Tetrahedron. Vol. 30, pp. 1683 to 1694. Pergamon Press 1974. Printed in Great Britain

THE CONFORMATIONAL CONSEQUENCES OF REPLACING METHYLENE GROUPS BY ETHER OXYGEN

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(*Received in the UK 8 February 1974*)

Abstract—A survey is given of experimentally established conformations of saturated compounds containing the isolated ether group, or the 1,5-, the 1,4- or the 1,3-dioxa-grouping. The emphasis is on demonstrating common features for simple molecules, polymers, and medium and large rings.

INTRODUCTION

The tetrahedral arrangement of the substituents around "saturated" carbon is so well preserved in the isoelectronic amines and ethers that it has become customary to consider the non-bonding electron pairs as directed in space and sterically equivalent to the electron pairs forming the bonds to substituents. Not only the valency angles but also the preferred conformation of a methyl substituent, and even its torsional barrier, is strikingly preserved, as demonstrated in the structural data for propane,[1] dimethyl amine[2] and dimethyl ether[3] (Fig 1).

In the case of an amine there is no problem in defining the lone-pair electron-density maximum in the direction of the lacking substituent.[4] At ether oxygen, however, it is a question of dispute[5,6] whether the best description is in terms of two tetrahedrally directed electron-density maxima, a single maximum in the plane formed by the CO-bonds, or a broad continuous region. This is a rather elusive problem, since whenever there is chemical interaction (alkylation, protonation, metal complexing) with ether oxygen to give one or the other geometry, this may always be taken as the result of an accompanying change in electron distribution. Terms such as "parallel" or "opposed lone pairs" will therefore be used in the following discussion simply as a convenient geometric description without any implication of real electron distribution.

When one or several methylene groups of the higher alkanes are replaced by ether oxygen, there is the additional question of relative energy of *gauche*- and *anti*-conformations in the CO-bonds and neighbouring CC-bonds. In oxa-cycloalkanes it is not only of interest to know if the ring conformation is preserved or changed, but also whether certain ring positions for oxygen are favoured, and whether transannular CH ··· HC repulsions are relieved when replaced by CH ··· O or O ··· O interactions.

The aim of the present review is to present established conformations for simple (generally unbranched and unsubstituted) ether molecules, polymeric ethers, and cyclic ethers, particularly those of medium- and large-ring size, and to point out the typical features this great variety of molecules have in common.

SIMPLE ETHERS AND POLYETHERS WITH WELL SEPARATED ETHER GROUPS

Both methyl ethyl ether[7] and diethyl ether[7,8] crystallize in the same extended *anti*- (and *anti,anti*-) conformation as do butane and pentane. New IR bands in the liquid can be assigned to the presence of small amounts of the *gauche*- (and *anti,gauche*-) conformer.[7] The *anti*-preference of the CO-bond seems thus at least as strong as that of the CC-bond in the hydrocarbon, and is in fact expected[9] to be stronger, since the *gauche* 1,4-interaction takes place between one α and one β hydrogen occupying neighbouring positions on the diamond lattice, and the distance between them is somewhat shortened because of the shorter CO-bond (Fig 2a). On the other hand, the corresponding interaction for the $C_\alpha C_\beta$-bond (Fig 2b) takes place between a hydrogen of the γ-carbon and an oxygen lone pair, and is not expected to be repulsive, but slightly attractive.[10] The magnitude of the vicinal α,β spin-coupling constant of propyl ethers indicates slightly lower enthalpy for *anti* than for *gauche*.[11] The closely related 1,4-interaction between halogen and hydrogen of the methyl group in propyl halides seems on the other hand indeed to be attractive, since a clear *gauche* preference is observed in gas[12–14] and liquid.[15] A stabilization of this magnitude (0·5 kcal/mol) is, however, not reproduced by *ab initio* calculations on propyl fluoride.[16]

For poly(tetramethylene oxide) one would on this basis expect both CO-bonds and the central CC-bond to be strongly preferred in *anti*, and the two remaining CC-bonds to have no preference. The stable crystalline form contains[17] the planar all-*anti* chain (Fig 3) and no other form corresponding to any of the possible *gauche* varieties is observed.

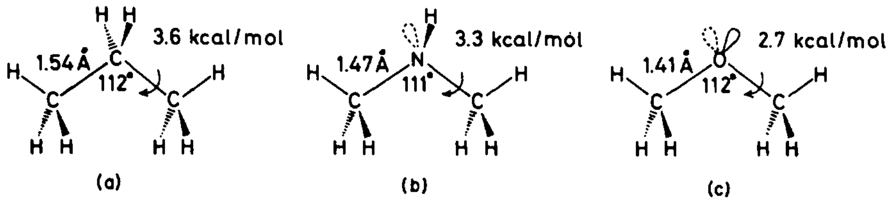


Fig 1.

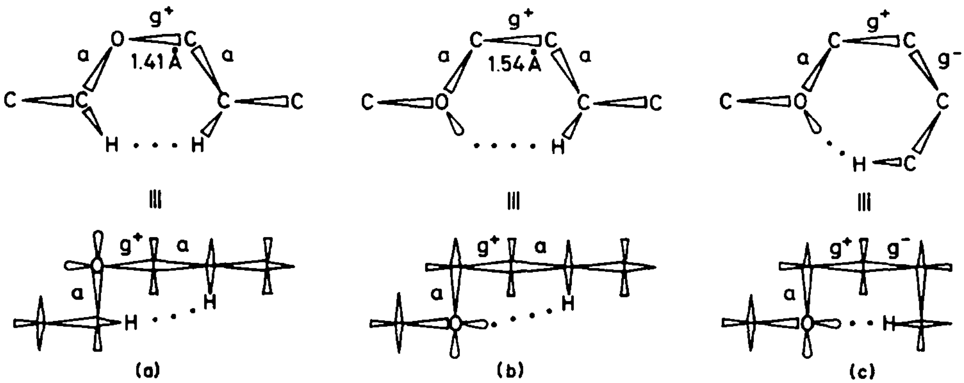


Fig 2.

Fig 3.

The all-*anti* chain is also the type of crystal conformation observed[18] for a series of higher homologues from poly(hexamethylene oxide) up to and including poly(dodecamethylene oxide) and of course for the extreme case, polyethylene. Although this may well be the result of a more efficient lattice packing of the extended chain, at least it suggests that any *gauche*-preference in solution for the $C_\alpha C_\beta$-bonds cannot be very strong.

The *gauche,gauche* 1,5-interaction between δCH and oxygen (Fig 2c) might also be expected to be non-repulsive so as to make the $g^\pm g^\mp a$ conformation of 1-methoxybutane allowed; the corresponding CH · · · CH 1,5-interaction is of course strongly forbidden. In gaseous 1-chlorobutane the $g^\pm g^\mp$ conformer with a similar interaction is in fact present to 24% and only outweighed by the *ag* conformer (37%).[19] The larger bromine atom changes the conformer distribution of 1-bromobutane dramatically to that of pentane with no $g^\pm g^\mp$ conformer present.[20]

Among cyclic monoethers there is no known case where the observed ring conformation is not of the same type as for the corresponding cycloalkane. Trimethylene oxide (oxetan) has for symmetry reasons a unique conformation (Fig 4a), and this is less puckered[21,22] and has a lower inversion barrier (0·04 kcal/mol)[21] than observed for cyclobutane (1·5 kcal/mol),[23] presumably connected with the lower eclipsing energy in the CO-bond and to its shorter bond length. Tetrahydrofuran (oxolan) is also flatter than cyclopentane[24] and displays a slightly impeded pseudorotation[22,25,26] due to the differing energies of the various positions that

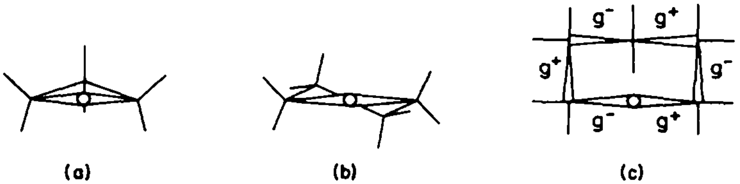


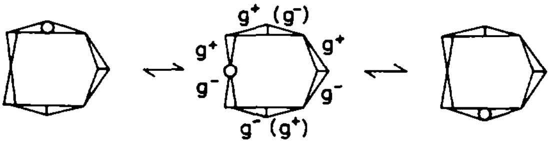
Fig 4.

oxygen can occupy on the envelope and the twist-envelope; the decisive pseudorotation barrier is nevertheless only 0·15 kcal/mol higher than the lowest minimum, a twist-envelope with oxygen on the two-fold axis (Fig 4b). This becomes of course much favoured in the 3,3,4,4-tetrol derivative.[27] Tetrahydropyran (oxan), on the other hand, adopts again a unique conformation (Fig 4c) since all ring positions are equivalent in the cyclohexane chair. Its inversion barrier[28] is close to that of cyclohexane.

The only higher cyclic monoether which has been examined is oxacyclooctane.[29,30] There are five non-equivalent positions on the boat-chair, or [26] conformation,* of cyclooctane, and the NMR spectrum suggests[29,30] that the oxygen atom occupies preferentially one or both of those two (Fig 5) which in cyclooctane have inner hydrogen atoms in the most serious transannular conflict. From this it may be concluded that 1,4- and 1,5- CH · · · O interactions are less repulsive than the corresponding CH · · · HC interactions

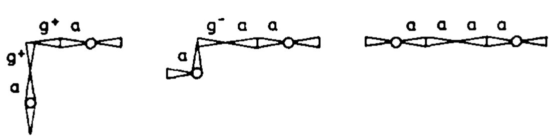
The 1,5-*dioxa-grouping*

Assuming that a clear *anti*-preference exists for the CO-bonds of 1,3-dimethoxypropane, and that a $g^{\pm}g^{\mp}$ sequence is as strongly forbidden as in pentane, there are only three possible conformers; $ag^{\pm}g^{\pm}a$, *agaa*, and *aaaa* (Fig 6). Since the more acidic α-CH might be expected to impart to the 1,4-CH · · · O interaction some attractive character, and a sequence of two *gauche* bonds of the same sign adds no extra energy term beyond the sum of the two,[32] it is the $ag^{\pm}g^{\pm}a$ conformer (Fig 6a) which should become favoured. A mixture of $ag^{\pm}g^{\pm}a$ and *agaa* is in fact indicated by the magnitude of the observed vicinal spin-coupling constant and the observed dipole moment.[11]



(a) (b) (c)

Fig 5.



(a) (b) (c)

Fig 6.

Electron diffraction of the analogous halogen compound 1,3-dibromopropane,[33] where similar CH · · · lone-pair interactions are possible, shows that the gas-phase contains predominantly the $g^{\pm}g^{\pm}$ conformer (67% *gg*, 30% *ga*, 3% *aa*); corrected for symmetry number and multiplicity, the *gg* conformer is 0·9 and 1·4 kcal/mol more stable than the *ag* and the *aa* conformers respectively. A similar situation exists also for 1,3-dichloropropane.[34] Definitely therefore, this kind of interaction must be attractive in these molecules, although semiempirical calculations for 1,3-dibromopropane fail to reproduce the energetic preference for the $g^{\pm}g^{\pm}$ conformer.[33]

In accord with the preceding data, poly(trimethylene oxide) adopts in its stable (orthorhombic) crystal form a folded conformation with a repeating $ag^{\pm}g^{\pm}a$ unit always of the same sign within each chain (Fig 7).[35] Two other less stable crystal modifications occur;[35] a trigonal form has the repeating conformational unit† $aag^{\pm}a|aag^{\mp}a$ and is also of folded type, while the monoclinic form, stable only as a monohydrate, is all-*anti*. This again points to a clear *anti*-preference for the CO-bonds (estimated 0·9 kcal/mol more stable than *gauche*[10]) and a slight *gauche* preference for the $C_{\alpha}C_{\beta}$-bonds (estimated 0·2 kcal/mol more stable than *anti*[10]).

The cyclic analogue, 1,5,9,13-tetraoxacyclohexadecane, a tetramer of trimethylene oxide, which must have eight *gauche* bonds to be able to form the ring, adopts a square, diamond-lattice [4444] conformation (Fig 8b) which is in every detail identical with the most stable polymer chain, except that the *gauche* sign alternates from corner to corner.[36,37] This type of ring conformation is also the most stable (but not exclusive)[31,36] for cyclohexadecane and found in the low-temperature crystal phase.[36] Neither of the other two possible dispositions of the oxygen atoms of this square ring skeleton, nor on any of the non-diamond-lattice ring skeletons for cyclohexadecane, would have satisfied the *anti*-requirement of all eight CO-bonds and at same time enabled the use of only CC-bonds to form the four corners. The near-zero dipole moment[36] (0·3 D as compared with 2·6 D expected for a totally flexible molecule) suggests a very rigid molecule, as do the equally sharp IR bands in solution as in the solid.[36] The conclusion

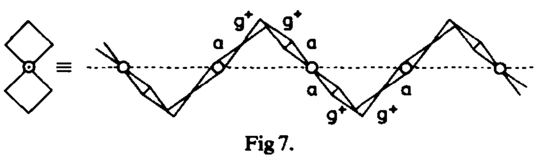


Fig 7.

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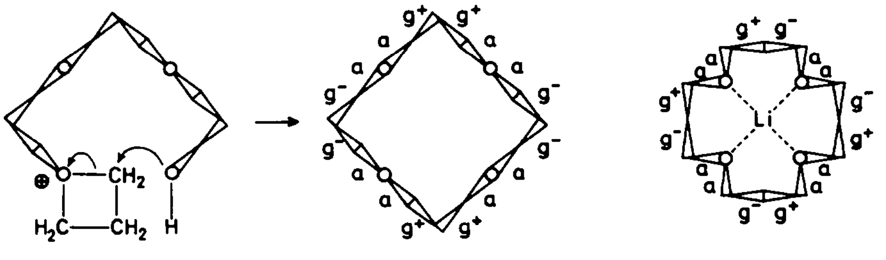
*In this notation each digit within the brackets gives the number of ring bonds in each of the sides connecting $g^{\pm}g^{\pm}$ corner atoms.[31]

†The conformational repeat unit of polymer fibers is not necessarily identical with the crystallographic repeat unit because of systematic deviations from ideal dihedral angles. In this paper idealized conformations are drawn throughout to facilitate comparison.



(a) (b) (c)

Fig 8.

seems unavoidable that the eight 1,4-CH · · · O interactions are attractive.

It is significant that this tetramer is the only cyclic oligomer formed rapidly during polymerization of trimethylene oxide,[38] although lower cyclic oligomers are also formed under equilibrium conditions.[39] The probability that the growing chain folds back to form a square ring must be high; only three corners of alternating sign are needed to bring the reacting ends together for cyclization (Fig 8a).

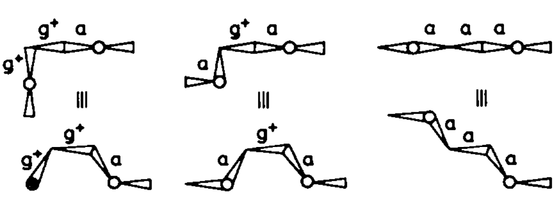
Even if the [4444] conformation of the cyclic tetramer is highly persistent and unique also in solution,[36] complexing with lithium salts (2:1) induces a complete conformational change.[40] The symmetry suggested by the low-temperature NMR-spectrum is satisfied by an $ag^{\pm}g^{\mp}a$ type conformation (Fig 8c) having one Li-cation above and one below; such a conformation is of course forbidden for the hydrocarbon.

The 1,4-*dioxa-grouping*

The simplest representative of this class is 1,2-dimethoxyethane. A variety of spectroscopic studies[41] indicate that the CC bond is predominantly *gauche*.* Infrared spectroscopy at − 196° shows more specifically[7] that the crystal has the *aga* conformation, while the melt at 25° contains also *aaa* and others, presumably $g^{\pm}g^{\pm}a$ (Fig 9).

Conformation-dependent physical properties of polyoxyethylene and its solutions[9,32,43] are compatible not only with the expected strong *anti* preference for the CO-bond (estimated 0·9 kcal/mol more stable than *gauche*)[32] but demand also a *gauche* preference for the CC-bond (estimated 0·4 kcal/mol more stable than *anti*).[32] These conclusions are further supported by the crystal structure of the polymer[44] which reveals a helix with a single repeating conformational unit *aga* of like sign within each chain (Fig 10).

Since the *gauche* interaction for a CC-bond is here really a 1,4-interaction of two oxygen lone-pairs, one would at most have expected[32] that the steric CH · · · CH repulsion of the hydrocarbon were eliminated, or perhaps replaced to some extent by electrostatic and dipole repulsion. The unquestionable attraction is difficult to understand, but it has been pointed out[32] that the O · · · O distance corresponds well to an attractive van der Waals distance. A similar situation is encountered on the one hand in the *gauche*-preference for liquid[45] and gaseous[46] 1,2-difluoroethane and other liquid 1-fluoro-2-haloethanes,[47] and on the other hand in the *cis*-preference for 1,2-dimethoxyethylene[48] and 1,2-dihaloethylenes.[49] *Ab initio* calculations on 1,2-difluoroethane[16] fail to reproduce the observed *gauche*-preference, and in the case of ethylene glycol the lower calculated energy of the *gauche*-form comes from internal hydrogen bonding,[16] and thus would not be obtained for ethers. Experimentally, internal hydrogen bonding seems to be unimportant in ethylene glycol,[43]



(a) (b) (c)

Fig 9.

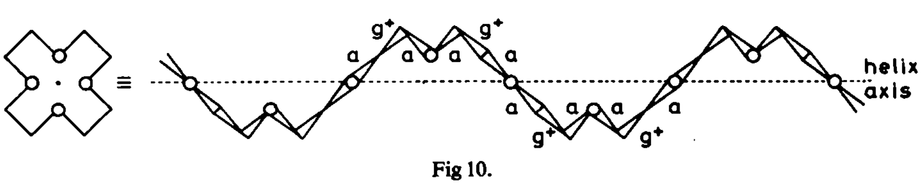


Fig 10.

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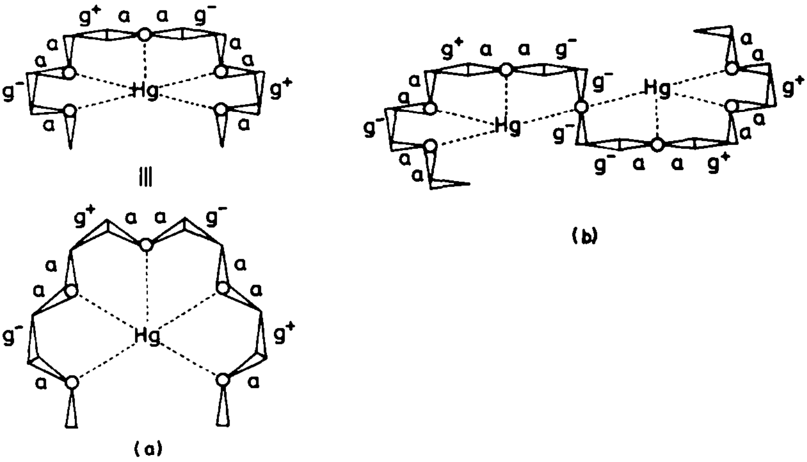
*In one case[42] it has been concluded that *anti* CC is more stable than *gauche* on the basis that the spectrum of its $HgCl_2$ complex, which is necessarily *gauche*, is different. However, it is the opinion of this writer that the changes are marginal and do not permit such a conclusion.

since its vicinal spin-coupling constant shows the same temperature variation as does 1,2-dimethoxyethane.

The tendency for *anti* CO-bonds and *gauche* CC-bonds does not preclude the existence of *gauche* CO or *anti* CC when necessary in ring formation (see below) or cation complexing. Thus, the polymer chain employs *anti* in each alternate CC-bond in the 4:1 complex between polyoxyethylene and $HgCl_2$,[50] which has the repeating conformational tetramer unit $ag^{\pm}a|aaa|ag^{\mp}a|aaa$, and only *anti* CC-bonds in a metastable crystal modification obtained by mechanical stretching,[51] while in a 1:1 complex with $HgCl_2$ also *gauche* CO-bonds are used,[52] the repeating dimer unit being $g^{\pm}g^{\pm}a|g^{\mp}g^{\mp}a$. It should be noted, however, that the *anti* CC-bond has then the normal 180° dihedral angle, whereas the *gauche* CO-bond takes the abnormally large dihedral angle value of 81°, reflecting the impossibly short 1,4- CH ··· HC distance for a torsional angle of 60°. Particularly interesting is the 1:1 complex of tetraethylene glycol dimethyl ether with $HgCl_2$,[53] since the favoured *aga* unit is used with alternating sign to obtain the necessary folding around the cation (Fig 11a). In the 1:2 complex of hexaethylene glycol diethyl ether with $HgCl_2$[54] the chain makes two folds (Fig 11b), but has then to use two $g^{\pm}g^{\pm}a$ units in the central region, and again the *gauche* CO-bond takes an unusually large dihedral angle value of 88°.

Among the cyclic oligomers containing the oxyethylene unit, dioxan has a completely normal cyclohexane chair conformation (Fig 12a) with a normal inversion barrier.[55] That the imposed unit $g^{\pm}g^{\mp}g^{\pm}$ is of high energy in an open chain is irrelevant for small ring systems where 1,4- and 1,5-interacting atoms are bonded together. Dioxan may be considered strainfree and is the final product[56] in the thermodynamic equilibrium between oxyethylene rings due to the higher entropy of the system with the greatest number of molecules.

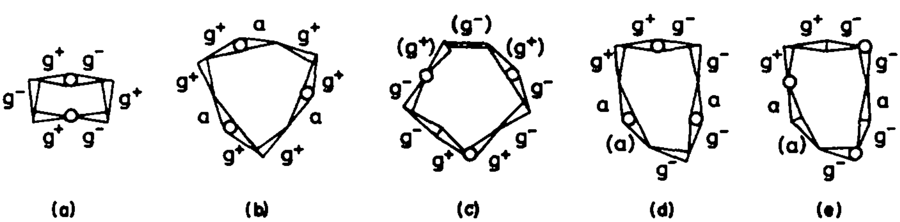
The next homologue, 1,4,7-trioxacyclononane, has been shown by IR and ^{13}C-spectroscopy[57] to adopt an unsymmetrical triangular[31] conformation [234], and none of the two which were considered most likely and are derived from the [333] conformation of cyclononane itself (Fig 12b) and from the quinquangular [12222] conformation (Fig 12c) found for some derivatives.[31] On the basis of relative barrier heights of the two observed conformational processes, the conformer having only oxygen in "side" positions (Fig 12d) seems most likely, whereas the observed dipole moment (1·55 D) fits best an alternative oxygen location (Fig 12e). However, as measured molecular dipole moments of the higher oligomers in the oxyethylene



(a)

(b)

Fig 11.



(a) (b) (c) (d) (e)

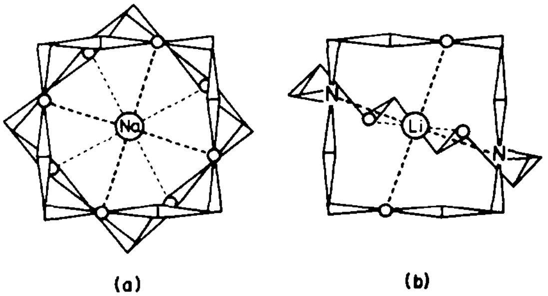
Fig 12.

series are found to be meaningless[58, 59] (those which should be small are too large and those which should be large are too small), the dipole moment argument in favour of the latter is disregarded. The smaller number of transannular hydrogen interactions, the greater number of *anti*-like CO-bonds, and the presence of only *gauche* CC-bonds also support the former. The reason for the flexible nature of these systems is unclear; it may be connected with the low energy of the CC *gauche* minimum, which might be expected to parallel lowered torsional barriers and shallow minima producing large vibrational amplitudes. In fact, the barriers are found to be extraordinarily low in 1,2-difluoroethane[60] (2·0 and 4·6 kcal/mol for ± 120° and 0°), and calculations on 1,2-diaminoethane[61] indicate that the *syn*-barrier is even lower than the barriers at ± 120°. Also, when *gauche* CO-bonds are imposed, the fact that the equilibrium dihedral angle is as large as ~ 90°, may have as a consequence that the 120° barrier is in that case only little higher and so again a shallow minimum is indicated.

The cyclic tetramer, 1,4,7,10-tetraoxacyclododecane,[59] adopts the same square type of conformation as the hydrocarbon, cyclododecane, with identical $g^{\pm}g^{\pm}a$ monomer units of the same sign, whereby the oxygen atoms must occupy "side" positions (Fig 13b). This asymmetric disposition of the oxygen atoms has the consequence that the single hydrogen site exchange process observed for cyclododecane splits into two processes for the tetraether.[59] Since the tetraether is the major product in the cyclooligomerization of ethylene oxide,[62] even if not the thermodynamically most stable, this suggests that the growing chain has a certain tendency of starting also another helix consisting of repeating $g^{\pm}g^{\pm}a$ units of like sign (Fig 13c), which after just three chain bends will bring the reactive ends in position for cyclization (Fig 13a). The ring conformation is actually not a diamond-lattice conformation, but one turn of an alpha-like helix (which *is* derived from the diamond lattice); it looks like the helix projection along its axis. No conformational change occurs with this ring when it forms complexes with cations, only sharpening of the IR bands betrays the stiffening of the otherwise loose ring.[59] The cation sits above the ring on the side to which the four oxygens are pointing. Lithium salts are complexed by one ring molecule, sodium salts symmetrically by two[59] like a sandwich[63] (Fig 14a).

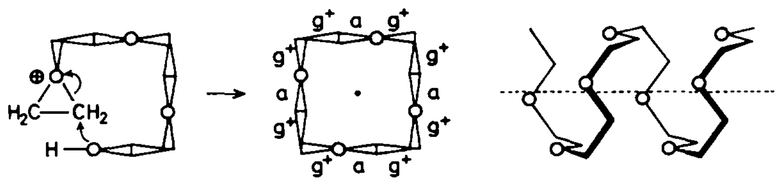
It is of great interest that in the bicyclic (211) cryptate of lithium iodide[64] the two short bridges form exactly the same type of 12-membered ring with the cation above and the long bridge spanning over the cation (Fig 14b). Again the torsion angles are small for the *gauche* CC-bonds (56°, 55°), large for the *gauche* CO-bonds (89°); CN-bonds are intermediate (79°).

Among the higher cyclic oxyethylene oligomers, only the hexamer, 1,4,7,10,13,16 - hexaoxacyclooctadecane, has been investigated in the crystalline state, both as free ether[65, 66] and as complex with cations.[65–67] In this case, the X-ray structures reveal two entirely different conformations, as shown also by a dramatic change from a complicated IR-spectrum with broad bands for the free ether to a simple one with sharp lines for the complex.[58] Neither of these correspond to the rectangular type of conformation [3636] which is most likely[68] for the hydrocarbon (Fig 15a). The ring conformation in the 1:1 complex of the hexaether with potassium and several other[58, 65–67] salts is simplest, since it consists (Fig 15b) of only one type of monomer unit, ***aga***, the same as in the polymer, but now of alternating sign (as in the complexing tetraethyleneglycol dimethyl ether already mentioned). The reason why this conformation is not also the best for the non-complexing ring is no doubt that all six dipoles would then point together.[58] The conformation actually chosen[65, 66] is also of diamond-lattice type (Fig 15c), but one that is forbidden for the hydrocarbon[68] because of two



(a) (b)

Fig 14.



(a) (b) (c)

Fig 13.

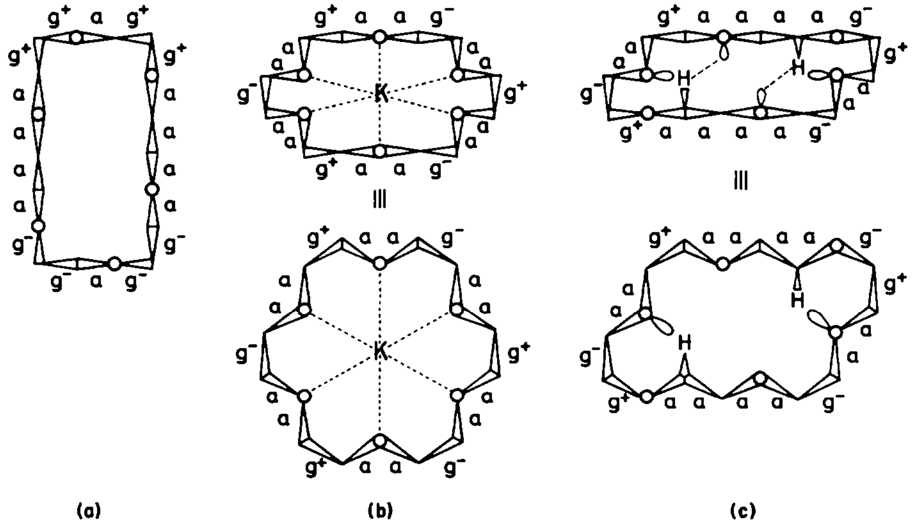


Fig 15.

1,5- CH · · · HC interactions; these are here replaced by 1,5-CH · · · O interactions. This is the only example of such close interaction found in ethers; it may be significant that it can be defined as being of $ag^{\pm}g^{\mp}a$ type and that the ring is large enough to permit adjustment of these torsional angles (– 170°, 80°, – 75°, 155°) whereby not only the short distance from the CH to the 5-oxygen is increased, but also the more distant 8-oxygen is brought closer. Compared with the alternative [3636] conformation (Fig 15a), the one found (Fig 15c) has the advantage of having fewer CO-bonds forced into *gauche* and no parallel neighbouring dipoles, and is of course more compact.

That cyclization to the hexamer occurs less readily than to the tetramer,[62] may be associated with the lower probability of making the required five chain bends of alternating sign, even if the *aga* unit is in itself favoured. In the absence of a cation the product is also energetically unfavourable.

The (222) cryptate is the bi-cyclic compound most closely related to the mono-cyclic hexaether. It is of considerable interest that in its complex with potassium and other cations,[69] where the oxygen lone pairs point towards the central cation, all twelve CO-bonds are *anti*, whereas in the free ligand[69] three of these become "gauche", but with typically large torsion angles (92°, 92°, 109°).

Another class of monocyclic oligoethers of oxyethylene type, the so-called benzo- and dibenzo-crowns,[70] is of less interest here since each benzo-group fixes four ring-atoms rigidly in one plane. Only the very large ring of the dibenzo 30-- crown - 10 provides sufficient freedom for the two tetraoxyethylene chains that their choice of conformation can be considered significant. In the crystal of the centrosymmetric non-complexing ring,[71] each of the two chains form essentially the same helix as the polymer (Fig 10), one right- and one left-handed, except that one CO-bond is *gauche*-like (95°) instead of *anti*: $ag^{\pm}a|ag^{\pm}a|ag^{\pm}a|g^{\pm}g^{\pm}a$. In the potassium iodide complex[71] the ring has a two-fold axis, and both tetraoxyethylene chains have identical $ag^{\pm}g^{\pm}|ag^{\pm}g^{\pm}|ag^{\pm}a|g^{\pm}g^{\pm}a$ conformations of the same sign, resembling in large part the helix (Fig 13c) from which the cyclic tetramer conformation is derived.

The 1,3-*dioxa-grouping*

Among the four conformations conceivable for dimethoxymethane (Fig 16) only the $g^{\pm}g^{\mp}$ conformer can *a priori* be excluded because of its severe 1,5- CH · · · HC interaction. Electron diffraction of the gas[72] shows that te $g^{\pm}g^{\pm}$ conformer (Fig 16c) is strongly dominant. This can be qualitatively rationalized equally well in terms of attractive 1,4- CH · · · O interactions as in terms of repulsion between parallel lone pairs in the other conformers, although quantitatively the energetic preference is not predicted by theory to be so strong.[32,73] The same $g^{\pm}g^{\pm}$ unit is also found in polyoxymethylene,[74] which crystallizes in a helix consisting of only *gauche* bonds of the same sign (Fig 17).

The smallest unstrained oxymethylene ring, 1,3,5V-trixan, is the thermodynamically most stable[75] of the cyclic oligomers of formaldehyde, even if the $g^{\pm}g^{\pm}$ sequence is precluded in the chair conformation (Fig 18a) which it is found to adopt.[76] The presence of three parallel lone pairs is probably the reason why there is nevertheless some driving force for the polymerization of 1,3,5-trioxan to the (crystalline) polymer,[77] provided the temperature is

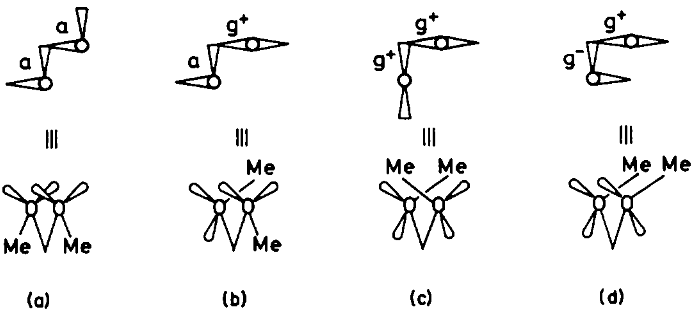


Fig 16.

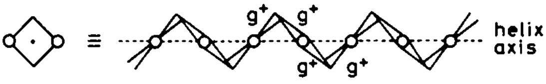


Fig 17.

below a so-called "ceiling temperature" defined by $\Delta H = T\cdot\Delta S$.[78]

The cyclic tetramer, 1,3,5,7-tetraoxacyclooctane (tetraoxocan) is formed kinetically even more easily under certain conditions,[79] and this again is expected on the basis that a chain of $g^{\pm}g^{\pm}$ units with alternating sign (Fig 18b) will lead directly to an 8-membered ring after three bonds (Fig 18c). This [2222]-conformation is, however, not the ring conformation observed; presumably, the two transannular 1,5- O ··· O interactions are repulsive, and the solution contains instead[29,80] a mixture of the usual boat-chair [26] and of a crown [8] (Fig 18d,e), the latter being also the crystal conformation.[81]

Among the larger rings, the crystal conformations have been determined for the pentamer[82] (1,3,5,7,9-pentaoxacyclodecane) and the hexamer[83] (1,3,5,7,9,11 - hexaoxacyclododecane). The hexamer (Fig 18g) is seen to be able to adopt a sexangular [222222] ring conformation by using $g^{\pm}g^{\pm}$ units of alternating sign, although valency and dihedral angles must thereby deviate from 112° and 60° (115° and 85°).[83] The odd number of monomer units in the 10-membered ring cannot be assembled similarly, and the conformation which is found (Fig 18f)[82] is intermediate between the crown type and the diamond-lattice type, and may be described as [55].

Summarizing, a tendency to use whenever and as much as possible the $g^{\pm}g^{\pm}$ unit is recognized also in these cyclic compounds.

Mixed systems: Polymeric and cyclic formals of diols

When a 1,3 - dioxa - grouping is isolated in a hydrocarbon environment in an open chain, it retains without any known exception its preferred $g^{\pm}g^{\pm}$ conformation. The adjacent CO-bonds adopt also normally their favoured *anti*-conformation (for an exception, see below), as do the more distant CC-bonds of CH_2CH_2–CH_2CH_2 type. The interesting question is whether an expected slight *gauche*-preference for the $C_\alpha C_\beta$-bonds due to the 1,4- CH ··· O interaction will show up in polyformals. The more efficient crystal packing of the all-*anti* form, which has been considered a possible

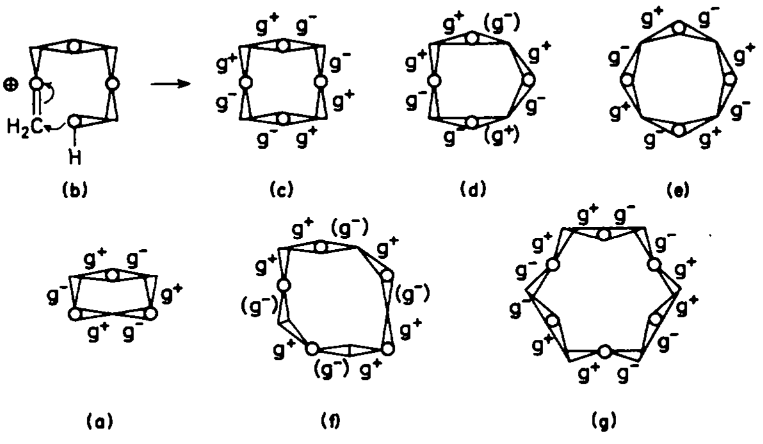


Fig 18.

reason why $C_\alpha C_\beta$-bonds occur in *anti* in crystalline simple polyethers (see above), is anyway precluded by the $g^\pm g^\pm$ formal group, and in fact no planar zig-zag all-*anti* conformation has ever been found in polyformals; all known crystal structures reveal the $C_\alpha C_\beta$-bond in *gauche*.

The crystal conformations of two members of the odd-numbered series (Fig 19a,b), poly - 1,3 - dioxonan[84] and poly - 1,3 - dioxepan,[85] are very similar and follow exactly the rules set out above with $g^\pm g^\pm ag^\mp aaag^\pm a$ and $g^\pm g^\pm ag^\mp ag^\pm a$ as repeat units with alternating sign. One might have expected then the lowest member of this series, poly - 1,3 - dioxolan, to behave similarly and adopt the loose helical structures obtainable by employing the $g^\pm g^\pm ag^\mp a$ repeat unit with same or alternating sign. However, the crystal modification II (three different modifications are found) which has been examined by X-rays,[86] shows very compact, tightly packed chains having the repeat unit $g^\pm g^\pm ag^\mp g^\mp$ of alternating sign (Fig 19c). One $C_\alpha O$-bond of each unit has thus chosen a *gauche*-conformation, and again, significantly, the torsion angle value is large (94°). Compactness seems to be the only imaginable motive for this choice.

The crystal conformation of poly - 1,3 - dioxocan,[84] the only representative of the even-numbered series, follows the normal pattern and has the $g^\pm g^\pm ag^\mp aag^\mp a$ repeat unit of like sign (Fig 20a). By extension, the unknown poly - 1,3 - dioxan may be predicted to take a chain-conformation with the repeat unit $g^\pm g^\pm ag^\mp g^\mp a$, also of the same sign (Fig 20b). Such a conformation is completely analogous to that established for the cyclic dimer of 1,3-dioxan (see below).

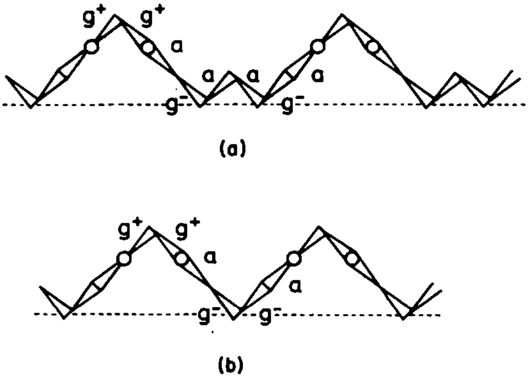


Fig 20.

Cyclic formals, acetals and ketals of 5- and 6-membered rings (1,3-dioxolans and 1,3-dioxans) have been studied extensively, and subtle conformational differences from the corresponding hydrocarbons mapped out in much detail.[5,24,87] We shall here just mention that 1,3-dioxolan is even more flattened than tetrahydrofuran,[24] has a similarly low pseudorotation barrier[25] and a symmetric twist-envelope (Fig 21a) as its lowest minimum; and that 1,3-dioxan has a chair conformation (Fig 21b) with a normal ring inversion barrier.[88] Of particular interest for our discussion is the fact that the 5-, the 6- and the 7-membered ring cannot accommodate the 1,3 - dioxa - grouping in its favoured $g^\pm g^\pm$ conformation, hence must be inherently unstable. The tendency for 1,3-dioxolan[89,90,91] and 1,3-dioxepan[92,93] to polymerize below a certain ceiling temperature, in spite of the accompanying entropy decrease, is

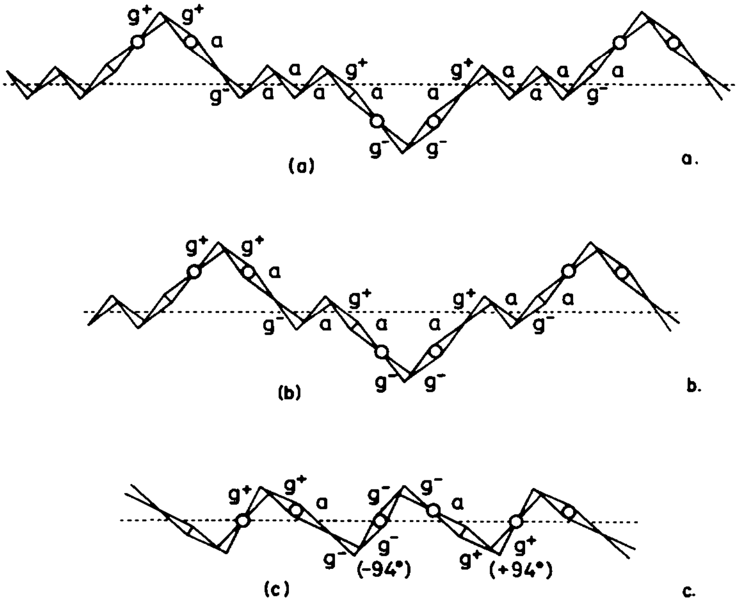
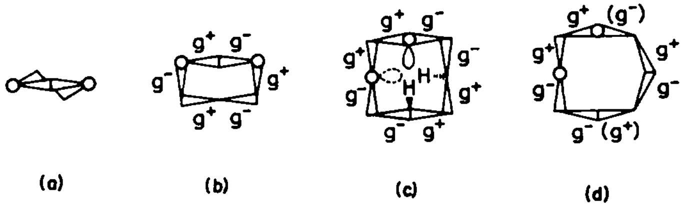


Fig 19.



(a) (b) (c) (d)

Fig 21.

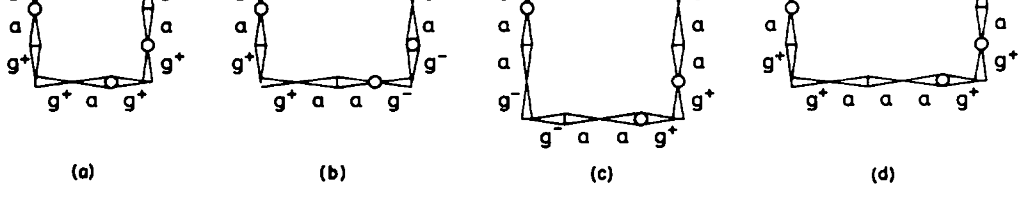
then due to release of both ring strain and conformational strain in the 1,3 - dioxa - grouping. 1,3-Dioxan should have negligible ring strain, so that only the latter part is responsible for its tendency to isomerize to the 12-membered ring.[92]

1,3-Dioxacyclooctane is the smallest ring which can accommodate the $g^{\pm}g^{\pm}$ 1,3 - dioxa - grouping. It was expected[80,94] that replacement of the two transannular 1,5- CH $\cdots$ HC interactions, which cyclooctane would have had in the diamond-lattice-type [2222] conformation, by CH $\cdots$ O interactions might allow 1,3-dioxacyclooctane to adopt this conformation (Fig 21c). Nevertheless, NMR-spectroscopy[30] showed that the boat-chair of the hydrocarbon (Fig 21d) is preserved, but with the 1,3 - dioxa - grouping fixed in $g^{\pm}g^{\pm}$ across one corner. The reason why the 1,5- CH $\cdots$ O interaction is thus also repulsive, has probably to do with the harder constraints of this ring hindering optimization of the distance. That 1,3-dioxacyclooctane, in spite of the fact that its formal group is in the favoured $g^{\pm}g^{\pm}$ conformation, polymerizes and cyclooligomerizes with extreme ease,[94] can of course be ascribed to its inherent medium-ring strain.

The dimeric cyclic formals, which are the main isomerization products from the liquid monomeric formals, have the properties characteristic of stable, rigid, conformationally homogeneous substances, such as high melting points and sharp IR bands,[94] and have been shown to have both 1,3 - dioxa - groupings $g^{\pm}g^{\pm}$ across opposite corners in quadrangular conformations (Fig 22). Thus, 1,3,7,9-tetraoxacyclododecane, m.p. 102°, is shown by dynamic NMR-spectroscopy[95] to have a symmetry only compatible with a square conformation (Fig 22a) and a much higher conformational barrier (~ 11 kcal/mol) than cyclododecane (7·3 kcal/mol), thus suggesting stabilizing CH $\cdots$ O interactions not only at the dioxa-groupings but also across the remaining corners, as observed for the trimethylene oxide tetramer (Fig 8b). A completely analogous conformation (Fig 22b) is found in the crystal for 1,3,8,10-tetraoxacyclotetradecane.[96] The observed dipole moment for 1,3,9,11-tetraoxacyclohexadecane[94] is so low (0·9 D) that it testifies to a stiffened molecule and the existence of attractive 1,4- CH $\cdots$ O interactions, and is thus in accord both with the square [4444] and the rectangular [3535] conformation (Fig 22c,d). NMR-spectroscopy[30] indicates the former for the unsubstituted formal, but a mixture of the two for the 2,2,10,10-tetramethyl derivative. The rectangular conformation has the advantage of having two $C_{\alpha}C_{\beta}$-bonds in *gauche*, but the disadvantage of not being of diamond-lattice type.

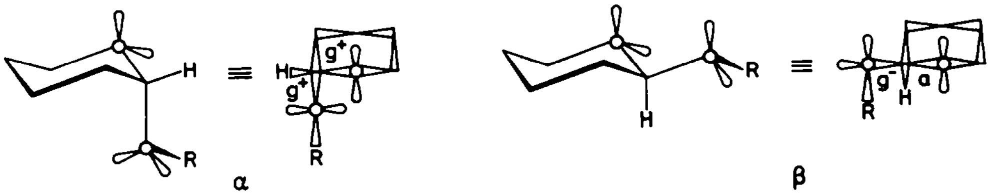
The well known anomeric effect in pyranose carbohydrates [5,24,97,98] is nothing other than a particular example of the $g^{\pm}g^{\pm}$ preference of the 1,3 - dioxa - grouping. This can most easily be shown by drawing the α- and β-forms in the same projection as used for the systems described above (Fig 23). The preference for axial halogen substituents in 1,4-dioxan[24] is another example of the anomeric effect. Even in 1,3-dioxans,[5] a 2 - methoxy - substituent is preferentially axial (by 0·4 kcal/mol), so that the 1,4-interactions of ether oxygen with axial CH in the 3- and 6-positions (Fig 24a) must be attractive in spite of the short distances. A 2-methyl substituent is for example strongly preferred equatorial,[5] and the energy difference (4·0 kcal/mol) can be taken as a measure of the double 1,4-CH $\cdots$ CH repulsion due to the short CO-bond when dihedral angle is forced near 60°.

1,3-Dioxans also give good examples of the



(a) (b) (c) (d)

Fig 22.



(a) (b)

Fig 23.

largely cancelled 1,5-repulsion when one CH is replaced by a lone pair, since a 5-t-butyl substituent is not totally forbidden axially[5] as it is in the hydrocarbon (Fig 24d).

CONCLUSIONS

Ethers are very similar to alkanes as regards the basic stereochemistry, having roughly tetrahedral COC valency angles and three staggered minima in the potential for rotation about CO- and adjoining CC-bonds.

On the other hand, the CO-bond gets a stronger *anti*-preference than the CC-bond whenever the alternative *gauche* 1,4-interaction is of CH · · · HC type, and this can be easily rationalized on simple geometric grounds.

A weakened repulsive or even an attractive interaction between CH and an oxygen lone pair, depending on CH-acidity, must be postulated to explain why both CC- and CO-bonds lose the *anti*-preference or even gain a *gauche*-preference whenever the *gauche* 1,4-interaction is of CH · · · O type. The very strong preference for the $g^{\pm}g^{\pm}$ conformation of the 1,3 - dioxa - grouping can be understood on the basis of the additional repulsion between parallel lone-pairs.

Quite unexpected is the observed *gauche*-preference for CC-bonds when the 1,4-interaction is of O · · · O type. Theoretical calculations fail to reproduce this experimental finding.

The 1,5- CH · · · O interaction in cyclic ethers may be slightly repulsive or slightly attractive depending on ring constraints.

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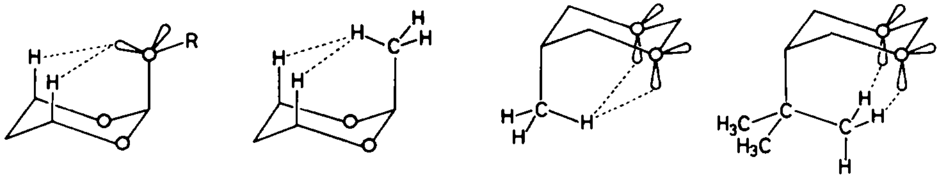

-0.4 kcal/mol (a) 4.0 kcal/mol (b) 0.8 kcal/mol (c) 1.4 kcal/mol (d)

Fig 24.

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