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Advances in the Study of *s-cis-trans*-Isomerism—Stereochemistry of Carbonyl Derivatives of Five-membered Heterocycles

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Results obtained on the stereochemistry of carbonyl derivatives of five-membered heteroaromatic systems—furan, thiophen, selenophen, tellurophen, pyrrole, and azoles—are summarised and systematised. Factors responsible for the stereochemical behaviour of conformationally non-rigid *s-cis-trans*-isomers of carbonyl derivatives of five-membered hetaryls are isolated. A list of 287 references is included.

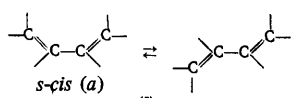
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I. INTRODUCTION

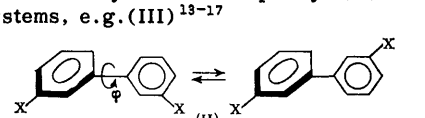
An important problem in the present-day stereochemistry of organic compounds is *s-cis-trans*-isomerism[1-3], involving the appearance of conformationally non-equivalent structures as a result of restricted rotation of molecular fragments about a single bond situated between two multiple bonds. The conjugation of double bonds through a single bond raises the energy barrier to rotation about the latter and increases significantly the latter's double-bonded character (the situation is analogous to *cis-trans*-isomerism, which is the reason for the fundamental similarity in the terms used for the isomers).

The phenomenon of *s-cis-trans*-isomerism, discovered[4] in butadiene systems

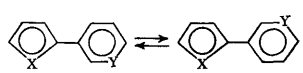


s-cis (*a*) (I) *s-trans* (*b*)

has proved to be widespread in aliphatic[1,2,5], aromatic[1,6-10], and heterocyclic[3,11-18] systems. Both planar structures, characterised by maximum conjugation, can be realised in butadiene and other aliphatic systems of type (I).[19] With conjugated aromatic systems like biphenyl (II)[6,7] and heteroaromatic systems, e.g. (III)[13-17]



X,X-*cis* ($0° < \varphi < 90°$) (II) X,X-*trans* ($180° < \varphi < 270°$)

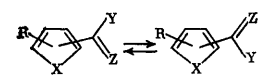


X,Y-*cis* (III) X,Y-*trans*

steric hindrance gives rise to non-planar structures corresponding to the optimum balance between conjugation and repulsion interactions. Unsymmetrical structures (II) and (III) may also give rise to *s-cis-trans*-isomerism. Finally, this can occur also in systems in which an aromatic or a heteroaromatic ring is conjugated with an unsaturated acyclic fragment, e.g. C=Z, where Z = C<, O, S, Se, N−, P<−†.

† Henceforward we shall arbitrarily apply the term "conformationally mobile" to such fragments.

This type of isomerism arises in aromatic systems only on the introduction of a second substituent into the ring (*ortho* or *meta* to the C : Z group).[3,20] With heterocycles, in contrast, introduction of a single conformationally mobile group is sufficient for the appearance of two isomers (IV), owing to diminution in the symmetry of the molecule to C_s and C_1:



X,Z-*cis* (IV) X,Z-*trans*

Among isomers of C : Z-containing heterocycles a most important place is occupied by carbonyl-containing derivatives (IV: Z = O), which have been investigated intensively by almost all current physical, physicochemical, and quantum-chemical methods (>80% of all the papers considered in the present Review have been published during the past decade).

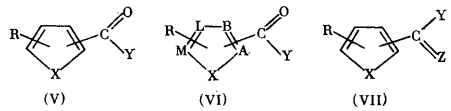
The reason for such heightened interest in the stereochemistry of carbonyl derivatives of five-membered heteroaromatic systems is that they form a convenient model for establishing general laws and elucidating the factors that explain various aspects of *s-cis-trans*-isomerism. Furthermore, knowledge of conformational transitions in such systems is necessary to establish the mechanism of several chemical[21] and photochemical[22] processes, and also to explain the biological action of preparations based on them[23,24]. Carbonylfurans have been used as internal and external standards in dynamic carbon-13 nuclear magnetic resonance spectroscopy for accurate temperature measurement[25].

However paradoxical it may appear, this particular type of isomerism has been inadequately discussed in well known monographs[2,5,6,8,26-28].# Yet progress in the study of *s-cis-trans*-isomerism and the huge quantity of publications make a review of this topic necessary.

The present Review gives a critical analysis of results on the *s-cis-trans*-isomerism of carbonyl-substituted five-membered heteroaromatic systems—furan, thiophen, selenophen, tellurophen, and pyrrole (Va-e), azoles (VI) and their

This problem is raised in certain reviews[3,5,18,29-32].

arylated derivatives—as well as structural analogues of carbonyl compounds (VII)



(V) (VI) (VII)

(V)-VII): (a) X = O; (b) X = S; (c) X = Se; (d) X = Te;
(e) X = NR′ (where R′ = H, Alk, Ar);
R = n-Alk, Ar, cyclo-C_4H_4, NO_2, Hal, CO.Y;
Y = H, Alk, Ar, Het, OH, OR″ (where R″ = Alk, Ar), Cl, NH_2;
(VI): A, B, L, M = N;
(VII): Z = CH.R″′ (where R′″ = H, Alk, Ar, Het), N.OH, N.Ar.

Attention is paid to the influence of the nature of the heterocycle, the character and the position of the conformationally mobile group and the substituent R in the heterocycle, the medium, and complex formation on the stereochemistry of systems of types (V)–(VII).

II. METHODS OF INVESTIGATION OF *s-cis–trans*-CONFORMERS

Vibrational Spectroscopy

In many cases analysis of vibrational spectra is an extremely effective method for establishing the presence of a conformational equilibrium[2,6,7,32-34]. It is usually assumed in such investigations that the normal vibration frequencies of the conformers differ somewhat owing to kinematic or dynamic factors. On such a hypothesis the main criteria of the presence of a mixture of conformers in liquids, solutions, or gases are complication of the spectra, variation in relative band intensities with temperature and solvent polarity, and simplification of the spectrum ("freezing" of the bands) in the liquid–crystal transition[6,34].

In the infrared, *s-cis–trans*-isomerism in carbonyl derivatives (V) and (VI) is usually indicated by a carbonyl absorption doublet ν_{CO} in the range 1660–1790 cm^{-1}. However, the nature of this doublet has been a matter of controversy. For 2-furaldehyde and 2-formylpyrrole it is explained by the presence of *s-cis–trans*-isomers[35-43], Fermi resonance[44-48], and also molecular association[42-51]. The doublet in the infrared spectrum of 2-formylthiophen is attributed mainly to Fermi resonance[52-54], although other workers[41] ascribe it to conformational equilibrium.

Thus existing data do not permit unambiguous interpretation of the behaviour of ν_{CO} nor definite conclusions on the conformations of carbonyl derivatives of five-membered heterocycles. Theoretical analysis of vibrational spectra[45, 48,55,56] has helped to explain the differences in the spectra of conformers and to give a more profound interpretation of the modes of vibration of each. Calculation has shown[56] that the doublet in the range 1670–1710 cm^{-1} is indeed due to the presence of both conformers, the ν_{CO} vibration being composite: the position of the carbonyl group affects not only the 1680- and 1700-cm^{-1} vibrations (X,O-*cis* and X,O-*trans*) but also the absorption at 1570 cm^{-1}, which is due to a fragment of the heterocycle ($\nu_{C(2):C(3)}$).

Frequency assignments for furaldehyde in other infrared regions, also used[40] for the study of *s-cis–trans*-isomerism, have been refined[55,56]. The integral absorption band intensities necessary to determine the state of conformational equilibrium were found[55,56]. The ratio of the conformers cannot[55] be evaluated solely from the experimental intensity ratio of ν_{CO} bands in the infrared spectra of furaldehyde.

The above discussion shows that, although infrared spectral data can be used to assess *s-cis–trans*-isomerism in a series of carbonyl derivatives of five-membered heteroaromatic systems, reliable results can be obtained only by combining empirical and calculated values for the vibrational spectra.

Dielectric and Electro-optical Investigations

Several dielectric and electro-optical investigations have been made on conformational equilibrium in the above systems. However, even in this case the solution depends on the choice of additive scheme, so that the use of group moments for aromatic substituents may not always be successful[57-59].

In connection with this the dipole moment of the aldehyde group was determined[60] for compounds of the furan series on the assumption that furaldehyde exists only in the O,O-*cis*-form. Dipole moments have been calculated theoretically[61-63] for both isomers of a series of aldehydes.

The controversial aspect of the vector calculation of dipole moments for heterocyclic aldehydes is to allow for the moment of interaction between heteroatom and carbonyl oxygen, first introduced for furaldehyde[64]. Values from 0 to 0.3 D have been assigned to this quantity[65-67].

A contradictory explanation has been given for dielectric results for carbonyl derivatives of thiophen (V: X = S, Y = R = H)[68], selenophen (V: X = Se, Y = R = H)[59,69,70], tellurophen (V: X = Te, Y = R = H)[71], and benzimidazole (VI: X = NAlk, A = L = M = CH, B = N, R = cyclo-C_4H_4).

Application of the Kerr effect has also led to opposite conclusions[58,68] concerning the preferential conformation of furaldehyde. These discrepancies are due both to difference in the valency–optical scheme used and to disagreement in the experimental results.

In several cases the above contradictions are due mainly to incorrect choice of vector additive and valency–optical schemes for the theoretical calculation of dipole moments and anisotropy of polarisability of the molecules of carbonyl derivatives of five-membered heteroaromatic systems. Therefore a definite advance in the use of dielectric measurements and the Kerr effect to assess the *s-cis–trans*-isomerism of these systems was determination of the polarisability tensors for several fundamental heterocycles[74-76] and the construction of valency–optical and vector–additive dipole schemes for calculating azole molecules[77-79]. Finding the formyl group moments for 2-furaldehyde and 2-formylthiophen from independent data was of great value[80,81].

Thus the limitations of the dielectric and electro-optical methods are inherent in their very foundations, in the problem of choosing adequate group moments and polarisability tensors. Since a correct solution of such a problem is often difficult or even impossible, the results may not agree and may differ from those obtained by other methods. However, with a right choice of these quantities a simultaneous application of the methods may be extremely fruitful for solving problems of conformational analysis.

Resonance Spectroscopy

Nuclear magnetic resonance spectroscopy has recently become one of the most widely used methods for investigating *s-cis–trans*-isomerism. It was first shown[82] that the conformations of 2-formyl derivatives of five-membered heterocycles can be assessed from the stereospecific spin–spin coupling constants in the ^1H n.m.r. spectra. It was later

found possible[83] to determine the position of the *s-cis–trans*-isomeric equilibrium and its thermodynamic parameters from such spectra. Unfortunately, errors were made in the detailed investigations[83], which led to a wrong conclusion on the ratio of the stable conformers. Nuclear magnetic resonance (^{1}H), together with stereospecific constants, chemical shifts, the Overhauser effect, and shift reagents, has been used to investigate the structure of carbonyl derivatives of furan[36,55,82–89], thiophen[85,88–96], selenophen[84,89], pyrrole[97,98], tellurophen[71,95,99], and azoles[100–104]. Isolated results have appeared on the application of carbon-13 and fluorine-19 n.m.r. in the conformational analysis of carbonyl derivatives of five-membered heterocycles[105–107]. However, the possibilities of n.m.r. spectroscopy are also limited, since its use presupposes either the availability of stereospecific hyperfine coupling constants, adoption of a definite model of diamagnetic shielding, or measurements at temperatures below the coalescence point. The postulates necessary also in application of the Overhauser effect and shift reagents restrict the use of these methods. The work is greatly complicated by increase in the order of the n.m.r. spectrum and sparing solubility of the compound. Nevertheless, n.m.r. spectroscopy is one of the most promising methods of investigation in the conformational analysis of *s-cis–trans*-isomers.

Use of electron spin resonance spectroscopy becomes possible for heterocyclic aldehydes only when they generate radical-anions[12,108,109]. The range of such compounds is limited, and the position of conformational equilibrium in the radical system differs from that for the neutral molecule.

The conformations of carbonyl derivatives of five-membered heterocycles have been analysed not only by the above main methods of investigation but also on the basis of data of microwave spectroscopy[110–113] (in the gas phase), ultrasonic[114] and dielectric[103,115] relaxation, X-ray examination[116–120] (of the crystalline phase), and electronic spectra[121–124].

Quantum-chemical Methods

The *s-cis–trans*-conformations of carbonyl derivatives of five-membered heterocycles (mainly aldehydes) have been widely assessed by quantum-chemical methods. Furaldehyde[5,62,63,123,125–129] has been investigated in the greatest detail by the Pariser–Parr–Pople, INDO/2, and extended Hückel methods, although the conclusions concerning realisation of a particular conformer obtained from the calculations are contradictory. A similar situation obtains in the assessment from quantum-chemical calculations of conformers of formylpyrrole[63,123] and formylthiophen[93,130,131].

Such a discrepancy in the conclusions concerning the configurations of carbonyl derivatives of five-membered heterocycles can be explained by the very small energy difference between the two conformers, hundredths of an electron-volt; i.e. the result may change depending on the approximations and the method of calculation. The role of *d*-orbitals in calculations on the conformations of the 2-formyl-thiophen and -selenophen is equally debatable[93,123,130].

Application of the comparatively simple extended Hückel method of calculation[132,133] led to important conclusions also on *s-cis–trans*-isomerism and barriers to internal rotation in heteroaromatic aldehydes[134,135].

The results in the present section can be summarised by emphasising the inconsistency of individual conclusions reached by different physicochemical methods on the conformations of carbonyl derivatives of five-membered heterocycles. Therefore only those results are reliable that coincide for different methods and produce a single, internally consistent picture in series of compounds with variation in heterocycles, substituents, and conformationally mobile groups.

III. FACTORS INFLUENCING THE POSITION OF CONFORMATIONAL EQUILIBRIUM§

Among factors responsible for the conformation of carbonyl-substituted five-membered heterocycles we have isolated the structure of the hetero-system with the exocyclic substituent, the medium, and intra- and inter-molecular interactions.

1. Structure of *C*-Carbonyl-substituted Heterocycles

(a) Substituents Attached to the Carbonyl Group (COR)

Aldehydes (R = H). No generally accepted view can be found on the most stable conformers of the simplest 2-formyl derivatives of five-membered heterocycles: the position of conformational equilibrium determined by different methods even under closely similar conditions often varies so widely that all the data available are insufficient to determine which form is the most stable and predominant.

The situation is especially characteristic of 2-furaldehyde: whereas it has been stated[42,64,83] that the O,O-*trans*-form is energetically the most advantageous, other workers[85,88,95,106,136,137] regard the O,O-*cis*-conformer as the most stable. More unambiguous conclusions have been reached on the structure of 2-formylthiophen, which most investigators[85,88,90–96,110,111,138–142] regard as existing solely in the form of the S,O-*cis*-conformer. Yet the agreement between experimental and calculated dipole moments led to the conclusion[140] that thiophen-2-aldehyde exists as a non-planar S,O-cisoid structure with a non-coplanarity angle of 35°, and other workers[68] assume the existence of an equilibrium mixture of conformers containing up to 27% of the S,O-*trans*-form.

2-Formylselenophen is regarded[59,70,84] as conformationally a more rigid system than 2-formylthiophen. The Se,O-*cis*-isomer is the more stable[59,69,70,95,143], although the conformational mixture may contain a considerable percentage of the *trans*-form[84,143].

Nuclear magnetic resonance and infrared spectroscopy[99], and also dipole moments[59,144], suggest that 2-formyltellurophen exists in solution as a mixture of two conformers, with a lower content of the *trans*-form than in the case of furaldehyde. However, even with this aldehyde shift reagents reveal exclusively the Te,O-*cis*-conformer[95]. Thus, despite appreciable discrepancies in the results, the X,O-*cis*-conformers are the most stable in 2-formylhetaryls containing

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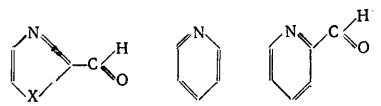
§ In most cases the solvents in which investigations have been made are not stated in the present Review if change in them does not lead to fundamentally different results. The solvents mainly used in the work cited were as follows: tetrachloromethane, benzene, and dioxan in dielectric measurements; tetrachloromethane, chloroform, dichloromethane, dioxan, and mineral oil in infrared spectroscopy; and tetrachloroethylene, chloroform, methanol, dichloromethane, tetrachloromethane, and acetonitrile in radiospectroscopy.

elements of subgroup VI*b* as heteroatom¶, the content of this form diminishing in the sequence—selenophen > thiophen > tellurophen > furan.

The authors of the majority of the investigations consider[49-51,97,103,115,145-148] that pyrrole-2-aldehyde exists as the N,O-*cis*-conformer. Yet other results[83,98,103,115,145,149,150] indicate a definite contribution by the N,O-*trans*-form, though this can be explained[151] also by the possible existence of a non-planar conformer of 2-formylpyrrole. Stabilisation of the N,O-*cis*-conformers in this compound was originally explained[146] by a hydrogen bond of the type NH...O=C. Later, however, it appeared[98,152,153] that no significant increase† in the proportion of the N,O-*trans*-conformer occurs even in *N*-alkyl derivatives of this aldehyde. The N,O-*cis*-form is characteristic also of 2-formylindole[155].

Thus the factors causing stabilisation of the X,O-*cis*-conformers of the 2-formyl derivatives are common to all the five-membered heterocycles considered, and hence independent of the nature of the heteroatom X. A decisive role is played by Coulombic interaction of the charges of the cyclic heteroatom and the carbonyl oxygen atom. ππ-Conjugation of exo- and endo-cyclic parts of the molecules is not decisive (in the presence of Coulombic interactions), and can merely be superposed on the predominant Coulombic effect, either strengthening or weakening it. For these aldehydes both effects give the X,O-*cis*-forms[156-158].

2-Aldehydes of the azole series are characterised[159,160] mainly by conformationally rigid *cis*-structures (VIII)#. To understand the factors stabilising the *cis*-configuration of the 2-formylazole systems it must be borne in mind that molecules of aldehydes of the 1,3-diazole series (VIII) include fragments of the fundamental five-membered heterocycles (V) and six-membered nitrogenous heteroaromatic systems [azines, in particular pyridine (IX)]. Examination of the structure 2-formylpyridine[11,43,63,82,113,123,161-169] indicates almost complete formation§ of the rigidly fixed N,O-*trans*-isomer (X)



(VIII) (IX) (X)

This is well explained by both the above factors responsible for stabilising conformers in the *s-cis*–*trans*-equilibrium of formyl-containing heterocycles.

Indeed, both Coulombic interaction (repulsion of negatively charged nitrogen and oxygen atoms) and ππ-conjugation effects stabilise the planar N,O-*trans* form of pyridine-2-aldehyde (X). The above results suggest that both effects should tend to stabilise the X,O-*cis*(N,O-*trans*)-conformers (VIII) in the case of 2-formylazole systems, as has been confirmed experimentally[73,159,160] and by calculation[159].

In this connection the conclusion[72] that up to 50% of the X,O-*trans*-isomer of 2-formyl-*N*-methylimidazole is present in benzene solution appears unexpected, though it is difficult to deny the actual possibility that the X,O-*trans*-isomeric form may be involved in the conformational equilibrium of aldehydes of the azole series[73,160].

Ketones (R = Alk, Ar, Het). The attachment of aliphatic, aromatic, and heterocyclic substituents to the carbonyl group changes the barrier to rotation about the single bond



and in most cases leads to structural non-coplanarity of ketone derivatives of five-membered heterocycles[134,154,171]. Even the simplest alkyl substituent, methyl, yields two isomers, with the O,O-*trans*-form predominating in 2-acetylfuran[42,68,93,94,136,137,171-174]. Yet 2-acetylthiophen, 2-acetylselenophen, and 2-acetylpyrrole are characterised exclusively or predominantly by the planar X,O-*cis*-structure[69,92,103,124,140,152,175-178]. However, some data even for these compounds indicate both the establishment of a conformational equilibrium[59,68,94,152] and the presence of a substantially non-planar structure[152,178,179] with a dihedral angle $\phi \cong 30-55°$. Increase in the proportion of the *trans*-conformer (from 28% to 53%) is observed on passing from formyl to acetyl derivatives of tellurophen[59,99,144]. The inconsistency of all these results on the three-dimensional structure of the acetyls is due to the difficulty usually encountered in choosing unambiguously, on the basis of individual data, between non-planar rotamers and equilibrium systems containing planar *s-cis*- and *s-trans*-conformers.

A non-planar structure is characteristic of hetaryl phenyl and dihetaryl ketones[178,180,181]. That of furyl phenyl ketone is due solely to displacement of the phenyl group from the plane of the rest of the molecule[180], whereas the corresponding thienyl ketones exhibit simultaneous displacement of the hetaryl group from the plane of the carbonyl group[181]. This result is due to the greater gain in energy on conjugation of the carbonyl with the less aromatic[182] furan ring than with the thiophen ring, as is confirmed by quantum-chemical calculation[123].

Thus the conformational analysis of ketones, in contrast to that of aldehydes, must take into account not only *s-cis*(*trans*)-conformers but also the possibility of a non-planar molecular structure for the carbonyl-containing five-membered heteroaromatic systems[23,67,68,92,121,124,183-186]. Like the corresponding aldehydes, ketones of azoles usually have predominantly a structure with maximum separation of pyridine-type nitrogen atoms and carbonyl oxygen[187,188]. Addition of two heterocycles to a carbonyl group usually complicates the task of conformational analysis, since the possibility arises

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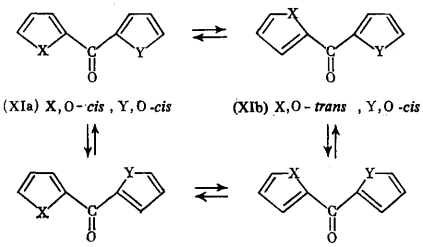
¶ However, other studies[83,145] suggest that the X,O-*trans*-conformer predominates in the 2-aldehydes of furan and pyrrole.

† It must be emphasised, however, that the presence of significant steric hindrance (in *N*-aryl- and *N*-hetaryl-2-aldehydes)[154] leads to the O,N-*trans*-structure, in which Coulombic repulsion is minimal.

To avoid confusion we retain for the carbonylazole systems (VIII) the names of conformers analogous to the formyl derivatives of the fundamental five-membered heterocycles.

§ Yet other workers[82,165,170] regard pyridine-2-aldehyde as a stereochemically non-rigid system with up to 30% of the N,O-*cis*-form involved in the conformational equilibrium.

of four planar conformers (XIa–d):



(XIa) X,O-*cis*, Y,O-*cis* (XIb) X,O-*trans*, Y,O-*cis*

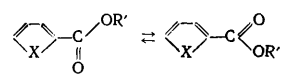
(XIc) X,O-*cis*, Y,O-*trans* (XId) X,O-*trans*, Y,O-*trans*

A non-planar structure is also possible for the ketones, as a consequence of electronic and steric effects of interaction between the heterocyclic rings and with the carbonyl group.

According to n.m.r. data difuryl ketone probably exists as a mixture of equal quantities of two forms, O,O-*cis*,O,O-*trans* and O,O-*trans*,O,O-*trans*[185]. Infrared[189] and n.m.r.[185] spectroscopy lead to fundamentally opposite conclusions on the structure of fur-2-yl fur-3-yl ketone. Whereas changes in dipole moments could not give an unambiguous indication of the spatial structure of dithienyl ketone[67], application of this method together with the Kerr effect has shown[68,181] a non-coplanar *cis,cis*-structure with the thienyl diverging from the carbonyl plane by 30–55°. Dielectric measurements and n.m.r. spectroscopy have demonstrated an unsymmetrical planar structure for a series of thioketones of pyrazole, thiophen, and several other heterocycles[190].

Carboxylic acids (R = OH). In contrast to aldehydes and ketones, *s-cis–trans*-isomerism in carboxylic acids of five-membered heterocycles has remained almost uninvestigated. X-Ray structural studies indicate that thiophen-, selenophen-, and tellurophen-carboxylic acids exist in the crystalline phase as planar X,O-*trans*-configurations, whereas furancarboxylic acid is characterised by the O,O-*cis*-form[119]. 1,3-Dimethylpyrazole-5-carboxylic acid has a planar N,O-*trans*-structure in the solid state[118].

Carboxylic esters (R = OR'). The esters have been investigated in greater detail. It can be accepted that the *s-cis–trans* equilibrium



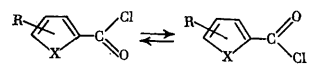
(XIIa) X, O_{carb}-*cis* (XIIb) X, O_{carb}-*trans*

is established in solution[47,59,65,106,191–193], but the clear dependence on the nature of the heterocycle characteristic of aldehydes is not observed[59]. Furancarboxylic esters (XII: X = O, R' = H) exist mainly as the X,O-*trans*-form (XIIb), which according to dipole moments[65] and n.m.r. spectra[106] constitutes 50–70%. Increase in the degree of branching of the group R' entails lowering of the barrier to rotation, which makes the identification of conformers difficult[106]. The content of the *cis*-conformer in conformational equilibrium is according to the dipole moments respectively 33%, 59%, and 42% in thiophen-, selenophen-, and tellurophen-carboxylic esters, in contrast to aldehydes and ketones.

These quantitative relations can hardly be regarded as sufficiently accurate, since it has been reported that conformational processes in thiophen- and furan-2-carboxylic acids have similar enthalpies, and also that furan- and tellurophen-carboxylic esters have equal contents of the two conformers[191].

In contrast to the above esters, methyl pyrrole-2-carboxylate exists in solution predominantly (73%) in the planar N,O_{CO}-*cis*-form: the rather higher content of the N,O-*trans*-isomer than in aldehydes and ketones is attributed to the ability of the imino-group to form a hydrogen bond not only with the carbonyl but also with the ethereal oxygen of the carboxyl group[194].

Acid halides (R = Hal). The barrier to rotation is higher in the chlorides of carboxylic acids of five-membered heterocycles than in the hetaryl methyl ketones, with a consequent conformational equilibrium between two planar conformations:



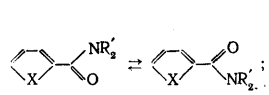
(XIIIa) (XIIIb)

Data on the conformations of acid halides are restricted to furan and thiophen derivatives[47,65,105,106,195,196].

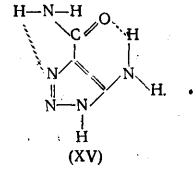
According to ^{1}H n.m.r. spectra[106] the equilibrium mixture of molecules of the chloride of furancarboxylic acid contains at low temperatures (~193 K) up to 90% of the O,O-*cis*-form (XIIIa). The same form (XIIIa) is predominant also in chlorides of thiophencarboxylic acids[195,197], although infrared spectra suggest[105] a significant contribution by the S,O-*trans*-form (XIIIb). The sequence is reversed on passing from chlorine to fluorine derivatives, and the proportion of the X,O-*cis*-form diminishes: under comparable conditions (solvent, temperature) the proportion of the O,O-*cis*-conformer of the fluoride of furancarboxylic acid is 75%, but in the corresponding thiophen derivative it has even dropped to 55%. This is obviously due to the strongly electronegative fluorine substituent, which is able to compete with the carbonyl oxygen in its ability to interact electrostatically with the endocyclic sulphur atom ($S^{\delta+}...F^{\delta-}$ and $S^{\delta+}...O^{\delta-}$), and this leads to approximate equivalence of the two forms in the thiophen derivative. In fluorides of furancarboxylic acids, on the other hand, the Coulombic repulsion between the terminal oxygen and the fluorine atom exceeds that between the two oxygen atoms, so that the proportion of the O,O-*cis*-form in them is higher[105] than in the corresponding aldehydes of the furan series.

Similar conclusions on the competitive electrostatic interaction of halogen and carbonyl oxygen with the cyclic heteroatom were reached in an investigation of conformational changes in series of chlorides of furan-2-carboxylic acids[196]. A detailed investigation showed, on the basis of infrared spectral data together with measurements of dipole moments and the Kerr effect, that such chlorides are present in solution as mixtures of two conformers, the proportion of the O,O-*trans*-form increasing with the acceptor properties of 5-substituents in the furan ring and with decrease in solvent polarity, whereas chlorides of thiophencarboxylic acids are characterised by a single O,S-*cis*-conformation (XIIIa).

Amides of carboxylic acids (R = NH_2, $NAlk_2$). In amides of carboxylic acids of five-membered heterocycles the barrier to rotation is much lower than in the aldehydes, which leads to predominance of a non-planar X,O-*trans*-structure (XIVb)[94,95,171]:



(XIVa) (XIVb)



(XV)

Measurements of dipole moments indicate[59] that the 2-dimethylcarbamoyl derivatives contain in the equilibrium mixture respectively 89% (furan, tellurophen), 67% (selenophen), and 44% (thiophen) of the X,O-*trans*-isomers.

Whereas the non-planar structure of these compounds is apparently due to steric effects, formation of a predominantly X,O-*trans*-structure is a consequence of X...N and X...O electrostatic interactions[95]. Crystallographic examination[198] of 5-amino-1,2,3-triazole-4-carboxamide reveals in the solid state a structure of *trans*-type stabilised by fairly strong intramolecular hydrogen bonds. Furthermore, such an $N_{(3)}$,O-*trans*-conformation is consistent with the principle of maximum distance between a negatively charged oxygen atom and the pyridine nitrogen atom of the heterocycle.

The carbothioamides possess a considerably lower energy barrier (2.4–4.4 kcal $mole^{-1}$)[199] than the 2-carboxamides of five-membered heterocycles and pyridine, but this hinders free rotation of the thiocarbamoyl group. Dielectric measurements show that furan-2-carbothioamide exists in benzene solution as a mixture of both planar conformers in the approximate proportions 2 : 1 (excess of the S,O-*trans*-form). On the other hand, the thiophen analogue is characterised by a fivefold excess of the S,S-*cis*-conformer. On the whole these results are consistent with what is known for the corresponding formyl and carbamoyl derivatives. However, the low energy barriers and the small difference in energy of the two forms (0.2 kcal $mole^{-1}$) facilitate appearance of the S,S-*trans*-form in thiophen-2-carbothioamide[199].

We note in conclusion that in none of the above carboxamide and carbothioamide derivatives could the coalescence point be reached (according to the ^1H n.m.r. spectra). This is due either to realisation of a single form (X,O-*trans*) or (more probably) to a low barrier to rotation (below 5–6 kcal $mole^{-1}$).[200]

Comparison of the structures of the various derivatives of carboxylic acids of five-membered heterocycles must take into account the great influence of the nature of the conformationally mobile group on the position of the conformational equilibrium. Compounds containing alkoxycarbonyl and dialkylcarbamoyl groups exhibit a shift in the equilibrium towards the X,O-*trans*-form. This is especially marked in carboxamides, with almost complete reversal of the equilibrium accompanied by a considerable lowering of the barrier to rotation and appearance of the ability to form non-planar structures. The situation is quite different with acid halides, where the state of the conformational equilibrium is determined by the halogen atom and its ability to compete with the carbonyl oxygen in attracting or repelling the heteroatom of the aromatic ring. This explains the marked difference in conformational equilibrium between acid chlorides and acid fluorides.

(b) Position of the Carbonyl Group in the Heterocycle

The remoteness of the carbonyl oxygen atom from the oppositely charged endocyclic atom X in 3-carbonyl derivatives facilitates the production of *s-trans*-conformations, which in individual cases may become the predominant or even sole form. This conclusion is confirmed theoretically for many 3-aldehydes[123,201]. Experimentally n.m.r. spectroscopy indicates[202–204] that the proportion of the *s-trans*-form in the 3-aldehydes of pyrrole, thiophen, and furan is respectively 78%, 82%, and 100%. Only introduction of a bulky (e.g. ester) substituent at position 2 in the heterocycle is able to change slightly the proportions of the conformers[203]. The structure of the latter has been confirmed by infrared spectroscopy[189] and by dielectric measurements[66,141,173,205].

The differences in the behaviour of 3-substituted furan and thiophen derivatives are explained[203] by the net effect of Coulombic (X...O_{ald}), dipole–dipole ($C_{(2)}$=$C_{(3)}$ and O=C), and resonance interactions. These three factors, acting in the same direction, lead to exclusive formation of the O,O-*trans*-modification in 3-formylfuran, but to both planar forms, with the S,O-*trans*-conformer predominating, in the thiophen analogue. Investigation of the conformations of the 3-formylselenophen gives more contradictory results. Thus the dipole moments indicate[143] that in benzene solution this aldehyde contains both conformers, in roughly equal quantities with the Se,O-*cis*-form in slight excess, whereas other dielectric measurements and proton n.m.r. spectroscopy suggest that the content of the Se,O-*cis*-form does not exceed 20%.[70,99]

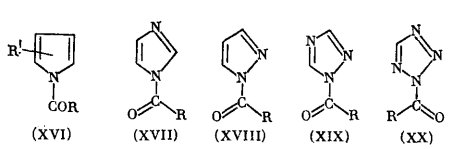
In the case of pyrrole-3-aldehyde the planar N,O-*trans*-structure is the most highly populated[97,115,206,207] and apparently[147] the only form. Substituents and solvents are able merely to disturb the ratio of the conformers, but not to change the general tendency. Pyrazole-4-aldehyde, in which the formyl group is arranged approximately as in the previous compound, exists according to the ^1H n.m.r. spectra as an equilibrium mixture of N,O-*cis*- and N,O-*trans*-isomers[208]. The activation energy of isomerisation is smaller by 1.5 kcal $mole^{-1}$ than for the corresponding pyrrole-3-aldehyde[208].

The content of the more stable X,O-*trans*-form in the 3-acetyl derivatives of five-membered heterocycles increases in the same sequence—from *N*-methylpyrrole through thiophen to furan—as for their formyl analogues[202]. However, the proportion of the conformers is less displaced towards this form than in the case of aldehydes: according to n.m.r. spectral results obtained by the use of shift reagents of the Overhauser nuclear effect[202] its content is on the average 52%, 56%, and 70% respectively (in the aldehydes 78%, 82%, and 97%). When the temperature is lowered to −100 °C coalescence of the signals cannot be observed in either 3-acetylfuran or 3-acetylthiophen, which indicates a low barrier to rotation in these compounds and less conjugation in 3- than in 2-substituted derivatives[185]. As in other five-membered heterocycles, the content of the X,O-*cis*-conformer in 3-acetylselenophen is double that in the 3-formyl analogue (30% and 15%).[99] 4-Acetylimidazole exists in the crystalline state solely in the $N_{(3)}$,O-*trans*-form[187].

Conformational equilibria in other 3-carbonyl derivatives of five-membered heterocycles (acids, esters, acid halides, and amides) remain almost uninvestigated.

2. *N*-Acyl Derivatives of Five-membered Heterocycles

In nitrogenous five-membered heterocycles derivatives are also possible in which a COR group is directly attached to the nitrogen atom—derivatives of pyrrole (XVI) and of azoles (XVII)–(XX)



(XVI) (XVII) (XVIII) (XIX) (XX)

The structure of *N*-acylazoles, though investigated by several workers[101–103,107,162,209–213], has not until recently received an unambiguous interpretation. Authors were one in accepting a planar structure[101,102,210–212,214], but attributed

to these compounds a *cis*-structure[101,102,107,212] or a *trans*-structure[215,216] on the basis of different methods of investigation, the contents of these forms varying within wide limits in papers by different authors[101-103,209,210].

In assessments of the conformations of *N*-acylazoles a detailed investigation was therefore made into their stereochemistry by measuring dipole moments, the Kerr effect[217], and n.m.r. spectra with the use of shift reagents[104]. Among the main conclusions[104,217] are that *N*-acetylimidazole (XVII) exists as a mixture of non-planar isomers (dihedral angle 21°) containing 75% of the $N_{(3)}$,O-*trans*-form and 25% of the N,O-*cis*-form, and that *N*-acetylpyrazole (XVIII) gives a mixture of almost planar conformers (10°) containing 90% of the $N_{(2)}$,O-*trans*-form (XVIII). A non-planar $N_{(2)}$,O-*trans*-form (dihedral angle $\phi = 30°$) is characteristic also of *N*-acetyl-1,2,4-triazole (XIX). In $N_{(1)}$-acetyl-1,2,3,5-tetrazole the $N_{(3)}$,O-*trans*-form (XX) is energetically advantageous.

Thus with all the *N*-acetylazoles studied the $N_{(2(3))}$,O-*trans*-form predominates significantly in solution. The energetic advantage of this form can be attributed to attainment of maximum distance between the negative charges of the acetyl oxygen atom and the nearest "pyridine" nitrogen atom of the azole ring. A nitrogen atom at position 2 in the azole ring leads to a greater content of the *trans*-form of *N*-acetylazole than when this atom is located at position 3. The apparent reason is strengthening of electrostatic repulsion as the acetyl oxygen atom approaches the cyclic nitrogen atom. The same factor leads to flattening of the $N_{(2)}$,O-*trans*-structure.

The influence on conformation of the cyclic nitrogen atom closest to the acetyl group is especially marked in *N*-acetyltriazole (XIX), since the $N_{(2)}$,O-*trans*-form observed for it is also a disadvantageous *cis*-form with respect to the $N_{(4)}$ atom.

These conclusions were confirmed by theoretical analysis of the stability of conformers of *N*-acetylazoles (energy of barrier to rotation, difference in energy of conformers, order of bonds in planar and orthogonal forms)[218]. In contrast to Otting's views[213] the results indicate that the rise in the frequency ν(CO) on passing from *N*-acetylpyrrole to *N*-acetylazoles is due not so much to a change in aromaticity of the heterocycles as to the non-planar structure of *N*-acetylazoles.

Among other *N*-carbonyl derivatives of pyrrole and azoles only the *N*-methoxycarbonyl derivative of the former and *N*-carboxamides of pyrazole and imidazole have been investigated[101].

3. Substituents in the Heterocycle

The chief effects of substituents on the state of conformational equilibrium in carbonyl derivatives of five-membered heterocycles can be divided into three types: (A) electronic effects of substituents are transmitted through the conjugated bond system of the heterocycle, with consequent changes in degree of conjugation of hetaryl with formyl group and in charges on heteroatoms and carbon atoms; (B) direct electrostatic or other specific interaction (e.g. hydrogen bonding of a substituent with a conformationally mobile group) tends to favour one of the forms; and (C) steric hindrance by a sufficiently bulky or closely adjacent substituent tends to prevent flattening of the system or causes a change in the state of conformational equilibrium. Separation of these factors is clearly a quite complicated task, which can be successfully accomplished only in isolated cases.

Type A

Interactions of the first type can be isolated only when the two cyclic substituents (conformationally mobile, e.g. formyl, and conformationally inert) are sufficiently far apart to exert no mutual influence. This occurs in 2-aldehydes of 4- and 5-substituted furans, thiophens, selenophens, and pyrroles.

A change from electron-donor to electron-acceptor substituents produces a decrease in the proportion of the X,O-*cis*-form[42,67,219-221]. This is especially characteristic of conformationally mobile ring-substituted 2-furaldehydes. Thus for 5-substituted 2-furaldehydes the proportion of *cis*-conformer decreases from 90% to 30% in the sequence from dimethylamino through halogeno, methyl, and hydrogen to nitro[219,221]. Introduction of a 5-nitro-group leads to accumulation of the X,O-*trans*-form even in formyl derivatives of thiophen[80,135], selenophen[69,75,135], and pyrrole[23,97,147,194]. It changes the position of the conformational equilibrium in pyrrole-3-aldehyde from the pure O,O-*trans*-form to a mixture of equal quantities of the two conformers, brings their energies closer together, and lowers the barrier to rotation[97,206]. Introduction of an electron-accepting ester group has the same effect[97,206,207,211,222]. Nevertheless, in contrast to 2-furaldehyde, in the conformationally less mobile 2-aldehydes of thiophen[138,140,141,175,176], selenophen[75,80], and pyrrole[97,148,207] electron-donor substituents have little effect on the position of conformational equilibrium (in these cases almost 100% of the X,O-*cis*-form is present).

5-Substituted 2-acetylfurans, in contrast to the 2-aldehydes, exhibit no clear electronic effects of substituents on the position of conformational equilibrium: electron-donor and electron-acceptor substituents lower the relative content of the X,O-*cis*-form[223].

Substituents at positions 4 and 5 have hardly any effect on the conformations of 2-formyl- and 2-acetyl-thiophens: these derivatives exist in solution[67,92,124,140,176,177] and in the crystalline phase[92,175] in the single planar S,O-*cis*-form. The same situation is found with 4- and 5-substituted formylpyrroles[211].

Infrared spectra and dielectric measurements indicate[196] that 5-substituents have a significant influence on the position of conformational equilibrium in furancarboxylic acids and their chlorides: as in the case of the aldehydes, the content of the O,O-*cis*-form decreases from 100% to 41% on passing from 5-methyl to 5-nitro-derivatives.

Annelation at positions 4 and 5 of the heterocycle should have had the same effect as the introduction of electron-accepting substituents[224]. However, fusion of a benzene ring usually has no significant influence on the conformational equilibrium[54,155]. Conformations similar to those considered above for formyl derivatives of five-membered heterocycles appear also in 2-aldehydes of 4,5-benzo-derivatives of thiophen[225], pyrrole[154,155], and imidazole[73,226].

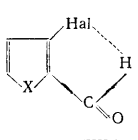
Substitution in the aryl ring of *N*-methylbenzimidazole-2-aldehyde seems unable to change the state of conformational equilibrium[73], whereas ring substitution in pyrrole-2-aldehydes leads in many cases to appearance of a second conformer[159].

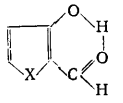
In contrast to *C*-carbonyl derivatives, in the corresponding *N*-derivatives benzannelation has a very substantial effect on the position of conformational equilibrium. Thus whereas in *N*-acetyl- and *N*-formyl-pyrroles the two conformations are equivalent ($\Delta H^{\neq} = 12-13$ kcal mole^{-1}),[212] two planar forms—$H_{(7)}$,O-*cis* and $H_{(7)}$,O-*trans*—can already be distinguished on passing to the corresponding indole and indazole derivatives. In this case the content of one of the conformers may vary within the range 10–90% depending on the nature of the mobile fragment and the substituent. Such

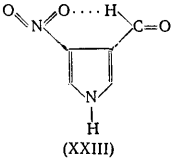
mobility of the position of conformational equilibrium in arene-annelated systems is due to steric effects and is clearly evident in derivatives of *N*-formylbenimidazole and *N*-formylindole[155]. (On further annelation—on passing to symmetrical *N*-carbonyl derivatives of carbazole—the two forms, of course, again become equivalent, as in the case of *N*-formylpyrrole[100].)

Type B

The second type of interaction of the conformationally mobile group (COR) with a substituent comprises direct (electrostatic or dipole–dipole) interaction or other specific effects of a substituent located *ortho* with respect to the COR group. In general steric and electronic effects of substituents may be superimposed on this interaction, but we can isolate quite reliably the specific effects of *ortho*-substituents.


(XXI)


(XXII)


(XXIII)

3-Alkylated and 3-halogenated (XXI) 2-aldehydes of the heterocyclic systems exist predominantly (75–100%) in the X,O-*cis*-form[44,97], but 3-hydroxy-derivatives (XXII) in the X,O-*trans*-conformation[219,227–229]. This is attributed to promotion of the X,O-*cis*-form in (XXI) by a hydrogen bond of type H...Hal, forces of repulsion $O_{carb}...Cl$,[97] and also steric effects of 3-substituents hindering formation of the X,O-*trans*-form. Similarly, a hydrogen bond of type H...O stabilises the *s*-*cis*-form of 4-nitropyrrole-3-aldehyde (XXIII)[97,194,206].

Replacement of the nitro-group by iodine leads to roughly equal contents of the two forms[194]. Such an intermediate position of the conformational equilibrium for 4-iodopyrrole-3-aldehyde is due to I...O repulsive interactions, which destabilise the N,O-*trans*-form, and to the absence of a stable intramolecular hydrogen bond between iodine and aldehydic hydrogen, sufficient to stabilise the *cis*-form[194,206].

The proportion of the O,O-*cis*-form in thiophen-3-aldehyde increases depending on the substituent, and on passing to the 4-bromo(iodo)-derivative reaches 100% owing to Br...H interaction[141,203], but in 4-hydroxythiophen-3-aldehyde falls to zero because of formation of the chelating hydrogen bond $C_{(4)}O–H...O=C$.[203] Similarly, 2-iodothiophen-3-aldehyde exists solely as the S,O-*cis*-form, as a consequence of the characteristics of I...H interaction[141].

It is very significant that introduction of bromine at position 4 in selenophen-3-aldehyde also yields the Se,O-*cis*-form alone, in contrast to the unsubstituted aldehyde, which exists predominantly (80–100%) in the Se,O-*trans*-form[70].

Type C

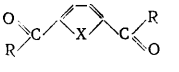
It is a complicated task to isolate in any pure form the steric influence of substituents adjacent to the aldehyde group on the ratio of the conformers, since this group is comparatively small to produce considerable steric hindrance. At the same time the bulky substituents investigated are usually extremely polar, so that their steric influence cannot be segregated from their electronic effects.

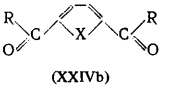
Steric effects on the position of conformational equilibrium can be traced more clearly for carbonyl derivatives of *N*-alkylated (*N*-arylated) five-membered heterocycles. The introduction of bulky substituents (e.g.t-butyl) at position 1 in pyrrole-2-aldehyde leads to accumulation of an N,O-*trans*-form or a non-planar conformer in the conformational mixture[152,153,230]. *N*-Aryl (*N*-hetaryl) substituents have a still stronger influence on the conformations of these compounds: *N*-phenyl derivatives of pyrrole[154] exist almost completely in the X,O-*trans*-form, which is not characteristic of the unsubstituted aldehydes.

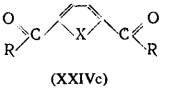
The above examples do not exhaust the whole variety of effects of substituents on conformational equilibrium in carbonyl derivatives of five-membered heteroaromatic systems.

The conformations of dicarbonyl derivatives of five-membered heterocycles must also be discussed in terms of the above three effects. In fact, each carbonyl group, being an electron-accepting substituent, attracts to itself the electron density of the ring and diminishes the conjugation of the other carbonyl group with the heterosystem. Furthermore, adjacent carbonyl groups may promote formation of a particular conformer by electrostatic interaction, specific interactions (e.g. hydrogen bonding), and steric effects.

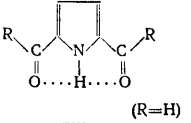
Introduction of a second carbonyl group into a heterocycle complicates the conformational problem: four conformers or three forms are formally possible in a molecule of symmetry C_2. Of the three conformers

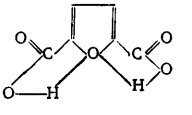

(XXIVa)


(XXIVb)

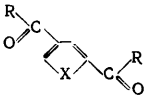

(XXIVc)

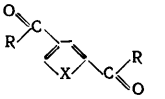
possible for 2,5-diformyl-thiophens[12,108,109,138,140,141,231,232] and -selenophens[70,143] two have been observed: the X,O-*cis*–*cis*-form (XXIVb) predominates or may even be present alone (when X = S)[231,232], and the content of the *s*-*cis*–*trans*-configuration (XXIVa) in the conformational mixture reaches 25%. A similar situation occurs[194,222] in the case of 2,5-diformylpyrrole, but the percentage of the *trans*–*trans*-form (XXIVc) is smaller[222]. It has been suggested[194] that this latter compound exists solely as the N,O-*cis*-form (XXV) stabilised by an intramolecular hydrogen bond.


(XXV) (R=H)


(XXVI)

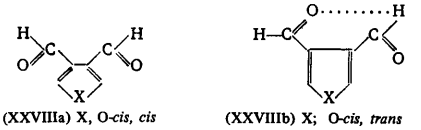
On passing from 2,5-diformyl to the corresponding diacetyl derivatives the proportion of the *s*-*cis*–*trans*-conformers (XXIVa) increases (for the thiophen derivative[140] to 55%). In 2,5-diacetylpyrrole only one carbonyl group forms the N,O-*cis*-structure, while the second is in the *trans*-position[49], which casts doubt on the possibility of a structure of type (XXV) in this case[49,222]. Diesters of 2,5-dicarboxylic acids of these heterocycles contain a mixture of roughly equal quantities of the two conformers[233] (for dimethyl tellurophen-2,5-dicarboxylate the proportion of the *cis*–*trans*-conformer[59] exceeds 50%). Furan-2,5-dicarboxylic acid itself, however, has the O,O-*trans*-structure (XXVI)[42,234].


(XXVIIa) X, O (2)-*cis*, X, O (4)-*cis*

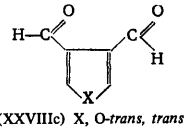

(XXVIIb) X, O (2)-*cis*, X, O (4)-*trans*

In the case of 2,4-dicarbonyl derivatives of the heterocycles only two (XXVIIa,b) of the four possible conformers are present in solution[70,97,138,143]. However, very contradictory values have appeared for their ratio[97,143,235]. Thus selenophen-2,4-dialdehyde has been regarded[143] as existing solely in the *cis*-form (XXVIIa), but has also been assigned[70] the *cis–trans*-configuration (XXVIIb). Similarly inconsistent results have been obtained for the conformations of pyrrole-2,4-dialdehydes: either the N,$O_{(2)}$-*cis*–N,$O_{(4)}$-*cis*-form[143,194] or the N,$O_{(2)}$-*cis*–N,$O_{(4)}$-*trans*-conformer (57%)[97] predominates.

The three planar structures

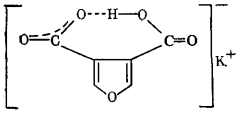


(XXVIIIa) X, O-*cis*, *cis* (XXVIIIb) X; O-*cis*, *trans*

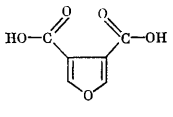


(XXVIIIc) X, O-*trans*, *trans*

are possible in 3,4-diformylhetaryls. The structure (XXVIIIc) is energetically disadvantageous because of the strong Coulombic repulsion of the two carbonyl oxygen atoms. The more advantageous of the remaining two structures is (XXVIIIb), in which additional stabilisation by hydrogen bonding is possible. For this reason the structure (XXVIIIb) apparently predominates in thiophen-3,4-dialdehyde[138], and is the sole form in the selenophen analogue[70,143]. X-Ray results suggest that a similar structure is stabilised by a hydrogen bond also in the anion of potassium furan-3,4-dicarboxylate (XXIX)[117]. In this connection it seems strange that the O,O-*trans*–*trans*-structure (XXX) has been ascribed[236,237] to the acid itself in the crystalline phase.

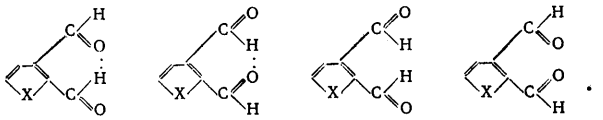


(XXIX)



(XXX)

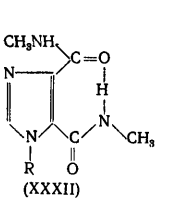
Contradictory results have been obtained also on the conformers of 2,3-dicarbonyl derivatives of five-membered heterocycles. From electrostatic considerations, the most favourable conditions for intramolecular hydrogen bonding, and repulsive interactions, the conformers of 2,3-dicarbonyl derivatives should arrange themselves according to energetic stability in the sequence *cis–cis* (XXXIa) > *trans–trans* (XXXIb) > *cis–trans* (XXXIc) > *trans–cis* (XXXId)



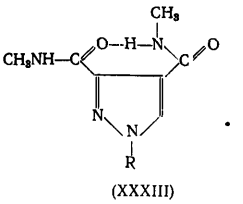
(XXXIa) (XXXIb) (XXXIc) (XXXId)

This conclusion has been confirmed for thiophen-2,3-dialdehyde[70] and ethyl 3-formylpyrrole-2-carboxylate[194]. The view is also held that 2,3-diformyl derivatives of thiophen[138] and selenophen[143] exist predominantly in the *cis–trans*-form (XXXIc). Predominance (70%) of the *trans–cis*-configuration (XXXId) attributed[70] to furan-2,3-dialdehyde therefore appears extremely doubtful.

Results of ^{1}H n.m.r. infrared spectra, and also theoretical analysis have shown that bismethylamides of the imidazole (XXXII) and pyrazole (XXXIII) series have the structure[22]



(XXXII)



(XXXIII)

In the *NN*-dimethylamide of thiazole-2-carboxylic acid only the S,O-*trans*-conformation is populated[200], which is surprising, as neither N,O-*cis*- nor S,O-*trans*-forms are normally characteristic of *o*-carbonyl derivatives. This can be explained both by the steric effect of the dimethylamino-group and by Coulombic attraction between this group and the sulphur atom preventing production of the traditional forms.

4. Influence of Cyclic Heteroatoms

Published information indicates that the nature of the cyclic heteroatom has a significant influence on the position of conformational equilibrium and the stereochemical rigidity of carbonyl-substituted five-membered heterocycles. Coulombic interactions between heteroatom and carbonyl oxygen have a decisive effect on the conformational rigidity of the system, since increase in the positive charge on the former in the sequence X = O, NH, S, Se is accompanied by increase in the X...O_{CO} electrostatic attraction, and hence also stabilisation of the X,O-*cis*-conformer. It must be added that the negative charge on the β-carbon atoms of the heterocycle increases in the same sequence[238], which further stabilises the X,O-*cis*-form by $C_{(3)}$...H_{ald} Coulombic interaction (in the case of formyl derivatives).

Since in butadiene derivatives the conformer with a *trans*-arrangement of the double bonds relative to the carbon–carbon single bond is thermodynamically the more stable, a similar phenomenon would be expected with carbonyl derivatives of five-membered heterocycles. Indeed, according to the Del Re criterion[243] the weakening of aromaticity in the series of heterocycles containing sulphur, selenium, imino, tellurium, and oxygen, caused by the nature of the heteroatom[71,120,239–242], should tend to increase the role of conjugation, and in the most "dienic" system (furan) lead to the highest content of the O,O-*cis*-conformer for furaldehyde. Experimentally, however, this is not observed: i.e. Coulombic X...O interaction has a greater influence than conjugation in stabilising the conformer.

Quantum-chemical calculations[134] show some increase in energy difference between the two conformers, corresponding to stabilisation of the X,O-*cis*-form, in the series of carbonyl derivatives of furan, pyrrole, thiophen, and selenophen. Attempts to explain[162] stabilisation of certain conformers by dipole–dipole interaction between heterocycle and formyl group have not been confirmed for 2-aldehydes: thus according to theoretical calculation[134] the minimum energy of dipole–dipole interaction corresponds to the energetically less stable X,O-*trans*-conformer. Furthermore, the increases in the positive charge on and the size of the cyclic heteroatom diminish its ability to retain $p_\pi(pd_\pi)$-orbitals and simultaneously enlarge them, so that the contribution of overlap between the heteroatom orbitals and the lone pair of the carbonyl oxygen becomes somewhat greater with selenium than with sulphur; this also favours a more stable partial Se...O bond[244].

The role of the bridging heteroatom X in azole-containing systems has not been investigated separately, but on the basis of published results[73,159,160,218] conclusions can be

transferred from monoheteroatomic to azole rings. On passing from carbonyl derivatives of the fundamental five-membered heterocycles to the corresponding azoles, i.e. on replacing a cyclic methine group by a nitrogen atom, the energy difference between the conformers increases sharply[218]. In the establishment of conformations of *N*- and *C*-carbonyl derivatives of azoles both factors—Coulombic interaction of nitrogen atoms of pyridine type with carbonyl oxygen and minimisation of the energy of the system with the dipoles of the acyl group and of the ring directed antiparallel—play an important part and act together. However, electrostatic $N_{pyr}...O$ repulsion makes a decisive contribution, since on removal of the conformationally mobile group the energy difference diminishes (also the height of the barrier in the case of *N*-acetyl derivatives). In *N*-acetylazoles the "pyrazole" and "imidazole" nitrogen atoms have different roles in the establishment of certain conformers. This example reveals especially clearly the "Coulombic" nature of the stabilisation of rotational isomers. Thus, although the 3-nitrogen atom bears a considerably more negative charge than does the 2-nitrogen atom, the greater distance of the former than of the latter from the carbonyl oxygen leads to appearance of a greater proportion of the $N_{(3)}$,O-*cis*-form in *N*-acetylimidazole than in *N*-acetylpyrazole[104,217].

5. Influence of Nature of Solvent

The influence of the medium, mainly its polarity, on rotational isomerisation and conformational changes is well known. These results have been summarised and supported by numerous examples in an exhaustive review[6]. According to the reactive field model[6] the solvating effect of a solvent can be estimated on the basis of the Onsager theory by means of the formula

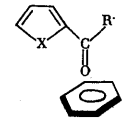
$$\Delta E_i^s = E_i^{vap} - E_i^{soln} = \frac{\mu_i^2}{a_i^3} \cdot \frac{\varepsilon_s - 1}{\varepsilon_s + 2}, \qquad (1)$$

where ΔE_i^S is the energy of solvation for the *i*th conformer of dipole moment μ_i and molecular radius a_i in a medium of dielectric constant ε_S. This equation shows that solvents of high dielectric constant have a greater solvating power and stabilise the more polar conformer. Taking into account the polarisability and the quadrupole moment of the solute molecules yields a more complete expression, regarded[6] as giving the best agreement between theoretical and observed solvation energies. A few other attempts have been made to improve the theory of solvation or to establish a new theory on the same premises[127,245-247].

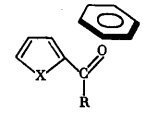
All these investigations involve several postulates restricting their application, but they support the well known rule that a polar isomer is stabilised by a polar solvent. When applied to 2-carbonyl derivatives of five-membered heterocycles, it explains the accumulation of the more polar X,O-*cis*-forms with increase in the dielectric constant of the solvent. Increase in the content of the O,O-*cis*-form with solvent polarity has been shown for 2-furaldehyde[6,202,219,248-251] and its derivatives[85,176,219], as well as for 2-acetylfuran[172] and the chloride and fluoride of furan-2-carboxylic acid[105,196,252].

Special attention should be paid to the work of Abraham[6,251], who has used his theoretical ideas to calculate energy differences between the two conformers of 2-furaldehyde and has compared the results with experimental values. On this basis he has explained the apparently contradictory results for the proportions of conformers in various media. It seems that the *s*-*trans*-form should be stabilised by polar solvents even in the case of carbonyl derivatives of thiophen, selenophen, and tellurophen, but relevant experimental results are lacking. In 2-carbonylpyrroles, on the other hand, the N,O-*trans*-conformer is more polar than the *cis*-isomer. This is why increase in solvent polarity leads in these compounds to stabilisation of the N,O-*trans*-form[97,103,123,147,206,222,253]. However, it must be borne in mind that a general solvation effect cannot explain stabilisation of the N,O-*trans*-form of 5-nitropyrrole-2-aldehyde[194,206] or the peculiar effect of benzene, which stabilises the X,O-*cis*-form of carbonyl derivatives of five-membered heteroaromatic systems more than would be expected from its dielectric constant[6,251] and several other factors[197,219,228].

All these phenomena can be explained by specific solvation effects. Thus the stabilising influence of benzene can be attributed[92] to its electron-accepting properties with respect to carbonyl oxygen. The steric accessibility of the latter is greater in the X,O-*cis*-form (XXXIVa) than in the X,O-*trans*-form (XXXIVb).



(XXXIVa)



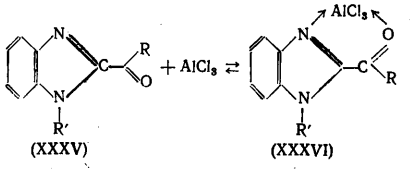
(XXXIVb)

Another example of the specific effect of a solvent on the position of conformational equilibrium is its ability to form intermolecular hydrogen bonds with the solute. Thus dielectric measurements indicate that pyrrole-2-aldehyde contains less of the *s*-*cis*-conformer in dioxan than in benzene solution (73% and 86%). This is attributed[194] to the proton-accepting properties of dioxan, which tend to break the NH...OC type of intramolecular hydrogen bond that usually stabilises the N,O-*cis*-form. Indeed, the content of the *cis*-form of pyrrole-2-aldehyde in dioxan is close to that for *N*-methylpyrrole-2-aldehyde. Similarly, whereas the S,O-*trans*-form of 3-hydroxythiophen-2-aldehyde, stabilised by an intramolecular hydrogen bond, appears in inert solvents[219,228], in proton-accepting solvents the hydrogen bond is broken with formation of the S,O-*cis*-structure.

6. Complex Formation

Interaction with Lewis acids influences significantly the conformations of stereochemically non-rigid systems and in several cases leads to stabilisation of isomers that are uncharacteristic of the free molecules used as ligands. An attempt to relate theoretically the complex-forming power of conformationally mobile ligands with their three-dimensional structure has shown[254] that complex formation is accompanied by a change in conformation only when the sum of the free energies of complex formation and solvation of the complex exceeds in absolute magnitude the sum of the energies of desolvation of the metal ion and the ligand and of spatial reorientation of the latter. This general principle is valid also for carbonyl derivatives of five-membered heterocycles[159,255-258]. Thus the coordination of aluminium chloride yields well defined conformers of 2-formyl derivatives of furan[257] and thiophen[258,259] as well as 2-acetylthiophen[258]. In the case of 2-carbonylazole derivatives complex formation with aluminium chloride may convert the X,O-*cis*-form (XXXV) into

the *trans*-conformation (XXXVI):



(XXXV) (XXXVI)

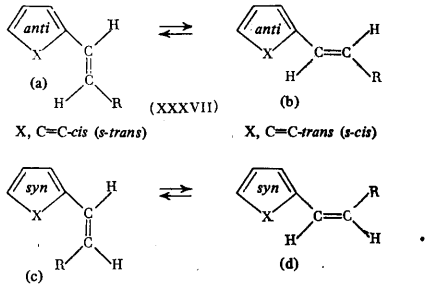
With 2-acetylbenzimidazole (XXXV: R′ = H, R = CH_3), in which the *cis*-form is stabilised by an intramolecular hydrogen bond of type NH...OC, however, this inversion of conformations is not observed. Similarly, conformations characteristic of uncoordinated carbonyl-azoles are preserved[159] even in their complexes with Lewis acids weaker than aluminium chloride—titanium tetrachloride and indium trichloride.

It must be emphasised that many shift reagents are also able to form complexes with carbonyl derivatives of heterocycles. Therefore conclusions concerning the conformations of the above stereochemically non-rigid systems, based on n.m.r. results obtained with the use of shift reagents, must be approached with great caution.

IV. CONFORMATIONAL PROCESSES IN SERIES OF STRUCTURAL ANALOGUES OF CARBONYL DERIVATIVES OF FIVE-MEMBERED HETARYLS

Among structural analogues of the above carbonyl compounds can be included heterocycles containing in the side-chain ethylenic, azomethine, oxime, or thiosemicarbazone groups directly attached to the ring by a single bond. The justification for such inclusion is not only that many of these compounds are obtained from carbonyl derivatives but mainly also that they resemble the latter in possessing multiple bonds capable of conjugation with the heterocycle, so that *s-cis–trans*-isomerism about the single bonds becomes possible.

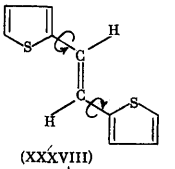
Among representatives of these compounds are hetarylethylenes containing additional substituents attached to the ethylene group and therefore capable not only of *s-cis–trans*-conformational changes but also *syn–anti*-isomerism, e.g.



(XXXVII)

X, C=C-*cis* (*s-trans*) X, C=C-*trans* (*s-cis*)

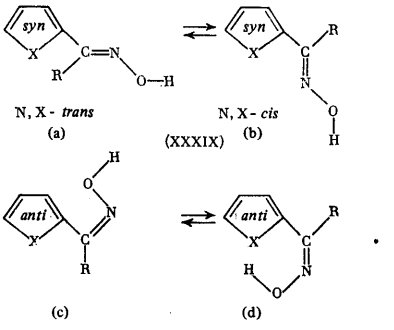
2-Vinyl-furans and -thiophens exist in solution[260–262] solely or predominantly as the *anti*-X,C:C-*cis*-conformer (XXXVIIa), whereas their styryl analogues[235] are present almost completely as the planar X,C:C-*trans*-conformer (XXXVIIb). In the latter the hetaryl and phenyl groups are arranged *anti* with respect to the ethylenic group. If, however, they are located in *syn*-positions, the aryl rings diverge from the ethylene plane because of steric effects. A similar situation is observed with ethylenic derivatives of five-membered heterocycles, i.e. substituted 2-vinyl-furans, -thiophens, and -pyrroles[264–266]. *anti*-1,2-Dithien-2′-ylethylene



(XXXVIII)

exists in the crystalline state as the S,C:C-*cis*-form, with each of the thienyl groups diverging by ~32° from the ethylene plane[267].

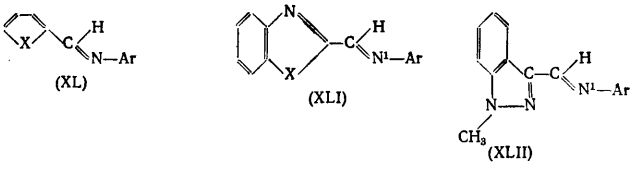
In the crystalline state 5-vinylimidazole exists as a mixture of both planar forms[268]. The thiophen analogues of chalcones exist exclusively in the S,O-*cis*–S,C:C-*cis*-form[269–272], except when a sufficiently bulky substituent is present at position 3 in the heterocycle[270]. Oximes of aldehydes of five-membered heterocycles are also able to exist in two stable isomeric forms—*syn* and *anti* (XXXIXa–d)—for each of which in turn two planar forms—N,X-*cis* and N,X-*trans*—are possible[126]:



N,X-*trans* (a) N,X-*cis* (b) (XXXIX)

(c) (d)

Investigations on oximes of furan (X = O, R = H) by n.m.r. and infrared spectroscopy together with quantum-chemical results have shown[126,273–275] that the N,O-*trans*-conformer is energetically advantageous for the *anti*-form ($\Delta H_{cis-trans}$ = 1.7 kcal mole^{-1} calculated by INDO), and is exclusively present in solution. In contrast, the *syn*-isomer is characterised by the simultaneous presence of two conformers with some predominance of the N,O-*cis*-form (59%), which is energetically more advantageous[276].

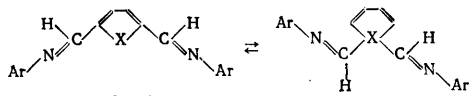


(XL) (XLI) (XLII)

All azomethines containing a five-membered heterocycle as the aldehydic moiety retain the X,N-*cis*-conformation (e.g. (XL)[277] and (XLI)[278,279]) characteristic of the corresponding formyl derivatives¶. Yet an *s-trans–trans*-conformation (XLII) has been very unexpectedly reported[280] for azomethines of 1-methylindazole-3-aldehyde. Equilibrium between the X,N-*cis–cis*-form (XLIIIa) and the X,N-*cis–trans*-form

¶ It must be stressed than anils of six-membered heteroaromatic systems are characterised by the N,N-*trans*-conformation[277].

(XLIIIb) has been found with dianils of thiophen-2,5-dialdehyde:



(XLIIIa) (XLIIIb)

In nitro-derivatives of these compounds the contents of the conformers vary within wide limits (100–40% of the *cis–cis*-form) depending on the position of the nitro-group in the aryl fragment[140]. Removal of the heteroatoms—the cyclic X and oxygen of the N → O group in aldonitrones (VII)



facilitates the appearance of X,O-*trans*-conformers in comparison with the corresponding aldehydes[281,282].

Investigation of the stereochemistry of 2-formylthiophen derivatives[283] suggests that thiosemicarbazones retain the same *cis*-structure as do 2-aldehydes of five-membered heteroaromatic systems.

V. CONCLUSION

Combination of all the above results, despite some inconsistency and in some cases inadequate experimental confirmation, enables several general conclusions to be drawn on the state of the conformational equilibrium in carbonyl derivatives of five-membered heterocycles.

Firstly, there is no doubt of the existence of two planar isomers (*s-cis* and *s-trans*) in the great majority of 2-carbonyl derivatives of furan in solution, with the exception of those cases in which, under the influence of substituents or external conditions, appearance of one of the conformers is energetically disadvantageous or sterically impossible. With few exceptions, but with the same reservations, the corresponding thiophen and selenophen derivatives exist solely in the X,O-*cis*-form. Carbonyl derivatives of tellurophen and pyrrole are conformationally more mobile than those of thiophen, but less mobile than the furan derivatives.

Secondly, several carbonyl derivatives of five-membered heterocycles, in particular ketones, are characterised in most cases by a non-planar structure, with the phenyl group in hetaryl phenyl ketones usually diverging considerably from the trigonal carbonyl plane, while the heterocyclic group is less non-coplanar owing to Het–CO conjugation.

Thirdly, the predominant structure in all carbonyl derivatives of azoles is that in which the carbonyl oxygen atom and the pyridine type of cyclic nitrogen atom are as far apart as possible.

In all cases the predominant structure in carbonyl derivatives of five-membered heteroaromatic systems is governed by Coulombic interaction between the nearest heteroatoms and the carbonyl oxygen atom. Other factors—conjugation between carbonyl and heterocycle, compensation of dipole moments in one of the forms, etc.—can merely be superposed on the dominant Coulombic effect, which is either strengthened or weakened. Despite the many studies of the stereochemistry of carbonyl derivatives of heteroaromatic systems, they exhibit several defects.

1. Compounds have been chosen for investigation without sufficient regard to their relevance. With respect to thoroughness of study (apparently depending on synthetic difficulties) we have, for the same conformationally mobile groups (COR) but different heteroatoms X, the **sequence** O ≈ S ≫ NR > Azoles > Se > Te. The corresponding **sequence** for identical heterocycles but different COR groups is

$$CHO \gg COAlk > COAr > COOH > COHet > COHal > CONH_2 \gg COF.$$

Although the use of carbonyl derivatives of five-membered heterocycles in which X is an element from subgroup VIb can be accepted as satisfactory, heteroaromatic systems based on Group V are represented only by nitrogen (pyrrole, azoles).

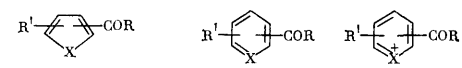
2. Only isolated studies have been made of the influence of external factors (temperature, general and specific solvation, complex formation, state of aggregation) on the position of conformational equilibrium.

3. A weak point is the heterogeneous character of quantitative data on the stereodynamics of *s-cis–trans*-isomeric processes, with inadequate application of quantum-chemical calculations.

4. Too few conclusions on the position of conformational equilibrium have been reached on the basis of the aggregate results of diverse physicochemical and mathematical methods with the use of reliable schemes of theoretical calculation.

All the above defects constitute the main reason for inadequate conclusions concerning the stereochemistry of carbonyl derivatives of five-membered heteroaromatic systems.

In our opinion future research in this field should be concentrated on a more detailed study of the relation between the fine structure of the heterocyclic system and the conformations of carbonyl derivatives. For this purpose the range of compounds studied should include carbonyl derivatives of phosphole, arsenole, and antimonole (XLIV)[284,285].



X = PR'', AsR'', SbR'' (XLIV) X = N, P, As (XLV) X = O, S, Se (XLVI)

However, if we approach the more general problem—of studying the stereochemistry of carbonyl derivatives of heteroaromatic systems and their analogues—with use of the information in the present Review and without restriction to results for pyridine derivatives we must investigate the stereodynamics of carbonyl derivatives of six-membered heterocycles (XLV) and (XLVI) and also larger heterocycles[241, 286,287]. The remaining directions of research are clear: the defects formulated under (1)–(4) above must be eliminated (ways for achieving this are quite well known to chemists).

The present survey of *s-cis–trans*-isomerism in five-membered heterocycles shows convincingly that the fine structure of a stereochemically non-rigid system, and also intra- and inter-molecular interactions, are the main factors responsible for the conformations of *s-cis–trans*-isomeric systems. Detailed analysis and generalisation of published information in this field are necessary for the reliable establishment of stereochemically non-rigid structures for various classes of chemical compounds.

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