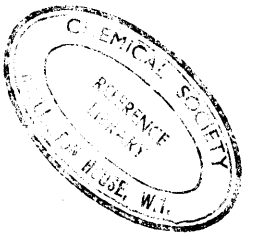
RUSSIAN CHEMICAL REVIEWS
Uspekhi Khimii

April 1971



U. D. C. 541.63 : 547.12

The Anomeric Effect

N.S.Zefirov and N.M.Shekhtman

One of the problems of dynamic stereochemistry and conformational analysis—the anomeric effect—is surveyed, and is shown to be a general conformational phenomenon occurring widely in acyclic and heterocyclic compounds. A theoretical discussion is given of the nature of this effect. The bibliography comprises 189 references.

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I. INTRODUCTION

At the present time conformational analysis is based, in its most general form, on examination of the energy contributions made by changes in bond angles and lengths, by eclipsed conformations, and by interaction between non-bonded atoms. The energy of the molecule can be written as a sum

$$E_{mol} = E_l + E_p + E_Q + E_V,$$

where E_l is the sum of the energies due to change in bond lengths from the normal to the observed value, E_p the sum of "Pitzer stresses", E_Q the sum of the angular stresses, and E_V the sum of the van der Waals interaction energies of non-bonded atoms. An additive scheme involving all these steric factors enables the conformations of a wide range of compounds to be calculated fairly accurately[1-4].

Quite a large number of cases have now accumulated in the literature in which the stability of the conformations actually observed cannot be explained solely by steric factors. This type of discrepancy is usually regarded as specific to a given grouping, and is often given a special name, e.g. "anomeric effect"[5,6], "the rabbit's-ears effect"[7-10], the Δ^2 instability factor[5,11], etc. In principle these factors can be taken into account by introducing new terms into the expression for the energy of the molecule.

The present paper examines one such effect—the so called "anomeric" effect.

II. HISTORICAL SURVEY

The oxan ring is able to exist as conformational isomers differing in stability. In contrast to cyclohexane, the

asymmetry of the oxan ring increases the number of possible conformational isomers for derivatives of this series [12]: whereas two conformations (chair and boat [13-15]) are possible for cyclohexane, the oxan ring can exist as two chair conformations (1C and C1) and several boat conformations [16], e.g. (see Ref. 12 for greater detail)



As with cyclohexane the boat conformations are energetically less advantageous. Taking the barrier to rotation in methanol as 1.1 kcal mole^{-1} indicated that for oxan the energy of the boat form exceeded that of the chair form by 3.9 kcal mole^{-1}. [17] As a comparison, ΔH for the chair $\rightleftharpoons$ boat equilibrium in cyclohexane is 5.9 kcal mole^{-1}. [18] This estimate is undoubtedly too low, since it would be more logical to base it on the barrier to rotation in dimethyl ether [19], which is 2.7 kcal mole^{-1}. [20,21] This is confirmed by the estimate of 2.2 kcal mole^{-1} for the difference in energy between chair and boat conformations of 1,3-dioxan, based on the barrier to rotation in methanol, whereas experimental determination gives ΔG = 5.7 kcal mole^{-1}, ΔH = 7.1 kcal mole^{-1}, and ΔS = 4.8 e.u. [22-24]

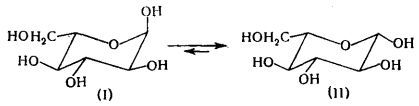
The barrier to chair $\rightleftharpoons$ boat conversion for oxan is 9.9 kcal mole^{-1}, [25,26] which is close to the value (10.3 kcal mole^{-1} [25]) found for cyclohexane.

The presence of chairlike conformations in a large number of pyranoses has been shown by X-ray examination [27-29], microwave spectroscopy [30], and nuclear magnetic resonance spectroscopy [25,26]. The R-factor which enables the departure from a chairlike conformation to be assessed, also has similar values—1.9 in oxan [31] and 2.2 in cyclohexane [32].

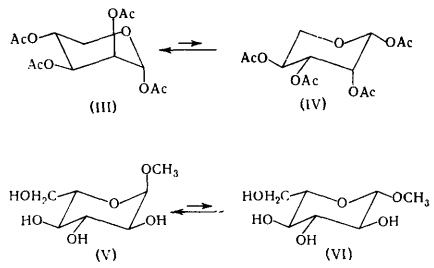
Thus the similarity in the geometry of oxan and cyclohexane enables us to apply general conformational rules to derivatives of the former compound.

The introduction by Reeves of conformational ideas into carbohydrate chemistry showed their complete applicability to this class of compounds, but also revealed the influence of specific "factors" on the relative stability of the conformations [16]. In particular we may mention e.g. the so called Δ^2 instability factor [11,16].

With free sugars both α- and β-forms are usually stable in solution (see Ref. 33 for a detailed scheme of the conformations of pyranoses). For the mutarotation of glucose in aqueous solution, for example, the equatorial form (II) has been shown to be the more stable, with ΔG_{OH} = 0.34 kcal mole^{-1}. [34,35] However, Lemieux [5] and other workers [36-39] have shown that several simple aglycones among pyranose derivatives tend in general to occupy the axial position. Lemieux termed this phenomenon the "anomeric effect" [6].



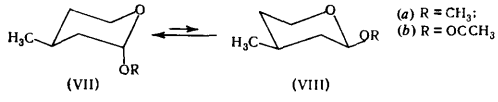
Detailed studies of the anomeric effect have been made on the $\alpha\beta$-anomerisation of pentose acetates [5], methyl pentosides [36,37,40-42], and halogeno- and acetoxy-derivatives of carbohydrates [38,43-46]. For example, 1,2,3,4-tetra-*O*-acetyl-α-D-lyxopyranose exists predominantly as the conformation (III), [5] whereas with methyl glucoside the α-anomer (V) is more stable than the β-anomer (VI). [42]



The first attempt to explain the anomeric effect was made by Edward [42], whose main idea was to examine the dipole–dipole interaction between the electronegative substituent and the ring oxygen atom. Such electrostatic interaction should be fairly large for an equatorial substituent, and slight for an axial substituent, in position 2.

Several quantitative estimates have been made of the anomeric effect in derivatives of monosaccharides. For example, Bishop [40] found a value of ~ 1.2 kcal mole^{-1} for the anomerisation of methyl pentosides in methanol. The most complete estimates of the anomerisation of sugars were given by Lemieux [5], with 1.5 and 1.3 kcal mole^{-1} respectively for the anomeric effect of the acetoxy-group in hexoses and in pentapyranoses. On the bases of these results he proposed a convenient additive scheme for calculating the preferential conformations of derivatives of monosaccharides.

In 1964 Anderson and Sepp found that the equilibrium mixtures of 2-methoxy- and 2-acetoxy-4-methyloxans contain 65% and 70% respectively of the axial forms of the compounds (VII*a*) and (VII*b*), [47] and thus showed that the anomeric effect should be a general phenomenon.



The impossibility of allowing for all the factors—all the dipole–dipole interactions, solvation, hydrogen bonds, deviations in the conformations from the standard chair forms in polysubstituted compounds, etc.—also makes it difficult to study the anomeric effect on models of monosaccharides. During recent years, therefore, various aspects of the anomeric effect have been studied extremely intensively on simple models. The investigations have shown without question that the anomeric effect is a general conformational phenomenon, unconnected with the specific structure of sugars and extremely widespread among heterocyclic compounds.

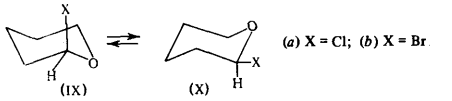
The literature on the anomeric effect has grown very rapidly since 1965. Several reviews have been published during recent years [5,33,48-50], but they are very concise and do not contain the full results. It therefore appeared to us useful to summarise in a special review the existing literature on the anomeric effect. It is systematically based on differences in the structural fragments comprising the cyclic heteroatom and the substituent atom directly attached to the ring.

III. THE ANOMERIC EFFECT IN SIX-MEMBERED CYCLIC STRUCTURES

1. The O–C–Hal Fragment

(*a*) Halogenated oxans

The conformational equilibrium of 2-halogeno-oxans can be represented by the equation



(*a*) X = Cl; (*b*) X = Br

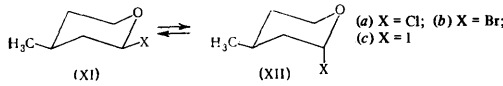
The conformational free energy of chlorine and bromine in the cyclohexane series is 0.43 [51] (0.53 [52]) and 0.38 [51] (0.48 [52]) kcal mole^{-1} in favour of predominance of the equatorial form.

Nuclear magnetic resonance has been used by Booth and Ouellette [53] and by Zefirov and Shekhtman [54,55] to study the conformational equilibrium of 2-chloro- and 2-bromo-oxans. They showed that the proportion of the equatorial form is very small in both compounds, the equilibrium being displaced almost completely towards the axial isomer (IX). The free energy of the conformational equilibrium (IX) $\rightleftharpoons$ (X) was estimated as 1.8 kcal mole^{-1}. The magnitude of the anomeric effect can be written

$$\Delta G_{AH} = \Delta G_0 - \Delta G_x,$$

where ΔG_0 is the equilibrium free energy and ΔG_X the conformational free energy of the substituent in the cyclohexane series [47] (this view has been criticised [56]). In this case the anomeric effect is estimated as 2.3 kcal mole^{-1}. Variation in the polarity of the solvent has very little influence on the position of the conformational equilibrium (IX) $\rightleftharpoons$ (X). [53] It is interesting that the n.m.r. spectrum of (IX*a*) shows a reversal of the chemical shifts of the signals from the axial and the equatorial proton attached to $C_{(6)}$. [55]

The above results [53–55] were based on a semi-quantitative estimate of the equilibrium position from the spin–spin interaction constants. A more exact estimate of the anomeric effect was made by Anderson and Sepp [57] in a study of the epimerisation of 2-halogeno-4-methyloxans (XI) and (XII) (*a*–*c*)

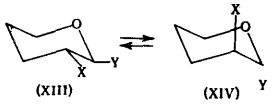


(*a*) X = Cl; (*b*) X = Br; (*c*) X = I

From data on the epimerisation equilibrium the anomeric effect for chlorine was estimated as 2.65 and 2.0 kcal mole^{-1} for non-polar and polar solvents respectively. The anomeric effect for bromine and iodine was ~ 3.1 kcal mole^{-1}.

Gas chromatography showed that 2-chloro-oxan comprises a mixture of equal quantities of axial and equatorial forms (IX*a*) and (X*a*). [58] However, this conclusion is undoubtedly erroneous, since it contradicts all the work cited above. Furthermore, the preferred axial conformation of this compound has recently been proved by measuring the Kerr constants and the dipole moments [59].

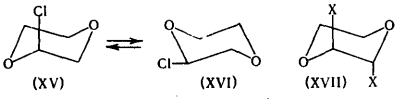
Lemieux and Fraser-Reid [43] found that *trans*-2,3-dichloro- and bromo-oxans exist predominantly as the *trans*-diaxial conformation (XIV).



In this case the position of the conformational equilibrium is determined not only by the anomeric effect but probably also by 1,2-repulsion of the halogen atoms in the diequatorial conformation. This effect has been studied in some detail among cyclohexane derivatives [60–62].

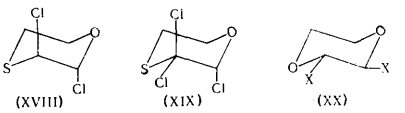
(*b*) Halogenated dioxans and oxathians

Zefirov and Fedorovskaya [63] observed a distinct anomeric effect with 2-chloro-1,4-dioxan. The equilibrium (XV) $\rightleftharpoons$ (XVI) was extensively displaced towards the axial isomer (XV), the position of the conformational equilibrium being as little affected by the polarity of the solvent as in the case of 2-halogeno-oxans.

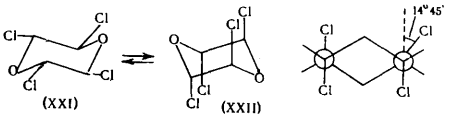


(X = Cl, Br)

Much work has been done on elucidating the configurations and preferred conformations of 2,3-dihalogeno-1,4-dioxans [64–68]. X-Ray examination has shown that the *trans*-isomers of 2,3-dichloro- and 2,3-dibromo-1,4-dioxans exist in the diaxial conformation (XVII). [64,65] Nuclear magnetic resonance has shown that in solution *trans*-2,3-dichloro-, -2,3-dibromo-, and -2,5-dichloro-1,4-dioxans also occur in the diaxial conformation [64,65,67–70]. Wolf and his coworkers [71,72] have studied the conformations of many polychlorinated oxathians and established a distinct anomeric effect in the halogenated derivatives. For example, *trans*-2,3-dichloro-oxathian and 2,3,3-trichloro-oxathian have the more stable conformations (XVIII) and (XIX) respectively.



It is probable that, as with 2,3-dichloro-oxan, the axial conformations of 2,3-dihalogenodioxans and 2,3-dichloro-oxathian are due not only to an anomeric effect but also to repulsion of the halogen atoms in the diequatorial conformation (XX).

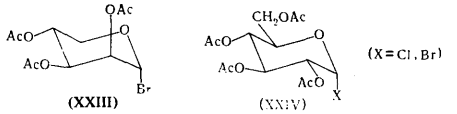


Extraordinarily interesting results have been obtained in a study of the crystalline structure of *trans*-2,3,5,6-tetrachloro-1,4-dioxan [73]. In spite of strong 1,3-interactions, the stable conformation is (XXII), in which all four chlorine atoms are axial. The C–Cl bond is inclined at an angle of 14°45′ to the vertical position.

(*c*) Pyranosyl halides

Numerous examples of pyranosyl halides have shown that the form in which the halogen is in an axial position is usually the more stable [5,11,38,39,45,74]. Thus (XXIII) and

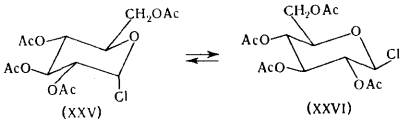
(XXIV) are the stable conformations of tri-*O*-acetyl-D-lyxopyranosyl bromide and tetra-*O*-acetyl-α-D-glucopyranosyl halides respectively.



(XXIII) (XXIV)

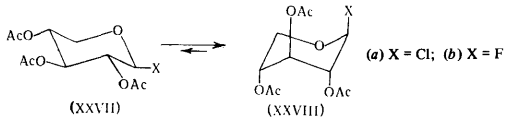
The anomerisation of pyranosyl halides should occur extremely readily, since the halogen atom is capable of nucleophilic detachment and the cyclic oxygen atom greatly stabilises the resulting carbonium ion. Since anomerisation occurs smoothly, therefore, the main factor determining the relative stability of the epimers is the anomeric effect.

Lemieux and Hayami [75] estimated the anomeric effect of the chlorine atom attached to $C_{(1)}$ in acetochloroglucose as ~ 2 kcal mole^{-1} in acetonitrile (taking into account ΔG_{Cl}), which corresponds to the presence of 93–95% of the α-anomer (XXV) in the equilibrium mixture.



(XXV) (XXVI)

In several cases the anomeric effect is sufficiently large to displace the equilibrium to a "completely" axial conformation. Very interesting examples of this type are provided by β-D-xylopyranosyl chloride and fluoride, the most stable conformations of which are (XXVIII*a*) and (XXVIII*b*), in which all four constituents are in axial positions [33,76–79]:

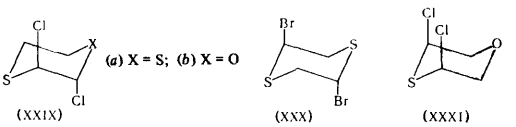


(XXVII) (XXVIII)

The 1,3-diaxial repulsion of two acetoxy-groups in the cyclohexane series has been estimated as 2.0 kcal mole^{-1}. [80] Although the structure (XXVIII) involves two 1,3-diaxial repulsions, this conformation is the more stable.

2. The S–C–Hal Fragment

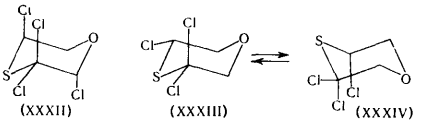
The repulsion between sulphur and halogen atoms is sufficient to destabilise the equatorial conformation. Kalff and Romers [81,82] made an X-ray examination of *trans*-2,3-dichlorodithian and *trans*-2,5-dibromodithian, and found them to have the conformations (XXIX*a*) and (XXX) respectively.



(XXIX) (XXX) (XXXI)

Few data are available on the conformations of compounds of this type in solution. Study of the infrared spectra and dipole moments of *trans*-2,3-dichloro- and *trans*-2,5-dibromo-1,4-dithians has shown [72] that these compounds have the same conformations as in the crystal.

It has been found [71,72,83] that *trans*-2,3-dichloro-, *cis*-3,5-dichloro-, *trans*-2,3,3,5-tetrachloro-, and 3,3,5-trichloro-oxathians have the preferred conformations (XXIX*b*) and (XXXI)–(XXXIII) respectively.



(XXXII) (XXXIII) (XXXIV)

These results are based on the vicinal spin–spin splitting constants. When compounds (XXXI)–(XXXIII) are compared, however, it remains obscure why the diaxial repulsion of the halogen atoms destabilises the conformation (XXIV), although this does not occur with compound (XXXI). It is also noteworthy that in several cases the quantity J_{ee} was of the order of 6–8 c/s, which perhaps indicates the presence of a mobile equilibrium, e.g. (XXXIII) ⇌ (XXXIV).

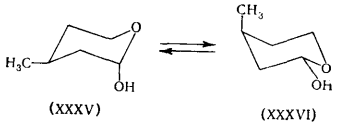
3. The O–C–OR Fragment

(*a*) Hydroxy-derivatives (R = H)

Oxan-2-ol is a cyclic tautomer of hydroxyvaleraldehyde, and according to the infrared spectra [84] exists in the hemiacetal form. It is well known that cyclic hemiacetal forms predominate with monosaccharides. It has already been remarked that the polarity of the solvent has relatively little effect on the position of the conformational equilibrium in 2-halogenated oxans, but the situation is quite different with the 2-hydroxylated derivatives.

The position of the conformational equilibrium is considerably changed by transfer from aprotic solvents to water, being displaced towards the equatorial form. This applies also to cyclohexanols, for which the mean values of ΔG_{OH} are 0.54 and 0.87 kcal mole^{-1} in aprotic solvents and in water respectively [51]. Stabilisation of the equatorial conformation of 2-hydroxylated oxans in water may be due either to an increase in the dielectric constant of the medium, which diminishes the anomeric effect, or to strong solvation of the hydroxy-group, which increases its effective volume.

In fact, Anderson and Sepp [85] found that the transfer from aprotic solvents to water produces a marked change in the conformational equilibrium for *trans*-4-methyloxan-2-ol: in water this compound exists to the extent of 66% in the equatorial conformation, whereas in carbon tetrachloride the conformation (XXV) with an axial hydroxyl predominates (60%):



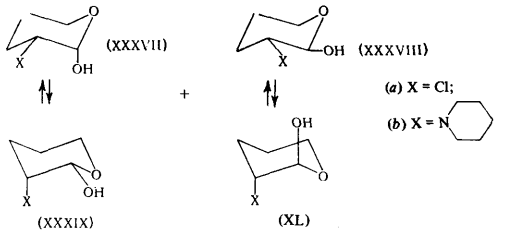
(XXXV) (XXXVI)

Pierson and Runquist showed by means of n.m.r. spectroscopy that the proportion of the axial isomer in oxan-2-ol is 77% in non-polar solvents [86]. This result is confirmed by infrared spectroscopy. Thus in 5% solution in carbon tetrachloride, for example, the conformation having an axial hydroxyl predominates, its proportion increasing further with dilution [85].

It is interesting that a distinct anomeric effect has been observed [87] with chroman-2-ol both in acetonitrile and in carbon tetrachloride, the proportion of the axial isomer (80–85%) being independent of the concentration.

The equilibrium mixture of oxan-2,3-diol in deuterochloroform has been shown by the n.m.r. spectra to comprise 30% of *cis*- and 70% of *trans*-diequatorial isomers[88]. The decisive part in stabilisation is probably played by an intramolecular hydrogen bond[89].

In dimethyl sulphoxide the addition product of hypochlorous acid and dihydropyran comprises a mixture of *cis*- and *trans*-isomers in the proportions 37 : 63, with $J_{2,3} = 5.6$ c/s for the *trans*-isomer, which suggests the presence in conformational equilibrium (XXXVIII) ⇌ (XL*a*) of an appreciable fraction of the diaxial form (XL*a*).[90]



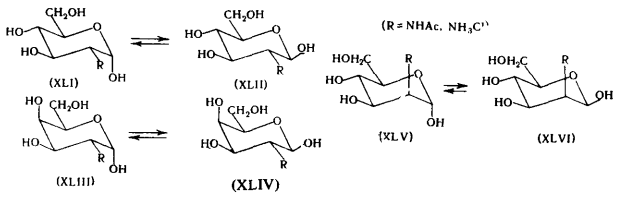
The equilibrium mixture of 3-piperidino-oxan-2-ol comprises 46% of the *cis*-isomer (XXXVII) ⇌ (XXXIX*b*) and 54% of the *trans*-isomer (XXXVIII*b*) ⇌ (XL*b*). For the *trans*-isomer $J_{2,3} = 6.6$ c/s,[91] which also indicates predominance of the diequatorial conformation (XXXVIII*b*).

Thus with oxan-2-ol derivatives in protic solvents the conformation in which the hydroxyl is in an equatorial position is usually the more stable.

The conformation of sugars and their $\alpha\beta$-anomerisation are well known[5,33,40,48,74,92,93], and we shall not discuss this subject in detail. We note merely that the magnitude of the anomeric effect in monosaccharides may be affected by a far larger number of factors than in the case of oxan-2-ol. As with the latter, the anomeric effect is influenced primarily by the nature of the solvent. Thus the equilibrium mixture of glucose in absolute methanol contains equal quantities of α- and β-forms, which gives an anomeric effect of 0.9 kcal mole^{-1},[94] but in water the proportions of the two forms are 36 : 64.[48,95] In a pyridine solution of mannose the equilibrium mixture contains 85% of the α-form[96] (the calculated anomeric effect is 1.15 kcal mole^{-1} [94]). The magnitude of the effect increases in non-polar solvents[94].

It has been found with aldopyranoses that the configuration of the hydroxyl attached to the $C_{(2)}$ atom greatly influences the magnitude of the anomeric effect[48]. Angyal showed that, in the absence of a 2-hydroxyl, the effect in pyranoses is 0.85 kcal mole^{-1}; if the hydroxyl is axial the effect is 1.0 kcal mole^{-1} (except when the 3-hydroxyl is also axial); and finally the anomeric effect is 0.55 kcal mole^{-1} when the 2-hydroxyl is equatorial (all values of the anomeric effect were calculated with ΔG_{OH} taken into account).

Polarimetric data and n.m.r. spectra have shown that replacement of the 2-hydroxyl in a series of D-gluco- and D-galacto-pyranoses by an acetamido-group or by an ammonium group results in greater stability of the α-forms (XLI) and (XLIII), whereas with D-mannose the β-form (XLVI) is stabilised[97,98].



Thus a great variety of factors—solvent, intramolecular hydrogen bonds, specific solvation, nature of substituent adjacent to anomeric centre, etc.—influence the conformational equilibrium of oxanols.

(*b*) Alkoxyoxans

Alkoxyoxans are very convenient models for examining various factors influencing the anomeric effect, as a consequence of which they are probably the most thoroughly studied. Zefirov and Shekhtman[54,55] and Pierson and Runquist[86] have made semi-quantitative assessments of the position of the conformational equilibrium and the magnitude of the anomeric effect for a wide range of 2-substituted oxans. These workers have found that 2-alkoxyoxans do exhibit an anomeric effect, whose value varies somewhat with the polarity of the solvent. Thus the anomeric effect for a series of 2-alkoxyoxans varies over the range 1.3–2.8 kcal mole^{-1} in non-polar solvents, and over the range 1.25–1.9 kcal mole^{-1} in acetonitrile[49,54,55].

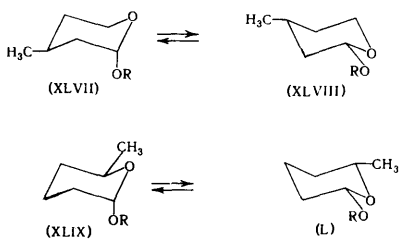
The electronegativity of the substituent undoubtedly affects the position of conformational equilibrium. There is probably a general tendency for the anomeric effect to increase slightly with electronegativity. Quantitative correlation is difficult, however, because of the lack of reliable and accurate data on the position of conformational equilibrium for a wide range of substituents. Pierson and Runquist[86] tried to correlate the free energy for the equilibrium in a series of 2-alkoxyoxans with the Taft inductive σ^*-constants for the radical in the alkoxy-group. However, the resulting correlation can hardly be regarded as in any way reliable owing to the crudity with which the equilibrium position was estimated.

The position of conformational equilibrium in 2-alkoxyoxans appears to be relatively insensitive to the size of the radical in the alkoxy-group[7,54,55,86,99].

It is interesting that α-fenchol reacts with dihydropyran to yield two compounds, which have been regarded as conformational isomers containing an axial and an equatorial fenchyloxy-group[100]. Such separation of conformers is obviously unprecedented, and it is probable that these workers were actually dealing with structural isomers.

The nature of the solvent has a relatively weak influence on the anomeric effect, although a certain tendency is observed for the content of the axial form to increase with decrease in the polarity of the medium[7,47,54,85,86,101].

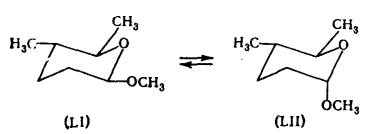
More exact data were obtained by Anderson and Sepp[57,101] and also by Eliel and Giza[56] in a study of the epimerisation of 2-alkoxy-4-methylpyrans (XLVII) ⇌ (XLVIII) and 2-alkoxy-6-methylpyrans (XLIX) ⇌ (L). They found a distinct dependence of the anomeric effect on the solvent. Thus ΔG for 2-methoxy-4-(and 6)-methyloxans in carbon tetrachloride is respectively 0.83 and 0.73 kcal mole^{-1} (corresponding to 80% and 67% of the anomer XLVII), whereas in acetonitrile the values are 0.42 and 0.35 kcal mole^{-1} (67% and 64% of the anomer XLVII).[56,102]



The size of the alkoxy-group has been considered[85] to have no significant influence on the position of the conformational equilibrium. In fact, the proportion of the *trans*-form (XLVII) remains almost unchanged on passing from the methoxy- to the isobutoxy-group. Thus in acetonitrile, for example, 65% of (XLVII) is present in the case of 2-methoxy-4-methyloxan, and 70% with 2-isobutoxy-4-methyloxan. Other workers[56], however, have noted a definite and monotonic decrease in the proportion of axial conformations (XLVII) and (XLIX) with increase in the bulk of the radical in the alkoxy-group. Thus $\Delta G(CCl_4)$ has the values 0.73, 0.64, and 0.5 kcal mole^{-1} for the methoxy-, isopropoxy-, and t-butoxy-groups in the 2-alkoxy-6-methyloxans.

The position of the conformational equilibrium in alkylated 2-alkoxyoxans is relatively insensitive to the location of the alkyl substituent in the ring[56,85,101]. Thus 2-methoxy-4-methyloxan in methanol contains 69%[101] (67.3%[56]) of the conformation (XLVII), while in 2-methoxy-6-methyloxan the content of the axial isomer (XLIX) under the same conditions is 70%[101] (62.5%[56]).

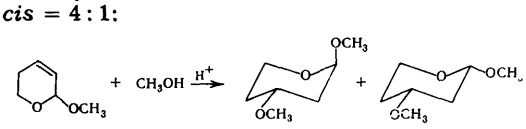
It has been pointed out[101] that the proportion of the axial form is greater with methyl glucoside than with methyl xyloside and 2-methoxyoxan. The explanation offered was that the presence of two bulky groups in positions $C_{(5)}$ and $C_{(6)}$ of the oxan ring in the equatorial position results in their steric repulsion, which may lead to a slight flattening of the ring and hence an increase in the distance between the axial 6- and 2-substituents, so that the steric repulsion of the 2-substituents is diminished. This effect has been confirmed experimentally on the isomeric 2-methoxy-5,6-dimethyloxans[101]. It was observed that the epimerisation of 2-methoxy-*trans*-5,6-dimethyloxans yields an equilibrium mixture in which the content of the isomer (LII) reaches 77%.



(LI) (LII)

Distinct anomeric effects have been observed also with oxanyloxy-,[103] trimethylsiloxy-,[54] t-butylperoxy-,[104] and alkylthio-oxans[103].

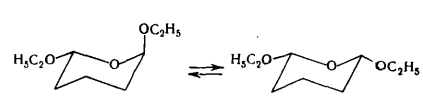
Sweet and Brown[105] showed that the addition of methanol to 5,6-dihydro-2-methoxy-2*H*-pyran yields a mixture of 2,4-dimethoxyoxans in which the ratio of the isomers is *trans* : *cis* = 4 : 1:



(LIII) (LIV)

Since the reaction was conducted in acid medium, the composition of the mixture was probably controlled thermodynamically. The n.m.r. spectra showed that the 4-methoxy-group occupied an equatorial position, while the anomeric effect in methanol was 1.4 kcal mole^{-1}. The difference in magnitude of the anomeric effect in (LIII) and (XLVII)—that of the latter compound in methanol is[85] 0.9 kcal mole^{-1}—was regarded[105] as a good illustration of the polar nature of the anomeric effect.

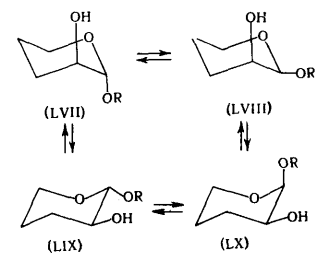
The anomeric effects of 2,6-diethoxyoxans



(LV) (LVI)

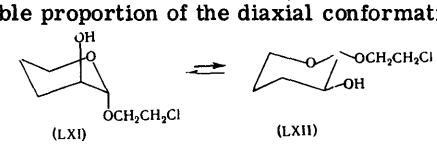
and of 2-ethoxy-4(or 6)-methyloxans are almost the same[56,108] when it is remembered that the *trans*-isomer (LV) is a DL-pair, so that ΔG is increased by $RT \ln 2 = 0.41$ kcal mole^{-1}. It is found also that with increase in the polarity of the solvent the equilibrium (LV) $\rightleftharpoons$ (LVI) is displaced towards the *cis*-isomer. Thus ΔG for this equilibrium has the values 1.16, 0.76, and 0.89 kcal mole^{-1} in carbon tetrachloride, acetonitrile, and ethanol respectively[56].

There is no published information on the conformations of 2,3-dialkoxyoxans, but 2-alkoxyoxan-3-ols have been studied by several workers. Although the n.m.r. data[107,108] are somewhat contradictory, there is no doubt about the predominance of the *trans*-diaxial form (LVII) and the presence of an anomeric effect; the size of the alkoxy-group has hardly any influence on the position of the conformational equilibrium[108].



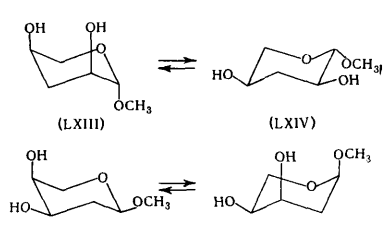
(LVII) (LVIII) (LIX) (LX)

The *trans*-isomer of 2-2′-chloroethoxyoxan-3-ol has $J_{3,2} = 5$ c/s in deuterochloroform[88], which also suggests a considerable proportion of the diaxial conformation (LXI).



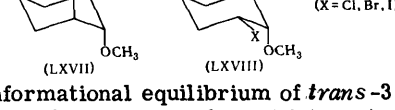
(LXI) (LXII)

Lemieux and Pavia[109] found that the nature of the solvent was the main factor determining the conformations of methyl 3-deoxy-β-L-erythropentapyranoside and 2-deoxy-L-erythropentapyranoside. In deuterium oxide the compounds exist in the conformations (LXIV) and (LXV), but in deuterochloroform as (LXIII) and (LXVI) respectively. The n.m.r. data correlate well with the specific rotations.



(LXIII) (LXIV) (LXV) (LXVI)

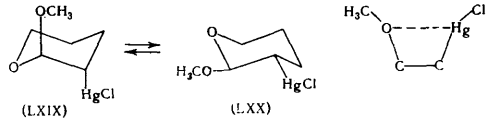
The halogenomethoxylation of dihydropyran yields a mixture of 3-halogeno-2-methoxyoxans. The *trans*-isomer exists in the diaxial conformation (LXVII), and the *cis*-isomer in the equatorial–axial conformation (LXVIII).[43] Iodomethoxylation results in the formation of 100% of (LXVII), whereas chloromethoxylation gives 75% of (LXVII) and 25% of LXVIII).



(LXVII) (LXVIII) (X = Cl, Br, I)

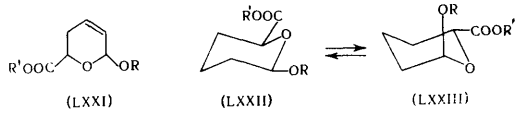
The conformational equilibrium of *trans*-3-chloromercuri-2-methoxyoxan is of great interest. Since $\Delta G_{HgCl} \simeq 0$ (the value of ΔG for the $HgOCOCH_3$ group is[52]

0 ± 0.09 kcal mole^{-1}), and also because of the anomeric effect of the methoxy-group, the conformation (LXIX) should predominate. According to Zefirov and Shekhtman[55], however, the diequatorial conformation (LXX) is stable. This was explained by the additional effect of coordination of the methoxyl oxygen and the mercury atom, which stabilises (LXX). The magnitude of this effect is 0.95 kcal mole^{-1} with ΔG_{OCH_3} taken into account.



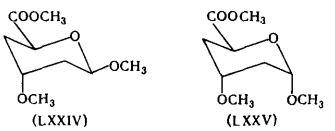
(LXIX) (LXX)

The n.m.r. spectra of Δ^3-dihydropyrans (LXXI) (obtained by Diels–Alder condensation of 1-alkoxyalka-1,3-dienes with carbonyl-containing compounds) and of the corresponding oxans indicate that isomers having shorter retention times in gas–liquid chromatography comprise more than 90% *trans-ax,eq*-isomers with the alkoxy-group in the axial position, whereas isomers having longer retention times comprise not less than 90% of *cis-eq,eq*-isomers[110,111]. Epimerisation in the presence of boron trifluoride leads to the conversion of *cis*-isomers (LXXII) into *trans*-isomers (LXXIII).



(LXXI) (LXXII) (LXXIII)

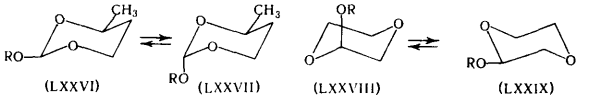
It is interesting that, in the case of methyl 4,6-dimethoxyoxan-2-carboxylate, the *ribo*-configuration (LXXV) is more stable than the *arabino*-isomer (LXXIV), in spite of the 1,3-diaxial arrangement of the methoxy-groups[112].



(LXXIV) (LXXV)

(*c*) Alkoxy-derivatives of saturated six-membered heterocycles containing two heteroatoms

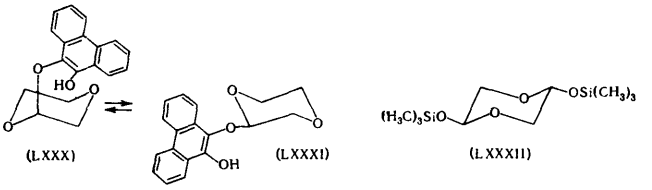
Eliel and Giza[10,56] observed a distinct anomeric effect with 2-alkoxy-1,3-dioxans. The epimerisation of 2-methoxy(and ethoxy)-4-methyl-1,3-dioxans (LXXVI) ⇌ (LXXVII) results in predominance of the *cis*-isomer (LXXVII), with ΔG_{OR} = 0.35 kcal mole^{-1} in carbon tetrachloride. For 2-methyl-1,3-dioxan ΔG_{CH_3} = 3.6–4.1 kcal mole^{-1}, which far exceeds the value of 1.7 kcal mole^{-1} observed for methylcyclohexane[51].



(LXXVI) (LXXVII) (LXXVIII) (LXXIX)

Zefirov and Fedorovskaya used the n.m.r. method to show that the anomeric effect applies to 2-alkoxy-1,4-dioxans[63,113]. In contrast to 2-alkoxyoxans[7,54,55,86,99], however, their conformational equilibrium (LXXVIII) ⇌ (LXXIX) is more sensitive to the volume of the substituent in the alkoxyl. Thus the (LXXIX) content increases by about 25% on passing from the methoxy- to the t-butoxy-group at position 2.[63]

Similar results have been obtained for 2-phenanthryloxy-1,4-dioxan, in which the steric effect predominantes over the polar effect, so that the conformational equilibrium is displaced towards the equatorial isomer (LXXXI):[114]



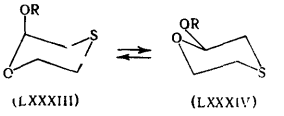
(LXXX) (LXXXI) (LXXXII)

A general explanation of this phenomenon can be given in terms of the "hockey-stick effect" (see below).

It is interesting that in the n.m.r. spectrum of 2,5-bistrimethylsiloxy-1,4-dioxan J_{AX} = 6.0 c/s and J_{BX} = 2.4 c/s (in carbon tetrachloride), so that a diequatorial conformation (LXXXII) was adopted for this compound[115]. For 2-t-butoxydioxan $J_{AX} + J_{BX}$ = 8.4 c/s,[62] and in both cases the content of the diaxial conformation is ~ 45%.

Another pecularity of alkoxy-1,4-dioxans is that the effect of the solvent on the position of conformational equilibrium is opposite to that observed with oxan derivatives[7,47,54,85,86,101]. With 2-alkoxy-1,4-dioxans the proportion of the axial conformation increases somewhat on passing from carbon tetrachloride to acetonitrile, which may be due to fine solvation effects at the 4-oxygen atom[63].

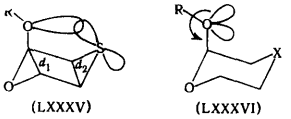
As already noted, introduction of the second heteroatom on passing from 2-alkoxyoxans to 2-alkoxydioxans has no great qualitative effect on the conformational behaviour. However, the situation changes radically on passing to 2-alkoxyoxathians, as Foster et al.[116] and Zefirov et al.[113,117] have shown. Thus with 2-methoxy- and 2-butoxyoxathians at least 50% of the equatorial conformation (LXXXIV) is present at equilibrium.



(LXXXIII) (LXXXIV)

A strict interpretation of this phenomenon is difficult because of the absence of experimental conformational analyses of other, analogous heterocyclic systems. However, it is obvious that destabilisation of the axial conformation cannot be explained simply by dipole–dipole repulsion of the 4-heteroatom and the substituent, for such repulsion should be more strongly developed in 1,4-dioxan than in 1,4-oxathian derivatives.

A general explanation of this phenomenon can evidently be based on the "hockey-stick effect"[118]. For the R–O–C–C–S fragment, in particular, the orbital of the oxygen atom (p or sp^3) may overlap an orbital of the sulphur atom (p- or sp^3-hybrid), as shown in formula (LXXXV). Since these orbitals are populated by four electrons, such overlap should lead to repulsion. Such repulsion will evidently depend on the geometry of the molecule, in particular on the relative distances d_1 and d_2, and also on the nature of the atoms having lone pairs of electrons. Experimental results must be accumulated for a more detailed study of this phenomenon.



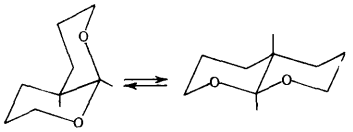
(LXXXV) (LXXXVI)

However, the "hockey-stick effect" enables an acceptable explanation to be given for the greater sensitivity noted above of the conformational equilibrium to the volume of the alkoxy-substituent in the 1,4-dioxan series than in

alkoxyoxans. In fact the most stable rotational conformation of the axial alkoxy-group is (LXXXVI), in which the radical R is directed outside the ring, and hence the orbitals of the oxygen atom containing lone pairs are directed inside the ring. Hence arises the possibility of repulsion of the 4-oxygen atom and the alkoxyl oxygen as a consequence of the "hockey-stick effect". If, however, the size of R is small, the group OR may adopt a more favourable rotational conformation, which will diminish such repulsion. When R is a bulky group, e.g. t-butyl, the mobility of OR is restricted significantly, and the orientation of OR observed with respect to $O_{(4)}$ leads to repulsion, which partly destabilises the axial conformation (LXXXVI).

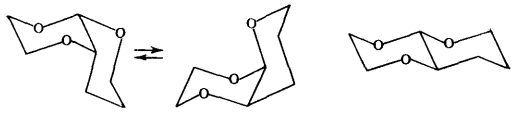
(*d*) Fused saturated systems

The axial forms of 3-alkoxy-4-oxa-5α-cholestanes and 3-methoxy-4-oxa-5α-oestranes are the more stable[119,120]. Thus an anomeric effect is clearly evident for the group O–C–O–C, which is a fragment of the polyfunctional fused systems.



(LXXXVII) (LXXXVIII)

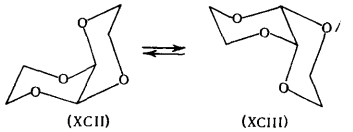
Descotes et al.[121] have shown by the n.m.r. method that the epimerisation of decahydro-1,8-dioxanaphthalene yields an equilibrium mixture of 57% of the *cis*-form (LXXXVII) and 43% of the *trans*-form (LXXXVIII), which differs markedly from the behaviour of decalin[122]. The relative stabilisation of the *cis*-isomer is explained by the anomeric effect, since the fragment O–C–O–C in this compound is analogous in (LXXXVII) to the O–C–O–R observed for the axial conformation of 2-alkoxyoxan, and the anomeric effect is of the same order in this case (1.4 kcal mole^{-1} [121]) as for simple 2-alkoxyoxans[84,101].



(LXXXIX) (XC) (XCI)

cis-Decahydro-1,4,5-trioxanaphthalene (LXXXIX) $\rightleftharpoons$ (XC) and the *trans*-isomer (XCI) were prepared by Sweet and Brown[88], and their structures proved by means of the n.m.r. spectra. Unfortunately these workers did not study the acid epimerisation, but it can be confidently stated that here the *cis*-isomer (XC) should be the more stable, as a consequence of the anomeric effect.

A *trans*-configuration was originally attributed to decahydro-1,4,5,8-tetraoxanaphthalene on the bais of X-ray data on its complex with mercurous chloride[123]. However, low-temperature n.m.r. spectroscopy has shown that this possesses a *cis*-configuration; the latter is more stable owing to the anomeric effect. The compound exists as two rapidly interconvertible conformations



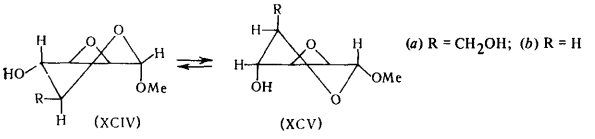
(XCII) (XCIII)

with $\Delta G^{\neq} = -11.5$ kcal mole^{-1}. [124–126]

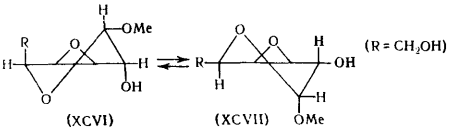
(*e*) Alkyl pyranosides

We have already mentioned in the Introduction that many examples have been shown of the preferential axial orientation of polar aglycones in the sugar series[36,37,40–42,67]. Lemieux[5] observed equilibrium proportions of 3 : 1 of α- and β-anomers in methyl 2,3,4,6-tetra-O-methyl-α- and -β-glucopyranosides in methanolic solution. Intramolecular rearrangement of methyl β-D-glucopyranoside triacetate catalysed by boron trifluoride and titanium tetrachloride gave a 90% yield of the α-anomer with an axial methoxy-group[127].

Methyl pyranosides contain approximately the same content (70%) of the axial isomer in conformational equilibrium[101] and exhibit a similar anomeric effect (1.2 kcal mole^{-1})[40] as the analogous 2-alkoxyoxans. The presence of many functional groups in alkyl pyranosides has enabled a broad study to be made of the various factors influencing the position of conformational equilibrium. Since most of the results of the large amount of work done on this problem can be found in review papers[5,33,48,50,101,128], we will not discuss it at length. We remark merely that an anomeric effect has been found also in polyacetylenic alcohols of glucosides[129].



(XCIV) (XCV) (*a*) R = CH_2OH; (*b*) R = H



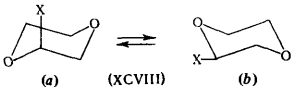
(XCVI) (XCVII) (R = CH_2OH)

In several cases the anomeric effect makes conformations having an axial alkoxy-group stable with 2,3- and 3,4-anhydroglucopyranosides[130–134]. In the case of the conformational equilibrium of methyl 2,3-anhydro-α-D-manno- and -lyxo-pyranosides, for example, the latter being especially interesting, (XCIV*a*) and (XCIV*b*) respectively are the stable conformations, but with methyl 3,4-anhydro-α-D-galactopyranoside the conformation (XCVII) is stable.

(*f*) Acetoxy-derivatives

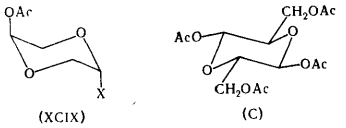
Anderson and Sepp[47,57,85] and Zefirov and Shekhtman[54] have shown that oxan-2-yl acetate and its alkyl derivatives have almost the same anomeric effect and similar contents (85–90%) of the axial form. The proportion of the axial isomer in the equilibrium mixture diminishes with increase in the polarity of the solvent.

The difference in electronegativity between the acetoxy- and the methoxy-group has a stronger influence on the position of conformational equilibrium in 2-alkoxy-1,4-dioxans. According to Zefirov and Fedorovskaya[63] the compound (XCVIII) in carbon tetrachloride consists of 68% of (XCVIII*a*) if X = OCH_3, and 95% if X = $OCOCH_3$.



(*a*) (XCVIII) (*b*)

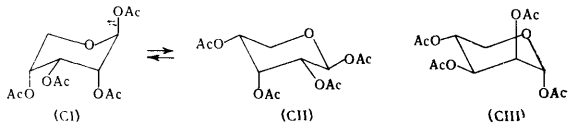
According to n.m.r. data 1,4-dioxan-2,5-diyl *trans*-diacetate consists almost entirely of the diaxial conformation (XCIX: X = $OCOCH_3$).[135] Nevertheless, the tetraequatorial conformation (C) of *trans*-2,5-diacetoxy-3,6-bisacetoxymethyl-1,4-dioxan is stable[135].



(XCIX) (C)

From results for the anomerisation and conformational equilibrium of pyranose acetates Lemieux[5] calculated the anomeric effects for hexoses and pentoses as 1.5 and 1.3 kcal $mole^{-1}$ respectively. The difference between these values is probably due to the electronegativity of the 5-substituents and in particular the inductive effect of the 6-oxygen atom.

The increased content (88%) of the axial isomer in glucose penta-acetate in comparison with xylose tetra-acetate (78.5%) and oxan-2-yl acetate (75%) is attributed by Anderson and Sepp[101] not only to the polar effect of the 6-hydroxymethyl group but also to interaction of the 3- and 4-acetoxy-groups.

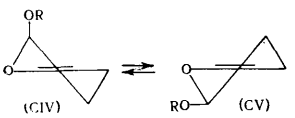


(CI) (CII) (CIII)

The conformational equilibrium of β-D-ribopyranose tetra-acetate (CI) ⇌ (CII) is displaced towards the *trans*-axial conformation (CII) by an anomeric effect[136]. α-D-Lyxopyranose tetra-acetate exists to the extent of 98% as the conformation (CIII).[138]

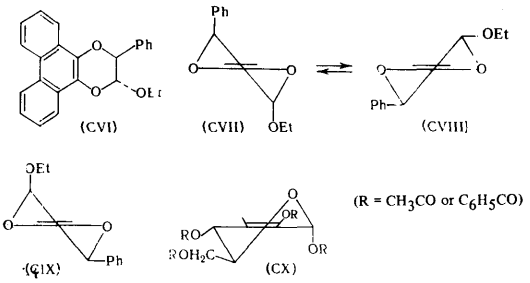
(*g*) Alkoxy-derivatives of dihydropyrans and dihydrobenzopyrans

The half chair is the preferred conformation of unsaturated and fused pyran derivatives containing a 5–6 double bond. Since ΔG_R decreases on passing from derivatives of cyclohexane to those of cyclohexene[137], a distinct anomeric effect was to be expected in dihydropyran derivatives. In fact Zefirov and Shekhtman found[54,87] with 2-alkoxy-3,4-dihydropyrans that the axial conformation (CIV) is predominant.



(CIV) (CV)

An anomeric effect has been demonstrated by nuclear magnetic resonance in 2-alkoxy-derivatives of chroman[86,139,140], 5,6-benzochroman[139], and dihydrophenanthro-1,4-dioxan[114]. Pfundt and Farid[114] observed with *trans*-2-ethoxy-5,6-dihydro-3-phenyl-5,6-phenanthro-1,4-dioxan (CVI) a mobile equilibrium with a considerable proportion of the diaxial conformation (CVII). Such a position of conformational equilibrium is undoubtedly due to a considerable decrease in ΔG_{Ph} on passing from oxan to dihydropyran derivatives. The *cis*-isomer exists as the conformation containing an axial ethoxy-group (CIX).



(CVI) (CVII) (CVIII)

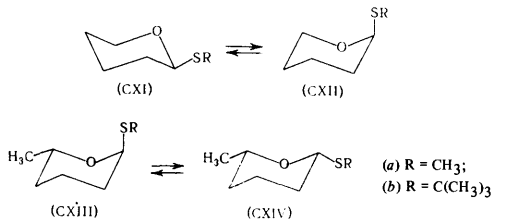
(CIX) (CX) (R = CH_3CO or C_6H_5CO)

Ferrier and Sankey[141] used nuclear magnetic resonance to show that, in esters of 2,3-didehydro-3-deoxyaldoses (CX), the allyl ester groups occupy preferentially (with respect to the double bond) a quasi-axial position, and the anomeric effect is 0.8 and 1.3 kcal $mole^{-1}$ for the acetoxy- and benzoyloxy-groups respectively.

4. The O–C–S Fragment

(*a*) Alkylthio-derivatives of oxygen-containing heterocycles

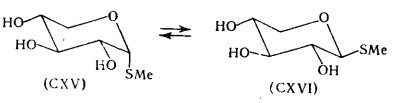
Semi-quantitative n.m.r. data have shown that 2-phenylthio- and 2-ethylthio-oxans possess an anomeric effect, although it is considerably weaker than in alkoxy-derivatives[54]. With 2-ethylthio-oxan, for example, the equilibrium mixture (in carbon tetrachloride) contains 65% of the axial isomer (CXII). This value agrees satisfactorily with results for the epimerisation of 2-methylthio- and 2-t-butylthio-6-methyloxans[56], the proportion of the axial *trans*-isomers (CXIII) being ~ 65% for both compounds. In acetonitrile, however, the equilibrium (CXIII) ⇌ (CXIV) is displaced in favour of the equatorial epimer, with values of ΔG of −0.08 and −0.12 kcal $mole^{-1}$ for cases (*a*) and (*b*) respectively.



(CXI) (CXII)

(CXIII) (CXIV) (*a*) R = CH_3; (*b*) R = $C(CH_3)_3$

The epimerisation of methyl 1-deoxy-1-mercapto-β-D-ribopyranoside yields a mixture containing 18.5% and 7.4% respectively of the α- and β-epimers (CXV) and (CXVI), and thus suggests the presence of an anomeric effect. However, these results are not very exact, since the mixture contains a considerable proportion of furanoside forms[142]. 2-Ethylthiodihydrophenanthro-1,4-dioxan also exhibits an anomeric effect[114], the equilibrium content of the axial conformation being ~ 60%.

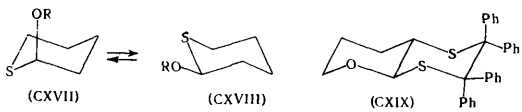


(CXV) (CXVI)

The above results show that the dipole interaction of oxygen and sulphur atoms is sufficient to destabilise the equatorial conformation.

(*b*) Alkoxythians

Since an anomeric effect is found with 2-alkylthio-derivatives of oxan, it should obviously occur also with alkoxylated six-membered sulphur-containing heterocycles. Zefirov et al. have shown[117,143] a distinct anomeric effect with 2-alkoxythians (CXVII) ⇌ (CXVIII). Thus the n.m.r. spectra indicate at least 90% of the isomer having the conformation (CXVII) at equilibrium in the cases of 2-methoxy- and 2-n-butoxy-thians, and the effect of solvents on the conformational equilibrium coincides with that observed for 2-alkoxyoxans[54,55].



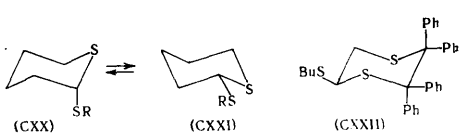
(CXVII) (CXVIII) (CXIX)

Distinct predominance of the axial conformation of alkoxy-derivatives has been found with 2-ethoxy- and 2-butoxy-5,5,6,6-tetraphenyl-1,4-dithians[144]. Thiobenzophenone reacts with dihydropyran to form *trans*-3,3,4,4-tetraphenyl-7-oxa-2,5-dithiabicyclo[4,4,0]decane (CXIX), the structure of which has been proved by n.m.r. spectroscopy[144,145]. In this connection it is of great interest to obtain the *cis*-isomer and also to study epimerisation.

It is interesting that according to the n.m.r. spectra[146] an anomeric effect occurs with thian-2-ol in deuterochloroform.

5. The S–C–S Fragment

Alkylthiothians (CXX) ⇌ (CXXI) exhibit a distinct anomeric effect[117], which has been estimated as 0.7 and 0.5 kcal mole^{-1} in carbon tetrachloride and in acetonitrile respectively.

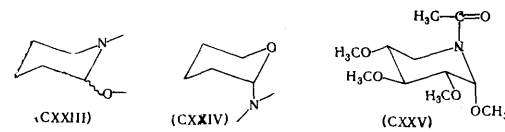


(CXX) (CXXI) (CXXII)

According to n.m.r. data, however, 2-butylthio-5,5,6,6-tetraphenyl-1,4-dithian exists predominantly as the equatorial conformation (CXXII).[144] This is probably due to strong 1,3-repulsion between phenyl and butylthio-groups, which predominates over the anomeric effect.

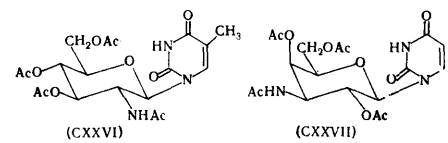
6. The N–C–O Fragment

The N–C–O fragment, containing an amino-nitrogen atom, can occur in two forms (CXXIII) and (CXXIV). In view of the variety of functional nitrogen groups, moreover, the conformational equilibrium of compounds of type (CXXIV) will obviously depend on the kind of nitrogen group present. Very few data are available on compounds of type (CXXIII).[147–149] Thus methyl *N*-acetyl-2,3,4-tri-*O*-methyl-α-D-xylopiperidinose occurs predominantly in the form (CXXV).[147] However, this effect may be due to purely steric factors (the conformation of 2-substituted *N*-acetylpiperidines will be discussed below). Compounds of type (CXXIV) containing an amino-group have been studied fairly thoroughly, but few data are available on the conformational equilibrium of such systems.



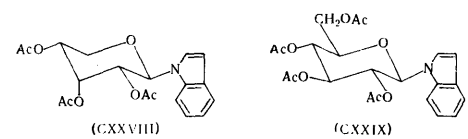
(CXXIII) (CXXIV) (CXXV)

A quite large number of examples have shown that substituents having an sp^2-hybrid nitrogen atom do not develop an anomeric effect. Thus epimerisation data for 1-(2-acetamido-3,4,6-tri-*O*-acetyldeoxy-β-D-glucopyranosyl)-thymine[150] and 1-(3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-β-D-galactopyranosyl)uracil[151] indicate that the equatorial conformations (CXXVI) and (CXXVII) respectively are the more stable.



(CXXVI) (CXXVII)

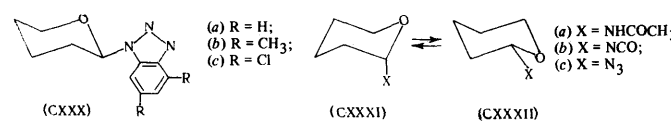
In a study of analogues of nucleosides Cushley et al.[152] discovered that an *N*-indolyl substituent on the $C_{(1')}$ atom of the pyranose ring also occupies the equatorial position, e.g. in



(CXXVIII) (CXXIX)

Similarly, the equatorial conformation (CXXX) is stable with benzotriazolyloxans[153].

A semi-quantitative estimate of the position of conformational equilibrium in *N*-oxan-2′-ylacetamide shows[104] that at least 85% of the conformation (CXXXII*a*) is present in the equilibrium (CXXXI) ⇌ (CXXXII).



(CXXX) (CXXXI) (CXXXII)

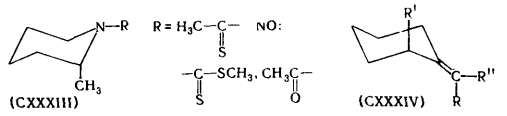
However, the situation changes markedly on passing to 2-substituted oxan derivatives containing linear functional groups in which nitrogen is present in the *sp*-hybrid state. Thus Zefirov and Shekhtman[104] showed by an n.m.r. method that the axial conformations (CXXXI*b*) and (CXXXI*c*) predominate at equilibrium in oxan-2-yl azide and isocyanate respectively, their proportions lying in the range 70–80%. It is interesting that, in the case of the azide, the proportion of the axial conformation diminishes on passing from acetonitrile to carbon tetrachloride.

7. The Fragments O–C–C, S–C–C, and N–C–C

The varied character of the functional groups containing a carbon atom makes it necessary to examine the conformational behaviour of compounds as a function of the type of hybridisation of the carbon atom. Consideration of the volume and electronegativity of the functional groups containing a tetrehedral carbon atom indicates absence of an anomeric effect with compounds containing simple alkyl groups. This principle is confirmed experimentally[154,155].

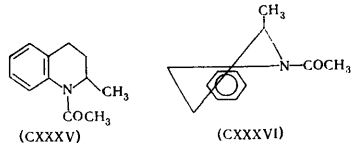
Anomalies might be expected with strong electron-acceptor groups such as trifluoromethyl and trichloromethyl, but experimental data on this aspect are lacking.

A very interesting phenomenon was discovered by Paulsen et al.[147,156,157], who found that a 2-methyl group in *N*-thioacetyl-, *N*-*syn*-nitroso-, *N*-methylthiothiocarbonyl-, and *N*-acetyl-piperidines occupies an axial position (CXXXIII). This phenomenon is most probably due not to a polar but to a steric effect. In fact, the cyclic nitrogen atom is trigonal in all the compounds, which produces strong steric repulsion between the *N*-substituents and the equatorial 2-methyl group.

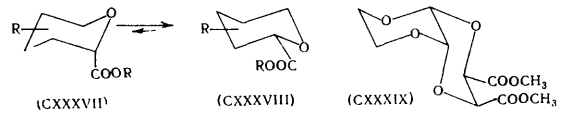


A similar effect has been found with cyclohexanes having an exocyclic double bond. Thus for compounds of type (CXXXIV) in which R = R′ = CH_3 the equilibrium mixture contains 85% of the axial conformations (CXXXIV).[158,159]

The methyl group in *N*-acetyltetrahydroquinaldine (CXXXV) has the axial conformation (CXXXVI).[155]



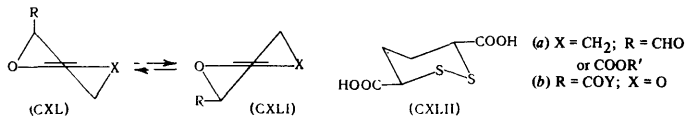
Available published data indicate that an anomeric effect is absent also from functional groups containing an sp^2-hybrid carbon atom. Thus epimerisation data on methyl alkyloxan-2-carboxylates (CXXXVII) ⇌ (CXXXIII) indicate that for the methoxycarbonyl groups ΔG = 1.62 kcal $mole^{-1}$.[160]



Using n.m.r. data Bramley et al.[161] showed that dimethyl decahydro-1,4,5,8-tetraoxanaphthalene-2,3-dicarboxylate has *cis*-fusion of the rings with a diequatorial arrangement of the methoxycarbonyl groups (CXXXIX).

A preferred equatorial position of methoxycarbonyl groups has been found also with isomeric methyl 6-alkoxyoxan-2-carboxylates[110,112].

Nuclear magnetic resonance has shown that the conformational equilibrium of 2-formyl- and 2-methoxycarbonyloxans is shifted towards the equatorial form (CXLI*a*).[137,162]



The absence of an anomeric effect in *trans*-1,2-dithian-3,6-dicarboxylic acid (CXLII) has been demonstrated by X-ray examination[163].

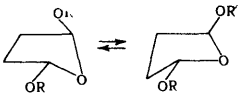
However, very interesting results have been obtained from a study of the conformational equilibrium of benzo-1,4-dioxan-2-carboxylic acid and its derivatives. The proportion of the axial conformation (CXL*b*) is 70%.[162,164] In this case the conformation is probably determined either by dipole–dipole attraction between the 4-heteroatom and the 2-functional group or by the inverse "hockey-stick effect", in which overlapping of the *p*-orbital of the carbon atom of the methoxycarbonyl group and the orbital of the 4:oxygen atm, which has a lone pair of electrons, leads to stabilisation of the axial conformation.

We may note in conclusion that data on functional groups having an *sp*-hybrid carbon atom are lacking, and therefore an experimental study of this question would be welcome.

IV. THE ANOMERIC EFFECT IN ACYCLIC AND NON-SIX-MEMBERED CYCLIC STRUCTURES

The anomeric effect should obviously apply to other types of structures containing an X–C–Y fragment.

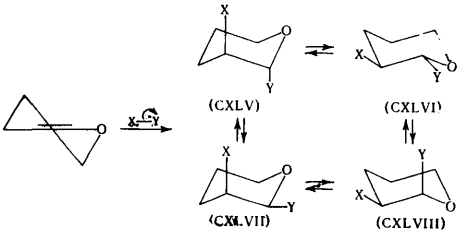
With cyclic structures interaction of this type should lead to stabilisation of the gauche conformation. Experimental data have shown that acetals exist predominantly in the gauche–gauche conformation[165], and a chloromethyl ether as a gauche conformation[166]. Polyformaldehyde, in contrast to polyethylene, forms a spiral chain[56,167].



A clear anomeric effect has been found in 2,5-dimethoxyoxolan[106]. Epimerisation in benzene yields an equilibrium mixture containing 63% of the *trans*-isomer (CXLIII). Increase in the polarity of the solvent shifts the equilibrium in favour of the *cis*-isomer (CXLIV). A similar situation has been found in 2-substituted 1,3-dioxolans[168]. This effect will obviously hold also for non-six-membered rings.

V. THE ANOMERIC EFFECT AS A FACTOR DETERMINING THE STEREOCHEMICAL COURSE OF REACTIONS

If a reaction is controlled thermodynamically, the anomeric effect will obviously be one factor determining the configuration of the products. This has already been shown in the examples of epimerisation. However, it applies also to certain other types of reactions. In particular, electrophilic addition at the double bond in Δ^2-dihydropyrans will lead under conditions of thermodynamic control to an appreciable quantity of a product having a *cis*-configuration. If a mechanism of *trans*-addition via the intermediate formation of an onium ion is accepted (for an alternative view see Ref. 169), the product will exist in the two conformations (CXLV) and (CXLVI). In this case epimerisation will yield the *cis*-isomer, which exists in the conformations (CXLVII) and (CXLVIII). In the absence of strong 1,2-repulsion between substituents X and Y to stabilise the conformation (CXLV), the conformation (CXLVIII) should obviously be the most stable. In fact, the halogenation of dihydropyran gives a mixture of *cis*- and *trans*-isomers[143,170], as discussed above, the proportion of the *cis*-isomer being greater in the dibromide than in the dichloride.



The addition of such electrophilic agents as nitrosyl chloride, oxalyl chloride, and acetals in the presence of boron trifluoride yields products having a *cis*-configuration of the type (CXLVIII).[169] The addition of ethanesulphenyl chloride to dihydropyran at low temperatures conforms to kinetic control and gives a normal product of *trans*-configuration, but at high temperatures the *cis*-isomer is obtained[171]. In the absence of added acid agents, which promote thermodynamic control, the formation of *trans*-products is more probable. In particular, as already noted above[55], the oxymercuration of dihydropyran yields the *trans*-isomer. It is noteworthy that *cis*-addition is very often observed in electrophilic additions at the double bond in polyfunctional derivatives of dihydropyran (glycals).[78,172-177]

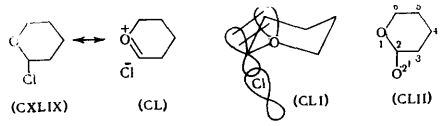
VI. THE NATURE OF THE ANOMERIC EFFECT

It is evident from the above discussion that an "anomeric effect" is exhibited by an extraordinarily wide range of compounds of various types and covers quite diverse phenomena. It therefore becomes necessary to refine this concept.

In a broad sense the term "anomeric effect" can be understood purely phenomenologically as the predominance of the axial conformation of a substituent in the α-position with respect to a heteroatom. Such an effect can obviously be due to a wide variety of causes, including purely steric factors, as has been discussed above for acetyl derivatives of piperidine.

In a narrower sense the anomeric effect can be understood as the predominance of an axial form as a consequence of specific non-steric interaction of a substituent with an adjacent heteroatom. This definition eliminates from discussion the effect of interaction of the substituent with a remote heteroatom, as discussed above for benzodioxan-2-carboxylic acid. In this sense the problem of the nature of the anomeric effect reduces to studying the interaction between the substituent and the heteroatom.

Two views are held on the nature of such interaction, according to one of which an explanation of the anomeric effect is to be sought in stereoelectronic factors. The concept of "double bond–no bond resonance"[178,180] is applied for this purpose. This concept has been used to explain various anomalies in the physical properties of compounds in which two electronegative substituents are attached to the same carbon atom. On this basis the resonance structures of 2-halogeno-oxans will be (CXLIX) and (CL).

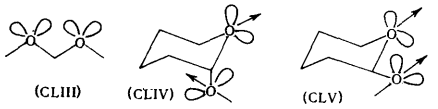


(CXLIX) (CL) (CLI) (CLII)

Such resonance is due to overlapping of the p_Z-orbital of the oxygen atom and the σ^*-orbital of the C–X bond (CLI).[7] The interaction between the p-electrons of the oxygen atom and the framework of σ-bonds for the fragment CH_2-O-CH_2-X has been examined[180-182]. Such overlapping will obviously be greatest with the halogen atom in the axial position. Therefore mixing of e.g. the p_Z-orbital of the ring oxygen atom and the σ^*-orbital of the carbon–halogen bond should result in stabilisation of the axial conformation. Conjugation of this type is supported by the shortening of the carbon–oxygen bond and lengthening of the C–X bond which are observed experimentally in several cases[183,184].

The situation is far more complicated, however, with alkoxy-derivatives[185-187]. Both the exocyclic $C_{(2)}-O_{(2')}$ bond (CLII) and in several cases also the $C_{(2)}-O_{(1)}$ bond are shortened. Shortening of the former bond has been observed also for the equatorial conformation[186,187].

Attempts have been made to relate the variation in bond lengths with the variation in angles and hence in hybridisation[187,188]. On the whole, however, this is a very complicated question, and a more detailed examination of this aspect of the "anomeric effect" encounters certain difficulties.



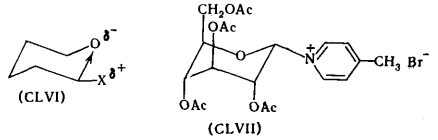
(CLIII) (CLIV) (CLV)

The second view relates the "anomeric effect" to dipole–dipole repulsion of substituent and heteroatom. The first to apply this idea was Edward[42]. Formulae (CLIV) and (CLV) show that dipole interaction is stronger in the equatorial than in the axial conformation. This view has been adopted in most papers. It is consistent with the influence of the solvent on the magnitude of the anomeric effect and with the qualitative changes observed with variation in the electronegativity of the substituent and the introduction of addition substituents[105,107,132]. Attempts have been made to calculate the electrostatic repulsion due to the dipole interaction[7]. However, although these calculations are consistent with the qualitative picture, they are unable to provide serious support for this view owing to the crudeness of the postulates involved.

A somewhat refined picture of such dipole–dipole interaction has recently become widespread. Since a considerable part of the negative charge is concentrated in the region of the lone pairs of the oxygen atoms, a rotational conformation of the type (CLIII) for the acetal fragment would be unstable. This phenomenon has been termed the "rabbit's-ears effect"[7-10]. An example is provided by the anomeric effect in alkoxyoxans. In several cases the "rabbit's-ears effect" enables the rotational conformations of alkoxy-groups to be predicted correctly, and it is applicable also to several nitrogen heterocycles and aliphatic compounds. In essence, however, this effect is also phenomenological, since the detailed causes of the instability of the conformation (CLIII) are unknown.

VII. THE INVERSE ANOMERIC EFFECT

In view of the polar nature of the anomeric effect, the converse effect can be imagined, in which there is dipole–dipole attraction between substituent and heteroatom of the type (CLVI). For a methyl alkyloxan-2-carboxylate, as noted above, $\Delta G_{COOR} = 1.62$ kcal mole^{-1},[160] which exceeds the value in methyl cyclohexanecarboxylate by 0.5 kcal mole^{-1}. Such an increase in the value of ΔG can be explained by two factors: a decrease in the distance between the atoms $C_{(2)}$ and $C_{(6)}$ in oxan will lead to an increase in 1,3-diaxial repulsion between the 6-hydrogen atom and the 2-substituent; it is also possible that this difference is due to an inverse anomeric effect.



(CLVI) (CLVII)

The clearest example of an inverse anomeric effect was observed by Lemieux and Morgan[189] with a glucopyranosylpyridinium salt. According to n.m.r. data this compound exists as the conformation (CLVII), in which the three acetoxy-groups and the acetoxymethyl group are present in axial conformations. Stabilisation of such a conformation is obviously due to an inverse anomeric effect—attraction of the heteroatom and the equatorial pyridinium group. Obviously, although very little study has been made of the inverse anomeric effect, it should also be a general phenomenon, applying to a wide range of compounds.

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As the present Review has shown, the anomeric effect is a general conformational phenomenon covering an extraordinarily wide range of compounds. Although the nature of this effect is a matter of controversy, we are able to predict it with a considerable degree of probability for a large number of compounds which have not yet been studied. It is quite obvious that further investigation of this effect with the use of new model compounds and a more profound study will lead to progress in understanding the nature of the forces determining the conformations of molecules.

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Chemical Faculty,
Lomonosov Moscow
State University