Reviews

Molecular design of tautomeric interconversions of heterocycles

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A classification and methodology of molecular design of ring—chain—ring (ring—ring) tautomeric systems by superposition of ring—chain equilibria in a structure of one molecule are considered.

Key words: ring—chain and ring—chain—ring tautomerism, heterocycles, ring transformation.

The main concepts and classification

Equilibrium ring transformations of heterocycles have been known for more than 100 years by the example of mutarotation of monoses. Ring—chain tautomerism[1—3] and ring transformation of heterocycles[4—6] have been comprehensively studied. Much later (in 1981), tautomeric interconversion was discovered in relation to thiobenzoylhydrazone of acetylacetone.[7] The results of the subsequent studies of processes of this type are reflected in reviews;[8,9] however, the current state of the problem requires further systematization and classification.

What does the notion "tautomeric interconversion" mean? The ring—chain tautomerism implies intramolecular interaction between a nucleophile (Nu) and an electrophile (E). Alternative cyclizations involving more than two reaction centers are also possible, for example, 2 Nu + 1 E, 2 E + 1 Nu, *etc.*, *i.e.*, those involving *superposition* of, at least, two ring—chain equilibria. When the stabilities of both cyclic forms are similar and the chain tautomer is less stable, *ring—ring tautomerism* is observed, and when the stabilities of the cyclic and chain forms are comparable, the *ring—chain—ring tautomerism* is involved. We call these types of tautomerism *tautomeric interconversions*. If the reaction of a molecule having a ring—chain system gives rise to an additional, more stable molecule, *ring transformation* takes place. The interconversions of diastereomers of the same cyclic derivative in which a chiral center is formed after the interaction of a single Nu—E pair should not be classified as tautomeric interconversions or ring transformations (see mutarotation and numerous published data[10,11]).

Basically, the situation is complicated due to an increase in the number of reaction centers and, as a consequence, the number of combinations (Scheme 1).

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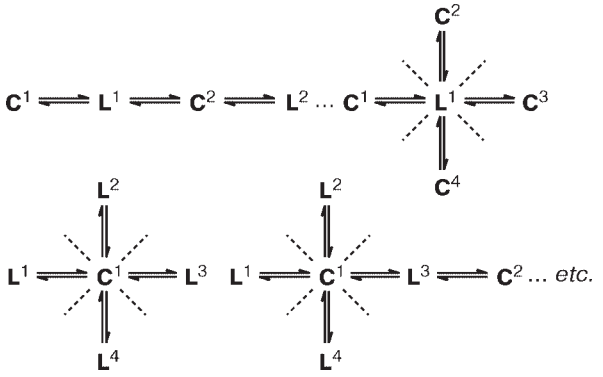
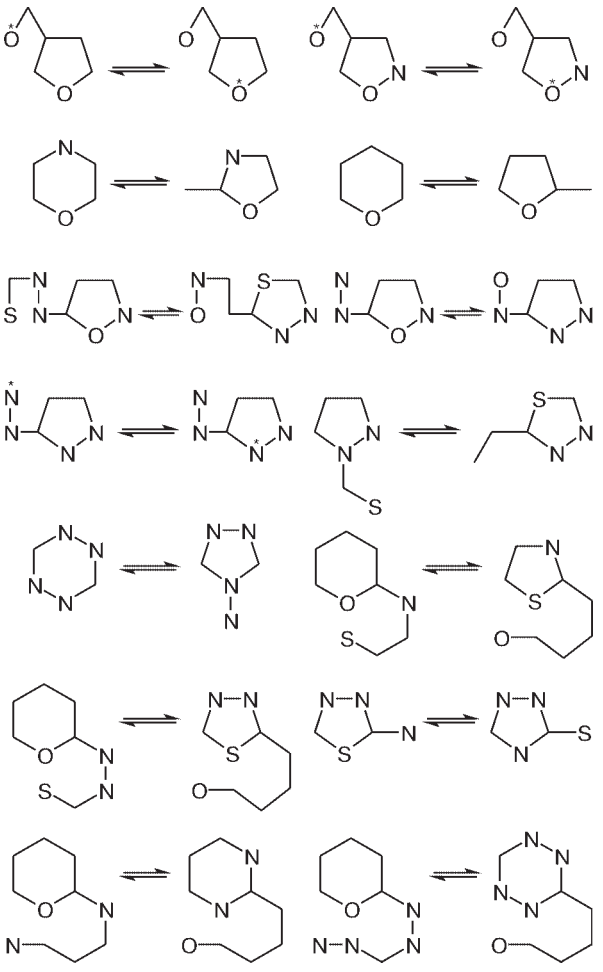
Scheme 1



$C^{1,n}$ are cyclic tautomers, $L^{1,n}$ are linear tautomers

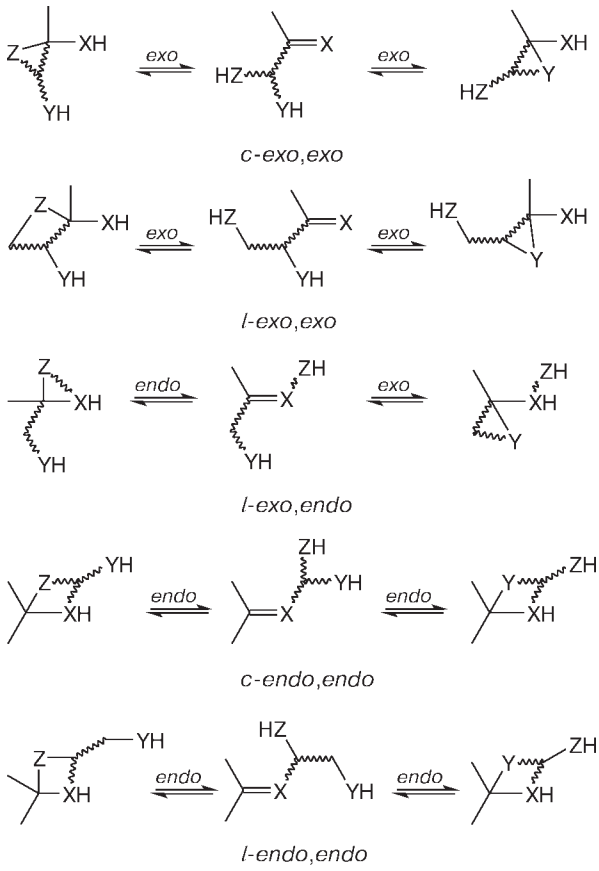
The combination of known tautomeric interconversions of heterocycles[9] is expressed as a set of topological equilibria (Scheme 2).

Scheme 2



Equilibrium ring transformations involving one electrophilic and two nucleophilic centers (1 E + 2 Nu) are represented by the set shown in Scheme 3.

Scheme 3

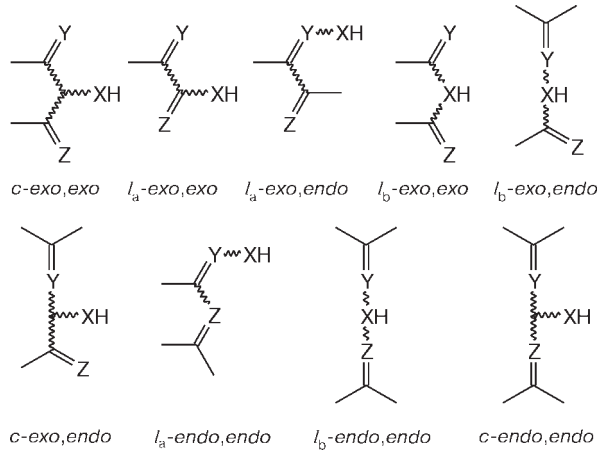


Linear structures able to undergo ring transformation and containing one nucleophilic and two electrophilic centers (1 Nu + 2 E, recyclizations are omitted for short), are presented in Scheme 4.

Analysis of the published data showed that most of ring—chain equilibria originate from the interaction of nucleophilic centers (OH, SH, or NH groups) with electrophilic ones (C=O, C=S, C=N, or, more rarely, C≡N). Therefore, the X, Y, and Z atoms in Schemes 3 and 4 are represented by O, S, or N, although these can also be C, P, and other atoms.

Let us classify Schemes 3 and 4 as *endo*- and *exo*-cyclizations[12] and introduce the designation *c* (*cross*) for the case where functions of the same type are located at a branching and *l* (*linear*) for the case where they belong to one chain. These designations do not suffice for Scheme 4; therefore, we will add the subscripts and superscripts a and b (the former standing for *after* and the latter standing for *between*) for the nucleophilic center being arranged after the electrophilic centers or between them.

Scheme 4

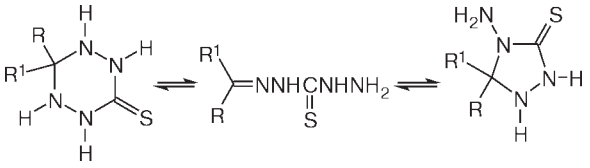


We will take into account the commonest rings, namely, five- and six-membered ones. Equilibrium ring transformations involving rings with other sizes (*e.g.*, a four and a seven-membered ring) are possible but unknown. Therefore, the l_a-*endo*,*endo* pathway (see Scheme 4), in which one of the rings contains not less than seven units is unlikely.

The sums of ring transformations for the above-indicated cases are presented in Tables 1 and 2, respectively.

Now we will use the proposed classification to characterize, for example, the tautomeric interconversion of heterocycles for ketone thiocarbonohydrazones[13,14] (Scheme 5).

Scheme 5



R = Me; R^1 = Alk, Bn, $—(CH_2)_5—$

This is an *l*-5-*endo*,6-*endo* (2 NH, C=N) ring transformation. The monose mutarotation should be described as an *l*-5-*exo*,6-*exo* (2 OH, C=O) ring transformation.

Of the 102 possible ring transformations of the (2 Nu + 1 E) type (see Table 1), five transformations are currently known, namely:

— *l*-5-*exo*,6-*exo* (2 OH + C=O) for carbohydrates[9,10] and (2 OH + C=N) for ribose and fructose thiosemicarbazones[15,16] (tetrahydropyran—tetrahydrofuran);

— *l*-6-*exo*,5-*endo* (OH, SH + C=N) for glucose β-mercaptoethylimine[17] (tetrahydropyran—1,3-triazolidine) and glucose thioacylhydrazones[15] (tetrahydropyran—2,3-dihydro-1,3,4-thiadiazole);

Table 1. Ring transformations involving two nucleophilic (Nu) and one electrophilic (E) centers

Ring transformation	E (X)	Nu (Y, Z)	The sum of five- and six-membered rings
c-exo,*exo*	O, S, NR	O, O	3
	The same	O, S	4
	»	O, NR	4
	»	S, S	3
	»	S, NR	4
	»	NR, NR	3
l-exo,*exo*	O, S, NR	O, O	1
	The same	O, S	2
	»	O, NR	2
	»	S, S	1
	»	S, NR	2
	»	NR, NR	1
l-exo,*endo*	N	O, O	4
	The same	O, S	4
	»	S, O	4
	»	O, NR	4
	»	NR, O	4
	»	S, S	4
	»	S, NR	4
	»	NR, S	4
	»	NR, NR	4
l-endo,*endo*	N	O, O	1
	The same	O, S	4
	»	O, NR	4
	»	S, S	1
	»	S, NR	4
	»	NR, NR	1
c-endo,*endo*	N	O, O	3
	The same	O, S	4
	»	O, NR	4
	»	S, S	3
	»	S, NR	4
	»	NR, NR	3
		Total	**102**

Note. X, Y, Z are atoms incorporated in the electrophilic and nucleophilic centers.

— *l*-6-*exo*,6-*endo* (OH, NH + C=N) for carbohydrate 3-aminopropylimines[17] (tetrahydropyran—piperimidine) and glucose and galactose thiocarbonohydrazones[15,18] (tetrahydropyran—hexahydro-1,2,4,5-tetrazine);

— *l*-5-*endo*,6-*endo* (2 NH + C=N) for ketone thiocarbonohydrazones[13,14] (4,5-dihydro-1,2,4-triazole—hexahydro-1,2,4,5-tetrazine);

— *c*-5-*endo*,5-*endo* (NH, SH + C=N) for alkanal thiosemicarbazones[19] (2,3-dihydro-1,3,4-thiadiazole—1,2,4-triazolidine).

Of the 55 possible ring transformations of the (1 Nu + 2 E) type (see Table 2), only two are currently known, namely, *c-exo*,*exo* (OH + 2 C=O) for 4-acyl-5-hydroxyisoxazolidines[20] (isoxazolidine—isoxazolidine´)

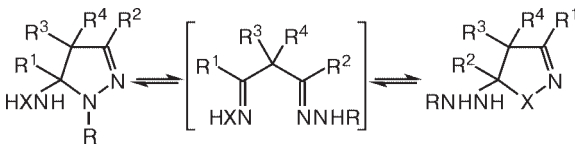
Table 2. Ring transformations involving one nucleophilic (Nu) and two electrophilic (E) centers

Ring transformation	E (X)	Nu (Y, Z)	The sum of five- and six-membered rings
c-exo,exo	O, S, NR	O	3
	The same	S	3
	»	NR	3
c-exo,endo	N; O, S, NR	O	4
	The same	S	4
	»	NR	4
c-endo,endo	N, N	O	1
	То же	S	1
	»	NR	1
l_a-*exo,exo*	O, S, NR	O	3
	The same	S	3
	»	NR	3
l_b-*exo,exo*	O, S, NR	N	3
l_a-*exo,endo*	N; O, S, NR	O	1
	The same	S	1
	»	NR	1
l_b-*exo,endo*	O, N	N	4
	N, S	N	4
	NR, N	N	4
l_a-*endo,endo*	N, N	O	1
	The same	S	1
	»	NR	1
l_b-*endo,endo*	N, N	N	1
		Total	**55**

and l_a-*exo,endo* (OH + C=O, C=N) for β-hydroxyethylimines of 1,2-dicarbonyl compounds[21,22] (5,6-dihydro-1,3-oxazine—oxazolidine).

Some known cases of the ring—ring tautomerism do not fit in the Scheme represented by Tables 1 and 2, because they involve two nucleophilic and two electrophilic centers (2 Nu + 2 E). These include ring transformations of oximo hydrazones,[23] oximo thioacylhydrazones,[24] asymmetrical bis-hydrazones[25,26] and thioacylhydrazones of 1,3-dicarbonyl compounds,[27—29] and 1,3,4,6-tetraketones.[30] However, they can also be classified. Indeed, the first transformation in Scheme 6 (X = O)[22] is *l*-5-*exo*,5-*endo* (OH + C=N, NH + C=N), while the second one (X = NR_5)[24,25] corresponds to an *l*-5-*exo*,5-*exo* (2 NH + 2 C=N) ring transformation.

Scheme 6

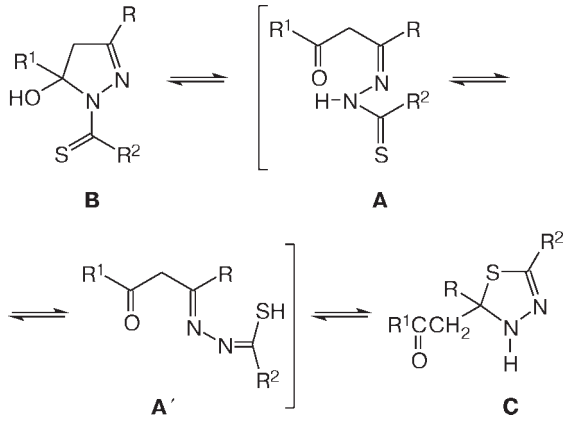


X = O; $R^1 = R^2 = R^4$ = Me; R = Alk, Bn, Ac, Bz
X = NR^5; $R^1 = R^2$ = Alk; $R^3 = R^4$ = H, Me; R = R^5 = ArCO

When analyzing individual examples of ring transformation, their real complexity should be taken into account.

First, ring—chain equilibria can be combined with prototropic shifts, which can, in particular, change the nature of the functional groups participating in the ring—chain transition. Indeed, the prototropy in the X=C—YH ⇌ HX—C=Y triad results in transposition of the nucleophilic and electrophilic centers. This may give rise to a new ring—chain equilibrium; this is the case with thioaroylhydrazones of 1,3-dicarbonyl compounds[7,27—29] (Scheme 7).

Scheme 7



R, R^1 = Alk, Ar; R^2 = Ar

In these compounds, the thioacylhydrazone—5-hydroxy-2-pyrazoline ring—chain system (**A** ⇌ **B**) with intramolecular interaction between the C=O (E′) and NH (Nu′) groups, after a prototropic shift occurring in the linear form (—NH—C=S ⇌ —N=C—SH) to give azinethiol tautomer **A′**, is combined with the azinethiol—1,3,4-thiadiazoline-2 (**A′** ⇌ **C**) ring—chain equilibrium due to the intramolecular reaction between the C=N (E″) and SH (Nu″) groups (*l*-5-*exo*,5-*endo* (C=O + NH, C=N + SH) ring transformation).

Second, one should also take into account the isomerism phenomena in both cyclic and linear forms, which may include hindered rotation in some fragments of the tautomers. In this case, we deal with multitautomer systems, which require thorough analysis.

Molecular design of ring—chain systems

Now we proceed to the proper *molecular design* of tautomeric interconversions of heterocycles.

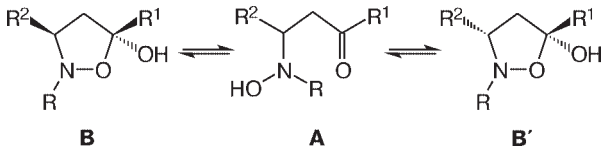
The first stage is the search for particular ring—chain systems in which a change of structural parameters and external factors can give rise to an equilibrium with pre-

dominance of the cyclic form. Numerous systems of this type are known;[1–3] however, the search for new ones is of interest by itself. Below we present some results of our investigations along this line.

Exo systems

5-*Exo* (C=O + OH) equilibria. According to previous publications,[31–33] the product of addition of *N*-substituted hydroxylamines to alkenals, *N*-hydroxyaminopropanals (**A**, Scheme 8), demonstrate the **A** ⇌ **B** equilibrium in which the 5-hydroxyisoxazolidine tautomers **B** and **B´** predominate in nonpolar solvents.

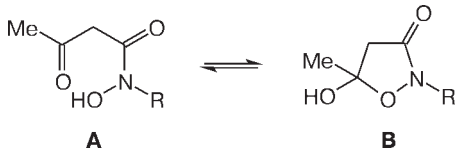
Scheme 8



R = Alk, Ar; R^1 = H; R^2 = H, Me

The same feature is found for the products of reaction of *N*-benzyl- and arylhydroxylamines with diketene (Scheme 9), which exist[34,35] as 5-hydroxyisoxazolidin-3-ones **B** in low-polarity media.

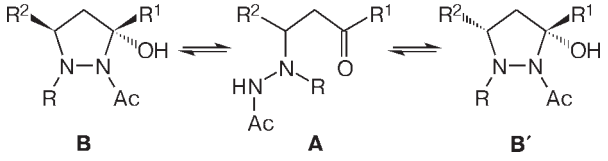
Scheme 9



R = Bn, Ar

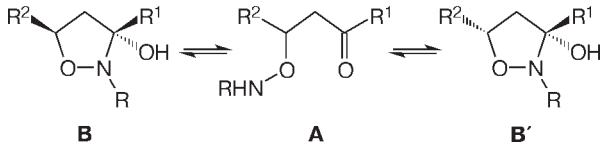
5-*Exo* (C=O + NH) equilibria. The products formed in the reactions of alkenals with 2-substituted hydrazides[36–38] (Scheme 10) and hydroxamic acids[31–33] (Scheme 11) have similar structures. In solutions, they occur in the **A** ⇌ **B** equilibrium in which cyclic forms **B** and **B´** predominate.

Scheme 10



R = Alk, Ar; R^1 = H; R^2 = H, Me

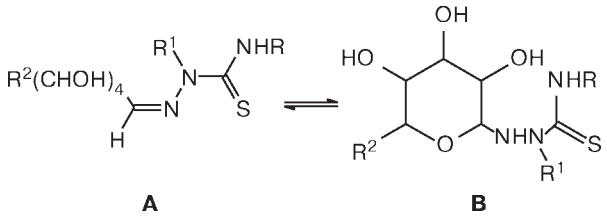
Scheme 11



R = acyl; R^1 = H; R^2 = H, Me

6-*Exo* (C=N + NH) equilibria. 4-Substituted monose thiosemicarbazones,[15] like aryl- and acylhydrazones and oximes of aldoses,[9] tend to undergo the **A** ⇌ **B** ring—chain tautomeric transition (Scheme 12).

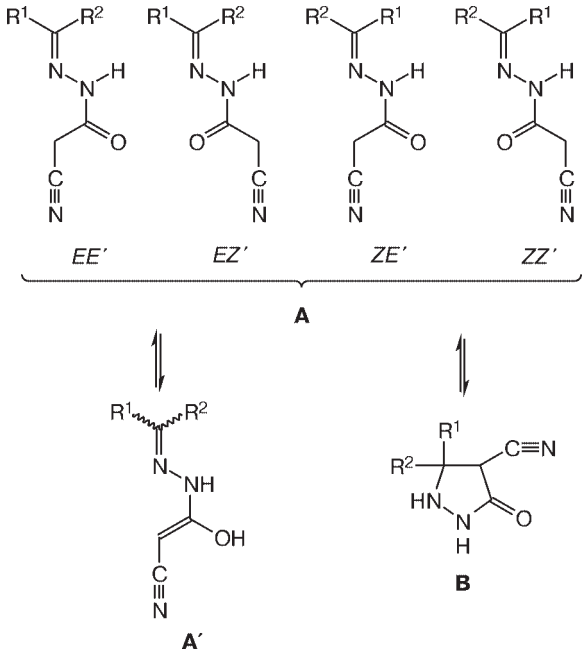
Scheme 12



R, R^1 = H, Alk; R^2 = H, CH_2OH

5-*Exo* (C=N + CH) equilibria are of special interest as potential ring—chain systems involving the C—H bond.

Scheme 13

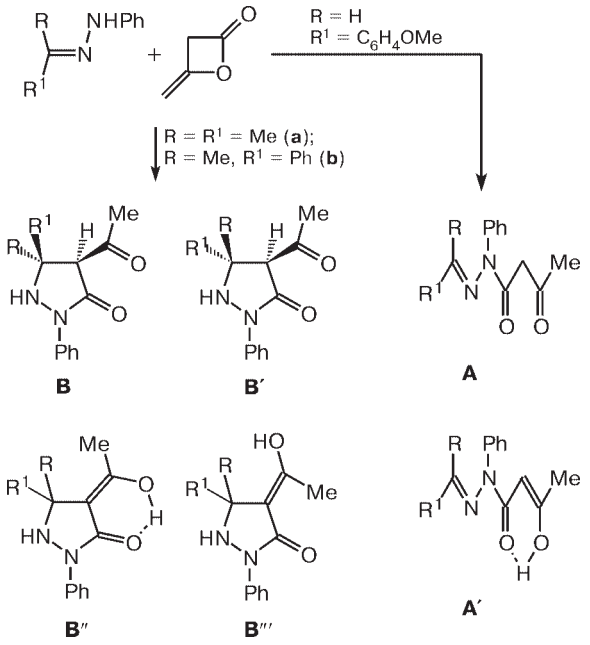


R^1, R^2 = H, Alk, Ar

Both the ring—chain equilibrium[39] **A** ⇌ **B** and the prototropic process[40] **A** ⇌ **A′** have been described for cyanoacetylhydrazones (Scheme 13). We found[41] that tautomerism is uncharacteristic of these compounds, the existence of different forms being due to *syn—anti* isomerism and hindered rotation in the amide fragment of hydrazone **A**.

N-Acetoacetyl-*N*-phenylhydrazones prepared by the reaction of diketene with aldehyde phenylhydrazones have linear structure **A** (Scheme 14), whicle in the case of hydrazones of ketones, these are pyrazolidinone derivatives **B**.[42] Thus the existence of ring—chain tautomerism **A** ⇌ **B** can be suggested in this case. However, the transformations of these compounds are limited to prototropy both in the linear (**A** ⇌ **A′**) and ring forms (**B** ⇌ **B′** ⇌ **B″** ⇌ **B‴**), while the **A** ⇌ **B** equilibrium between them does not take place.[43]

Scheme 14



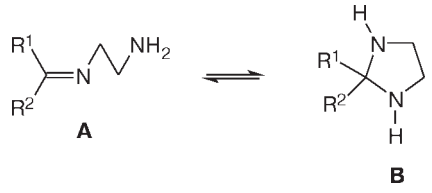
Thus, the cases of *exo*-equilibria that we found can, in principle, be used for the molecular design of ring transformations.

Endo systems

These systems proved to be less promising.

5-*Endo* (C=N + NH) cyclizations. We found[44] that monoimines **A** (Scheme 15) tend to undergo ring—chain tautomerism but the content of imidazolidines **B** in the equilibrium is low. Hence, these compounds are of little use for the molecular design of tautomeric interconversions.

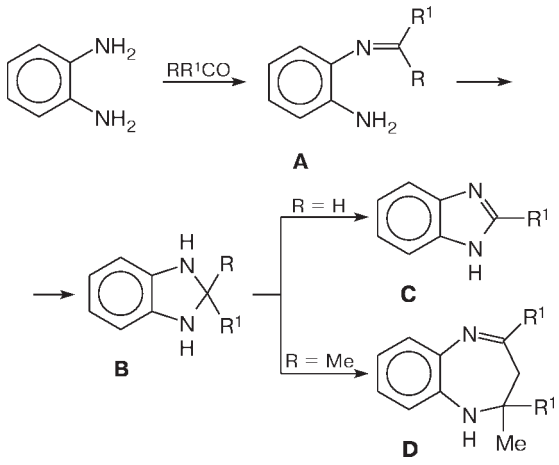
Scheme 15



R^1, R^2 = H, Me, Ar

Monoimines **A** derived from *o*-phenylenediamine (Scheme 16) are inapplicable for the design of ring transformation either. The intermediate formation of these species was also expected in the reactions of *o*-phenylenediamine with aldehydes (in the synthesis of benzimidazoles **C**) or with enolyzed ketones (in the synthesis of 1,3-benzodiazepine derivatives **D**). We found[45] that the reactions afford the corresponding monoimines **A**, which cyclize to benzimidazolines **B**; however, the **A** ⇌ **B** ring—chain tautomerism does not occur because benzimidazolines **B** are rapidly converted into products **C** or **D**.

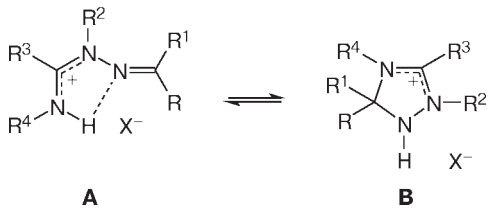
Scheme 16



R = H; R^1 = H, Me, Ar

1-Alkylidene(arylidene)amidrazonium, -aminoguanidinium, and -isothiosemicarbazinium salts[46—48] are capable of ring—chain transitions but in these equilibria, linear tautomer **A** predominates more often (Scheme 17).

Scheme 17

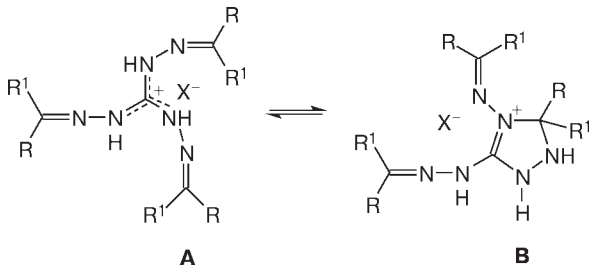


R, R^1 = H, Alk, Ar; R^2, R^4 = H, Me; R^3 = Me, Ph, NH_2, S-Alk

In addition, these salts are soluble only in polar media, which restricts their use.

The same is true for triaminoguanidinium salts,[49,50] for which the proportion of the cyclic form **B** in the **A** ⇌ **B** equilibrium is relatively low (Scheme 18).

Scheme 18

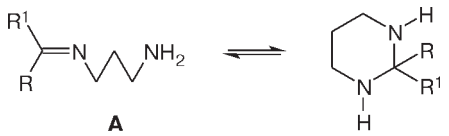


A **B**

R = Me; R¹ = Me, Ar

6-*Endo* (C=N + NH) cyclizations. We showed[51] that 1,3-diaminopropane monoimines **A** occur in solutions as equilibrium mixtures of linear and cyclic forms (Scheme 19), the corresponding piperimidines **B** being more stable.

Scheme 19

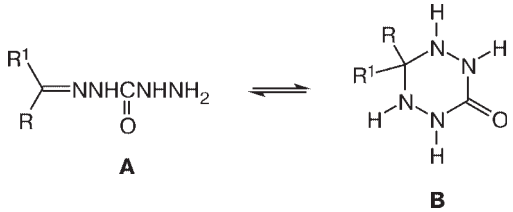


A **B**

R, R¹ = H, Me, Ar

Thus, they are suitable for the construction of equilibrium ring transformations, as opposed to hydrazones **A** (Scheme 20).[49] The **A** ⇌ **B** ring—chain equilibrium was observed only for some of their representatives, the proportion of cyclic tautomer **B** in the equilibrium being low.

Scheme 20



A **B**

R = H, Me; R¹ = Alk

5-*Endo* (C=N + SH) cyclizations have been studied systematically for thioacylhydrazones **A**[51—54] (Scheme 21), which exist predominantly as the cyclic 1,3,4-thiadiazoline form **B**.

Scheme 21

A **B**

R, R¹, R² = H, Alk, Ar

Thus, 1,3,4-thiadiazolines and piperimidines are suitable for the molecular design of ring—ring tautomeric systems.

The set of ring—chain tautomeric systems we generated can be supplemented by the rather broad range of equilibria already known.[1—3]

The range of *exo*-cyclizations will be extended by adding a number of objects corresponding to the above-formulated requirement, namely, monohydrazones of 1,3-dioxo compounds[7,27—29,55—57] (existing usually as the more stable 1-acyl(thioacyl)-5-hydroxy-2-pyrazoline form), monooximes of 1,3-dioxo compounds[1] (which exist as 5-hydroxy-2-isoxazolines), the products of reactions between alkenals and substituted thioureas (4-hydroxohexahydro-2-pyrimidine-2-thiones[58]), and monoses. This gives a universal (naturally, incomplete) set of *exo*-components.

The range of suitable *endo*-cyclizations we found is not large (piperimidines and 1,3,4-thiadiazolidines). However, the list can be readily extended by inclusion of alkylidene (arylidene) derivatives of amino alcohols and aminophenols (*o*-aminophenol, *o*-aminobenzyl alcohol, *o*-hydroxybenzylamine, aminoethanethiol, *o*-aminobenzenethiol), which are either known[1—3] or assumed by analogy (*o*-aminobenzylthiol, *o*-mercaptobenzylamine) to exhibit tendency for ring—chain tautomerism.

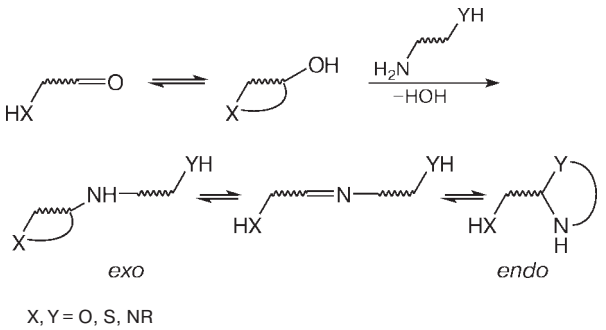
The structures of these systems can be varied over a broad range through modification of the linking unit. Thus β-aminopropionamide or, for example, asparagine, for which no data on the tautomerism of alkylidene derivatives are available, can be included in the range of 1,3-diaminopropane analogs. As noted above,[50] carbonohydrazones are not suited for our task; on the other hand, thiocarbonohydrazones tend to undergo not only ring—chain transitions but also tautomeric ring transformations[15,16,59,60] (see Scheme 5). 2-Aminomethylaniline, whose arylidene derivatives exist in a cyclic form will also be included in the set.[61]

The search for tautomeric interconversions of heterocycles

Having got the ample set of ring transformation variants (see Schemes 3 and 4), one perform the molecular design of such processes. We deliberately restricted the search to only *l-endo*,*exo* (1 E + 2 Nu) ring transformations (see Table 1).

The reason for this choice is the ease of replacement of the hemiacetal hydroxyl in the *exo*-ring—chain system upon the reaction with a functionally substituted amine or hydrazine (the *endo*-ring—chain-system bearer in the product) (Scheme 22).

Scheme 22



Superposition of the selected *endo*- and *exo*-ring—chain systems within the framework of Scheme 22 gives more than 100 different ring transformations (Table 3). Note that four of them have already been studied (see Table 3), ring—chain equilibria being observed for them.[15—18,24,62]

To embody the patterns presented in Table 3, it is expedient to extend the search, first of all, to a variant already checked, namely, ring—ring equilibria in the series of monose derivatives.

We found that this feature (Scheme 23, **B** ⇌ **C** equilibrium) is typical of 3-aminopropylimines of glucose, galactose and rhamnose[63] (*endo*,*exo* (C=N + OH, NH) ring transformation) and of 2-mercaptoethylimine of glucose[17] (*endo*,*exo* (C=N + OH, SH) ring transformation) (see Table 3, entries 97 and 98) but is not observed for aldose imines from ethylenediamine[63] or ethanolamine,[15] in which the pyranose form **B** is retained.

Many derivatives of this type exhibit ring transformations to give derivatives **C** (Table 4).

The next stage was to verify the validity of the data of Table 3 for arbitrarily chosen cases. As these cases, we tested entries 52 and 60 (see Table 3).

In the case of entry 52, 5-*endo*,5-*exo* (C=O + OH, SH) ring transformation[35,64] took place (Scheme 24).

The next randomly chosen examples were the condensation products of 5-hydroxyisoxazolidin-3-ones with 2-aminomethylaniline (see Table 3, entry 60). Their structures can be represented by all sorts of combinations of 11 tautomers (Scheme 25), three of which are cyclic (**B_1**, **B_2**, **C**).

We found[64] that the compounds shown in Scheme 25 exist in solutions as ring—chain—ring equilibria, **B_2** ⇌ *cis*-**A'_2** ⇌ *trans*-**A'_2** ⇌ **C**. This gave a new equilibrium ring transformation involving isoxazole

Scheme 23

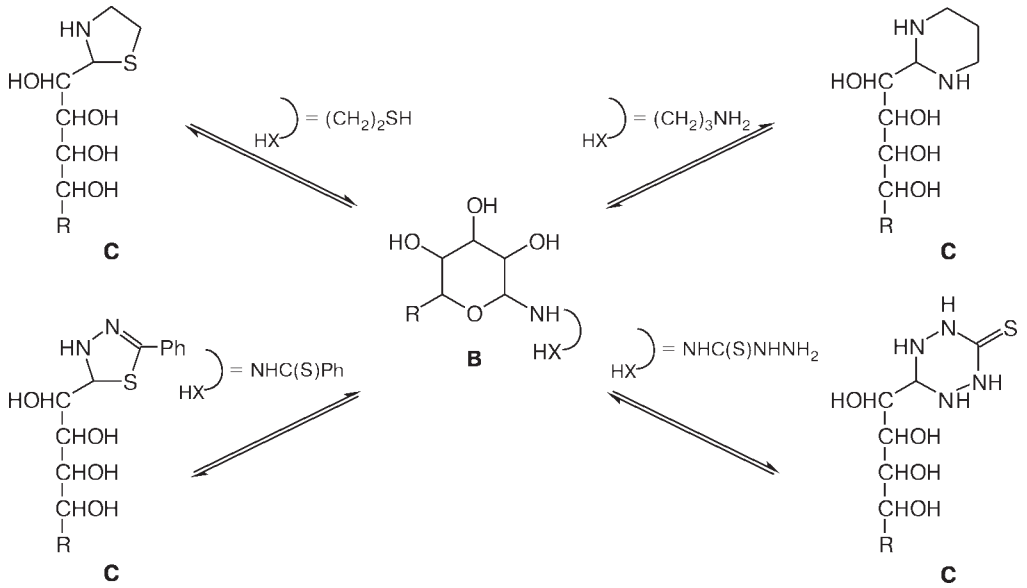
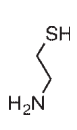
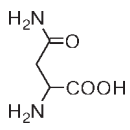
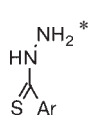
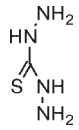
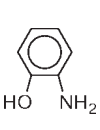
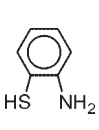
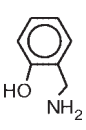
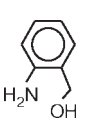
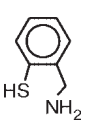
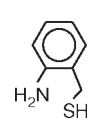
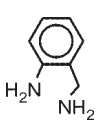
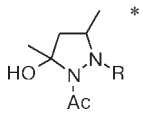
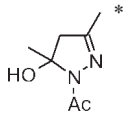
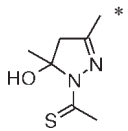
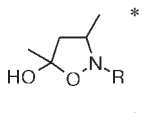
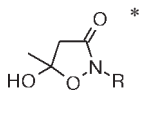
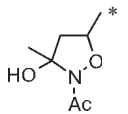
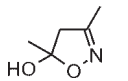
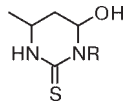
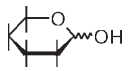
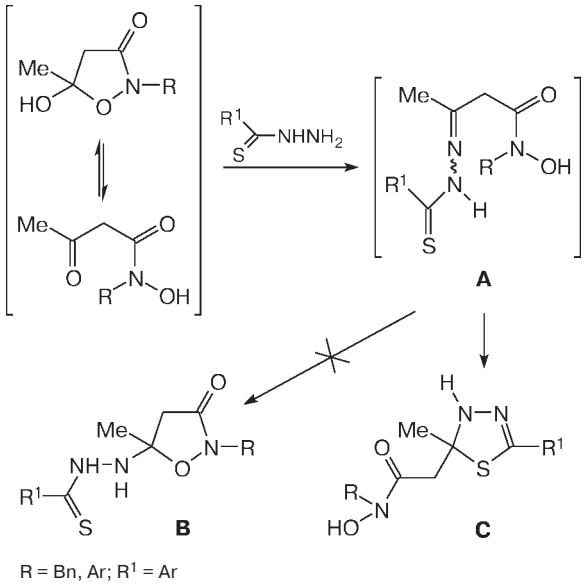


Table 3. Some possible variants of tautomeric interconversions of heterocycles (according to the *endo*,*exo*-pattern (2 Nu + 1 E))

Exo-component	*Endo*-component											
												
	1	2	3	4	5	6	7	8	9	10	11	12
	13	14	15	16	17	18	19	20	21	22	23	24
	25	26	27	28	29	30	31	32	33	34	35	36
	37	38	39	40	41	42	43	44	45	46	47	48
	49	50	51	52	53	54	55	56	57	58	59	60
	61	62	63	64	65	66	67	68	69	70	71	72
	73	74	75	76**	77**	78	79	80	81	82	83	84
	85	86	87	88	89	90	91	92	93	94	95	96
	97	98	99	100**	101**	102	103	104	105	106	107	108

* Our results. ** Known variants.

Scheme 24



R = Bn, Ar; R^1 = Ar

and 1,2,3,4-tetrahydroquinazoline rings (5-*exo*,6-*endo* (C=N + OH, NH) ring transformation).

Thus, Table 3 based on Scheme 22 can be regarded as a versatile (but not the only one) system for the molecular design of tautomeric interconversions of heterocycles.

The next stages are to be, first, systematic research of the variants outlined in Table 3, second, extension of this set of variants using other *endo*- and *exo*-components for reactions, and, third, consideration of the remaining variants (there are 141 of them) involving three reaction centers and numerous variants in which the number of reaction centers is greater than three.

Methodology of investigation of tautomeric interconversions of heterocycles

The methodology of investigation of ring—chain tautomeric processes is fully applicable to the study of equilibrium ring transformations.

NMR spectroscopy. ^{1}H and ^{13}C NMR spectroscopy are the most appropriate methods. ^{15}N NMR spectroscopy can also be used to study relatively large amounts of nitrogen-containing tautomers because ^{15}N chemical shifts vary over broad ranges (~1500 ppm[65]). Study of the structures of thiocarbonohydrazones can serve as an example.[13] However, due to the low natural abundance of the ^{15}N isotope (2%), on the one hand, and pronounced signal broadening in the ^{14}N NMR spectra, on the other hand, nitrogen NMR spectroscopy plays a minor role.

Even the routine one-dimensional NMR spectra can often provide useful structural information, in particular, information concerning direct, geminal, vicinal, and far spin-spin coupling constants. The standard pulse sequences such as DEPT and INEPT are used[65—67] in one-dimensional NMR spectroscopy to enhance the signals of low-sensitivity nuclei. A useful expedient is transfer of magnetization from sensitive nuclei (normally ^{1}H) to insensitive ones (for example, ^{15}N).

Homo- and heteonuclear correlated two-dimensional NMR spectroscopy techniques are especially suitable for the study of multicomponent tautomer mixtures.[68—72] The standard set of two-dimensional methods includes COSY spectroscopy (^{1}H—^{1}H COSY and ^{1}H—^{13}C COSY correlations).

The DSQ-COSY variant provides generally the same information as the COSY but it eliminates the undesirable dispersion broadening of signals.[65—67] The full correlation TOCSY spectroscopy is useful in the investigation of molecules containing long linear fragments. The heteronuclear HMBC spectroscopy identifies far C—H correlations, even those involving quaternary C atoms. The heteronuclear HSQC and HMQC methods also provide information about C—H correlations; an advantage of the former technique is that the signal multiplicity related to H—H interactions is eliminated. A large number of pulse sequences have been developed whose combination with the above-noted fundamental methods provides better quality of two-dimensional NMR spectra.[65—67,73,74]

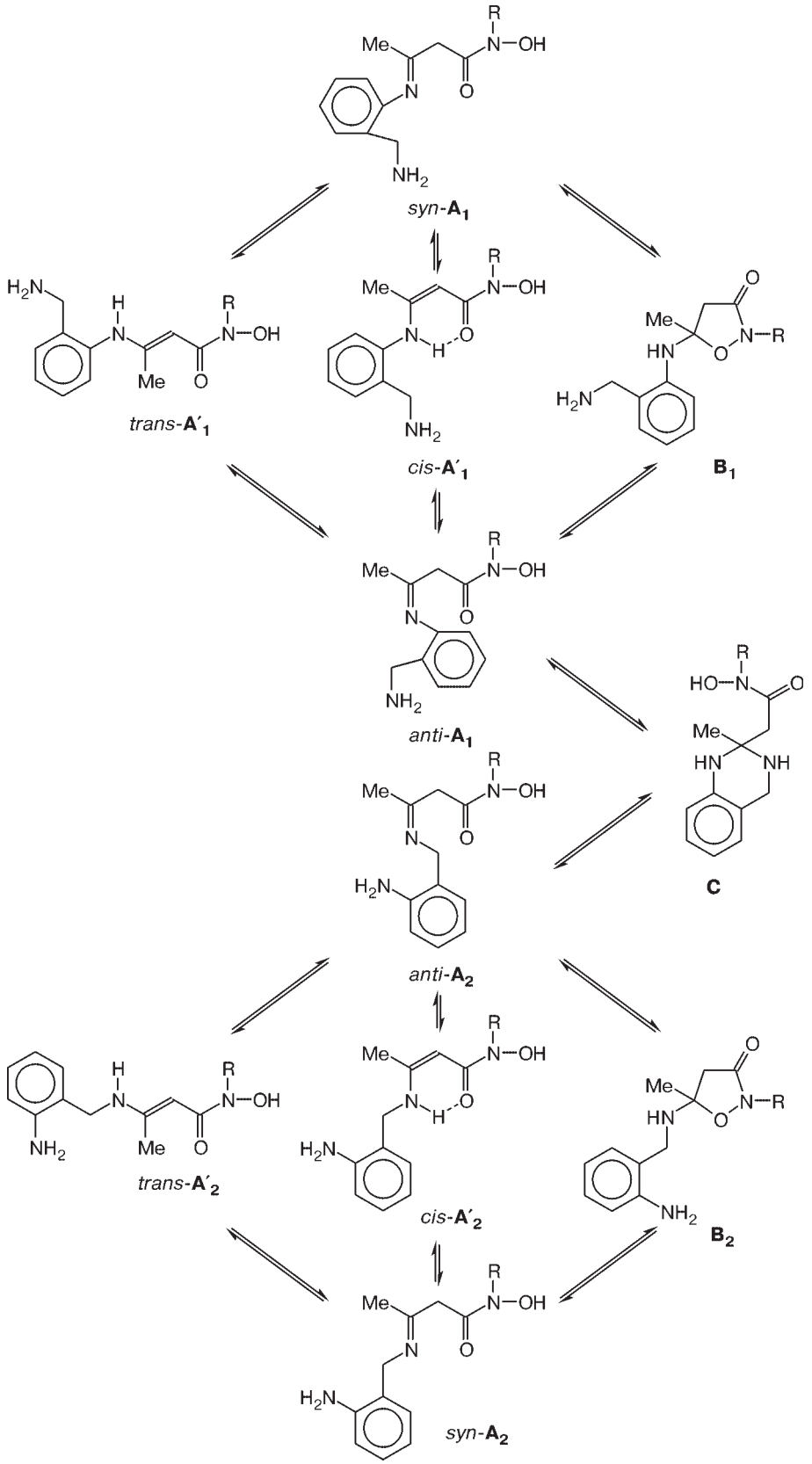
Methods based on the nuclear Overhauser effect (NOE)[65—67] should be specially mentioned. In the differential NOE spectroscopy, irradiation of one proton affects in a definite way the signal intensities of other protons located close in space. Two-dimensional NOESY

Table 4. Ring transformations of functionally substituted imines (hydrazones) of monoses*

Monoses	—$(CH_2)_2$SH	—NHC(S)Ph	—NHC(S)$NHNH_2$	—$(CH_2)_3NH_2$
Glucose	**B**, **C**	**B**, **C**	**B**, **C**	**B**, **C**
Galactose	**C**	**C**	**B**, **C**	**B**, **C**
Rhamnose	**C**	**C**	**C**	**B**, **C**
Mannose	**C**	**C**	**C**	**C**
Arabinose	**C**	**C**	**C**	**C**

* See Scheme 23.

Scheme 25



R = CH_2Ph, Ph

spectroscopy makes it possible to detect pairs of protons closely adjacent in space by comparing NOE spectra with conventional ^{1}H NMR spectra. This method, which is especially useful in studies of large biomolecules, has been used successfully to study dynamic (tautomeric or conformational) equilibria.[65–67,75]

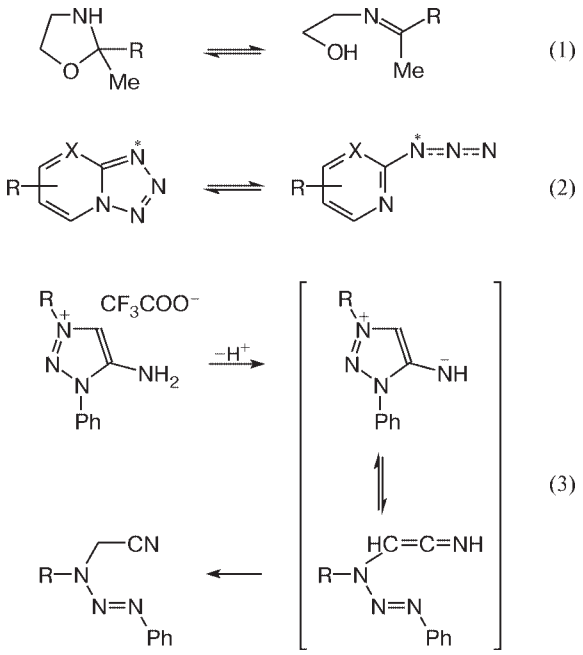
Thus, modern NMR techniques[65–67] allow one to study successfully both simple ring—chain[70,76–87] and more complex multicomponent tautomeric equilibria.[68,69,71,72,81,86,88,89] Due to the high resolving power of modern spectrometers, the key signals of the species involved can be detected in most cases even in conventional ^{1}H and ^{13}C NMR spectra, while the set of available pulse sequences and two-dimensional methods provides additional information concerning the order of binding of hydrogen and carbon atoms.

When the tautomeric transformation affects directly the N atoms present in the molecule, ^{15}N NMR spectroscopy can be a source of important information, despite the laboriousness of the relevant experiments. Thus the ^{15}N NMR spectra of 2,2-dialkyl-1,3-oxazolidines[90] (Scheme 26, reaction (1)) exhibit two clearly discernible signals at −305 to −316 ppm (cyclic form) and −69 to −76 ppm (linear imine). ^{15}N NMR spectra proved especially useful in the case of ring—chain tautomer systems of the azide—tetrazole[91,92] type (see Scheme 26, reaction (2)). The signals of the N atoms marked in the Scheme by an asterisk occur at −270 to −280 ppm for cyclic tetrazole forms but shift to −65 to −70 ppm (in $CDCl_3$ or DMSO) in the case of linear azides. When the equilibria are studied in CF_3COOH, the chemical shifts of the signals of these atoms in cyclic forms virtually do not change, while those in azides shift due to protonation to −95 to −160 ppm, and thus they are clearly resolved from the tetrazole signals. Previously,[92] it was concluded that the information content of NMR spectra with respect to the azide—tetrazole tautomerism increases in the sequence ^{1}H < ^{13}C < ^{15}N. It should be noted, however, that these equilibria have been studied successfully without ^{15}N NMR spectroscopy, for example, using H—C correlations.[93]

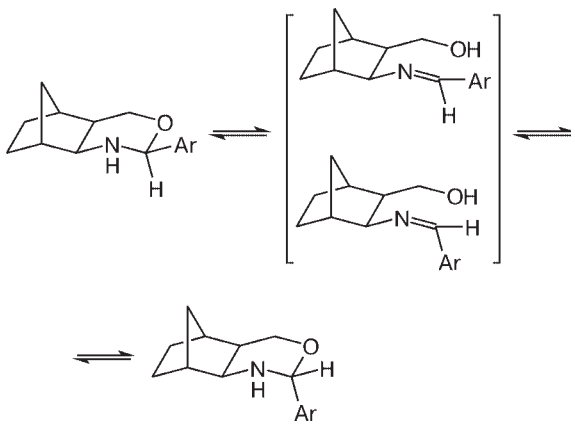
NMR spectroscopy at other nuclei have not virtually been used to study ring—chain systems, although a successful study of keto—enol tautomerism of 2-pyridones by ^{17}O NMR spectroscopy has been reported.[94] The fact that positively charged ^{14}N atoms give rise to somewhat narrower signals (1000—1500 Hz) than neutral atoms (which cannot be detected) made it possible to identify the position of the formal positive charge in mesoionic 1,2,3-triazoles[95] capable of ring—chain tautomerism (see Scheme 26, reaction (3)).

Except for specific cases of this type, many tautomeric systems can be studied successfully by much simpler methods. Thus a study of tautomeric equilibria in four-component systems comprising epimeric cyclic forms and *Z*,*E*-isomers of the open forms[88] (Scheme 27) was based on mere integration of the signals of methine and methylene protons in the case of oxazolidines,[76,78,81,85–87] 1,3-thiazolidines[79,83] (Fig. 1) and perhydrobenzo-1,3- and -3,1-oxazines.[76,77,85–88]

Scheme 26



Scheme 27



More complicated cases that required the use of 2D NMR techniques were encountered in a study of prototropic tautomerism of 1,2-dihydroquinazolin-4(3*H*)-ones,[68] dihydrobenzoazepinethiones, and dihydrobenzodiazepinethiones.[69]

The conformational diversity of 1,2,4-triazepinone forms and the corresponding linear hydrazones has been

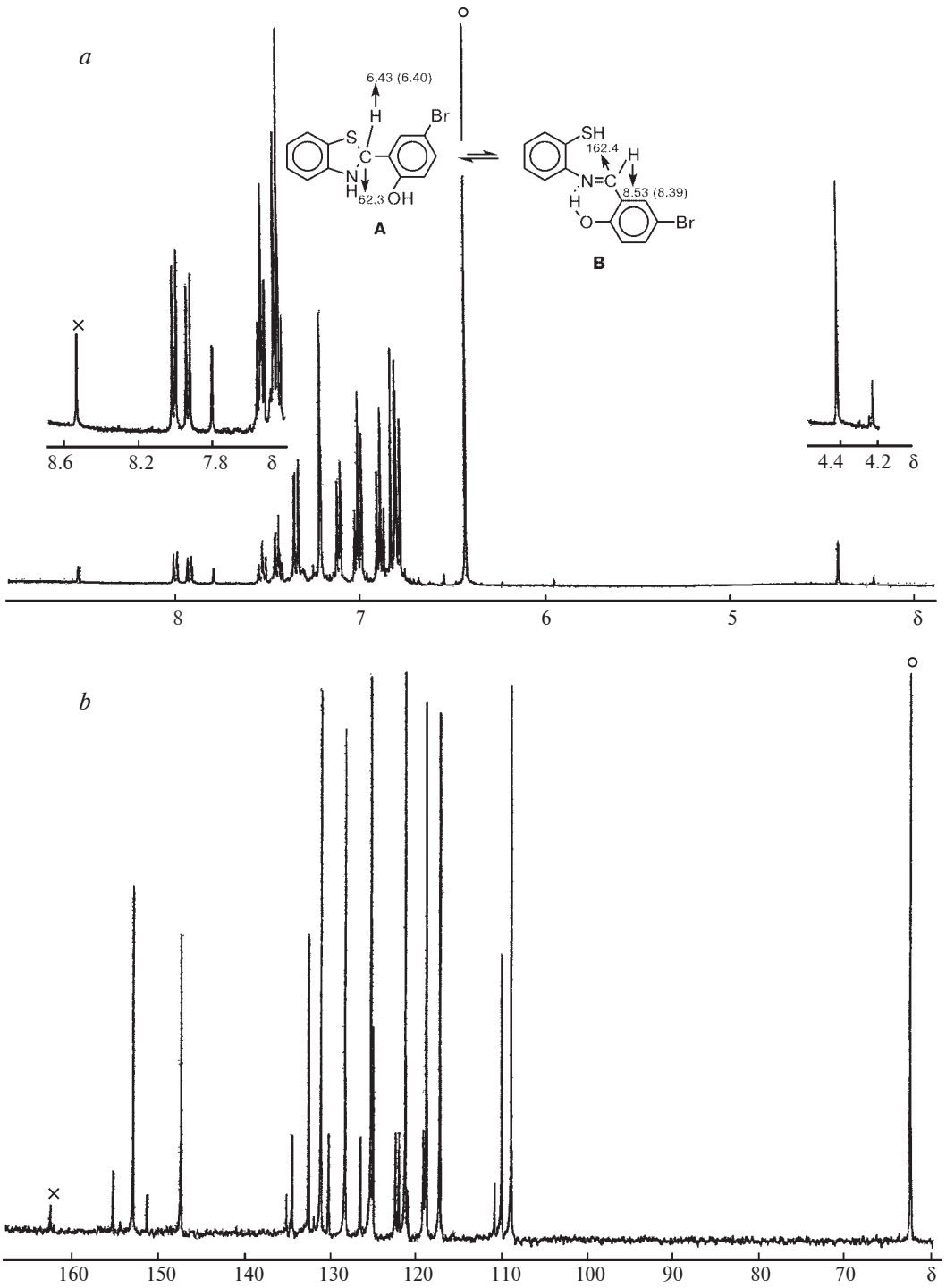


Fig. 1. ^{1}H (*a*) and ^{13}C (*b*) NMR spectra of the benzo-1,3-thiazoline (**A**)—2-mercaptophenylimine (**B**) ring—chain tautomer system[83] (the signals of some protons and ^{13}C atoms for structure **A** are marked by circles, and those for **B** are denoted by crosses; the ^{1}H NMR spectrum was recorded in $CDCl_3$ (the δ values for DMSO-d_6 are given in parentheses), the ^{13}C NMR spectrum was measured in DMSO-d_6).

studied using 1D and 2D NMR techniques at different temperatures.[71,72] Correlation analysis of the ^{13}C chemical shifts in 2-aminobenzoylhydrazones of substituted benzaldehydes allowed investigation of substituents along a heteroatom chain.[70] Important additional information on the dynamic processes in the 1,2,4-triazepinone—hydrazone system was gained by comparison of the thermodynamic parameters[71] found by NMR with the results of

theoretical calculations (MMX, MNDO, AM1, PM3) and X-ray diffraction data.[72]

Mass spectrometry. Investigation objects for organic mass spectrometry are gas-phase ions occurring under high-vacuum conditions, which exclude intermolecular interactions and influence of a solvent. Therefore, studies of tautomeric systems by mass spectrometry serve as an important source of information complementary to NMR spectroscopy. The most obvious way is to compare the fragmentation pathways and the intensities of the characteristic fragment ions formed directly from molecular ions corresponding to different forms of the initial compounds.

Ring—chain systems are convenient investigation objects because the alternative tautomers differ markedly in topology (unlike, for example, prototropic tautomers). The formation of definite characteristic fragments directly from molecular ions (so-called first-level fragmentations, which can be distinguished from subsequent fragmentation stages on the basis of spectra of metastable ions) is often possible for only one form. In the case of prototropic tautomerism, one has to face the fact that the transfer of the H atom either preceding or accompanying fragmentation of the molecular ion distorts the determined ratio of the tautomers.

The absence of interconversion of molecular ions having structures corresponding to different tautomers of the initial substance is a necessary prerequisite for mass-spectroscopic investigation. The accumulated experimental data indicate that this interconversion does not take place in the case of EI ionization (see Ref. 96). In many of the above-mentioned studies,[14,15,18,48] NMR data were supplemented by the results of mass-spectral studies.

It should be emphasized that the results obtained by EI mass spectrometry with direct injection of substances into the ion source do not fully conform to the situation in solutions because substances are evaporated from the solid phase and are ionized within a short period of time, which can be insufficient to attain the gas-phase tautomeric equilibrium. The true equilibrium position can be determined using an injection cylinder in which the vapor of the initial substance can be stored for a rather long period at a required temperature before it get to the ion source.

Yet another important method is GC/MS analysis. Thus ring and chain tautomers have been identified in the GC/MS spectra of mono- and dinitrogen derivatives acetylacetone.[97]

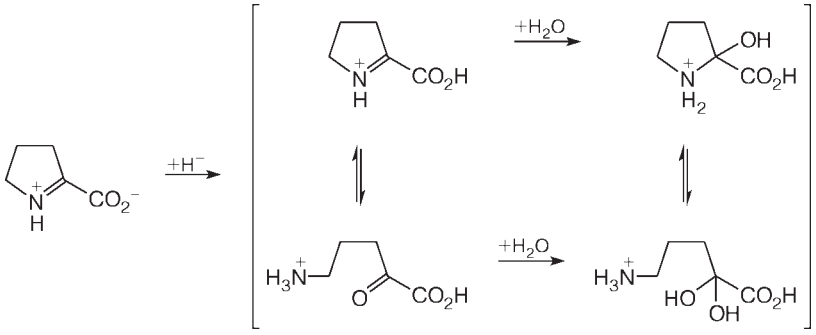
The "soft" ionization methods (for example, fast-atom bombardment (FAB) and electrospray ionization (ESI)) vigorously developing in recent years have a fundamental advantage over classical EI and CI methods in that the substance under study is transferred to the gas phase directly from a solution (ESI) or from the gas—liquid boundary layer (FAB). Moreover, these methods provide the possibility of investigating labile and polar molecules, which markedly extends the range of objects that can be studied in this way. Unfortunately, no systematic research of tautomeric systems by "soft" ionization techniques have been undertaken, despite their great potential illustrated by individual examples.

The ring—chain tautomerism in the product of metabolic degradation of the Tacrolimus immunosuppressing agent (FK-506, $C_{44}H_{69}NO_{12}$, M = 803), used in clinical practice, was discovered and studied by the FAB method. It was shown[98] that ring and chain forms differ in physiological activity.

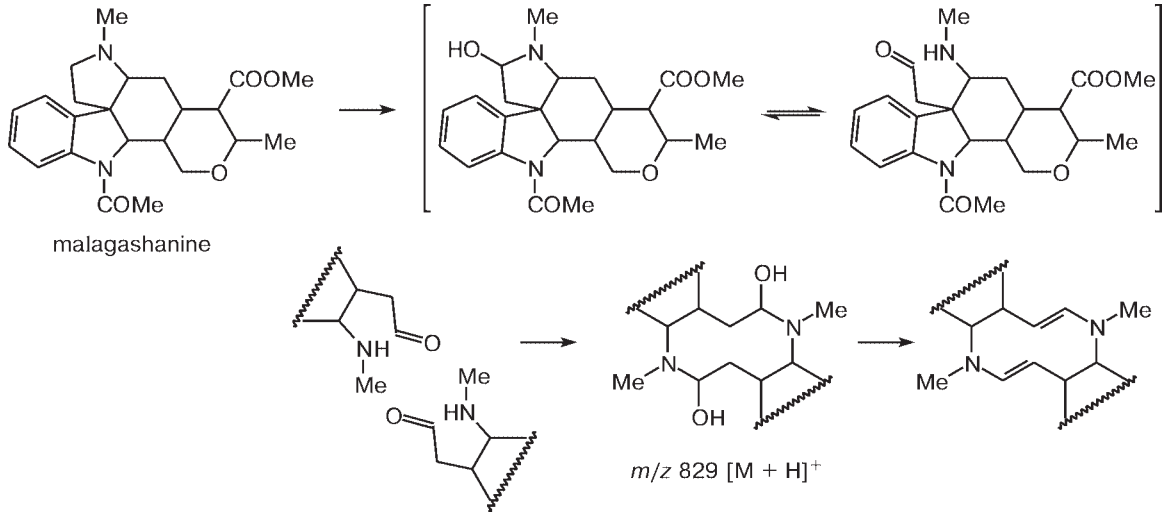
The ^{1}H NMR spectrum of Δ^1-pyrroline-2-carboxylic acid is known to be rather sensitive to the medium pH. The ESI mass spectra of this compound[99] confirmed the presence of at least four tautomeric forms (Scheme 28) including the hydrated analogs of the ring and chain tautomers, which resulted in the revision of the views on the structure of this compound in solutions.[100]

An alkaloid of the indole series, malagashanine ($C_{23}H_{30}N_2O_4$, M = 398), is hydroxylated during metabolism, being thus converted into carbinolamine, susceptible to ring—chain tautomerism. ESI mass spectra demonstrated the presence of ring and chain forms of the metabolite and made it possible to monitor dimerization and cyclodehydration of the linear form[101] (Scheme 29).

Scheme 28



Scheme 29



The examples considered above demonstrate the potential of modern organic mass spectrometry in the study of tautomeric processes. We hope that this review will promote interest in the investigation of tautomeric systems with integrated use of physicochemical methods.

Conclusion

Thus, a classification and methodology for the construction of ring—chain—ring (or ring—ring) tautomeric systems by superposition of ring—chain equilibria within one molecule has been proposed.

Undoubtedly, the range of equilibrium ring transformations will be extended due to the involvement of new heterocyclic structures in the superpositions. Multitautomeric systems, *i.e.*, multicomponent combinations of ring—chain, configurational, and conformational equilibria will serve as investigation objects; the first cases of chain—ring—chain tautomerism, equilibrium ring transformations involving large numbers of ring species, and so on are to be sought after.

Systematic analysis of all sorts of variants of ring transformations will provide information on the relative stabilities of derivatives of various heterocycles. A particular example available even now is represented by the data of Table 4 concerning the tautomeric equilibria in the series of monose derivatives, which can be used to estimate qualitatively the relative stabilities of the piperimidine, hexahydro-1,2,4,5-tetrazine, 1,3,4-thiadiazoline, and thiazolidine rings. A detailed investigation of the dependence of ring transformations on the structural factors and conditions is needed.

The quantitative aspect becomes topical. The available set of empirical rules is of low utility for predicting the existence of one or another tautomeric state. Well-posed calculation techniques are to be developed to gain data on the equilibrium constants and the energy barriers.

The molecular design of the tautomeric interconversions of heterocycles should be applied to synthetic problems, discovery of new chemical transformations, and to the search for valuable, specifically, physiologically active compounds.

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