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Ring-Chain Isomeric Transformations of Hydroxy-, Amino-, and Mercapto-Derivatives of Carbonyl Compounds and Their Heteroanalogues

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The ring-chain isomeric (including tautomeric) transformations of hydroxy-, amino- and mercapto-derivatives of aldehydes, ketones, other carbonyl compounds, imines, hydrazones, and nitriles are examined. The effect of molecular structure and the structure of substituents at the interaction functional groups and also of external factors on the relative stabilities of the isomers and on the nature of the equilibrium has been analysed.
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I. INTRODUCTION

Since the appearance of the first review[1] dealing with ring–chain tautomerism, numerous experimental studies in this field based on modern spectroscopic techniques have been published. The ring–chain isomerism of carboxylic acids with formyl and oxo-groups and their derivatives formed by the modification of the carboxy-group were discussed in a recently published review[2].

This review considers the advances during the last decade in the field of ring–chain isomeric (including tautomeric) transformations[3-6] of hydroxy-, amino-, and mercapto-derivatives of aldehydes, ketones, other carbonyl compounds†, imines, hydrazones, and nitriles. In the above series of compounds the formation of a cyclic isomer takes place via the intramolecular addition of a nucleophilic centre (OH, NH, SH) to the electrophilic carbon atom of the polar bond C=O, C=N, or C≡N (see Scheme 1).

It is possible to distinguish three fundamental types of ring–chain isomeric transformations[2,4].

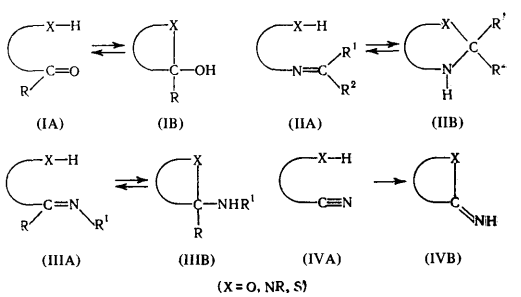
1. Tautomerism

Only one or, more rarely, both isomers are isolated in a pure form. With the aid of spectroscopic methods, it is possible to demonstrate a dynamic equilibrium between the open-chain (A) and cyclic (B) forms in solution at room temperature.

The case where only one isomer (for example A) is isolated in a pure form and its stability in solution has been demonstrated requires special consideration. One cannot then rule out the possibility of an equilibrium A ⇌ B displaced so much towards A that the concentration of the isomer B is below the limit of sensitivity of the identification procedure employed. Such a possibility can be rigorously excluded only by the isolation of both isomers in a pure form, provided that their stability in solution has been proved.

† With the exception of monosaccharides.

Scheme 1



2. Reversible Isomerism

Both isomers are obtained in a pure form. They are stable in solution at room temperature and equilibrium mixtures are not formed. The isomerisation processes A → B and B → A take place under the influence of specific reagents, acid or alkaline catalysts, or on heating.

3. Irreversible Isomerism

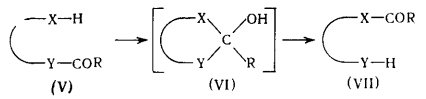
The isomerisation can take place in only one direction (A → B).

We shall also consider cases where either open-chain (A) or cyclic (B) isomers are formed, depending on the structure of the substituents at the interacting functional groups, but for a given set of substituents the isomeric interconversions cannot be achieved.

This review deals only with the results of studies where the structure of the isomers and the presence of a tautomeric equilibrium has been reliably established by spectroscopic methods (infrared, ^{1}H NMR, and ultraviolet spectroscopy). The formation of derivatives of both forms (A and B) in chemical reactions does not as a rule constitute a rigorous proof of a tautomeric equilibrium[1,7].

The electronic and steric effects of the substituents at the interacting functional groups and the effect of the structure of their connecting link on the relative stabilities of isomers and on the equilibrium are of greatest interest. It has been demonstrated in many instances that all the structural changes resulting in an enhancement of the nucleophilic properties of the oxygen, nitrogen, or sulphur atoms (OH, NH, SH) or the electrophilic properties of the carbon atoms in the C=O, C=N and C≡N bonds stabilise the ring form and displace the equilibrium towards it. The steric approach of the interacting groups is even more important. The open-chain form is stabilised by electronic effects acting in the opposite direction (the diminution of the nucleophilic properties of the XH groups or of the electrophilic properties of the carbon atom) and by the steric screening of the interacting groups by bulky substituents.

We are unable to discuss studies in which the isomers were not isolated or the ring–chain equilibrium was not demonstrated by spectroscopic methods and its occurrence in an intermediate stage is merely postulated to account for the mechanism of the formation of the final reaction products. However, such an equilibrium frequently constitutes the only possible explanation of the occurrence of the reaction in question. For example, the intramolecular rearrangement (V) → (VII), involving the migration of the acyl residue between two nucleophilic groups (OH, NH, SH), proceeds via the intermediate cyclic isomer (VI):

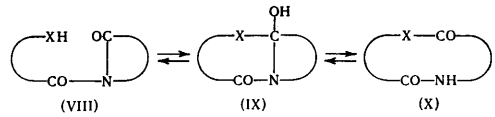


(V) (VI) (VII)

(X, Y = O, NR', S)

In view of its low stability, it is rarely possible to isolate this compound in a pure form or to demonstrate rigorously its presence in solution[4,8].

An interesting example of intramolecular transacylation is also provided by the reaction involving the inclusion of the residues of hydroxy- or amino-acids in lactam, peptide, or depsipeptide rings. This reaction proceeds via the intermediate formation of the so called cyclols [IX, X = O (oxacyclols) or X = NR (azacyclols)] and leads to cyclic peptides (X, X = NR) or depsipeptides (X, X = O):[9-16]



(VIII) (IX) (X)

(X = O, NR, S)

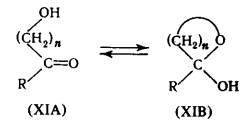
Studies on *N*-hydroxyacyl-lactams (VIII, X = O) showed that[9,14,17-21], depending on ring size and the structure of the hydroxyacyl group, either spontaneous isomerisation (VIII) → (X) takes place or it is possible to isolate the oxacyclols (IX, X = O), which are incapable of isomerisation to macrocyclic derivatives (X). In certain cases (*N*-glycolylvalerolactam[14], *N*-glycolylcaprolactam[20], *N*-hydroxyacyldioxopiperazines[22] and others[9,23]) the presence of the tautomeric equilibrium (VIII) ⇌ (IX) in solution was confirmed spectroscopically. *N*-Hydroxyacylbutyrolactams do not form cyclols.

The isomeric transformations (VIII) → (IX) → (X) have been observed also in the series of azacyclols. However, the azacyclols themselves (IX, X = NR) are relatively unstable and cannot be isolated[9,24-32]. The azacyclol formed from *N*-(2-methylaminobenzoyl)butyrolactam has been isolated in a pure form[33]. The tautomeric equilibrium (VIII) ⇌ (IX) ⇌ (X) occurs in solutions of thiacyclols (IX, X = S) formed from *N*-(thiosalicyloyl)-lactams[34,35]. With increase in the lactam ring size and also with increase of the dielectric constant of the solvent, the equilibrium shifts towards the macroring (X).

II. CARBONYL COMPOUNDS

Hydroxy-derivatives (IA ⇌ IB, X = O)

The simplest examples of hydroxycarbonyl compounds which can give rise to a cyclic form are hydroxyketones and hydroxyaldehydes[1,4,6,36]. The equilibrium (XIA) ⇌ (XIB) is rapidly established[36-38] in solutions of 5-hydroxy-2-pentanone (XIa) and 6-hydroxy-2-hexanone (XIb), with the open-chain form predominating slightly:



(XIA) (XIB)

a) R = Me, *n* = 3; b) R = Me, *n* = 4;
c) R = H, *n* = 3; d) R = H, *n* = 4

The contents of the tautomeric forms were determined[38] from the intensities of the proton signals of the methyl groups of both tautomers (the tautomeric transformations are slow on the ^{1}H NMR time scale) and also by measuring the intensities of the 265–280 nm bands observed in the ultraviolet spectra of the open-chain isomers (XIA).

Table 1. The tautomeric equilibrium constants in solutions of 5-hydroxy-2-pentanone (XIa) and 6-hydroxy-2-hexanone (XIb) determined[38] by ^{1}H NMR and ultraviolet spectroscopic methods.

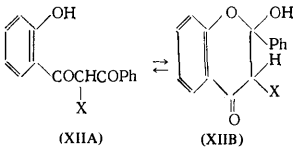
Solvent	K_T = [B]/[A]			
	^{1}H NMR at 37°C		u.v.spectra at 25.1°C	
	(XIa)	(XIb)	(XIa)	(XIb)
Pure liquid	0.83	0.85	—	—
Cyclohexane*	0.81	0.95	0.78	0.87
Dioxane	—	—	0.83	0.74
Carbon tetrachloride	0.73	0.95	0.75	0.96
Chloroform	0.82	0.85	0.75	0.81
Acetone*	0.82	0.82	—	—
Ethanol*	0.83	0.62	0.80	0.54
Methanol	—	—	0.81	0.51
Acetonitrile*	0.82	0.79	0.79	0.61
Dimethyl sulphoxide*	0.64	0.81	0.56	0.77
Water*	0	0	0	0

*The ^{1}H NMR spectra were recorded in deuteriated solvents.

An increase of temperature[38,39] and of solvent polarity[38] displaces the equilibrium towards the open-chain form, although the equilibrium constants in various solvents, with the exception of water, differ insignificantly (Table 1). The cyclic form predominates in aqueous solution. The addition of water to solutions of hydroxyketones in dioxane, ethanol, or dimethyl sulphoxide rapidly displaces the equilibrium towards the open-chain form. The thermodynamic properties (ΔH° and ΔS°) of the (XIA) ⇌ (XIB) transformation in various solvents have been determined[38].

Compared with hydroxyketones, in solutions of hydroxyaldehydes (XIc and XId) the equilibrium is displaced appreciably towards the cyclic form [in 75% aqueous dioxane at 25°C K_T = 7.8 for (XIc) and K_T = 15.4 for (XId)].[40]

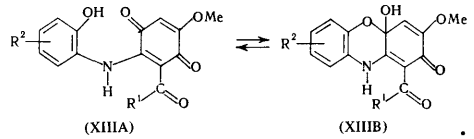
The formation of the cyclic form via the intramolecular addition of the phenolic hydroxyl to the formyl or keto-group has been observed in *o*-hydroxyphenylglyoxal[41], 2-(*o*-hydroxybenzyl)cyclohexanone[42], and in a series of substituted benzoyl(*o*-hydroxybenzoyl)methanes (XII, a–c).[43,44] In the crystalline state, the compounds (XII, a–c) have a cyclic structure, while in chloroform solution the equilibrium (XIIA) ⇌ (XIIB) is established rapidly [K_T = 3.7 for (XIIa) and K_T = 0.5 for (XIIb)]. The substitution of the hydroxy-group by bromine enhances the electrophilic properties of the carbon atom of the keto-group and shifts the equilibrium towards the cyclic form:



(XIIA) (XIIB)

a) X=Br; b) X=OH; c) X=OOCPh)

As a result of the intramolecular addition of the phenolic hydroxyl to the C=O group of the quinone, (XIIIA) ⇌ XIIIB) equilibrium mixtures are formed in solutions of substituted 2-(*o*-hydroxyphenylamino)-1,4-benzoquinones[45–47]. A similar tautomeric equilibrium was observed previously[48] in solutions of 2-(*o*-hydroxyphenylamino)-1,4-naphthoquinones. The amounts of the tautomers were determined by ultraviolet spectroscopy[48]:

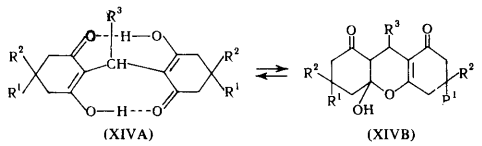


(XIIIA) (XIIIB)

a) R^1 = Me, and R^2 = 3' – Ac.

The long-wavelength band is at 470 and 394 nm respectively in the spectra of model compounds with fixed open-chain and cyclic structures[45,46]. In ethanol solution of 3-acetyl-2-(3'-acetylphenylamino-2'-hydroxy-)-5-methoxy-1,4-benzoquinone (XIIIa) the cyclic form predominates, while in non-polar solvents the equilibrium is displaced towards the open-chain form (XIIIA). The authors assume that[46] the open-chain form is stabilised by the intramolecular hydrogen bond O–H...O=C (3'-acetyl). Both isomers were isolated in a pure form: (XIIIa – A) as a black powder on crystallisation from benzene and (XIIIa – B) as yellow crystals on crystallisation from methanol. The ultraviolet spectra of solutions of both isomers are identical, i.e. after dissolution identical equilibrium mixtures are formed regardless of which isomer is used to prepare the solution.

Lielbriedis and Gudriniece[49–52] observed an interesting type of tautomerism in which the cyclic form is produced as a result of the intramolecular addition of the enolic hydroxyl to the keto-group:

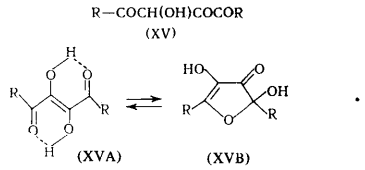


(XIVA) (XIVB)

a) $R^1 = R^2$ = Me; b) $R^1 = R^2$ = H;
c) R^1 = Ph, R^2 = H; d) R^1 = Me, R^2 = H

Bisdimedonylmethanes (XIVa), obtained by the condensation of dimedone with aliphatic aldehydes and also with *m*- and *p*-substituted benzaldehydes, have the open-chain structure (XIVa – A) in the crystalline state. This structure is stabilised by two intramolecular hydrogen bonds. The products of the condensation of dimedone with *o*-substituted benzaldehyde have the cyclic structure (XIVa – B). Both isomers of *p*-[*NN*-bis(β-chloroethyl)amino]phenyl bisdimedonylmethane [XIVa, R^3 = *p*-$(ClCH_2CH_2)_2NC_6H_4$] were isolated in a pure state. Isomerisations in both directions were achieved: (XIVA) → (XIVB) on refluxing in alcohol or on recrystallisation from acetic acid and (XIVB) → (XIVA) on slow crystallisation from dioxane. The products of the condensation of cyclohexane-1,3-dione and its 5-phenyl- and 5-methyl-substituted derivatives with aldehydes (XIV, b – d) were isolated either in the open-chain (XIVA) or cyclic (XIVB) forms, but no clear relation between the structure of the substituents and the preferential formation of one of these isomers could be traced in this instance.

As a result of the intramolecular addition of the enediol hydroxyl to the keto-group, the cyclic form of acetylformoins is produced[53–60]. The enolisation of acetylformoins (XV) can proceed to two direction. The symmetrical enediol has the open-chain structure (XVA) with two intramolecular hydrogen bonds, while the asymmetric enediol has the cyclic structure (XVB). Both forms can be readily identified from their infrared spectra [ν(C=O) = 1620 – 1630 cm^{-1} for (XVA) and ν(C=O) = 1695 – 1705 cm^{-1} for (XVB)] and ultraviolet spectra [λ = 355–360 nm for (XVA) with R = alkyl, λ = 390–410 nm for (XVA) with R = aryl, λ = 305–310 nm for (XVB) with R = alkyl, and λ = 355–360 nm for (XVB) with R = aryl][58]:



(XVA) (XVB)

Here R = Me(A)‡, i-Pr(B), t-Bu(B), *p*-XC_6H_4 [X = H(B), Me(B), MeO(A), t-Bu(B), Me_2N(A), Cl(A and B), Br(A and B), or NO_2(B)], 2,4,6-$Me_3C_6H_2$ (A), α-naphthyl (A), or β-naphthyl (A and B).

The introduction of electron-donating substituents (MeO, Me_2N) into the aromatic ring of aroylbenzoins diminishes the electrophilic properties of the carbon atom of the keto-group and stabilises the open-chain form, while electron-accepting substituents act in the opposite direction[59]. Both isomers of *p*-bromo- and *p*-chlorobenzoylformoins[58] and β-naphthoylformoins[60] were isolated in a pure form: (XVB) crystallises as yellow crystals from ethanol and (XVA) as red crystals from benzene after prolonged heating of the solution. When the cyclic isomers are fused, the isomerisation (XVB) → (XVA) takes place[54,58].

In proton-accepting solvents (ethanol, tetrahydrofuran) acylformoins exist exclusively in the cyclic form (XVB). This form is stabilised by the hydrogen bonds (OH...O<) between the hydroxyl of the cyclic form and the solvent molecule[56]. Mesitoylformoin, which does not give rise to a cyclic form, evidently due to the steric screening of the carbonyl group by the bulky substituent, constitutes

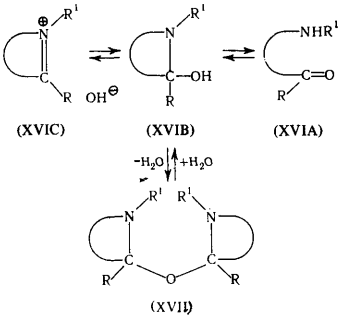
‡ The structure of the crystalline substance is indicated in brackets.

an exception (cf. Refs. 2, 61–63). In solvents which are not proton-acceptors the open-chain form (XVA) predominates[58,59].

In polar proton-accepting solvents the equilibrium involving the above examples of the ring-chain tautomerism of compounds (XIIIa), (XIV), and (XV), where the open-chain is stabilised by one or two intramolecular hydrogen bonds, is displaced towards the cyclic form. The formation of the latter as a result of the intramolecular addition to the C=O group of the hydroxy-group at a nitrogen atom (NHOH, =NOH) has also been observed[64,65].

Amino-derivatives (IA ⇌ IB, X = NR)

The aminoaldehyde or aminoketone ⇌ hydroxyalkylamine ring–chain tautomeric systems (XVIA) ⇌ (XVIB) can be formed on covalent hydration[66-69] of heterocycles containing an immonium nitrogen atom. The equilibrium (XVIC) ⇌ (XVIB) has been most frequently investigated. In a study of the hydroxyalkylamines obtained from isoquinoline or 3,4-dihydroisoquinoline bases, Beke[70,71] established that the less basic the nitrogen atom in the (XVIB) molecule the greater the probability of the formation of the open chain form (XVIA):



(XVIC) (XVIB) (XVIA)

(XVII)

Four cases are considered[70].

1. Strong bases. In the crystalline state and in non-polar solvents they exist as the hydroxyalkylamines (XVIB), while in polar solvents they exist in the ionic form (XVIC). The presence of the open-chain form (XVIA) cannot be demonstrated by either chemical or physical methods.

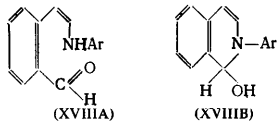
2. Moderately strong bases. In the crystalline state they have the structure (XVIB). The equilibrium (XVIC) ⇌ (XVIB) ⇌ (XVII) is observed in aqueous solution. The open-chain form (XVIA) is absent.

3. Hydroxyalkylamines incapable of giving rise to the ionic form (XVIC) isomerise to the open-chain form (XVIA). The existence of both forms can be demonstrated in solution or they can be actually isolated in a pure state[71].

4. Compounds showing no pseudobasic properties exist only in the open-chain form (XVIA). The hydroxyalkylamine (XVIB), formed when the solution of a quaternary salt of the nitrogen-containing heterocycle is made alkaline, is unstable and isomerises spontaneously to (XVIA).

It is clear from the foregoing that the equilibria (XVIC) ⇌ (XVIB) and (XVIB) ⇌ (XVIA) are not observed simultaneously. Hydroxyalkylamines capable of giving rise to the ionic form (XVIC) are not converted into the open-chain form (XVIA) and conversely.

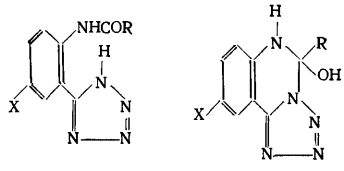
The products of the covalent hydration of *N*-arylpyridinium compounds[72] have an open-chain structure. On hydration of *N*-(2,4-dintrophenyl)isoquinolinium[71], both isomers, (XVIIIA) and (XVIIIB), were obtained and their interconversions were achieved. By investigating the esterification kinetics, it was established that under the reaction conditions the equilibrium (XVIIIA) ⇌ (XVIIIB) obtains. The absence of the open-chain form in the crystalline state and in solutions of covalent quinazoline hydrates has been demonstrated by infrared spectroscopy[66,73,74].



(XVIIIA) (XVIIIB)

[Ar-2,4-$(NO_2)_2C_6H_3$]

Postovskii[75-79] showed that the covalent hydrates of 5-R-9-X-tetrazolo[1,5-c]quinazolines have the structures (XIXA) or (XIXB) depending on the structure of the substituents R and X:

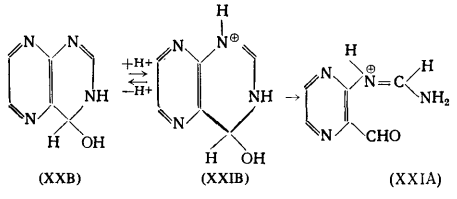


(XIXA) (XIXB)

Here X = R = H (A and B),[76] X = H and R = Me (B),[75] X = COOH and R = Ph (B),[78] X = Br and R = Me (A), and X = Br and R = Ph (A).[77,79]

Both isomers of the unsubstituted compound (XIX, X = R = H) were isolated in a pure state[76]. It has been shown for the methyl derivative (XIX, X = H, R = Me) that an acid medium stabilises the cyclic form and on dissolution in pyridine the isomerisation (XIXB) → (XIXA) takes place[75].

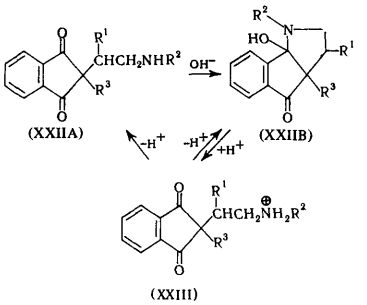
The covalent hydrates of pteridines[66,67,80,81] (XXB) and of 1,3,6-triazanaphthalenes[82] are rapidly converted in an acid medium into the open-chain isomers (XXIA). The opposite process takes place on neutralisation. Evidently the isomerisation (XXIB) ⇌ (XXIA) can be accounted for by the fact that the basicity of the nitrogen atom is sharply reduced by protonation:



(XXB) (XXIB) (XXIA)

Depending on the molecular structure, the protonation of aminocarbonyl compounds can stabilise either the cyclic or the open-chain form. Vanags and Dregeris obtained[83] both isomers of 2-β-(*N*-cyclohexyl)aminoethyl-2-phenylindan-1,3-dione—(XXIIa – A) and (XXIIa – B). The isomerisation (XXIIa – A) → (XXIIa – B) takes place in the

presence of bases. Such base-catalysed isomerisation has also been observed for a series of γ-ketoacid amides[2,84-86] and other aminocarbonyl compounds[87,88].

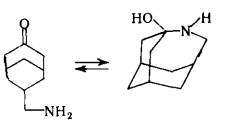


(XXIIA) (XXIIB) (XXIII)

a) R^1 = H, R^2 = cyclo-C_6H_{11}, and R^3 = Ph.

The protonation of the cyclic isomer entails ring opening, (XXIIB) → (XXIII), while deprotonation is accompanied by the reverse process[83,89].

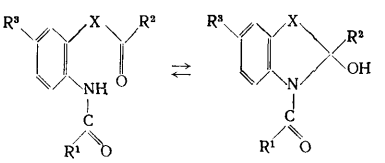
In solution 7-aminobicyclo]3, 3, 1]nonan-3-one gives rise to the equilibrium mixture (XXIVA) ⇌ (XXIVB).[90]



(XXIVA) (XXIVB).

The total absence of the C=O absorption from the spectrum of the hydrochloride suggests that the protonated form has a cyclic structure.

In the crystalline state, *o*-acetamidobenzil (XXV, R^1 = Me, R^2 = Ph, R^3 = H, X = CO) has the cyclic structure (XXVB), while in solution an equilibrium is established slowly[91]. A similar equilibrium has been observed[92-95] for a series of *N*-acyl-2-(2′-oxoalkyl)anilines (XXV, X = CH_2 or CHMe), the cyclic form predominating for the formyl derivatives (R^2 = H) and the open-chain form for the keto-derivatives (R^2 = Me). Analysis of the mass spectra established[96] that in the gas phase the equilibrium is completely displaced towards the open-chain form (XXVA):

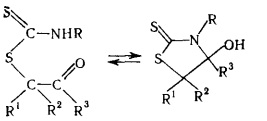


(XXVA) (XXVB)

(X = >CO, >CH_2, >CHMe)

There are many examples of ring–chain tautomerism in the series of aminocarbonyl compounds of more complex structure, where the cyclic isomer is a heterocycle with two or more heteroatoms.

The contents of the tautomers in solutions of S-(2-oxoalkyl)dithiocarbamates (XXVI) have been determined by infrared spectroscopy[97]. The open-chain isomer (XXVIa – A) and the cyclic isomer (XXVIa – B) were isolated on crystallisation from methylenechloride and from a methanol–water mixture respectively:



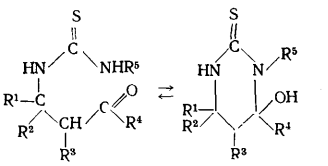
(XXVIA) (XXVIB)

a) R = Ph, R^1 = R^2 = H, and R^3 = *t*-Bu.

The introduction of the alkyl substituents R^1 and R^2 displaces the equilibrium towards the cyclic form (the *gem*-dimethyl effect[3,98]). The enhancement of the electron-donating properties of the substituent R^3 and the increase of the steric bulk of the substituents R and R^3 stabilise the open-chain form[97,99].

S-(3-Oxoalkyl)dithiocarbamates[100,101] exhibit a smaller tendency towards the formation of the cyclic form. However, compounds of this series, containing the *gem*-dimethyl fragment, have the cyclic structure in the crystalline state and in solution the equilibrium is displaced towards the open-chain form[101].

Unkovskii and coworkers[102-104] showed that *N*-(3-oxoalkyl)-*N*′-substituted thioureas have the cyclic structure in the crystalline state, with one exception[103], and in solution they give rise to the equilibrium mixtures (XXVIIA) ⇌ (XXVIIB), the equilibrium being established slowly (over a period of 6–15 days):



(XXVIIA) (XXVIIB)

The equilibrium concentrations of the tautomers were determined[104] from the intensities of the C=O band in the infrared spectra of the solutions. The introduction of methyl groups as the substituents R^1, R^2 and R^3 (R^4 = Me throughout) stabilises the cyclic form in the following sequence (the arrow indicates the direction of the increase of stability of the cyclic form):

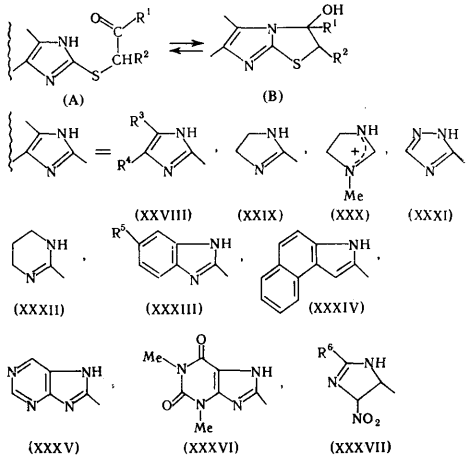
R^1	H	H	Me	Me	Me
R^2	H	H	H	H	Me
R^3	Me	H	Me	H	H

An increase of the effective bulk of the substituent R^5 is accompanied by an increase of the rate of ring opening and a shift of the equilibrium towards the open-chain form (XXVIIA). One cannot agree with the assertion[104] that the enhancement of the electron-donating properties of the substituent R^5 acts in the same direction. In contrast to keto-derivatives, the aldehydes (XXVII, R^4 = H) exist in solution entirely in the cyclic form.

A similar situation, where the crystalline compounds have the cyclic structure and equilibrium mixtures are produced in solution, has been described for a series of *S*-methyl-*N*-(3-oxoalkyl)isothioureas[105,106].

2-Ureido-,[107,108] 2-thioureido-,[109,110] and 2-guanidinoindan-1,3-diones[108] and 2-ureido- and 2-thioureidobenzophenones[111-113] have cyclic structures and there is no evidence for the occurrence of the ring–chain equilibrium in solution.

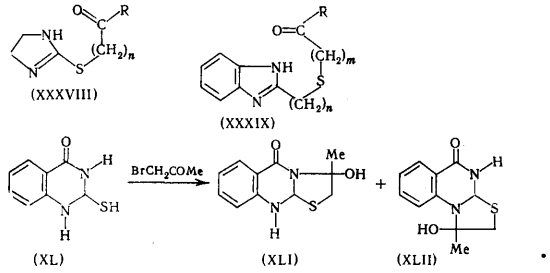
The ring–chain tautomerism of *S*-acylalkyl-substituted 2-mercaptoimidazole (XXVIII),[114-119] 2-mercaptoimidazoline (XXIX),[114,117,119-121] 2-mercapto-1-methylimidazolinium (XXX),[122] 3-mercapto-1,2,4-triazole (XXXI),[119] 2-mercapto-3,4,5,6-tetrahydropyrimidine (XXXII),[119] 2-mercaptobenzimidazole (XXXIII),[114,120,121,123-129] 2-mercaptonaphtho[1,2-*d*]imidazole (XXXIV),[114,130,131] 8-mercaptopurine (XXXV),[114,132] 8-mercaptotheophylline (XXXVI),[114,132] and 5-mercapto-4-nitroimidazole (XXXVII,[133,134] which were isolated in most cases as intermediates in the synthesis of imidazo[2,1-*b*]thiazoles and their condensed derivatives, was investigated by infrared and ^{1}H NMR spectroscopy. In a study of the effect of the structure and the state of aggregation on the stability of the tautomers and on the equilibrium, it was established[114,127] that 2-formylmethylmercaptoimidazoles and their condensed derivatives have cyclic structures both in the crystalline state and in solution. On passing from aldehydes to ketones of the aliphatic (R^1 = Me) and aromatic (R^1 = Ph) series, the stability of the open-chain form increases.



It has been shown[127] that in the series of 2-acylmethylmercaptobenzimidazoles (XXXIII, $R^2 = R^5 = H$) with a wide range of substituents R^1, the open-chain form is stabilised by bulky substituents R^1 and also by the conjugation of the carbonyl group with the aromatic ring and the ethoxycarbonyl or cyclopropyl group. The compounds (XXXIII, R^1 = *p*-XC_6H_4, COOEt, cyclo-C_3H_5, $R^2 = R^5 = H$) exist exclusively in the open-chain form (A) in the crystalline state and in solution. It is remarkable that the stability of the open-chain form is unaffected[125] by the introduction of electron-accepting substituents in the *para*-position of the aromatic ring (R^1 = *p*-$NO_2C_6H_4$), although it has been shown for the trifluoromethyl derivative (XXXIII, $R^1 = CF_3$, $R^2 = R^5 = H$) [126,127] that the presence of a powerful *I*-effect in the substituent R^1 completely displaces the equilibrium towards the cyclic form. The introduction of the nitro-group into the benzimidazole ring to give (XXXIII, R^1 = Me, $R^2 = H$, $R^5 = NO_2$) diminishes the nucleophilic properties of the nitrogen atom and displaces the equilibrium towards the open-chain form relative to the unsubstituted compound (XXXIII, $R^5 = H$).

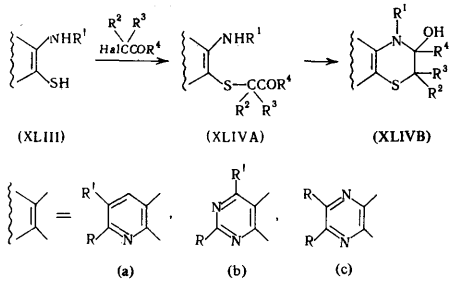
The crystalline state stabilises the cyclic form[114]. While the compound has the open-chain structure (A) in the crystalline state, in solution the equilibrium is completely displaced towards (A). Crystalline cyclic isomers (B) have either the cyclic structure also in solution or (A) $\rightleftharpoons$ (B) equilibrium mixtures are produced[127].

A study of the effect of the size of the ring formed on the stability of the cyclic isomer in a series of hydroxy-derivatives of imidazoline (XXXVIII, n = 1 or 2) and benzimidazole (XXXIX, n = 0 or 1 and m = 1 or 2) established[120,121] that the cyclic form is produced only on closure of a five-membered ring (XXXVIII, n = 1; XXXIX, n = 0, m = 1).



The reaction of 2-mercapto-4-oxotetrahydroquinazoline (XL) with bromoacetone results in the formation[135] of a mixture of products (XLI) and (XLII) in proportions of 9:1. On this basis, the authors conclude that the formation of the cyclic form involves preferentially the sterically less hindered nitrogen atoms even if the competing nitrogen atom is more basic.

In reactions of *o*-aminomercapto-derivatives of pyridine (XLIIIa),[136-140] pyrimidine (XLIIIb),[88,141-144] and pyrazine (XLIIIc)[145,146] with α-halogenocarbonyl compounds, Safonova and coworkers obtained in most cases only the most stable isomer [either (XLIVA) or (XLIVB)] and their dehydration products.



Electron-accepting substituents R^4 and electron-donating substituents in the heterocycle (R and R^1) stabilise the cyclic form[137,142,144-146]. Phenylacyl derivatives show a smaller tendency towards the formation of the cyclic form (XLIVB) than the products of the condensation with aliphatic halogenoketones. Both isomers were isolated in reactions of 5-amino-4-chloro-6-mercaptopyrimidine (XLIIIb, $R = R^1 = H$, R^1 = Cl) with phenylacyl bromides ($R^4 = C_6H_4X$, X = H, 4-Br, 3-NO_2, or 4-NO_2)[88,141] and of 3-amino-6-chloro-2-mercaptopyridine (XLIIIa, $R^1 = R' = H$, R = Cl) with *o*-substituted (F, Br, Me) phenylacyl halides[140]. In a medium close to neutrality 5-amino-4-chloro-6-phenylacylmercaptopyrimidines (XLIVb – A) are formed. The isomerisation (XLIVb – A) → (XLIVb – B) is base-catalysed. However, after the introduction of a methyl group into the amino group (R^1 = Me), such isomerisation could not be achieved[88].

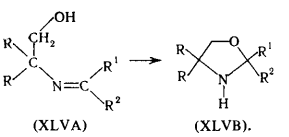
Tautomeric equilibria in solutions of 6-alkyl-4-chloro-6-hydroxy-5,6-dihydropyrimido[4,5-*b*][1,4]thiazines (XLIVb – B, R = R^1 = R^2 = R^3 = H, R′ = Cl, R^4 = Me, CH_2Cl, or CH_2COOEt) were not observed by infrared and ^1H NMR spectroscopic methods[144]. The derivatives of these compounds having a methyl group at the nitrogen atom (R^1 = Me) form equilibrium mixtures in solution. In deuteriochloroform solution of the 6-methyl derivatives (XLIVb, R^1 = R^4 = Me, R′ = Cl) the equilibrium is displaced towards the open-chain form and in solutions of the compounds (XLIVb, R^1 = Me, R′ = Cl, R^4 = CH_2Cl or CH_2COOEt) it is displaced towards the cyclic form. The addition of a proton-accepting agent (C_5H_5N-d_5) to the solutions displaces the equilibrium towards the cyclic form. The destabilising effect of the methyl group (R^1 = Me) at the nitrogen atom on the cyclic form cannot be accounted for in terms of electronic hypotheses, because the methyl group enhances the nucleophilic properties of the nitrogen atom and consequently should have the opposite effect. The experimentally observed influence of the methyl group can be explained[144] by the steric interaction of *peri*-substituents in the cyclic form (XLIVb – B, R′ = Cl, R^1 = Me), which destabilises the 1,4-thiazine ring.

Apart from the examples discussed above, there is evidence for ring–chain tautomerism (IA ⇌ IB, X = NR) in the series of monohydrazones of 1,3-dicarbonyl compounds[147,148], *N*-(2-oxoalkyl)triazenes[149,150], *N*-acylmalonodianilides[151], *O*-(3-oxoalkyl)hydroxylamines[152], urethanes derived from benzoin[153], 2-benzoylbenzenesulphonamide and 2-phenylacylbenzenesulphonamides[154], *NN*′-dimethylhydrazides of 2-acylbenzoic acids[155], and 6-hydroxycrinamines[156].

III. IMINES AND HYDRAZONES

Hydroxy-derivatives (IIA ⇌ IIB, IIIA ⇌ IIIB, X = O)

The tautomeric equilibrium (XLVA) ⇌ (XLVB) is observed in solutions of oxazolidines[1,157-161]. An increase in the steric bulk of the substituents R^1 and R^2 stabilises the open-chain form. It has been established that an enhancement of the electron-accepting properties of the substituents X in the aromatic ring in the series of 2-(3′- or 4′-X-phenyl)-4,4-dimethyloxazolidines (XLV, R = Me, R^1 = H, R^2 = 3′ or 4′-XC_6H_4) displaces the equilibrium towards the cyclic form[160]:

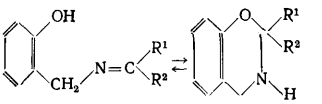


(XLVA) (XLVB).

A linear correlation has been observed between the tautomeric equilibrium constants K_T = [B]/[A] and the σ or better σ* constants of the substituents X in the aromatic ring [$\lg(K_T/K_0) = 0.86\sigma$, $r = 0.973$; $\lg(K_T/K_0) = 0.54\sigma^*$, $r = 0.999$]. The equilibrium constants were determined from the intensities of the signals of the geminal proton relative to the aryl group (R^1 = H) in both tautomeric forms[159,160].

The products of the condensation of 3-aminopropanol with carbonyl compounds were obtained either in an open-chain form or as tetrahydro-1,3-oxazines[162,163]. They show a greater tendency towards cyclisation than *N*-(2-hydroxyethyl)imines. 4-Aminobutanol gives rise to hexahydro-1,3-oxazepine in the reaction with formaldehyde and the products of its condensation with benzaldehyde and acetophenone have an open-chain structure[164].

In the crystalline state *N*-(2-hydroxybenzyl)imines of aromatic aldehydes (XLVI, R^1 = H, R^2 = 4′-XC_6H_4) have the open-chain structure (XLVIA), while in solutions the equilibrium (XLVIA) ⇌ (XLVIB) is established rapidly[165,166]:



(XLVIA) (XLVIB).

The tautomeric equilibrium constants are satisfactorily correlated with the σ or σ* constants of the substituents X [$\lg(K_T/K_0) = 0.74\sigma$, $r = 0.993$; $\lg(K_T/K_0) = 0.68\sigma^*$, $r = 0.999$].[160,166]. The *N*-(2-hydroxybenzyl)imines derived from aliphatic aldehydes and ketones have the cyclic structure (XLVIB) and in solutions the equilibrium is almost entirely displaced towards the cyclic form. It has been established by ^1H NMR [167] that protonation of the compounds (XLVI, R^1 = H, R^2 = alkyl or aryl; R^1 = R^2 = alkyl) in solution in trifluoroacetic acid results in the formation of open-chain immonium ions. Protonated cyclic forms were obtained only for the imines derived from formaldehyde and trichloroacetaldehyde.

The 1,3-oxazine–Schiff base tautomerism was observed also in solutions of the products of the condensation of 2-hydroxybenzylamine with α-dicarbonyl compounds[168]. 2,4-Diaryl-2,3-dihydro-1*H*-nathpho[1,2-*e*]-1,3-oxazines obtained[169] by the condensation of 1-(α-aminobenzyl)-2-naphthol with aromatic aldehydes have a cyclic structure in the crystalline state and in solution give rise to equilibrium mixtures; an equilibrium has also been observed between the cyclic and open-chain protonated forms in solution in trifluoroacetic acid.

Table 2. Effect of the proton-accepting properties of solvents on the constants of the tautomeric equilibrium (XLVA) ⇌ (XLVB) (R = Me, R^1 = H, R^2 = Ph).[159]

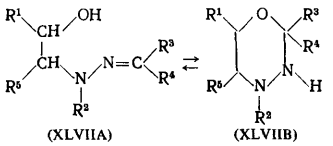
Solvent	$\Delta\nu^*_{OH}$, cm^{-1}	K = [B]/[A]**	Solvent	$\Delta\nu^*_{OH}$, cm^{-1}	K = [B]/[A]**
Carbon tetrachloride	0	1.89	Acetone	110	0.42
Chloroform	8	1.72	Tetrahydrofuran	156	0.51
Dimethyl carbonate	69	0.80	Dimethylacetamide	193	0.12
Acetonitrile	87	0.62	Dimethyl sulphoxide	224	0.10

* The shift of the hydroxyl band frequency in the infrared spectra of solutions of di-t-butylmethanol as a measure of the proton-accepting properties of the solvent.
** Determined by ^1H NMR at 38°C.

Under the influence of solvents, the constants of the tautomeric equilibria (XLVA) ⇌ (XLVB) and (XLVIA) ⇌ (XLVIB) vary over a wide range, but they are not correlated either with the dipole moments, or with the dielectric constants, or with Kosower's *Z* constants of the solvents[166]. A satisfactory correlation has been found[159], between the frequency shifts of the hydroxyl band $\Delta\nu$(OH) in the infrared spectra of solutions of di-t-butylmethanol on formation of intermolecular hydrogen bonds with the

solvent and the activation enthalpies ΔH° for the tautomeric transformations (XLVA) ⇌ (XLVB) (R = Me, R^1 = H, R^2 = Ph) in the same solvents. Consequently the ability of the solvents to form intermolecular hydrogen bonds with the hydroxy-group of the Schiff base plays the main role in determining the state of equilibrium. The enhancement of the proton-accepting properties of the solvent displaces the equilibrium towards the open-chain form (Table 2).[159]

Potekhin and coworkers[170-175] made a systematic study of the tautomerism (XLVIIA) ⇌ (XLVIIB) of *N*-(2-hydroxyalkyl)hydrazones. The tautomeric composition was determined by measuring the molecular refraction and by ^{1}H NMR. Freshly prepared products of the condensation of *N*-alkyl-*N*-(2-hydroxyalkyl)hydrazines with aldehydes and ketones in most cases have the cyclic structure of alkyl-substituted perhydro-1,3,4-oxadiazines (XLVIIB). On storage and in solution, they form the equilibrium mixtures (XLVIIA) ⇌ (XLVIIB). The equilibrium concentration of the open-chain form (XLVIIA) increases with increase of the number and steric bulk of the alkyl substituents at the carbon atom of the C=N bond (R^3, R^4).



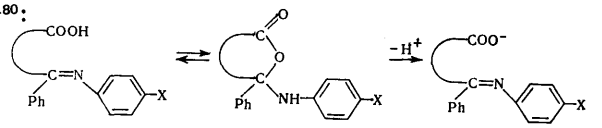
(XLVIIA) (XLVIIB)

The introduction of the methyl group in the hydroxyethyl group (R^1 = Me), the introduction of an alkyl substituent at the nitrogen atom (R^2 = alkyl), and an increase of the steric bulk of the latter substituent shift the equilibrium towards the cyclic form (XLVIIB). *N*-Unsubstituted 2-hydroxyethyl- and 2-hydroxypropyl-hydrazones (XLVIIA, R^1 = H or Me, R^2 = H) [172,173] and also products of the condensation of lactic acid hydrazide with carbonyl compounds[176] do not give rise to the cyclic form. In the series of *N*-aryl-*N*-hydroxyethylhydrazones (XLVII, R^1 = H, R^2 = *p*-XC_6H_4) a shift of the equilibrium towards the cyclic form was observed[175] with enhancement of the electron-accepting properties of the substituent X in the aromatic ring.

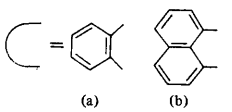
The greater tendency of aldehyde hydrazones to form the cyclic form (XLVIIB) compared with ketone hydrazones can be explained[172] by the fact that perhydro-1,3,4-oxadiazines with two alkyl substituents at $C_{(2)}$ have an increased conformational energy. An important factor facilitating intramolecular cyclisation is also the higher electrophilicity of the carbon atom in the C=N bond in aldehyde derivatives compared with ketone derivatives[38,177].

The tautomeric equilibrium constants of the products of the condensation of *N*-amino-(-)-ephedrine with aliphatic aldehydes (XLVII, R^1 = Ph, R^2 = R^5 = Me, R^3 = H, R^4 = alkyl) at different temperatures in solution in tetrachloroethylene were measured by ^{1}H NMR [178] in the presence of an acid catalyst (0.1% CF_3COOH), which increases the rate of tautomerisation. An increase of the polarity of the solvent, an increase of solution temperature (cf. Potekhin and Zaitsev[173]), and also an increase of the steric bulk of the alkyl substituent R^4 displace the equilibrium towards the open-chain form.

In the crystalline state the anils of 2-benzoylbenzoic acid[179,180] have the cyclic structure of 3-arylamino-3-phenylphthalides (XLVIIIa – B), while in solution the equilibrium (XLVIIIa – A) ⇌ (XLVIIIa – B) is appreciably displaced to the right. Electron-accepting substituents in the aromatic ring stabilise the cyclic form. The enhancement of the polarity and proton accepting properties of the solvents shift the equilibrium to the open-chain form[180]:



(XLVIIIA) (XLVIIIB) (XLIX)

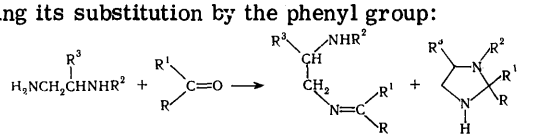


(a) (b)

Compared with the molecule of the anil of 2-benzoylbenzoic acid (XLVIIIa – A), in the (XLVIIIb – A) molecule the interacting COOH and C=N groups are sterically in greater proximity and therefore the equilibrium in solutions of 2-benzoylnaphthoic acid anils is fully displaced towards the cyclic form (XLVIIIb – B).[181] When (XLVIIIa) and (XLVIIIb) are treated with bases, the open-chain anions (XLIX) are formed.

Amino-derivatives (IIA ⇌ IIB, IIIA ⇌ IIIB, X = NR)

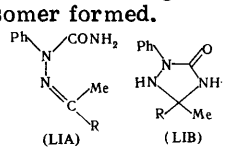
Mixtures of open-chain and cyclic isomers, (LA) and (LB), are formed in reactions of ethylenediamines with aldehydes and cyclic ketones. However, Chapuis et al.[182] were unable to confirm the existence of the tautomeric equilibrium (LA) ⇌ (LB) in solution. It has been shown by ^{1}H NMR that the fraction of the cyclic isomer in the mixture of reaction products decreases with increase of the steric bulk of the alkyl substituent R^1 (for R = H) or following its substitution by the phenyl group:



(LA) (LB)

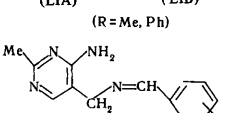
Acetone and acetophenone 2-phenylsemicarbazones have been obtained[183] in both the open-chain (LIA) and cyclic (LIB) forms. The isomerisation (LIA) → (LIB) takes place in the presence of acid.

The reactions of 4-amino-5-aminomethyl-2-methyl-(or phenyl)pyrimidine with aromatic aldehydes give rise to open-chain (LIIA) or cyclic (LIIB) condensation products or their mixtures[184]. However, it is impossible to find a relation between the electronic properties of the substituent in the aromatic ring of the aldehyde and the structure of the isomer formed.



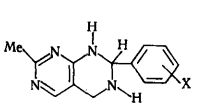
(LIA) (LIB)

(R = Me, Ph)



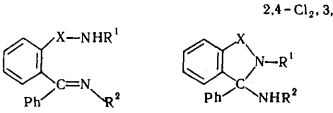
(LIIA)

(X = 4-Cl, 4-Br, 4-F)



(LIIB)

(X = 4-F, 4-MeO, 4-NO_2, 2,4-Cl_2, 3,4-Cl_2)



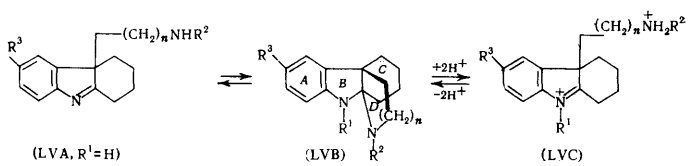
(LIII A, LIVA) (LIIIB, LIVB)

(LIII, X = CO; LIV, X = SO_2)

Both isomers have been obtained in the series of imines[154] and anils[185] derived from 2-benzoylbenzamides—(LIIIA) and (LIIIB). The imine derived from 2-benzoyl-*N*-methylbenzamide has been obtained only in the cyclic form (LIIIB, R^1 = Me, R^2 = H). The anilide has been isolated in the open-chain form (LIIIA, R^1 = Ph, R^2 = H). When its solution in deuteriochloroform is stored at room temperature or its solution in ethanol is heated, the isomerisation (LIIIA) → (LIIIB) takes place readily. A similar isomerisation occurs in a series of anils of *N*-alkyl-2-benzoylbenzamides (LIII, R^1 = n-Pr, $PhCH_2$, i-Pr, or t-Bu, R^2 = Ph[5]), obtained by treating 3-chloro-2,3-diphenylisoindolinone with alkylamines[185]. An increase of the steric bulk of the substituent R^1 hinders the isomerisation (LIIIA) → (LIIIB): the *N*-benzylamide isomerises more slowly at room temperature in ethanol solution than the *N*-propylamide, while the *N*-isopropyl- and *N*-t-butyl-amides are stable under these conditions. They isomerise on refluxing the ethanol solutions with added triethylamine. In solutions in dioxane at room temperature both isomers (LIIA and LIIIB, R^1 = alkyl, R^2 = Ph) are stable and equilibrium mixtures are not formed when the solutions are stored for 24 h.

The imine derived from *N*-methyl-2-benzoylbenzenesulphonamide has been obtained[154] in the cyclic form (LIVB, R^1 = Me, R^2 = H) and the *N*-phenyl derivative has been obtained as a mixture of both isomers with the open-chain form predominating.

Ring—chain tautomerism has been observed[186] for echiboline (LVB, $R^1 = R^2 = R^3$ = H, n = 1) and its derivatives. In all cases protonation results in the open-chain dication (LVC) and deprotonation is accompanied by cyclisation:

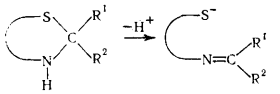


(R^1=H, Me; R^2= H, Me; R^3=H, OMe; n = 1, 2, 3)

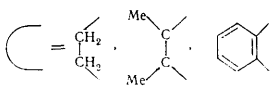
Certain echiboline derivatives (LV, R^1 = H, R^2 = H or Me, R^3 = MeO) exist in the cyclic form in solvents of low polarity, while in methanol solutions they form equilibrium mixtures with the open-chain form. Ring opening is facilitated by the presence of unsubstituted nitrogen atoms ($R^1 = R^2$ = H), by the introduction of the methoxy-group into the aromatic ring (R^3 = MeO) which decreases the electrophilicity of the carbon atom of the C=N bond in the molecule of (LVA), and by increase of ring size. Echiboline itself (LVB, $R^1 = R^2 = R^3$ = H, n = 1) exists in the cyclic form in solution, an equilibrium is observed with n = 2, and on further increase of ring size (n = 3) the cyclic form is not formed at all.

Mercapto-derivatives (IIA ⇌ IIB, X = S)

The products of the condensation of 2-mercaptoethylamine[187-189], 2-mercapto-3-butylamine[187], and 2-mercaptoaniline[190-192] with carbonyl compounds have exclusively the cyclic structure (LVIB). The formation of open-chain derivatives when the alkylation reactions are carried out in highly alkaline media is indirect evidence for the open-chain structure of the anionic form (LVIC):



(LVIB) (LVIC)

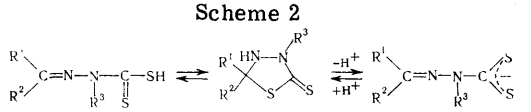


In reactions with formaldehyde and cyclohexanone, 3-mercaptopropylamine forms the corresponding tetrahydro-1,3-thiazines and the reaction with benzaldehyde gives a mixture of both isomers with the Schiff base predominating[193]. The reaction of 4-mercaptobutylamine with cyclohexanone gives rise to hexahydro-1,3-thiazepine[164].

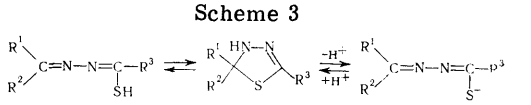
The concept of the ring—chain equilibrium of mercaptoalkylimines has been used[194] to explain the mechanism of ring contraction in the 5,6-dihydro-1,4-thiazines under the influence of hydrogen sulphide as well as the reverse reaction—the expansion of the rings of thiazolidines under the influence of elemental sulphur.

Mayer and Lauerer[195] quote interesting examples of the ring—chain tautomerism in the series of 1,3,4-thiadiazolidine and 1,3,4-thiadiazoline derivatives (Schemes 2—4). The state of equilibrium depends on the pH of the medium. The anionic forms (Schemes 2 and 3) have the open-chain structure.

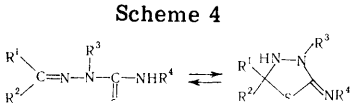
Scheme 2



Scheme 3



Scheme 4



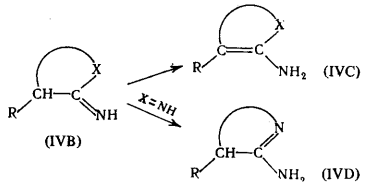
IV. NITRILES

(IVA → IVB, X = O, NR, or S)

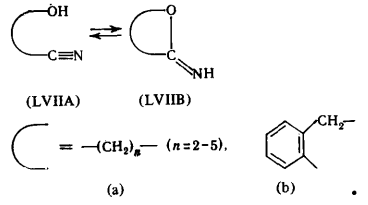
Numerous ways of synthesising heterocyclic imines or amines whose final stage is intramolecular nucleophilic addition of OH, NH, and SH groups to the C≡N bond have been developed[196,197]. The intermediates formed in these syntheses, namely hydroxy-, amino-, or mercapto-nitriles (IVA, X = O, NR, or S), were frequently not isolated.

Examination of studies where the compounds (IVA) were isolated in a pure form shows that the isomerisation (IVA) → (IVB) takes place readily and irreversibly on heating in polar solvents[198-200], in the presence of acids[201-206] and bases[197,207-218], or simply on heat treatment[198,200,203,218-220]. Double melting points, i.e. the crystallisation of the substance after fusion and its second fusion ar the melting point of the cyclic isomer, are important phenomena in the thermal isomerisation of

2-cyanobenzamide[219] and 2-thioureidobenzonitrile[198]. The heterocyclic imines (IVB) formed frequently isomerise to heterocyclic amines (IVC or IVD) as a result of the migration of the double bond to the ring:

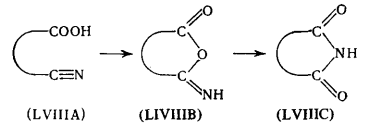


Matsui and also Renson observed $\nu(C\equiv N)$ and $\nu(C=N)$ bands in the infrared spectra of the ω-cyanoalcohols (LVIIa)[221] and 2-hydroxymethylbenzonitrile (LVIIb) [222] and concluded that the ring–chain tautomeric equilibrium (LVIIA) $\rightleftharpoons$ (LVIIB) occurs:



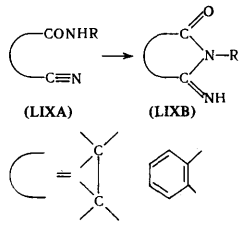
This conclusion requires additional confirmation, which can be secured by spectroscopic study of solutions of (LVIIa) and (LVIIb) in various solvents. Numerous data on the cyclisation reactions of hydroxynitriles[196,197,201] suggest that the isomerisation (IVA) → (IVB) (X = O) is irreversible. One cannot rule out the possibility that some investigators[221,222] did not work with the equilibrium system (LVIIA) $\rightleftharpoons$ (LVIIB) but with a mixture of isomers (LVIIA) and (LVIIB) (cf. des Abbayes[214]).

The mononitriles of phthalic[219], homophthalic[223], and other γ- and δ-dicarboxylic acids[197] readily isomerise to the imides (LVIIIC). This isomerisation can proceed through the stage involving the formation of the relatively unstable iminolactone (LVIIIB).[216,223] A study[218] of the infrared spectra of 2-cyanobenzoic acid in various solvents showed that the acid is stable in solution at room temperature and the equilibrium (LVIIIA) $\rightleftharpoons$ (LVIIIB) is not observed.

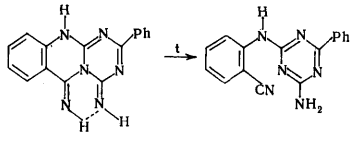


Both γ-and δ-aminonitriles[202,203,209,217,224-226], β-hydrazinonitriles[213,217,227], the hydrazones of cyanoketones[200], and β-cyanoacid hydrazides[190] isomerise to the corresponding heterocyclic imines or amines. The amides of β-cyanopropionic[208,210,215] and 2-cyanobenzoic acids (LIXA) [218-220] isomerise in the presence of bases (sodium alkoxides or triethylamine) or by a thermal process to the iminolactams (LIXB).

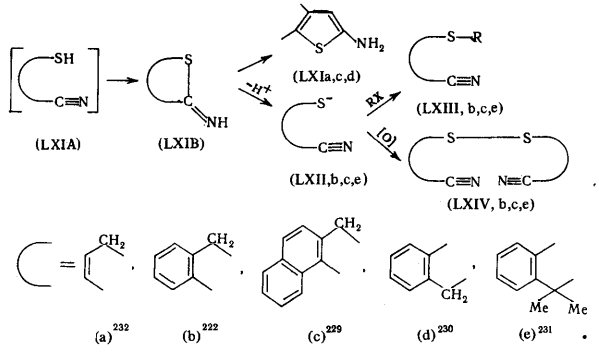
It has been shown that an increase in the bulk of the substituent R at the nitrogen atom in the series of 2-cyanobenzamides hinders the isomerisation (LIXA) → (LIXB) and for this reason *N*-(t-butyl)- and *N*-(1-adamantyl)-2-cyanobenzamides do not cyclise. In solutions in dioxane 2-cyanobenzamides and their cyclic isomers (LIXB) are stable and the equilibrium (LIXA) $\rightleftharpoons$ (LIXB) has not been observed by infrared spectroscopy[218]. 2-Ureido and 2-thioureido-benzonitriles[198,212,228] as well as urethanes derived from α-cyanohydrins[211] isomerise similarly.



Among amino-derivatives of nitriles, there is one unusual example[226] where the cyclic form undergoes thermal isomerisation to the open-chain form [(LXB) → (LXA)]. Evidently the gain of the aromatisation energy on formation of the *s*-triazine ring in the open-chain isomer (LXA) is of decisive importance here:



At the instant of their formation γ-mercaptonitriles (LXIA) cyclise[196,222,229-232] to iminothiophen derivatives (LXIB). If there is a hydrogen atom attached to the carbon atom which is α to the C=N bond, the latter undergo spontaneous further isomerisation to the aminothiophens (LXIa – c) and (LXId – C).[230,232] Stacy[229,231] and Renson[222] speak of the ring–chain tautomerism (LXIA) $\rightleftharpoons$ (LXIB), since the compounds (LXIb – B), (LXIc – B), and (LXIe – B) form both cyclic and open-chain derivatives. For example, alkylation in an alkaline medium gave the open-chain *S*-alkyl derivatives (LXIII, b, c and e) and on oxidation the products were the open-chain disulphides (LXIV, b, c, and e). Evidently the open-chain anion (LXII) is formed in an alkaline medium. However, the presence of the open-chain form either in the crystalline state or in solution could not be demonstrated by spectroscopic methods (Raman spectroscopy and ^{1}H NMR), i.e. the tautomeric equilibrium (LXIA) $\rightleftharpoons$ (LXIB) does not occur within the limits of the sensitivity of these methods.



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Thus the application of infrared, ^{1}H NMR, and ultraviolet spectroscopic methods permits a quantitative characterisation of the phenomenon of ring–chain tautomerism. However, few such studies have been made in this field. A quantitative assessment of these processes,

based on at least two spectroscopic methods, is of greatest interest and evidently such investigations will be the first to develop.

A common defect of the majority of the experimental studies carried out to date in this field is the narrow range of test systems. Whereas the influence of the substituents on ring–chain equilibrium has been very thoroughly characterised[160,166,233-237] by correlation constants, attempts to assess quantitatively the influence of the structure of the link joining the two interacting groups are not described in the literature. Nevertheless, the study of the relation between the quantitative characteristics of intramolecular reversible addition reactions and the steric disposition of the reacting functional groups in the presence of a fairly rigid connecting link is of great theoretical interest.

ADDED IN PROOF

During the preparation of the review for the press, a number of studies on the ring–chain tautomerism of hydroxyketones[238-241], hydroxyiminoketones[242,243], 2-oxoalkyltriazenes[244,245], and *N*-(β-hydroxyalkyl)hydrazones[246] were published.

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