their unexceptional inversion barriers (Tavernier et al., 1974).

(15)

The explanation proposed for the low barrier in 5,5-di-isopropyl-1,3-dioxane is corroborated by the inversion barriers of the isomeric spiro compounds (16) and (17), which again have two tertiary carbon atoms bonded to the 5-position of the 1,3-dioxane moiety. The cyclohexane part of 16 and 17
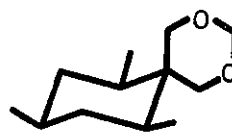
(16) (17)

assumes the conformation depicted (^{1}H-nmr parameters). The

molecular structure in the neighbourhood of the 1,3-dioxane
moiety is however very different. In 16, there is a methyl-
outside conformation, and the barrier to reversal of the
heterocyclic ring is normal (10.7 kcal.mole^{-1}). In 17, on
the contrary, the ground state of the molecule is a methyl-
inside conformation, and the barrier to ring reversal of the
1,3-dioxane ring is approximately 7.5 kcal.mole^{-1} (Tavernier,
Anteunis, 1975). The 1,3-dioxane nucleus has also been
used to look at another manifestation of methyl-inside strain,
namely a _raising_ of the inversion barrier. The idea was to
have a structure such that not the ground state, but the tran-
sition state would be subject to methyl-inside strain, or
something reminiscent of it. Consider the spiro compound (18).
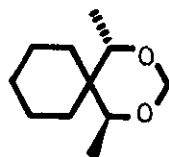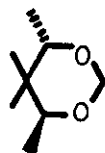
(18)   (19)

It can exist, in principle, in two pairs of identical all-
chair conformers, αα,ββ and αβ,βα (Fig.11). The forms αβ,βα
are the more stable ones. The transformation of αβ to βα
or vice-versa formally requires a reversal of the cyclohexane
and the 1,3-dioxane rings. Again formally, after reversal
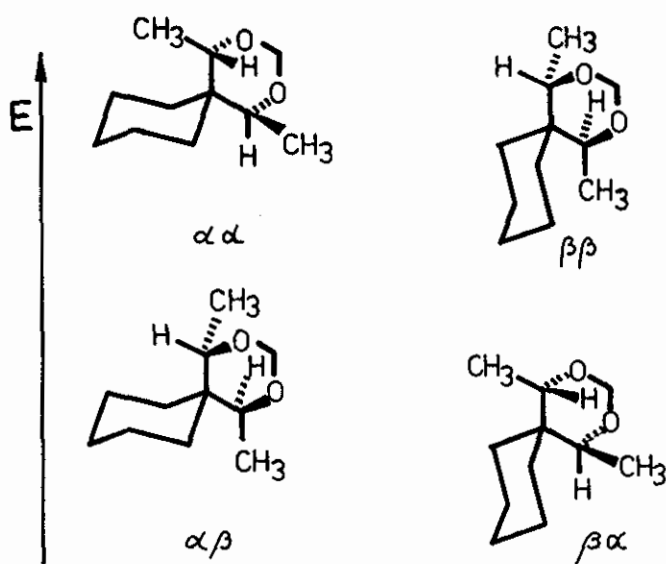of only one ring, αα or ββ is formed, and the strain present

Fig.11

in this conformation (or some cognate form encountered du-
ring the inversion itinerary) should cause an increase in
the inversion barrier. Experimentally, the barrier to re-
versal of the 1,3-dioxane moiety in $\underset{\sim}{18}$ is 11.4 $kcal.mole^{-1}$,
the highest one reported for a non-annellated 1,3-dioxane
derivative. The relatively high inversion barrier is not
a result of the heavy substitution pattern, because the si-
milarly substituted ($\underset{\sim}{19}$) has a barrier of only 10.0 $kcal.mole^{-1}$
(Tavernier et al., 1973).

V. Non-Chair Conformations.

A. Means of Detection.

There are two distinct twist-boat (TB) forms of 1,3-dioxane,
a symmetrical one, the 2,5-TB form, which has a C_2 axis, and
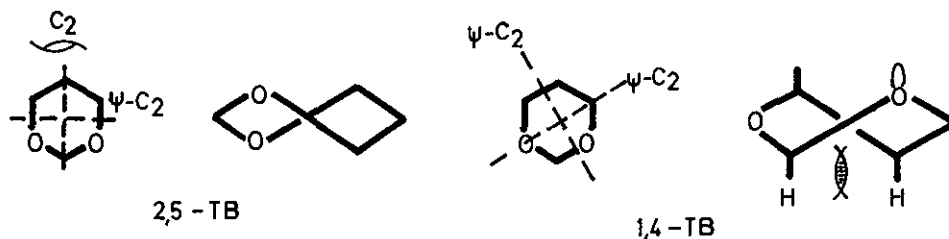an asymmetrical one, the 1,4-TB form (CHART 5). As the full

CHART 5

symmetry of the TB form of cyclohexane (point group V) is
approximately conserved in the TB forms of 1,3-dioxane, it
is possible to talk about pseudo C_2 axes (ψ-C_2) in these
forms. It was originally suspected that the boat form of
1,3-dioxane could be a relatively low energy conformation,
and perhaps this idea was lent credence by the prediction
that the (or a) boat form of 1,3-dioxane should be strained
over the chair form by no more than 2.2 kcal.mole^{-1}. It
turned out that this prediction was based on the understan-
dable but unfortunate choice of the rotational barrier in
methanol as a model for the rotational barriers around the
C-O bonds in 1,3-dioxane (Eliel et al., 1965). Subsequent

work has shown that the free energy difference between the chair and the TB forms of 1,3-dioxane is even larger than in the case of cyclohexane (see TABLE XIII). Clearly, it would be convenient to have at one's disposal criteria to distinguish chair and non-chair forms. In view of the profound conformational changes involved, it is not surprizing that several criteria have been advanced: (i) a low absolute value of $^2J(2)$ (Anteunis, Swaelens et al., 1971a) e.g. $^2J(2)$ = -2.8 Hz in a 2,5-TB form (Anteunis, Swaelens, 1970); (ii) an increased sum of vicinal coupling constants in the aliphatic part of the ring, e.g. for trans 4,6-dialkyl-1,3-dioxanes $\Sigma^3J(4,5) = ^3J^{cis} + ^3J^{trans} = 10.5$ to 11 Hz for a chair form and >15 Hz for a 2,5-TB form (Tavernier, Anteunis, 1967; Pihlaja et al., 1972); (iii) deviations of specific solvent effects in NMR, especially ASIS (aromatic solvent induced shifts)(Pihlaja, Äyräs, 1970b; Pihlaja, 1968); (iv) lowered values for the exocyclic coupling constant $^3J_{H-Me}$ in comparison with the one expected for axial methyl (Tavernier, Anteunis, 1971a); (v) substantial deviations of ring ^{13}C chemical shifts from those expected for a chair form (Riddell, 1970; Kellie, Riddell, 1971); (vi) substantial deviation of the experimental boiling point from the one excepted on the basis of empirical rules (Kellie, Riddell, 1972); (vii) thermochemical data (Pihlaja, Luoma, 1967); (viii) chiroptical properties (Tocanne, 1970).

By way of illustration, the temperature dependency of $^2J(2)$ in trans-4-t.butyl-6-alkyl-1,3-dioxanes (alkyl = methyl, isopropyl, cyclohexyl, trifluoromethyl) has made it possible to assay the minor amounts of flexible forms (Anteunis, Swaelens, 1970; Dirinck, Anteunis, 1972).

B. Chair-twist Equilibria.

TABLE XIII gives the chair-twist boat energy differences of some six membered rings. It is seen that the energy difference $\Delta H^{\circ}(C\text{-}TB)$ increases roughly with the "compactness" of the molecule, as a result of residual non-bonded repulsions (Eliel, 1970b). In a recent review (Riddell, 1974) rather divergent values for $\Delta H^{\circ}(C\text{-}TB)$ in 1,3-dioxane are reported.

TABLE XIII. Chair-Twist Boat Energy Differences of some six membered Rings.

	ΔG° kcal.mole^{-1}	ΔH° kcal.mole^{-1}	ΔS° e.u
cyclohexane	5.1	6.0	3.2
1,3-dioxane	8.0[a]	8.6[a]	<2.2
1,3-oxathiane	5.5	6.0	~2.2
1,3-dithiane	1.8	3.4	5.3
	2.6	4.0	4.5

(a) For the 2,5-TB form the difference seems to be lower, e.g. $\Delta H^{\circ} = 6.2$ kcal.mole^{-1}, see text for discussion.

In the opinion of the present authors, it has not always

been appreciated that these apparent discrepancies partly arise because of the difference in nature of the TB forms under consideration. Thus, torsional strain may be smaller in the 2,5-TB form (see half-chair forms, CHART 4, for comparison), and note the slightly higher di pseudo-axial H-H interactions in the 1,4-TB form (CHART 5).

When studying 2,5-TB-like compounds as in trans-4-t.butyl-6-alkyl-1,3-dioxanes (Anteunis, Swaelens, 1970) one would expect to obtain a lower ΔH° (T-C) value than when studying 1,4-TB-like compounds as trans-2,4,4,6-tetramethyl-1,3-dioxane (Pihlaja et al., 1972). Indeed, qualitatively one may state that (i) ψ-equatorial substitution is preferred over ψ-axial substitution; (ii) a t.butyl in 2-, and 4(6) position will end up in a ψ-axial position, rather than in an isoclinal (bisectional) position; (iii) gem.dimethyl will show up at an isoclinal position. Therefore trans-4-(1'-adamantyl)-6-t.butyl will escape almost exclusively in the 2,5-TB form, but trans-2,4,4,6-tetramethyl-1,3-dioxane will occur in the 1,4-TB form. (CHART 6).
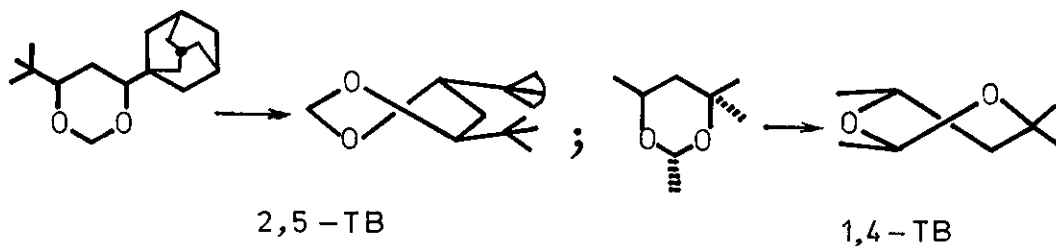

2,5 - TB   1,4 - TB

CHART 6

It may well be then that $H°(2,5$ TB-C) is $\sim$6.2 to 6.8 kcal.mole^{-1}
(Anteunis, Swaelens, 1970; Pihlaja, 1968) but that $\Delta H°(1,4$ T-C)
is $7.5 \sim 8.0$ kcal.mole^{-1} (Pihlaja, 1974; Pihlaja, Pasanen, 1974).
Actually, the values of $\Delta H°(C-T)$ of 6.2 kcal.mole^{-1} (Anteunis,
Swaelens, 1970; Dirinck, Anteunis, 1972) may even be somewhat
overestimated. These values were arrived at from the dependen-
cy of $^2J(2)$ on temperature, and the thermodynamic parameters
were corrected for the axial strain that must be present in
the chair form in equilibrium with the 2,5-TB form. However
it was <u>assumed</u> that no residual strain due to the alkyl groups
was present in the 2,5-TB form, and this is perhaps not exact-
ly so.

C. Deformed Chairs.

1. The buttressing phenomenon.
A number of changes in the ring shape of 1,3-dioxanes, brought
about by the presence of substituents, have been discussed
(Eliel et al., 1974; Danneels, Anteunis, 1975). It seems that
such "non-typical" forms occur more frequently in **six** membered
cyclanes than is usually accepted. Thus, in cyclohexane, in-
troduction of a "heavy" equatorial substituent such as tert.
butyl results in a puckering of the ring (Parthasarathy et al.,
1972; Johnson et al., 1973), a feature also found from calcula-
tions (Altona, Sundaralingam, 1970). This puckering gives an
enhanced interaction of the axial hydrogen geminal to tert.bu-
tyl with the syn-axial hydrogens (or other axial ligands) at

the γ-position. This interaction is accentuated when there is an additional equatorial γ-substituent. The importance of this so-called "Allinger buttressing" by alkyl groups in the 1,3-dioxane nucleus was examined (Eliel et al., 1974). Buttressing by an equatorial 5-tert.butyl or a 5-geminal dimethyl group seems to be unimportant; equatorial methyl at position 4 and 6 exert a sizeable buttressing effect on the axial substituents; equatorial alkyl groups at C-2 cause buttressing in the increasing order Ph < Me ∿ Et < i.Pr ∿ t.Bu. Buttressing originating from polar groups at position 2 was observed (Danneels, Anteunis, 1975) in cis-4,6-dimethyl-2-dichloromethyl and cis-4,6-dimethyl-2-trichloromethyl-1,3-dioxane. The dipole moment of the trichloroderivative deviates seriously (0.8 D) from the expected one, that of the dichlorocompound much less so. From NMR parameters (shift and coupling constants) the deformation of the C-4, C-5, C-6 part in the order t.Bu < $CHCl_2$ ≪ CCl_3 was established.

2. Non-Chair forms in C-sp^2 hybridized-1,3-dioxanes.
Conformational descriptions of 1,3-dioxanes that contain sp^2 ring carbon atoms are scarce. The ring shape of 4-oxo-1,3-dioxanes seems to depend on the substitution pattern: 3,4-monoplanar (half-chair), 2,5-TB and 2,5-B forms (or a time averaged mixture of these) have been proposed. Mesomeric overlap in the O-C=O part of the ring and minimized non-bonded interactions are at the origin of this behaviour (Äyräs, Pihlaja, 1973a,b; Äyräs, 1973).
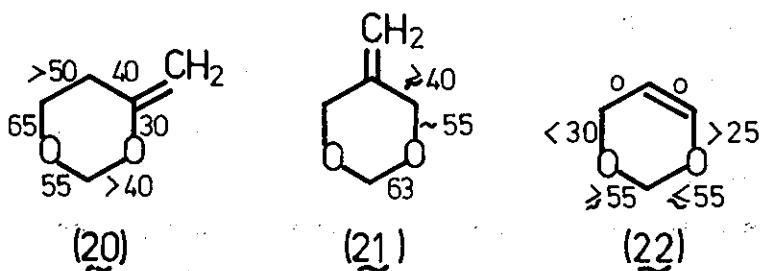
4-Methylidene-1,3-dioxane (20) was examined by NMR spectro-
scopy (Anteunis, Camerlynck, 1975a). The coupling constants
$^2J_{(2)}$, $^2J_{(5)}$, $^2J_{(6)}$, ^3J and ^4J disclosed the conformation of
20, and by reference to a rule of thumb (developed for cyclo-
hexane systems, Bucourt, 1974) a set of ring torsion angles
could be proposed. The conformation of 20 can differ slightly
from the corresponding 4-oxo-compound, not only because of the
unequal importance of mesomerism, but also because of the dif-
ferent spatial requirements of C=O and $C=CH_2$. A difference
is also perceptible in cyclohexane derivatives, e.g. 1,4-cyclo-
hexanedione exist as a 1,4-TB (Bastiansen et al., 1971; Groth,
1968), but 4-methylidene-cyclohexane and 1,4-bismethylidene
cyclohexane exist as flattened chairs (Rickborn, Wuesthoff,
1970; Jacques, Bernard, 1969). At variance with 20, 5-methyli-
dene-1,3-dioxane (21) assumes a flattened chair conformation
(Anteunis, Camerlynck, 1975b), which is not unexpected in view
of the behaviour of methylidene cyclohexane. 2-Methylidene-
1,3-dioxane is extremely unstable. It was not possible to in-
vestigate its conformational characteristics accurately (An-

teunis, Camerlinck, 1975).

It can be expected that it resembles a sofa form (cf. the
2-oxo-1,3-dioxane studied by Pihlaja et al., 1970). Also
Δ^4-1,3-dioxene (22) and some derivatives were investigated
and on the basis of ^{1}H-N.M.R. parameters a 1,2-diplanar
form was proposed (Anteunis, Camerlinck, 1975b).

REFERENCES.

R.J. Abraham, H.D. Banks, E.L. Eliel, O. Hofer, and M. Kalous-
    tian, J.Amer.Chem.Soc., 1972, 94, 1913.

N.L. Allinger, and M.T. Tribble, Tetrahedron Letters, 1971 ,
    3262.

C. Altona, and M. Sundaralingam, Tetrahedron, 1970, 26, 925.

C.B. Anderson, and D.T. Sepp, Tetrahedron, 1968, 24, 1707 .

J.E. Anderson, and J.C.D. Brand, Trans.Faraday Soc., 1966, 62,
    39.

J.E. Anderson, J.Chem.Soc.(B), 1967, 712.

J.E. Anderson, Chem.Commun., 1970, 417.

M. Anteunis, D. Tavernier, and F. Borremans, Bull.Soc.Chim.
    Belges, 1966a, 75, 396.

M. Anteunis, E. Coene, and D. Tavernier, Tetrahedron Letters,
    1966b, 4579.

M. Anteunis, Bull.Soc.Chim.Belges, 1966, 75, 413.

M. Anteunis, and G. Swaelens, Organic Magnetic Resonance, 1970,
    2, 389.

M. Anteunis, Bull.Soc.Chim.Belges, 1971, 80, 3.

M. Anteunis, G. Swaelens, F. Anteunis-De Ketelaere, and P.
     Dirinck, Bull.Soc.Chim.Belges, 1971a, 80, 409.

M. Anteunis, G. Swaelens, and J. Gelan, Tetrahedron, 1971b,
     27, 1917.

M. Anteunis, F. Anteunis-De Ketelaere, and F. Borremans,
     Bull.Soc.Chim.Belges, 1971c, 80, 701.

M. Anteunis, and P. Dirinck, Canad.J.Chem., 1972, 50, 423.

M. Anteunis, and F. Borremans, Canad.J.Chem., 1973, 51, 3170.

M. Anteunis, and M. Coryn, Bull.Soc.Chim.Belges, 1973, 82, 413.

M. Anteunis, D. Tavernier, and G. Swaelens, Rec.Trav.Chim.Pays-
     Bas, 1973, 92, 531.

M. Anteunis, R. Camerlynck, and R. De Waele, Bull.Soc.Chim.Bel-
     ges, 1974, 83, 483.

M. Anteunis, and M. Coryn, Bull.Soc.Chim.Belges, 1974, 83, 133.

M. Anteunis, C. Becu, and F. Anteunis-De Ketelaere, J.Acta Ci-
     encia Indica, 1974, 1, 1.

M. Anteunis, and R. Camerlinck, J.Chem.Soc., 1975a, in press.

M. Anteunis, and R. Camerlinck, Bull.Soc.Chim.Belges, 1975b,
     in press.

M. Anteunis, and D. Danneels, unpublished results (1975).

M. Anteunis, D. Tavernier, and N. Hosten, unpublished results
     (1975).

B.A. Arbuzov, Bull.Soc.Chim.France, 1960, 1311.

P. Äyräs, and K. Pihlaja, Acta Chem.Scand., 1973a, 27, 2511.

P. Äyräs, and K. Pihlaja, Tetrahedron, 1973b, 29, 3369.

P. Äyräs, Suomen Kemistilehti.B., 1973, 46, 151.

W.F. Bailey, Ph.D. Thesis, 1973, University of Notre Dame, as
     quoted in E.L. Eliel , et al. (1974).

W.F. Bailey, and E.L. Eliel, J.Amer.Chem.Soc., 1974, 96, 1798.

N. Baggett, M.A. Bukhari, A.B. Foster, J. Lehmann, and J.M. Webber, J.Chem.Soc., 1963, 4157.

C. Barbier, M. Davidson, and J. Delmau, Bull.Soc.Chim.France, 1964, 1046.

C. Barbier, J. Delmau, and J. Ranft, Tetrahedron Letters, 1964, 3339.

S.A. Barker, A.B. Foster, A.H. Haines, J. Lehmann, J.M. Webber, and G. Zweifel, J.Chem.Soc., 1963, 4161.

O. Bastiansen, H. Seip, and J. Boggs, "Perspectives in Structural Chemistry", 1971, Vol. IV, J. Wiley, New York.

O. Bastiansen, L. Fernholt, H.M. Seip, H. Kambara, and K. Kuchitsu, J.Mol.Structure, 1973, 18, 163.

E. Bernaert, M. Anteunis, and R. De Waele, Bull.Soc.Chim.Belges, 1973, 82, 795.

E. Bernaert, M. Anteunis, and D. Tavernier, Bull.Soc.Chim.Belges, 1974, 83, 357.

A.K. Bhatti, Ph.D. Thesis, 1973, State University of Ghent, Belgium.

A.K. Bhatti, and M. Anteunis, Tetrahedron Letters, 1973, 71

G. Binsch, E.L. Eliel, and S. Mager, J.Org.Chem., 1973, 38, 4079.

A.V. Bogatskii, and N.L. Garkovik, Russ.Chem.Revs.Engl.Trans., 1968, 37, 264.

H. Booth, Tetrahedron Letters, 1965, 411.

H. Booth, and P.R. Thornburrow, Chem. and Ind.(London), 1968, 685.

F. Borremans, Unpublished results, 1973.

F. Borremans, Ph.D. Thesis, 1975, State University of Ghent.

F. Borremans, and M. Anteunis, In preparation, 1975.

F. Borremans, M. Anteunis, and F. Anteunis-De Ketelaere,
     Org.Magn.Resonance, 1973, 5, 299.

W.A. Brown, G. Eglington, J. Martin, W. Packer, and G.A. Sim,
     Proc.Chem.Soc., 1964, 57.

R. Bucourt, Top.Stereochem., 1974, 8, 159.

H.R. Buys, Rec.Trav.Chim.Pays-Bas, 1969, 88, 1003.

H.R. Buys, and E.L. Eliel, Tetrahedron Letters, 1970, 2779.

H.R. Buys, and H.J. Geise, Tetrahedron Letters, 1970, 2991.

V.F. Bystrov, Russ.Chem.Revs., 1972, 41, 281.

A. Camerman, N. Camerman, and J. Trotter, Acta Cryst., 1965,
     19, 449.

G. Claeson, G.M. Androes, and M. Calvin, J.Amer.Chem.Soc.,
     1960, 82, 4428.

E. Coene, and M. Anteunis, Bull.Soc.Chim.Belges, 1970a, 79, 25.

E. Coene, and M. Anteunis, Tetrahedron Letters, 1970b, 595.

E. Coene, and M. Anteunis, Bull.Soc.Chim.Belges, 1970c, 79, 37.

P.M. Collins, A.S. Travis, K.N. Tsiquaye, P.F. Lindley, and D.
     Perratt, J.Chem.Soc., Perkin I, 1974, 1895.

R.C. Cookson, T.A. Crabb, Tetrahedron, 1972, 28, 2139.

M. Coryn, and M. Anteunis, Bull.Soc.Chim.Belges, 1974, 83, 83.

B. Coxon, Tetrahedron, 1966, 22, 2281.

D. Danneels, and M. Anteunis, Org.Magn.Resonance, 1974, 6, 617.

D. Danneels, and M. Anteunis, Tetrahedron, 1975, in press.

J. Dale, Tetrahedron, 1974, 30, 1683.

H. De Beule, and M. Anteunis, Bull.Soc.Chim.Belges, 1974, 83,
     295.

A.J. De Kok, and C. Romers, Rec.Trav.Chim.Pays-Bas, 1970, 89,
     313.

J. Delmau, and C. Barbier, J.Chem.Phys., 1964, 41, 1106.

J. Delmau, and J. Duplan, Tetrahedron Letters, 1966, 559.

J. Delmau, J.C. Duplan, and M. Davidson, Tetrahedron, 1968, 24, 3939.

P. Dirinck, and M. Anteunis, Can.J.Chem., 1972, 50, 412.

P. Dirinck, and M. Anteunis, Journal of Fluorine Chemistry, 1972-73, 2, 194.

R. Dratler, and P. Laszlo, Tetrahedron Letters, 1970, 2607.

G. Eccleston, and E. Wyn-Jones, Chem.Commun., 1969, 1511.

G. Eccleston, B. Walsh, E. Wyn-Jones, and H. Morris, Transact.Farad.Society, 1971, 67 (587)} 3223.

E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis", (1965), Wiley Interscience, New York.

E.L. Eliel, and G.A. Giza, J.Org.Chem., 1968, 33, 3754.

E.L. Eliel, and M.C. Knoeber, J.Amer.Chem.Soc., 1968, 90, 3444

E.L. Eliel, Bull.Soc.Chim.France, 1970a, 517.

E.L. Eliel, Accounts of Chem.Research, 1970b, 3, 1.

E.L. Eliel, Kemisk Tidskrift, 1969, 81, 22.

E.L. Eliel, and M.K. Kaloustian, Chem.Commun., 1970, 290.

E.L. Eliel, and D.I.C. Raileanu, Chem.Commun., 1970, 291.

E.L. Eliel, Angew.Chem.Int.Ed. Engl.Trans., 1972, 11, 739.

E.L. Eliel, and R.M. Enanoza, J.Amer.Chem.Soc., 1972, 94, 8072.

E.L. Eliel, and H.D. Banks, J.Amer.Chem.Soc., 1972, 94, 171.

E.L. Eliel, and S.A. Evans, J.Amer.Chem.Soc., 1972, 94, 8587.

E.L. Eliel, and O. Hofer, J.Amer.Chem.Soc., 1973, 95, 8041.

E.L. Eliel, J.R. Powers, and F.W. Nader, Tetrahedron, 1974, 30, 515.

E.L. Eliel, and F. Alcudia, J.Amer.Chem.Soc., 1974, 96, 1939.

O. Exner, V. Jehlicka, and B. Uchitil, Coll.Czescholowak Chem. Comm., 1968, 33, 2862.

J. Feeney, M. Anteunis, and G. Swaelens, Bull.Soc.Chim.Belges, 1968, 77, 121.

H. Friebolin, S. Kabuss, W. Maier, and A. Lüttringhaus, Tetrahedron Letters, 1962, 683.

H. Friebolin, H.G. Schmidt, S. Kabuss, and W. Faisst, Org.Magn. Resonance, 1969, 1, 67.

E.W. Garbisch, and M.G. Griffith, J.Amer.Chem.Soc., 1968, 90, 6543.

A. Geens, G. Swaelens, and M. Anteunis, Chem.Commun., 1969, 439.

A. Geens, M. Anteunis, F. De Pessemier, J. Fransen, and G. Verhegghe, Tetrahedron, 1972, 28, 1097.

H.J. Geise, H.R. Buys, and F.C. Mijlhoff, J.Mol.Structure, 1971, 9, 447.

G. Goor, and M. Anteunis, Heterocycles, 1975, 3, 363.

A. Greenberg, and P. Laszlo, Tetrahedron Letters, 1970, 2641.

A.I. Gren, Nguen Van D'en, A.V. Bogatskii, and Yu.Yu. Samitov, Khim.Geterotsikl.Soedin, 1973, 9, 1240.

P. Groth, Acta Chem.Scand., 1968, 22, 128.

L.D. Hall, and R.N. Johnson, Org.Magn.Resonance, 1972, 4, 369.

P.C. Hamblin, R.F.M. White, and E. Wyn-Jones, Chem.Commun., 1968, 1058.

P.C. Hamblin, R.F.M. White, and E. Wyn-Jones, J.Mol.Structure, 1969, 4, 275.

R.K. Harris, and R.A. Spragg, J.Chem.Soc.(B), 1968, 684.

L.M. Jackman, and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", 1969, 2nd Edt., Pergamon Press, Chapter 4.

M.S. Jacques, and M. Bernard, Can.J.Chem., 1969, 47, 2911.

F.R. Jensen, and B.H. Beck, J.Amer.Chem.Soc., 1968, 90, 3251.

F.R. Jensen, and R.A. Neese, J.Amer.Chem.Soc., 1971, 93, 6329.

P.L. Johnson, J.P. Schaefer, V.J. James, and J.F. McConnell,
    Tetrahedron, 1973, 28, 2901.

S. Kabuss, A. Lüttringhaus, H. Friebolin, and R. Mecke, Z.
    Naturforsch.B., 1966, 21, 320.

M. Karplus, J.Amer.Chem.Soc., 1963, 85, 2870.

G.M. Kellie, and F.G. Riddell, J.Chem.Soc.(B), 1971, 1030.

G.M. Kellie, P. Murray-Rust, and F.G. Riddell, J.Chem.Soc.,
    Perkin II, 1972 2384.

G.M. Kellie, F.G. Riddell, J.Chem.Soc., Chem. Commun., 1972,
    42.

G.M. Kellie, and F.G. Riddell, Top.Stereochem., 1974, 8, 225.

R. Kewley, Can.J.Chem., 1972, 50, 1690.

F.J. Koer, and C. Altona, Rec.Trav.Chim.Pays-Bas, 1974, 93,
    147.

P.A. Laurent, and P. Tarte, Bull.Soc.Chim.France, 1958, 1374.

J.B. Lambert, J.Amer.Chem.Soc., 1967, 89, 1836.

J.B. Lambert, R.G. Keske, R.E. Cahart, and A.P. Jovanovitch,
    J.Amer.Chem.Soc., 1967, 89, 3761.

J.B. Lambert, C.E. Mixan, D.H. Johnson, J.Amer.Chem.Soc.,
    1973, 95, 4634.

R.U. Lemieux, In "Molecular Rearrangements" (P. de Mayo, ed.),
    1964, Wiley Interscience, New York, 723.

S. Mager, and E.L. Eliel, Rev.Roumaine de Chimie, 1973, 18,
    2097.

P. Maroni, P. Gorrichon, and Tran le Trang, Bull.Soc.Chim.Fran-
    ce, 1972, 785.

P. Maroni, L. Cazaux, J.P. Gorrichon, P. Tisnes, and J.G. Wolf, Org.Magn.Resonance, 1973, 5, 517.

E.N. Marvell, and S. Provant, J.Org.Chem., 1964, 29, 3084.

F.W. Nader, and E.L. Eliel, J.Amer.Chem.Soc., 1970, 92, 3050.

M.M. Otto, J.Amer.Chem.Soc., 1937, 59, 1590

R. Parthasarathy, J. Orth, H.B. Kagan, and J.C. Fiaud, Tetrahedron, 1973, 28, 1529.

G.O. Pierson, and O.A. Runquist, J.Org.Chem., 1968, 33, 2572.

H.M. Pickett, and H.L. Strauss, J.Chem.Phys., 1970a, 53, 376.

H.M. Pickett, and H.L. Strauss, J.Amer.Chem.Soc., 1970b, 92, 7281.

K. Pihlaja, and J. Heikkilä, Acta Chem.Scand., 1967, 21, 2390.

K. Pihlaja, Ann.Univ.Turku. Ser.A, 1967, N° 114, cited in K. Pihlaja, and J. Heikkilä, Acta Chem.Scand., 1967, 21, 2390.

K. Pihlaja, Acta Chem.Scand., 1968, 22, 716.

K. Pihlaja, and S. Luoma, Acta Chem.Scand., 1968, 22, 2401.

K. Pihlaja, and P. Äyräs, Suomen Kemistilehti , 1969, B42, 65.

K. Pihlaja, K.J. Teinonen, and P. Äyräs, Suomen Kemistilehti, 1970, 43, 41.

K. Pihlaja, and P. Äyräs, Acta Chem.Scand., 1970a, 24, 531;

K. Pihlaja, and P. Äyräs, Acta Chem.Scand., 1970b, 25, 204.

K. Pihlaja, and P. Äyräs, Suomen Kemistilehti, 1970c, B43, 171.

K. Pihlaja, and J. Jalonen, Org.Mass.Spectr., 1971, 5, 1363.

K. Pihlaja, G.M. Kellie, and F.G. Riddell, J.Chem.Soc.(B), 1972, 252.

K. Pihlaja, J.Chem.Soc., Perkin II, 1974, 890.

K. Pihlaja, and P. Pasanen, J.Org.Chem., 1974, 39, 1948.

K.C. Ramey, and J. Messick, Tetrahedron Letters, 1965, 4423.

F.G. Riddell, Quart.Rev.London, 1967, 21, 364.

F.G. Riddell, and M.J.T. Robinson, Tetrahedron, 1967, 23, 3417.

F.G. Riddell, J.Chem.Soc.(B), 1970, 331.

F.G. Riddell, and M.J.T. Robinson, Tetrahedron, 1971, 27, 4163

B. Rickborn, and M. Wuesthoff, J.Amer.Chem.Soc., 1970, 92, 6894.

C. Romers, C. Altona, H.R. Buys, and E. Havinga, In "Topics in Stereochemistry" (E.L. Eliel and N.L. Allinger, Eds.), 1969, J.Wiley Interscience, New York, 39.

Z. Samek, Tetrahedron Letters, 1971, 1709.

Yu.Yu. Samitov, and R.A. Aminova, Zhur.Strukt.Khim., 1964, 5, 207.

H.G. Schmid, H. Friebolin, S. Kabuss, and R. Mecke, Spectrochim. Acta, 1966, 22, 623.

G. Schulz, and I. Hargittai, Acta Chim.Acad.Sc.Hung., 1974, 83, 331

C.W. Shoppee, F.P. Johnson, R.E. Lack, J.S. Shannon, and S. Sternhell, Tetrahedron, 1966, Supp.8, Part II, 421;

C.P. Smyth, J.Chem.Phys., 1937, 4, 209.

A. Snelson, and H.A. Skinner, Trans.Faraday Soc., 1961, 57, 2125.

G. Swaelens, and M. Anteunis, Bull.Soc.Chim.Belges, 1969a, 78 321.

G. Swaelens, and M. Anteunis, Bull.Soc.Chim.Belges, 1969b, 78 471.

G. Swaelens, Ph.D. Thesis, 1970, University of Ghent, Belgium.

G. Swaelens, and M. Anteunis, Tetrahedron Letters, 1970, 561.

G. Swaelens, M. Anteunis, and D. Tavernier, Bull.Soc.Chim. Belges, 1970, 79, 441.

D. Tavernier, and M. Anteunis, Tetrahedron Letters, 1966, 5851.

D. Tavernier, and M. Anteunis, Bull.Soc.Chim.Belges, 1967, 76, 157.

D. Tavernier, Ph.D. Thesis, 1971, State University of Ghent.

D. Tavernier, and M. Anteunis, Tetrahedron, 1971a, 27, 1677.

D. Tavernier, and M. Anteunis, Bull.Soc.Chim.Belges, 1971b, 80, 219.

D. Tavernier, and M. Anteunis, Bull.Soc.Chim.Belges, 1973, 82, 405.

D. Tavernier, M. Anteunis, and N. Hosten, Tetrahedron Letters, 1973, 75.

D. Tavernier, and M. Anteunis, J.Magn.Resonance, 1974, 13, 181.

D. Tavernier, M. Anteunis, and E. Bernaert, Bull.Soc.Chim.Belges, 1974, 83, 497.

D. Tavernier, and M. Anteunis, Unpublished results, 1975.

J.F. Tocanne, Bull.Soc.Chim.France, 1970, 750.

R. Van Cauwenberghe, Ph.D. Thesis, 1974, State University of Ghent.

R. Van Cauwenberghe, M. Anteunis, and L. Valckx, Bull.Soc.Chim. Belges, 1974, 83, 285.

M.-C. Vertut, J.-P. Fayet, G. Chassaing, and L. Cazaux, C.R.-Acad.Sci.Paris t.277, 1973, Série C, 635.

R. Walker, and M. Davidson, Can.J.Chem., 1959, 37, 492.

D.H. Williams, and N.S. Bhacca, J.Amer.Chem.Soc., 1964, 86, 2742.