Recent Developments in the Ring-Chain Tautomerism of 1,3-Heterocycles

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Some important results from the past seven years on the ring-chain tautomerism of 1,3-heterocycles are reviewed, including substituent effects on the tautomeric equilibria and synthetic applications of this phenomenon. The structures and reactivities of numerous five- and six-membered, saturated, *N*-unsubstituted 1,3-X,N-heterocycles (X = O, S, NR) can be characterized by the ring-chain tautomeric equilibria of the 1,3-X,N-heterocycles and the corresponding Schiff bases; this is often exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry. The selectivity of certain transformations can be explained on the basis of the ring-chain tautomeric equilibration of the intermediates, followed by a shift in the equilibrium.

1. Introduction

The reversible intramolecular addition of an XH (X = O, S, NR) group to a C=N double bound to form a cyclic structure is a well-known phenomenon in *N*-unsubstituted 1,3-X,N-heterocycles. This ring-chain tautomeric process influences the reactivity, and therefore the synthetic applicability, of these compounds. According to the Baldwin rules, the ring-closure of **1A** to **1B** is favoured for six-membered heterocycles (*6-endo-trig*), but disfavoured for five-membered ones (*5-endo-trig*) (Scheme 1).[1−3]

Because of the theoretical and practical importance of this process, the ring-chain tautomerism of 1,3-X,N-heterocycles has been thoroughly studied in recent decades. Tautomeric equilibria of type **1A** ⇄ **1B** have been investigated not only in solution, but also in the gas phase by mass spectrometry, and in the solid state by high-resolution NMR spectroscopic methods.

Developments in this field up to 1996 can be followed in earlier reviews,[1−3] but numerous papers discussing various

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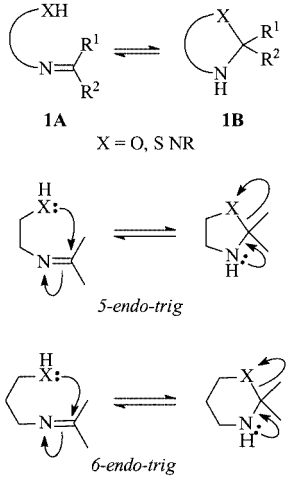
Ferenc Fülöp (left) was born in Szank, Hungary, in 1952. He received his MSc in Chemistry in 1975 and his PhD in 1979, from József Attila University, Szeged, Hungary, under the supervision of Professor Gábor Bernáth. He spent almost two years as a postdoctoral fellow in Turku, Finland, and three months in Bonn, Germany, working in the fields of heterocyclic and structural chemistry. In 1990, he received his DSc from the Hungarian Academy of Sciences in Budapest. After different teaching positions, he was appointed full professor at the Institute of Pharmaceutical Chemistry in Szeged, and since 1998 has been head of the Institute. He has a wide range of research interests in heterocyclic chemistry, including the ring-chain tautomerism of 1,3-oxazines and oxazolidines. His recent activities have focused on the use of amino alcohols and amino acids in enzymatic transformations, asymmetric syntheses and combinatorial chemistry, with a view to the development of pharmacologically active compounds.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.



Scheme 1

aspects of this topic have been published since then. A recent review of the tautomeric interconversion of heterocycles provides a few special details on 1,3-heterocyclic derivatives.[4] The aim of this review is to discuss some important results on the ring-chain tautomerism of 1,3-heterocycles published during the past seven years.

2. 1,3-O,N-Heterocycles

The 1,3-O,N-heterocycles are one group of saturated 1,3-X,N-heterocycles, the ring-chain tautomerism of which has been investigated intensively in recent years. Studies on the ring-chain tautomeric equilibria of 2-aryl-substituted oxazolidines and tetrahydro-1,3-oxazines suggested the conclusion that the proportions of the ring-closed forms strongly depend on the electronic character of the substituent on the aromatic ring. For these compounds, both in solution and in the gas phase, a linear correlation has been found between the log K_X values of the equilibria (K_X = [ring]/[chain]) and the Hammett−Brown parameters σ^+ of the substituents X on the 2-aryl group [Equation (1)]. The value of ρ in Equation (1) proved to be dependent on the temperature and on the nature of the solvent.[1−3]

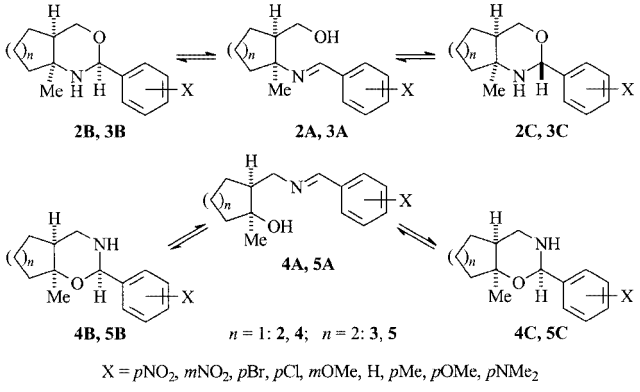
$$\log K_X = \rho\sigma^+ + \log K_{X=H} \quad (1)$$

A relative ring stability constant has been introduced in order to characterize the electronic and steric effects of the substituents at positions 4−6 on the stability of the ring forms. The value of *c* was calculated as the difference between the value of log $K_{X=H}$ for a 2-aryl-1,3-O,N-heterocycle bearing substituents at positions 4−6 and the intercept value (log K_0) for the parent unsubstituted 2-aryl-1,3-O,N-heterocycle ($c = \log K_{X=H} - \log K_0$).[2,3]

The scope and limitations of Equation (1) have been thoroughly studied from the aspect of the influence of the steric and/or electronic effects of the substituents at positions other than 2 on the parameters in Equation (1), and the applicability of Equation (1) in the case of complex tautomeric mixtures containing several types of open and/or cyclic forms.

The proportions of the chain and ring forms of the tautomeric equilibria are usually determined at 300 K by integration of the well-separated O−C*H*−N (ring) and N=C*H*Ar (chain) proton singlets in the ^{1}H NMR spectra. So that the equilibria are reached, the samples are dissolved in an appropriate deuterated solvent and the solutions are allowed to stand at ambient temperature for some period before the ^{1}H NMR spectra are run.

On annelation, a methyl group caused opposite effects on the stabilities of the ring forms in the three-component tautomeric equilibria of 2-aryltetrahydro-1,3-oxazines bearing a *cis*-condensed cyclopentane or cyclohexane ring at positions 4,5 (**2** and **3**) or 5,6 (**4** and **5**) (Scheme 2). In the equilibria of **2** and **3**, the ring-closed tautomers (**B** and **C**) were present in higher proportions than in the corresponding oxazines that did not contain this methyl group, but the opposite was found for **4** and **5** (Table 1). It was presumed that this reverse stabilization effect of the bridgehead methyl group arose from relative destabilization of the open tautomers of **2** and **3**, and from relative destabilization of the cyclic forms of **4** and **5**.[5]



Scheme 2

A double substituent effect was studied in 3-aryl- and 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **6**−**12** and the regioisomeric 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines **13**−**18** derived from Betti base analogue aminonaphthols (Scheme 3). The *major* ring forms in the tautomeric equilibria of **7**−**18** contained the 1,3- or 2,4-diaryl substituents in the *trans* position (**B**). As a consequence of the annelated naphthalene ring, increased ring stability relative to the parent unsubstituted compound was observed for **6B** and for all 1,3-diarylnaphth[1,2-*e*][1,3]oxazines bearing *trans*-diaryl substituents (**7B**−**12B**) (Table 1). The double substituent effects on the tautomeric ratios for the equilibria involving the *trans*-cyclic (**B**) and the open forms (**A**) could be characterized by a Hansch-type equation [Equation (2)] for both regioisomeric naphthoxazines (**7**−**12** and **13**−**18**). The field effect (σ_F) of substituent Y was found to have a significant effect on the equilibria ($\rho_F^{(Y)}$ = 0.33 for **7**−**12** and 0.27 for **13**−**18**), but the resonance effect (σ_R) of Y proved to be insignificant ($\rho_R^{(Y)} \approx 0$) for both sets of compounds.[6]

Table 1. Substituent effects on the ring-chain equilibria of 2-aryltetrahydro-1,3-oxazines in $CDCl_3$; linear regression analysis data according to Equation (1)

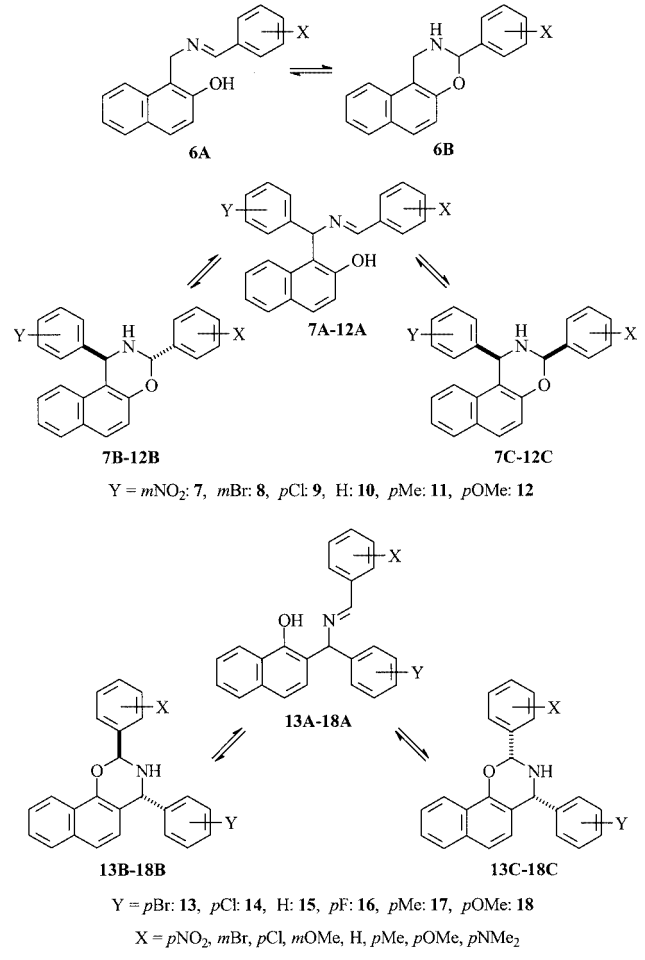
Equilibrium	Number of points	Slope (ρ)	Intercept (log $K_{X=H}$)	Correlation coefficient	c	Ref.
2A ⇄ **2B+C**	9	0.69	1.21	0.994	1.36	[5]
3A ⇄ **3B+C**	8	0.81	1.39	0.986	1.54	[5]
4A ⇄ **4B+C**	9	0.76	−0.07	0.988	0.08	[5]
5A ⇄ **5B+C**	7	0.76	−0.73	0.971	−0.58	[5]
6A ⇄ **6B**	7	0.81	0.52	0.994	0.67	[6a]
7A ⇄ **7B**	7	0.93	0.70	0.995	0.85	[6a]
7A ⇄ **7C**	6	1.04	−0.33	0.999	−0.18	[6a]
8A ⇄ **8B**	7	1.00	0.64	0.985	0.79	[6a]
8A ⇄ **8C**	6	1.01	−0.33	0.985	−0.18	[6a]
9A ⇄ **9B**	7	0.96	0.62	0.993	0.77	[6a]
9A ⇄ **9C**	6	0.81	−0.42	0.979	−0.27	[6a]
10A ⇄ **10B**	7	0.92	0.53	0.988	0.68	[6a]
10A ⇄ **10C**	6	0.98	−0.34	0.983	−0.19	[6a]
11A ⇄ **11B**	7	0.95	0.49	0.989	0.64	[6a]
11A ⇄ **11C**	6	0.95	−0.42	0.993	−0.27	[6a]
12A ⇄ **12B**	7	0.95	0.52	0.991	0.67	[6a]
12A ⇄ **12C**	6	0.94	−0.40	0.986	−0.25	[6a]
13A ⇄ **13B**	7	0.93	−0.18	0.977	−0.03	[6b]
13A ⇄ **13C**	7	0.91	−0.41	0.988	−0.26	[6b]
14A ⇄ **14B**	7	0.93	−0.20	0.981	−0.05	[6b]
14A ⇄ **14C**	7	0.91	−0.39	0.991	−0.24	[6b]
15A ⇄ **15B**	7	0.92	−0.27	0.981	−0.12	[6b]
15A ⇄ **15C**	7	0.90	−0.40	0.994	−0.25	[6b]
16A ⇄ **16B**	7	0.83	−0.20	0.941	−0.05	[6b]
16A ⇄ **16C**	7	0.79	−0.34	0.954	−0.19	[6b]
17A ⇄ **17B**	7	0.97	−0.33	0.983	−0.18	[6b]
17A ⇄ **17C**	7	1.03	−0.46	0.965	−0.31	[6b]
18A ⇄ **18B**	7	0.92	−0.26	0.991	−0.11	[6b]
18A ⇄ **18C**	7	0.86	−0.36	0.994	−0.21	[6b]
19A ⇄ **19B+C**	9	0.67	−0.48	0.991	−0.33	[7]
21A ⇄ **21D**	7	0.72	−1.32	0.983	−1.17	[8]
21A ⇄ **21E**	7	0.74	−0.22	0.986	−0.07	[8]
22A ⇄ **22D**	7	0.75	−0.05	0.968	0.10	[8]
22A ⇄ **22E**	7	0.75	−0.68	0.976	−0.53	[8]
26A ⇄ **26B**	6	0.68	0.36	0.995	0.51	[11b]
26B ⇄ **26C**	6	0.69	0.35	0.992	0.50	[11b]
27A ⇄ **27B**[a]	–	–	0.09	–	0.24	[11b]
27B ⇄ **27C**[a]	–	–	−0.78	–	−0.68	[11b]
28A ⇄ **28B**	6	0.65	0.80	0.999	0.95	[11b]
28B ⇄ **28C**	6	0.52	1.19	0.993	1.34	[11b]
29A ⇄ **29B**[a]	–	–	1.15	–	1.30	[11b]
29B ⇄ **29C**[a]	–	–	−1.32	–	−1.17	[11b]

[a] For the equilibria in $(CD_3)_2SO$.

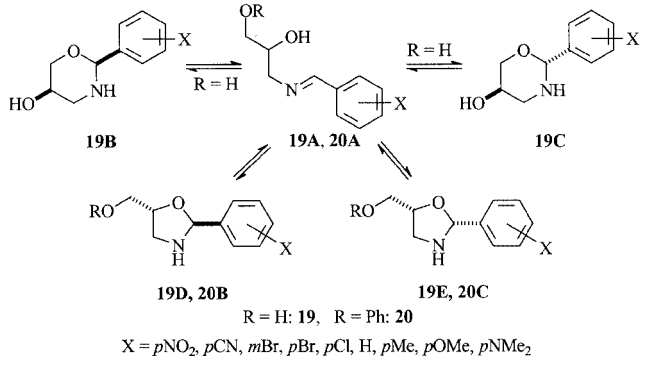
$$\log K_X = \rho^{(X)}\,\sigma^{+(X)} + \rho_F^{(Y)}\,\sigma_F^{(Y)} + \rho_R^{(Y)}\,\sigma_R^{(Y)} + k \qquad (2)$$

The ring-chain tautomerism of the Schiff bases (**19A**) containing 1,2- and 1,3-amino alcohol moieties resulted in five-component tautomeric mixtures containing C-2-epimeric 2-aryltetrahydro-1,3-oxazines (**19B** and **19C**) and 2-aryloxazolidines (**19D** and **19E**) (Scheme 4). The proportion of the oxazine forms (**B** and **C**) was high enough for the C-2 epimers to be distinguished by direct NMR spectroscopic methods in the five-component tautomeric mixture. The characteristic 2-H proton lines of the minor oxazolidine tautomers (**19D** and **19E**) could be identified only by comparison with the NMR spectroscopic data for the three-component equilibria of **20**. The equilibria of **19A**−**E** proved that, when two types of ring closure are possible in a ring-chain tautomeric process, the favoured *6-endo-trig* route does not exclude ring closure by the disfavoured *5-endo-trig* route. The ratios of the two types of ring-closed forms in the equilibria of **19** could be characterized by Equation (1) (Tables 1 and 2).[7]

Both single and double cyclizations occurred in the condensations of *cis*- and *trans*-aminocyclohexanediols **25** and **26** with equivalent amounts of aromatic aldehydes to give multicomponent tautomeric mixtures containing monocyclized ring forms of oxazolidine (**B** and **C**) and tetrahydro-1,3-oxazine (**D** and **E**), product types **21** and **22**, together with the ring-open tautomers **21A** and **22A**, and 7,11-dioxa-9-azatricyclo[7.2.1.$0^{1,6}$]dodecane diastereomers **23** and **24** (Scheme 5). The tautomeric ratios were found to be characterized by Equation (1) (Tables 1 and 2) and influenced by the stereochemistry of the starting amino alcohol. For the equilibria derived from the *cis*-amino diol, **21E** was the



Scheme 3



Scheme 4

major monocyclized tautomer and **23D** the *major* tricycle. For the *trans*-amino diol derived equilibria, however, **22D** and **24B** proved to be the corresponding *major* components. The unusual formation of the tricycles **23** and **24** was explained in terms of aldehyde transfer reactions between the Schiff bases **21A** or **22A** and the *major* monocyclic forms **21E** or 23**D**.[8]

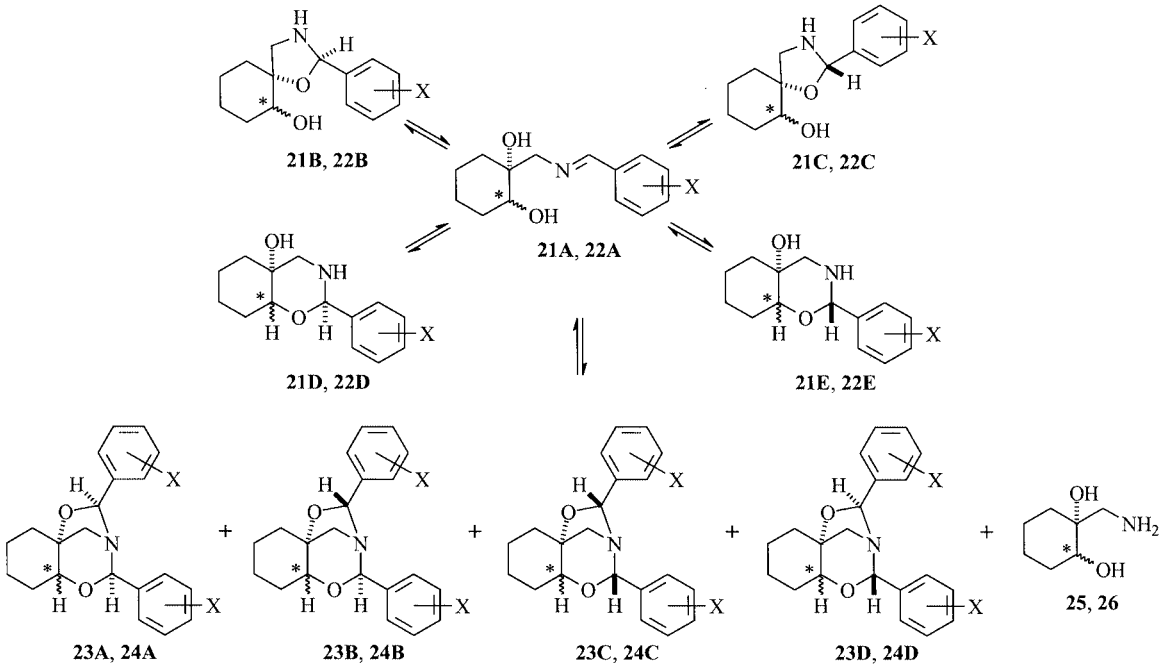
When the 1,2-amino diol moieties in the Schiff base form contained different substituents, complex tautomeric mixtures containing C-2 epimers of regioisomeric oxazolidine forms were obtained. Such ring-chain tautomeric processes have been thoroughly investigated in the case of 2-amino-1-phenyl-1,3-propanediol (phenylserinol) derivatives.[9,10] In the equilibria of (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol derivatives **27** in $(CD_3)_2SO$, only the *major* ring-closed tautomers **27D** and **27E** could be distinguished by NMR analysis; traces of the other ring forms **27B** and **27C** could be seen only in cases of some strongly electron-withdrawing 2-aryl substituents.[9] In the ring-chain tautomeric equilibria of the compounds derived from (1*S*,2*S*)- and (1*R**,2*S**)-2-amino-1-phenyl-1,3-propanediol **28** and **29**, the proportions of the ring forms in $CDCl_3$ allowed unequivocal identification of all four cyclic tautomers **B**−**E** by NMR methods (Scheme 6). The tautomeric ratios at equilibria were found to follow Equation (1) (Table 2). The relative stabilities of the isomeric ring forms were strongly affected by the relative configurations of the substituted carbon atoms and the steric interactions of the substituents in the cyclic tautomers.[10]

In the case of 1,3-O,N-heterocycles derived from primary diamino diols and 2 equiv. of aldehydes, two-step ring-chain tautomeric equilibria are possible. Compounds **30**−**33**, obtained from the *threo* and *erythro* isomers of 1,4-diamino-2,3-butanediol and 2,3-diamino-1,4-butanediol, proved to participate in multicomponent tautomeric equilibria involving 1,3-oxazine (**B**) and dioxadiazadecalin (**C**) tautomeric forms, as well as the Schiff bases (**A**) (Scheme 7). On addition of the β-hydroxy groups to the C=N bonds, oxazolidine derivatives were also formed as *minor* cyclic tautomers (< 10%). Both consecutive ring-closures to give 1,3-oxazines were stereoselective, yielding the mono- and bicyclic forms **B** and **C** as the main diastereomers, with the configurations depicted in Scheme 7. Each equilibrium of **A** ⇄ **B** type and of **B** ⇄ **C** type for the *cis*-fused compounds **30** and **32** in $CDCl_3$ or in $(CD_3)_2SO$ could be characterized by Equation (1), but the values of log $K_{X=H}$ could also be determined for the equilibria of *trans*-fused dioxadiazadecalins **31** and **33**. In contrast to the cyclohexane-condensed 2-aryltetrahydro-1,3-oxazines, in which the *trans*-fused rings increased the stability of the ring-closed tautomers to a greater extent than the *cis* ring junction, the values of *c* indicated more stability for the *cis*-fused dioxadiazadecalins **30C** and **32C** than for their *trans*-fused counterparts **31C** and **33C**.[11]

Substituent effects on the stabilities of the ring and chain forms in a tautomeric equilibrium of 2-aryl-substituted oxazolidines and tetrahydro-1,3-oxazines have been studied with the aid of ^{13}C NMR spectroscopy and PM3 charge density and energy calculations. The reaction energies of the isodesmic reactions showed that electron-donating substituents stabilized both the chain and the ring tautomers, but that the effect on the stability of the chain form was stronger than that on the stability of the ring form. It was concluded that the substituent dependence of the relative stability of the ring and chain tautomers in equilibrium was governed by several different electronic effects. At least intramolecular hydrogen bonding between the imine nitrogen

Table 2. Substituent effects on the ring-chain equilibria of 2-aryloxazolidines in $CDCl_3$; linear regression analysis data according to Equation (1)

Equilibrium	Number of points	Slope (ρ)	Intercept (log $K_{X=H}$)	Correlation coefficient	c	Ref.
19A ⇄ **19D+E**	9	0.62	−1.03	0.990	0.07	[7]
20A ⇄ **20B+C**	9	0.55	−0.80	0.992	0.30	[7]
21A ⇄ **21B**	7	0.65	−1.19	0.988	−0.09	[8]
21A ⇄ **21C**	7	0.62	−1.04	0.999	0.06	[8]
22A ⇄ **22B**	7	0.63	−0.27	0.988	0.83	[8]
22A ⇄ **22C**	7	0.64	−0.50	0.995	0.60	[8]
28A ⇄ **28B**	10	0.51	−0.33	0.985	0.77	[10]
28A ⇄ **28C**	10	0.61	−0.01	0.996	1.09	[10]
28A ⇄ **28D**	10	0.50	0.15	0.983	1.25	[10]
28A ⇄ **28E**	10	0.64	−0.69	0.990	0.41	[10]
29A ⇄ **29B**	10	0.55	−0.63	0.995	0.47	[10]
29A ⇄ **29C**	10	0.48	−0.83	0.983	0.27	[10]
29A ⇄ **29D**	10	0.50	−0.84	0.982	0.26	[10]
29A ⇄ **29E**	10	0.55	−0.60	0.997	0.50	[10]

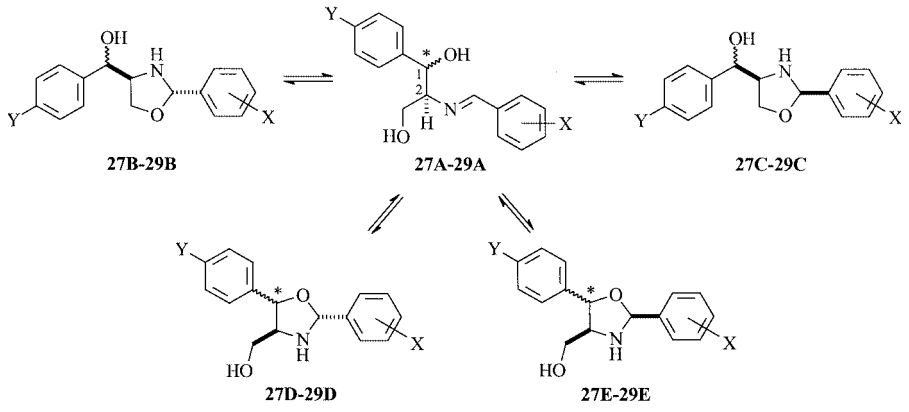


Scheme 5

atom and the hydroxy group and polarization of the C=N bond were found to contribute in the chain form. The increase in stability of the ring form caused by the presence of electron-donating substituents was explained in terms of stereoelectronic and electrostatic effects.[12]

The C-2 epimerization reactions of spirooxazolidines obtained from amino polyols with alicyclic ketones can be explained in terms of ring-chain tautomerism. Despite the absence of a detectable amount of the open tautomer **34A** in the NMR spectra, the solvent-dependent [$(CD_3)_2SO$ and $CDCl_3$] *cis*/*trans* ratios of the spirooxazolidines **34B** and **34C** prepared from 1,1,1-tris(hydroxymethyl)aminomethane and 2-, 3- or 4-substituted cyclohexanones could be explained by the tautomeric interconversion of the cyclic forms (Scheme 8).[13]

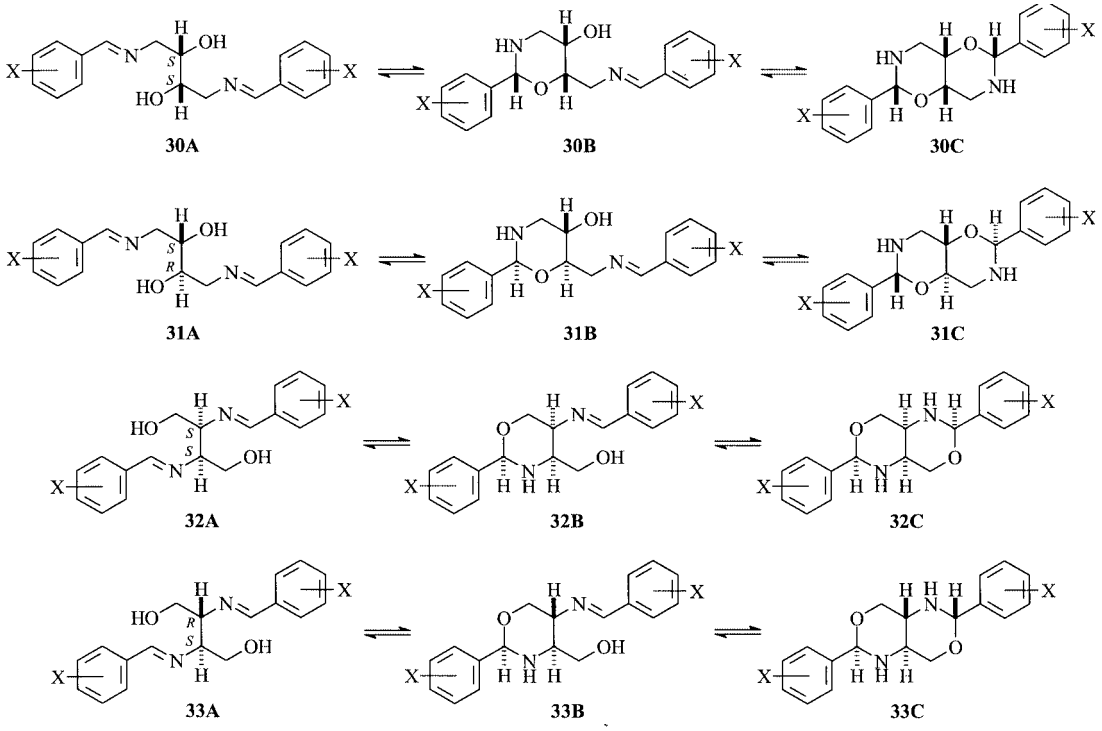
For the dispirooxazolidines **35** and **36**, the C-2 epimerization process through the undetectable open tautomers is even more complicated, since not only the *cis*-*trans* geometry of the heteroatoms attached to the cyclohexane ring, but also the relative configurations of the asymmetric centres in the oxazolidines are involved (Scheme 9). The proportions of the tautomers **A**−**D** in the equilibria for **35** and **36**, determined by NMR methods, exhibited a considerable solvent dependence, but in each solvent



(*1S,2S*), Y = NO_2: **27**; (*1S,2S*), Y = H: **28**; (*1R*,2S**), Y = H: **29**

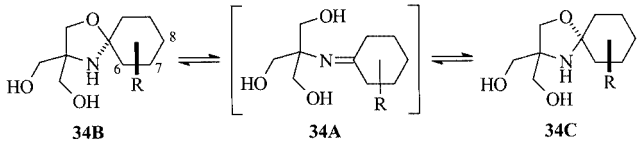
X = *p*NO_2, *m*NO_2, *m*Br, *p*Cl, *p*F, H, *p*Me, *p*OMe, *p*NMe_2

Scheme 6



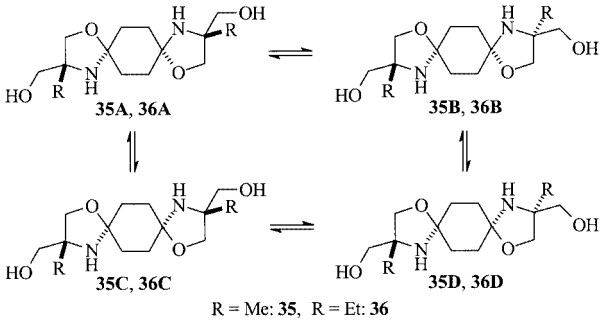
X = *p*NO_2, *p*Br, H, *p*Me, *p*OMe, *p*NMe_2

Scheme 7



R = 6-Me, 7-Me, 8-Me, 8-*t*Bu

Scheme 8



R = Me: **35**, R = Et: **36**

Scheme 9

[(CD_3)$_2$SO, $CDCl_3$ and D_2O] the *trans-unlike* diastereomer (**B**) proved to be the *major* component.[13]

When (1*S*,2*S*)-2-amino-1-phenyl- and 1-(*p*-nitrophenyl)-1,3-propanediol were treated with terephthalaldehyde, the

condensation products **37** and **38** proved to be complex tautomeric mixtures. The two C=N bonds allowed consecutive ring closures, and because of the two non-equivalent hydroxy groups, the formation of diastereomers of two regioisomeric oxazolidine ring forms was possible (Scheme 10). NMR analysis revealed that the cyclizations occurred regioselectively: only the 4,5-disubstituted oxazolidines were detectable. The equilibria of **37** and **38** in $(CD_3)_2SO$ involved only diimine (**A**) and double oxazolidine (**D**−**F**) ring forms, the open diimine form being the *major* component. Among the cyclic tautomers, oxazolidines of type **E** were found to be the dominant diastereomers.[14] More complicated tautomeric mixtures **39** and **40** were formed from methyl- and ethylserinols with terephthalaldehyde, in which the number of possible diastereomers was increased by the relative configurations of C-2 and C-4 in the cyclic tautomers (Scheme 10). The methyl and ethyl substituents exerted significant effects on the tautomeric ratios in the equilibria of **39** and **40** in $(CD_3)_2SO$; in **39** and **40**, the relative proportions of the components were **B**,**C** > **A** > **D-I** and **D-I** > **B**,**C** > **A**, respectively.[14]

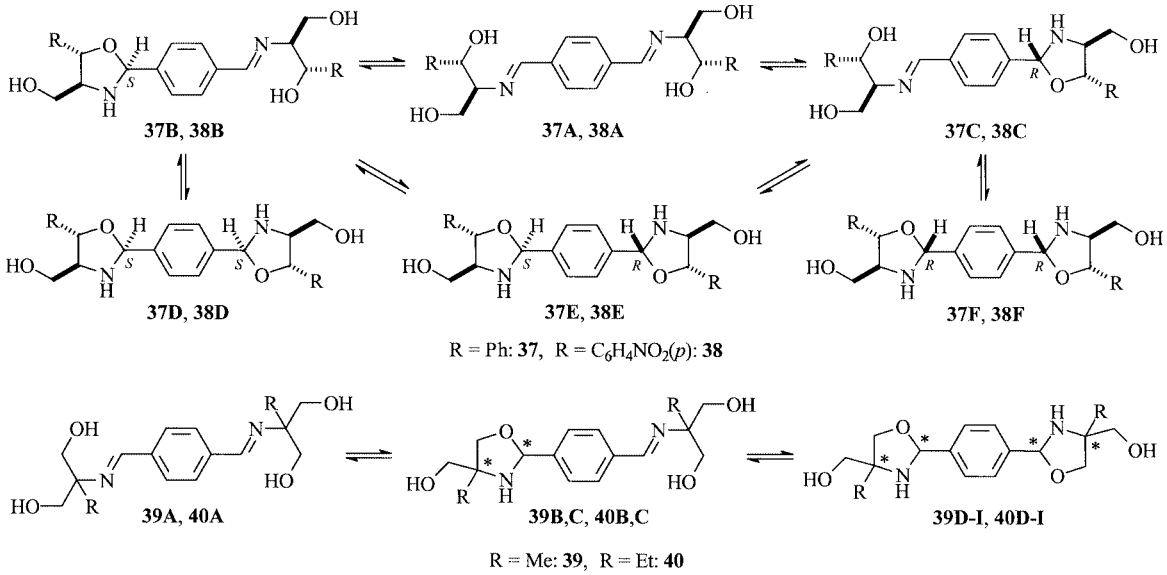
Highly diastereoselective ring closures were found in the ring-chain tautomeric equilibria of dioxadiazadecalin macrocycles **41** and **42** (Scheme 11), as in the analogous bicyclic derivatives **30**−**33**. The equilibria of **41** and **42** at 298 K were shifted towards the double ring-closed tautomers (**C**) both in $CDCl_3$ and in $(CD_3)_2SO$ solution. Heating of the solutions caused no change in the tautomeric ratios for **41** in $CDCl_3$ or for **42** in either solvent, but elevated temperatures produced increases in the proportions of the open and the monocyclic tautomers (**A** and **B**) in the equilibria of **41** in $(CD_3)_2SO$. The ring-chain tautomerism exerted a strong influence on the cavity size and therefore on the metal ion complexation processes of **41**. Ni^{2+}, Cd^{2+} and Pb^{2+} were complexed by **41** in different tautomeric modes, depending on the size of the cation. The metal ion complexation properties of **42** were not influenced by the ring-chain tautomerism. The analogous macrocycles **43** and **44** proved to exist as tautomeric mixtures in $CDCl_3/CD_3OD$ and in $(CD_3)_2SO$, without apparent preference for any tautomer.[15]

In the reaction between tris(hydroxymethyl)aminomethane and methylglyoxal, two regioisomeric Schiff bases (**45Aa** and **45Ab**) and a complex tautomeric mixture were formed. The cyclizations of the open forms (**45Aa**,**b**) occurred either through *endo-trig* or through *exo-trig* ring closures to yield regioisomeric oxazolidine (**45Ba**,**b**) and dihydro-1,4-oxazine tautomeric forms (**45Ca**,**b**). The consecutive cyclizations afforded methyl-substituted regioisomers of 3,6-dioxa-8-azabicyclo[3.2.1]octanes (**45Da**,**b** and **45Ea**,**b**), the structures of which were characterized by their ^1H and ^{13}C NMR parameters (Scheme 12).[16]

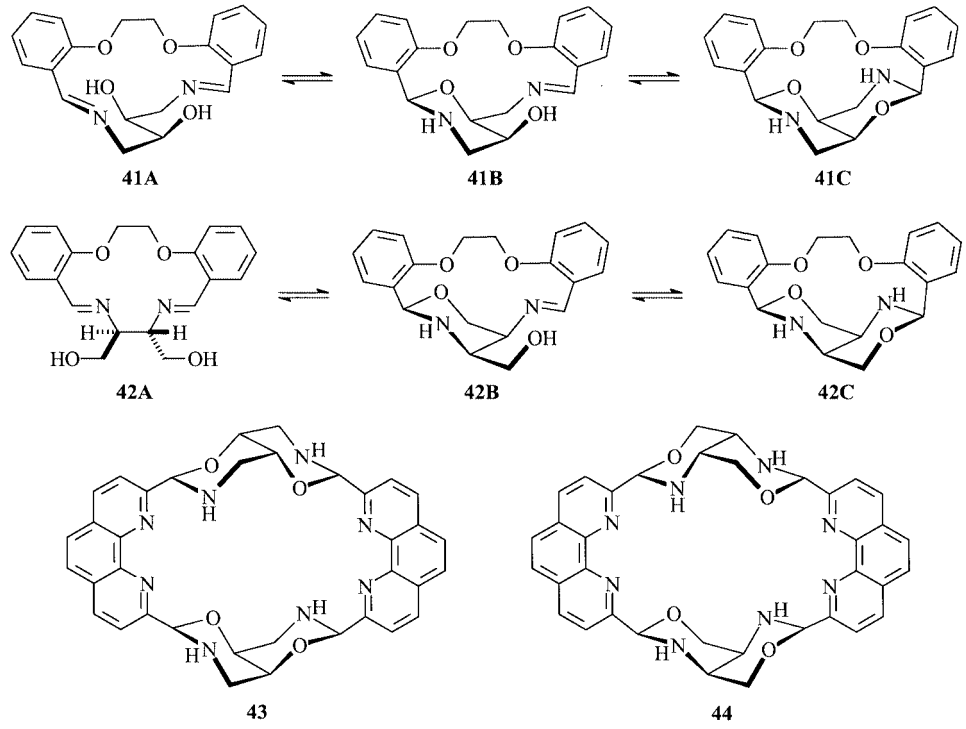
There are numerous examples of ring-chain tautomerism among 1,3-O,N-heterocyclic hydroxylamine derivatives, in which the cyclic tautomer is formed as a result of the intramolecular addition of a hydroxy group to the C=N double bond of the corresponding nitrone.[1−3] Peracid oxidation of 2,3,5-substituted isoxazolidines produced equilibrium mixtures of nitrones and their cyclic hydroxylamine tautomers of tetrahydro-1,3-oxazine type (**46**). The tautomeric ratios for **46** were found to depend strongly on the substituents. The nitrone/hydroxylamine equilibrium could be shifted by acetylation, which gave the *O*-acetyl derivatives (**47**) of the cyclic tautomers (Scheme 13).[17]

3. 1,3-S,N-Heterocycles

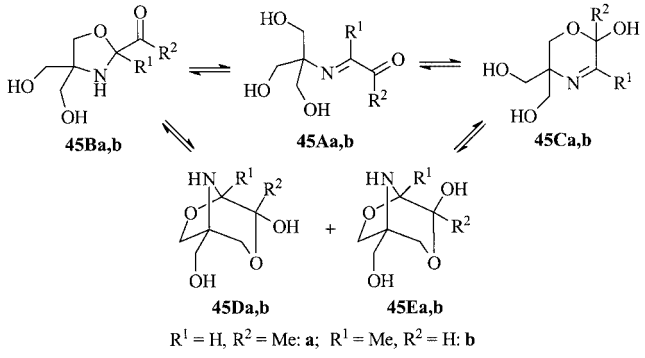
The ring-chain tautomeric character of thiazolidines and tetrahydro-1,3-thiazines can usually be deduced only from indirect evidence, such as the formation of metal chelates,



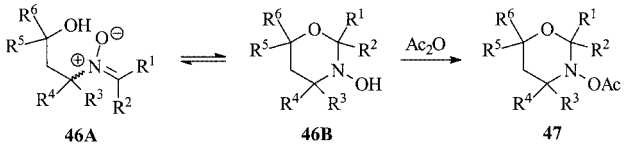
Scheme 10



Scheme 11



Scheme 12

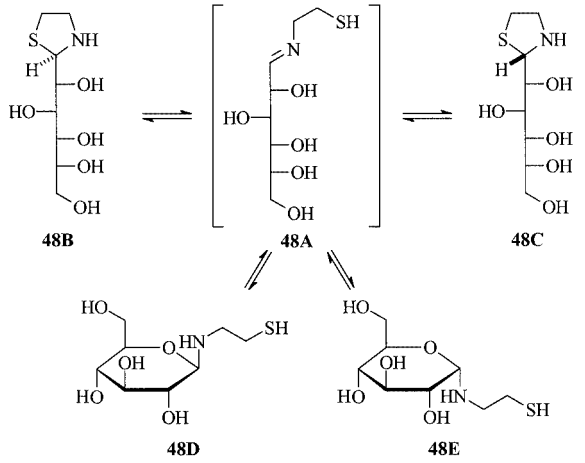


Scheme 13

hydrolysis, C-2 epimerization and carbon-transfer reactions. The tautomeric equilibria of these compounds are completely shifted towards the ring-closed forms; open tautomers have been detected only in special cases.[1–3] There are only two examples from recent years that concern the ring-chain tautomerism of a 1,3-S,N-heterocyclic system.

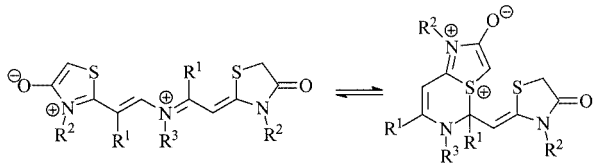
As with other thiazolidine derivatives, no open forms could be detected in the condensation products obtained from 2-aminoethanethiol and aldoses (arabinose, rhamnose, glucose, mannose and galactose). Depending on the competing addition of SH and OH groups, both *endo-trig* and *exo-trig* ring closures of the open forms (**A**) are possible, yielding diastereomeric cyclic forms of thiazolidine (**B** and **C**) or pyranose (**D** and **E**) types (Scheme 14). The tautomeric equilibria in $(CD_3)_2SO$ involved only the C-2 epimeric thiazolidine tautomers (**B** and **C**), with the exception of the glucose derivative **48**, in which a considerable proportion of the β-pyranose ring form (**D**) also participated in the equilibrium. In the oxa analogues, prepared from 2-aminoethanol and aldoses, the tautomeric equilibria in $(CD_3)_2SO$ were completely shifted towards the pyranose forms.[20]

In the reactions between 3-substituted 3-aminothioacrylanilides and ethyl bromoacetate, *N*-bridged 1,3-thiazolium-



Scheme 14

4-olates **49** were synthesized. The deep-blue compounds **49** displayed an unusual ring-chain tautomeric equilibrium, in which the interconversion of the open and cyclic forms was accomplished by valence tautomerism instead of proton migration (Scheme 15). The tautomeric ratios for **49** were found to be dependent on the solvent and influenced by the pH.[21]



49A **49B**

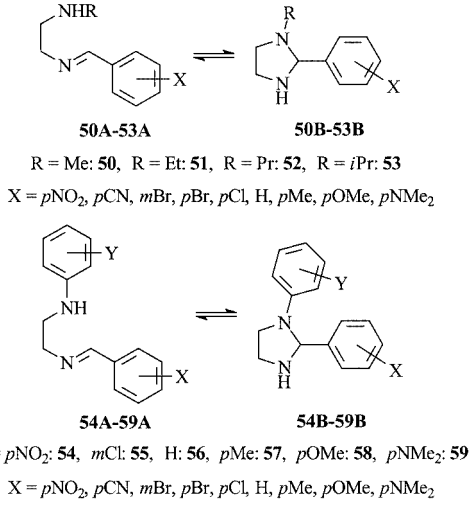
R^1 = Me, Ph; R^2, R^3 = Ph, $C_6H_4Me(p)$

Scheme 15

4. 1,3-N,N-Heterocycles

A large number of examples of quantitative investigations of the ring-chain tautomerism in 1,3-N,N-heterocyclic compounds have emerged in recent years. A large proportion of these studies were aimed at extension of the applicability of Equation (1), well known to characterize the equilibria of 2-aryl-1,3-O,N-heterocycles, to the ring-chain tautomerism of the corresponding diaza analogues.

1-Alkyl-substituted 2-arylimidazolidines **50**−**53** proved to be ring-chain tautomeric mixtures, the equilibria of which in $CDCl_3$ could be described by Equation (1) (Scheme 16). The tautomeric ratios and the parameters in Equation (1) were strongly influenced by the steric effect of substituent R on the nitrogen atom at position 1. The proportions of the open forms (**A**) and the slopes (ρ) of the regression lines for the equilibria **50**−**53** according to Equation (1) increased with increasing bulkiness of substituent R (Table 3). In the tautomeric equilibria of 1,2-diarylimidazolidines **54**−**59**, the electronic effect of the aryl group at position 2 on the ring-chain ratios could also be characterized by Equation (1). The aryl substituent at position 1 similarly influenced the slopes of the regression lines according to Equation (1), a more strongly electron-donating substituent Y producing a higher value of ρ. The aryl groups on the nitrogen atom considerably decreased the proportions of the cyclic tautomers in the equilibria. To express the effect of the substituted nitrogen atom at position 1 on the stability of the ring-closed tautomeric form, a heteroatom effect parameter (c_h) was introduced, referring to the stability difference of the corresponding 1,3-N,N- and -O,N-heterocycles ($c_h = \log K^{N,N}_{X=H} - \log K^{O,N}_{X=H}$). For five-membered 1,3-Y,N-heterocycles, the stability of the ring form increases in the following heteroatom (Y) sequence: O < N*i*Pr < NPh < N*n*Pr ≈ NEt < NMe < S.[22]



50A-53A **50B-53B**

R = Me: **50**, R = Et: **51**, R = Pr: **52**, R = *i*Pr: **53**

X = *p*NO_2, *p*CN, *m*Br, *p*Br, *p*Cl, H, *p*Me, *p*OMe, *p*NMe_2

54A-59A **54B-59B**

Y = *p*NO_2: **54**, *m*Cl: **55**, H: **56**, *p*Me: **57**, *p*OMe: **58**, *p*NMe_2: **59**

X = *p*NO_2, *p*CN, *m*Br, *p*Br, *p*Cl, H, *p*Me, *p*OMe, *p*NMe_2

Scheme 16

The mass spectra of **50**−**53** and **56** showed that these compounds also participate in ring-chain tautomeric equilibria in the gas phase. The tautomeric ratios proved to be dependent on the electronic effect of substituent X on the 2-phenyl ring, but more ring forms were found for electron-donating substituents X than for electron-withdrawing ones, which is the opposite of the situation for these equilibria in $CDCl_3$. The unusual behaviour of **50**−**53** and **56** in the gas phase was explained in terms of the differences in fragmentation efficiency between chain forms with different substituents X on the phenyl group.[23]

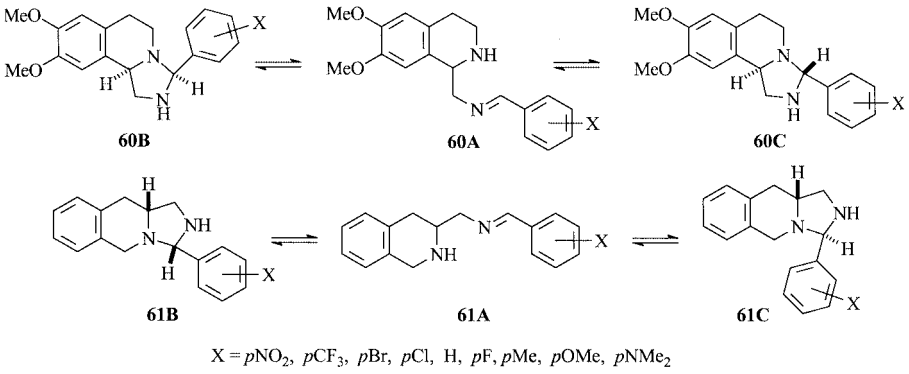
Isoquinoline-condensed, aryl-substituted imidazolidine derivatives **60** and **61** also proved to be of a ring-chain tautomeric character in $CDCl_3$ (Scheme 17). Their equilibria, involving diastereomeric ring forms (**B** and **C**) besides the open tautomer (**A**), could be described by Equation (1). The relative configuration of the cyclic tautomer exerts only a small influence on the values of ρ and the intercept (log $K_{X=H}$) for the equilibria of angular compounds (**60**), whereas considerable differences in the values of ρ and log $K_{X=H}$ were found for the equilibria of the *major* and *minor* ring forms of the linear imidazoisoquinolines **61**. For **61**, X-substituent-dependent hyperconjugative interactions were observed between the nitrogen lone pair and the C-3-attached antibonding orbitals. This anomeric effect is presumed to play an important role in the ring-chain tautomeric equilibria of conformationally inflexible 2-aryl-1,3-N,N-heterocycles.[24]

Both the substituent on the nitrogen atom and the presence of an annelated ring had marked effects on the ring-chain tautomeric processes of 2-arylhexahydropyrimidines. No open tautomer could be detected in $CDCl_3$ solutions of the *N*-methyl-substituted derivatives **63** and **66**. The *N*-unsubstituted, the *N*-isopropyl-substituted and the *N*-phenyl-substituted compounds **62**, **64**, **65**, **67** and **68** proved to be tautomeric mixtures (Scheme 18), the equilibria of which could be described by Equation (1).[25,26] As with the analogous 1,3-O,N-heterocycles, the presence of a condensed benzene ring increased the stability of the ring form. To characterize the stabilizing effects of the annelated ring, a substituent effect parameter (c_s) was calculated as the differ-

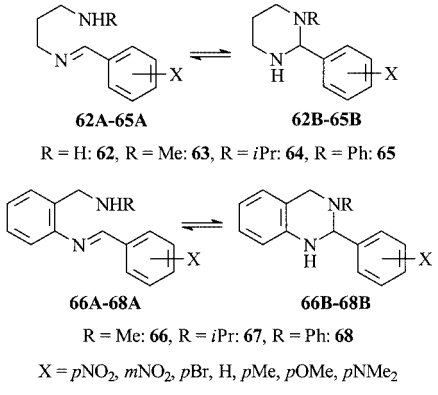
Table 3. Substituent effects on the ring-chain equilibria of 2-arylimidazolidines in $CDCl_3$; linear regression analysis data according to Equation (1)

Equilibrium	Number of points	Slope (ρ)	Intercept (log $K_{X=H}$)	Correlation coefficient	c_h	Ref.
50A ⇄ **50B**	9	0.53	0.75	0.990	1.85	[22a]
50A ⇄ **50B**[a]	8	0.61	0.84	0.970	–	[22a]
51A ⇄ **51B**	9	0.59	0.25	0.984	1.35	[22a]
52A ⇄ **52B**	9	0.62	0.25	0.989	1.35	[22a]
53A ⇄ **53B**	8	0.82	−0.97	0.973	0.13	[22a]
54A ⇄ **54B**	9	0.49	−0.27	0.991	0.83	[22b]
55A ⇄ **55B**	9	0.58	−0.25	0.999	0.85	[22b]
56A ⇄ **56B**	9	0.67	−0.20	0.997	0.90	[22a]
56A ⇄ **56B**[a]	9	0.72	−0.48	0.993	–	[22a]
57A ⇄ **57B**	9	0.67	−0.15	0.997	0.95	[22b]
58A ⇄ **58B**	8	0.68	−0.20	0.989	0.90	[22b]
59A ⇄ **59B**	7	0.77	−0.20	0.996	0.90	[22b]
60A ⇄ **60B**	9	0.56	0.44	0.961	–	[24]
60A ⇄ **60C**	9	0.60	0.72	0.903	–	[24]
61A ⇄ **61B**	9	0.44	1.02	0.982	–	[24]
61A ⇄ **61C**	9	0.65	−0.22	0.985	–	[24]

[a] For the equilibria in $(CD_3)_2SO$.



Scheme 17



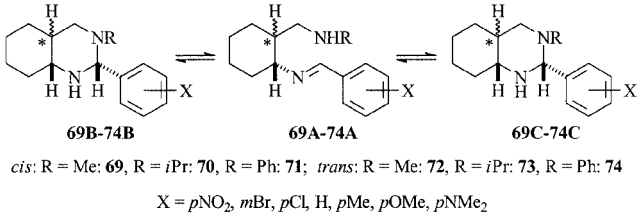
Scheme 18

ence in the intercepts for the given 4-, 5- and 6-substituted 2-aryl-1,3-N,N-heterocycle and the corresponding monocyclic 2-aryl-1,3-N,N-heterocycle bearing the same substituent on the nitrogen atom (Table 4). From a comparison of the heteroatom parameters for **62**−**65** and the corresponding 2-aryltetrahydro-1,3-oxazines, the stability of the ring form increases in the following heteroatom (Y) sequence: NPh < N*i*Pr < O < NH < NMe; while for the tetrahydroquinazolines **66**−**68** and the related 2-aryl-3,1-benzoxazines, the sequence of Y is NPh < O < N*i*Pr < NMe.[26]

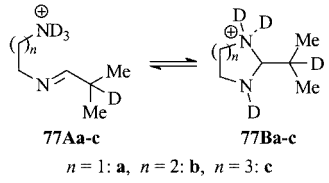
The substituents on the nitrogen atom and the stereochemistry of the ring junction strongly influenced the ring-chain tautomerism of *cis*- and *trans*-2-aryldecahydroquinazolines **69**−**74**. For the methyl-substituted derivatives **69** and **72**, no open-chain tautomeric forms **A** could be detected. The *cis*- and *trans*-3-isopropyl- and *trans*-3-phenyl-substituted compounds **70**, **73** and **74** proved to be three-component ring-chain tautomeric mixtures containing open and C-2-epimeric cyclic forms **B** and **C**. In the case of the *cis*-3-phenyl derivatives **71**, the tautomeric equilibria were shifted towards the open form; cyclic tautomers could be detected only for compounds bearing electron-withdrawing substituents X (Scheme 19). The annelated cyclohexane ring was found to have a stabilizing effect on the ring-closed tautomers: the values of c_s were higher for the *trans* isomers (Table 4). The stabilities of the ring-closed forms of *cis*- and *trans*-2-aryldecahydroquinazolines **69**−**74** and the corre-

Table 4. Substituent effects on the ring-chain equilibria of 2-aryl-substituted hexahydropyrimidines, 1,2,3,4-tetrahydro- and perhydroquinazolines in $CDCl_3$; linear regression analysis data according to Equation (1)

Equilibrium	Number of points	Slope (ρ)	Intercept (log $K_{X=H}$)	Correlation coefficient	c_h	c_s	Ref.
62A ⇄ **62B**	7	0.84	0.93	0.99	1.08	–	[25b]
64A ⇄ **64B**	6	0.77	−1.04	0.997	−0.89	–	[26]
65A ⇄ **65B**	7	0.42	−1.28	0.988	−1.13	–	[26]
67A ⇄ **67B**	7	0.72	1.49	0.978	0.38	2.53	[26]
68A ⇄ **68B**	7	0.93	0.67	0.984	−0.44	1.95	[26]
70A ⇄ **70B**	7	0.51	−0.06	0.994	−0.72	0.98	[27]
73A ⇄ **73B**	7	0.57	0.72	0.957	−0.40	2.00	[27]
73A ⇄ **73C**	6	0.71	−0.43	0.952	0.26	0.85	[27]
74A ⇄ **74B**	7	0.85	−0.59	0.985	−1.71	0.69	[27]
74A ⇄ **74C**	6	1.21	−1.39	0.998	−0.70	−0.11	[27]



Scheme 19



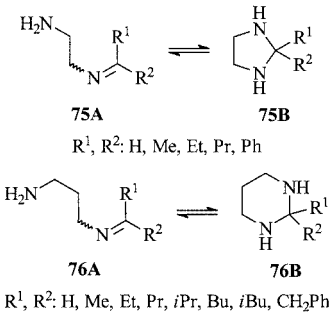
Scheme 21

sponding 2-aryloctahydro-3,1-benzoxazines were found to increase in the following sequence of the heteroatom at position 3: NPh < N*i*Pr < O < NMe.[27]

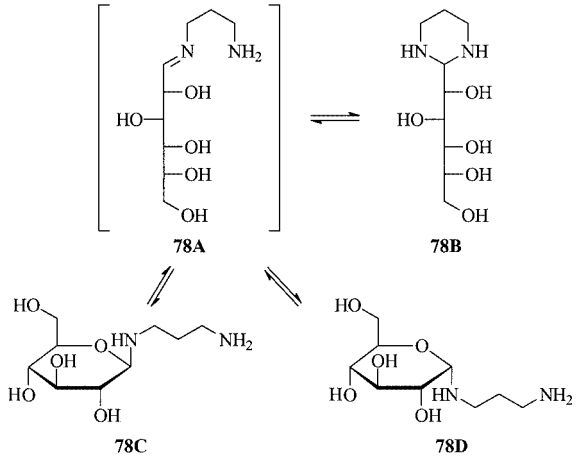
The 1,3-unsubstituted imidazolidines and hexahydropyrimidines bearing non-branched chain alkyl substituents (**75** and **76**: R^1 = Me, Et, Pr, R^2 = H) proved to exist in $CDCl_3$ exclusively as the ring-closed tautomers (**B**). However, 2-isopropyl- (**75** and **76**: R^1 = *i*Pr, R^2 = H) and 2,2-dialkyl-substituted derivatives (**75** and **76**: R^1, R^2 = alkyl) participated in ring-chain tautomeric equilibria (Scheme 20). For the 2-phenyl-substituted imidazolidine (**75**: R^1 = Ph, R^2 = H), the tautomeric equilibrium was totally shifted towards the open tautomer (**A**).[25b,28] The mass spectra of 2,2-dialkyl-substituted imidazolidines (**75**: R^1, R^2 = Me, Et) also pointed to the ring-chain tautomeric character of these compounds in the gas phase.[29]

According to NMR analysis, the deuterated 2-isopropyl-substituted 1,3-N,N-heterocycles **77a**−**c** also formed ring-chain tautomeric mixtures in $(CD_3)_2SO/D_2O$ (Scheme 21). For the five- and six-membered compounds **77a**,**b**, the equilibrium was shifted towards the cyclic tautomer **B**; while for hexahydro-1,3-diazepine **77c** the open form **A** was found to be the predominant tautomer. Free energies, enthalpies and entropies of activation were determined for all three equilibria.[30]

Multicomponent equilibria involving regioisomeric cyclic forms are also known among 1,3-N,N-heterocycles. As with the 2-aminoethanethiol derivatives (e.g., **48**), the condensation products (in the case of glucose: **78**) of 1,3-diaminopropane and aldoses were found to participate in tautomeric equilibria involving the corresponding anomeric pyranose and the hexahydropyrimidine cyclic forms **B**−**D**, the interconversion of which took place via the undetectable open tautomer (**A**) (Scheme 22). Tautomeric ratios were deter-



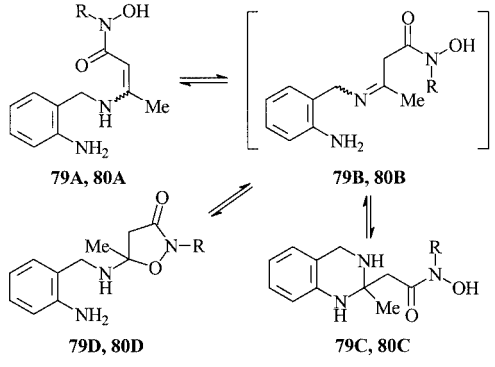
Scheme 20



Scheme 22

mined by ^{13}C NMR spectroscopy. In each equilibrium, the hexahydropyrimidine forms were the main components (50−100%). In the homologous 1,2-diaminoethane derivatives, only the anomeric pyranose forms could be detected in the tautomeric mixtures.[31]

The regioisomeric Schiff-base formation, the imine/enamine and (*Z*)/(*E*) isomerization of the double bond and the competing *exo* or *endo* ring closures of the open tautomer resulted in multicomponent tautomeric mixtures for the compounds **79** and **80** obtained from *N*-phenyl- or *N*-benzyl-substituted 5-hydroxyisoxazolidin-3-one with 2-(aminomethyl)aniline (Scheme 23). Because of the higher nucleophilicity of the benzylamine nitrogen atom, no Schiff bases of aniline type, and probably therefore no anilino-substituted isoxazolidine ring forms, could be detected in the equilibria. According to ^{1}H, ^{13}C and ^{15}N NMR measurements, the equilibria involved (*Z*) and (*E*) isomers of the enamine open forms (**A**) together with the benzylamino-substituted isoxazolidine (**D**) and the tetrahydroquinazoline cyclic forms (**C**), the proportions of which varied, depending on the solvents [$CDCl_3$, $(CD_3)_2SO$ and CD_3CN].[32] The (*Z*) and (*E*) isomers of the corresponding enamine open form were also detected in the ring-chain equilibrium of 2-methyl-2-(morpholinocarbonylmethyl)-1,2,3,4-tetrahydroquinazoline in $(CD_3)_2SO$.[33]

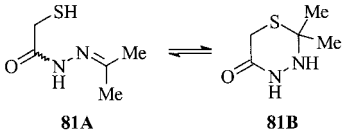


Scheme 23

5. 1,3-Heterocycles with Additional Heteroatoms

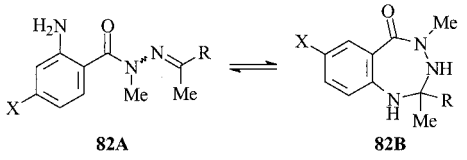
Ring-chain tautomerism is also observed in 1,3-X,N-heterocyclic derivatives containing an extra heteroatom in the ring. A large group of these compounds is made up of the 1,3,4-X,N,N-heterocycles formed by the corresponding hydrazones bearing an XH group capable of reversible intramolecular addition to the C=N bond.[1−3]

In the reaction between mercaptoacetylhydrazine and acetone, a 1,3,4-thiadiazine derivative **81** was formed, and was found to be the cyclic tautomer in the solid state. In [D_5]pyridine and in $(CD_3)_2SO$ solutions, however, **81** was a mixture of open (**A**) and cyclic (**B**) tautomers (Scheme 24), as demonstrated by the ^{1}H and ^{13}C NMR spectroscopic data.[34]



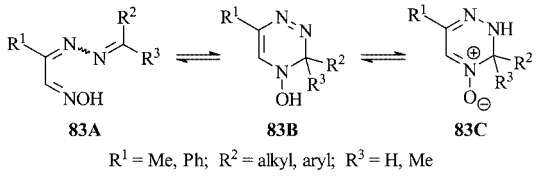
Scheme 24

The condensation products of anthranilic acid *N*-methylhydrazide and ketones participated in ring-chain tautomeric equilibria of the open hydrazones **82A** and the corresponding cyclic 2,2-substituted 4-methyl-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-5-one **82B** forms in CD_2Cl_2, $CDCl_3$ and $(CD_3)_2SO$ solutions (Scheme 25). The molecular rearrangements of **82**, involving interconversions of the tautomers, isomerizations of the amide and C=N bonds of the open form, pseudorotation of the ring form and N-inversion processes, were monitored by NMR methods. Increases in the bulkiness of substituent R and elevated temperatures decreased the proportions of the ring forms (**B**) in the equilibria. Because of the complex rearrangement processes, the electronic effect of substituent Y on the 2-phenyl ring on the tautomeric ratios could not be described by Equation (1) for 2-aryl-substituted derivatives.[35]



Scheme 25

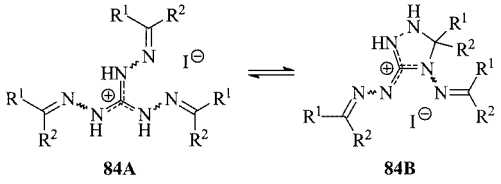
The double hydrazones **83A** prepared from isonitrosoacetone and isonitrosoacetophenone hydrazones with aldehydes or ketones proved to participate in ring-chain tautomeric equilibria with the corresponding 1,2,4-triazine-4-oxides **83B**,**C** in $(CD_3)_2SO$ solution or in the gas phase (Scheme 26). In the case of alkyl- and hydroxyphenyl-substituted derivatives, there were considerable differences in the proportions of the open and cyclic forms measured in solution and in the gas phase. No connection between the electronic effects of the 2-aryl groups and the tautomeric ratios was found.[36]



Scheme 26

Condensation of triaminoguanidinium iodide with aldehydes or ketones produced tris(alkylidene/arylideneamino)-guanidinium iodides (**84**), the ring-chain tautomerism of which was strongly dependent on the substituents. Both tautomeric forms could be detected in $(CD_3)_2SO$ solutions of the compounds prepared from aliphatic ketones (except

pinacolone). The aldehyde and pinacolone derivatives existed entirely as the open tris(hydrazone) forms **A**. Either open or cyclic tautomeric forms of the acetophenone and propiophenone derivatives could be prepared, but no equilibrium was observed between these compounds (Scheme 27).[37]



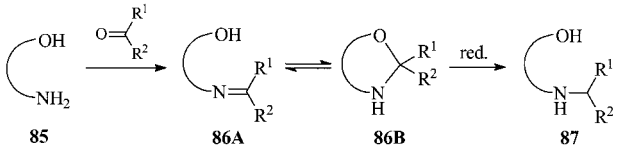
Scheme 27

6. Applications

Recent examples provide clear evidence that the ring-chain tautomeric character of 1,3-heterocyclic derivatives can often be exploited successfully in organic synthesis, and also in physical, medicinal or peptide chemistry.

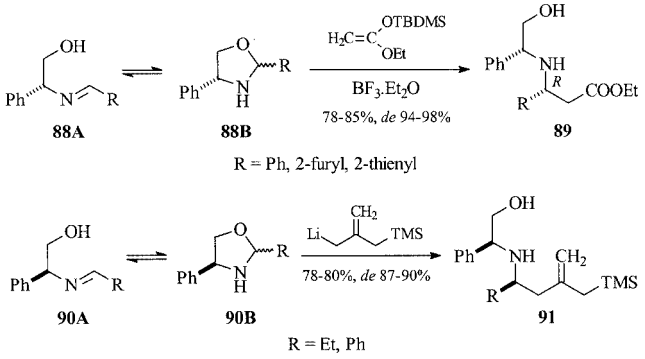
The determination of σ^+ values for aryl or *X*-substituted phenyl substituents at position 2 of a ring-chain tautomeric 1,3-O,N-heterocycle is possible by means of Equation (1). The values of ρ have been accurately determined for numerous 1,3-O,N-heterocycles, and the electronic character of a substituent at position 2 can therefore be calculated according to Equation (1) by measuring the ring-chain ratios. This principle was recently applied for determination of the σ^+ values for *para*-1-imidazolyl, -1-benzimidazolyl, -1-benzotriazolyl, -2-benzotriazolyl, and -1,2,4-triazolo[2,3-*a*]pyridin-2-yl substituents on a phenyl ring.[38]

The *N*-substitution of amino alcohols **85** containing a primary amino group can easily be achieved through their ring-chain tautomeric 1,3-O,N-heterocyclic derivatives **86**. Reduction of the open forms of the mixture results in *N*-substituted amino alcohols **87** (Scheme 28).[39] A similar transformation, based on the ring-chain tautomeric character of the intermediate, can also be performed by starting from *N*-monosubstituted amino alcohols.[40]



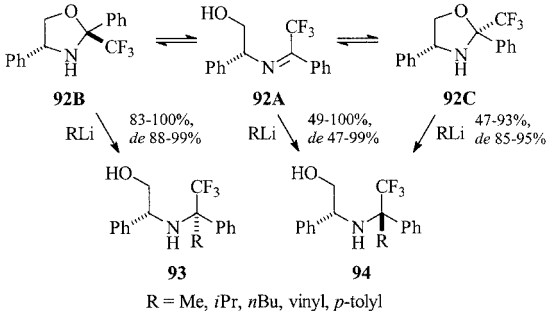
Scheme 28

Thanks to the presence of the C=N double bond in the open form, ring-chain tautomeric 1,3-O,N-heterocycles can also be applied in addition reactions. Substituents on the carbon atom in the C=N bond proved to exert a decisive influence on the stereochemistry of the new chiral carbon atom formed. The reactions between (*R*)-phenylglycinol-derived oxazolidines (**88**) and silyl enol ether in the presence of $BF_3{\cdot}Et_2O$ resulted in β-substituted β-amino esters (**89**) with the (*R*) configuration at the new centre of asymmetry, in good yields and with high diastereomeric excesses.[41] The additions of {2-[(trimethylsilyl)methyl]prop-2-enyl}lithium to (*S*)-phenylglycinol-derived oxazolidines (**90**) also afforded β-amino alcohols **91** with high diastereoselectivities (Scheme 29).[42]



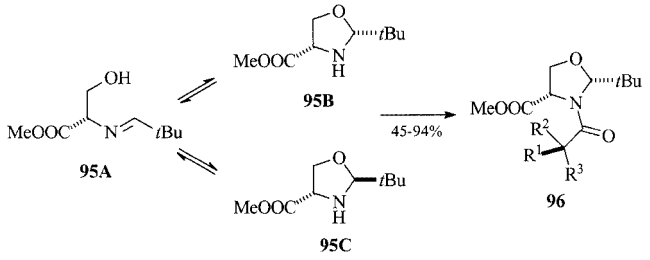
Scheme 29

Probably because of a slow tautomeric equilibration process, an open (**A**) and two C-2-epimeric cyclic (**B** and **C**) tautomers of the condensation product **92** derived from (*R*)-phenylglycinol and 2,2,2-trifluoroacetophenone could be isolated. When compounds **92A**−**C** were treated with various organolithium reagents, *N*-substituted amino alcohol derivatives **93** or **94** were obtained with moderate to excellent diastereoselectivities. Both yields and diastereomeric excesses were influenced by the tautomeric form of the substrate. The open and the (*R*,*R*) cyclic tautomer **C** gave the same amino alcohol diastereomer **94** (Scheme 30).[43]



Scheme 30

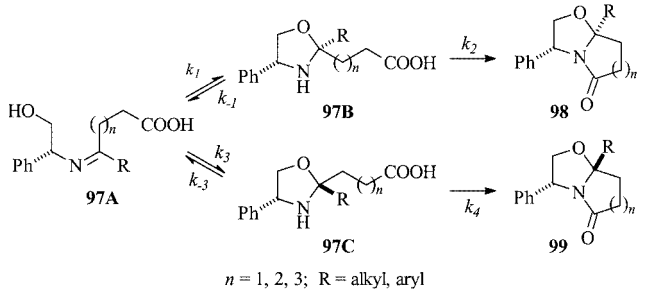
As with other tautomeric equilibria, selective reactivity of the tautomeric forms can shift a ring-chain equilibrium entirely towards the most reactive component. When oxazolidine **95**, prepared from serine methyl ester and pivalaldehyde, was acylated with various acid derivatives under different conditions, the *N*-acylated products **96** were obtained as the sole diastereomers, although **95** was a 1:1 mixture of *cis* and *trans* cyclic tautomers (**B** and **C**). The selective transformations were explained in terms of the different rates of acylation for the cyclic diastereomers, which caused



Scheme 31

the total shift of the ring-chain equilibrium (Scheme 31).[44]

The diastereoselective formation of bicyclic lactams **98** in the domino ring-closure reactions between (*R*)-phenylglycinol and γ-, δ- or ε-oxo acids was also explained in terms of the differences in the rates of the acylation steps ($k_2 > k_4$) for the ring-chain tautomeric intermediates **97**, shifting the equilibrium towards the cyclic form **B** (Scheme 32). The highest difference in k_2 and k_4, and therefore the highest diastereoselectivity, was observed for the formation of five-membered lactams ($n = 1$). Thanks to the increased flexibility of the larger ring size, elongation of the carbon chain ($n = 2, 3$) resulted in better conditions for the ring-closure towards **99**, which decreased the diastereoselectivity of the reaction.[45]



Scheme 32

The shifts of the ring-chain equilibria in the intermediates of bicyclic lactams, caused by the difference in the acylation rates of the cyclic tautomers, can also be applied for the development of dynamic kinetic resolution procedures, if the equilibration process involves all of the centres of asymmetry to be resolved. This was the case in the reaction between (*R*)-phenylglycinol and racemic methyl 5-oxo-4-phenylpentanoate, for which the acylation steps in the intermediate cyclic tautomers **100D−G** were significantly different ($k_1 > k_2 >> k_3$, k_4) and racemization of both new centres of asymmetry was possible either by the ring-chain tautomeric process or by the imine-enamine isomerization of the open forms **100A−C** (Scheme 33). Enantiopure bicyclic lactams **101** and **102** were isolated in a ratio of 49:9. This method was also successfully applied for other racemic or prochiral oxo esters.[46]

Thanks to their ring-chain tautomeric character, 1,2-disubstituted saturated 1,3-N,N-heterocycles can be exploited as intermediates in the selective functionalization of *N*-monosubstituted ethylene- or propylenediamines. The reactions between 1-methylhexahydropyrimidine derivatives **105** and several electrophiles afforded products of types **107** and **108** or, after hydrolysis, the regioisomerically substituted diamines **109** and **110**. The ratio of the compounds formed from the cyclic or from the open tautomer was found to depend mostly on the bulkiness of substituent R^1 at position 2 of the starting hexahydropyrimidine **106** and, to a lesser extent, on the nature or the size of the electrophiles. The reactions of the methyl or ethyl-substituted hexahydropyrimidines occurred mainly on the cyclic tautomer to yield compounds **108** or **110**, while for isopropyl- or phenyl-substituted compounds, derivatives of the open forms **107** and **109** were the main products (Scheme 34).[47]

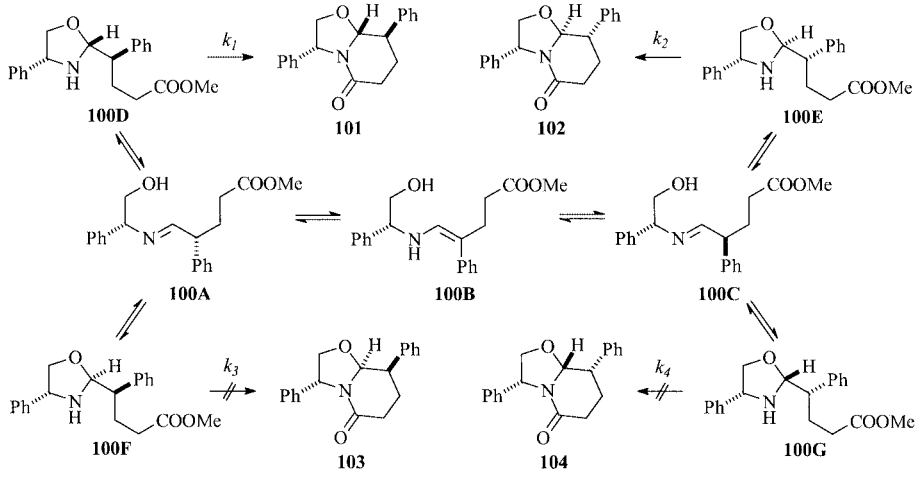
For chiral 1,3-O,N-heterocyclic derivative **111**, obtained from (2*S*,3*S*)-2,3-diamino-1,4-butanediol and salicylaldehyde or 3,5-di-*tert*-butylsalicylaldehyde, the ring-chain tautomeric equilibria were strongly shifted towards the open tautomer **111A**. The Mn^{3+} complexes **112** of the open form were tested as chiral catalysts for the epoxidation of indene **113**. No asymmetric induction was observed for the epoxidation in the presence of **112a**, but the tetra-*tert*-butyl derivative **112b** produced an enantiomeric excess of 48% in favour of (1*S*,2*R*)-1,2-epoxyindane (**114**) (Scheme 35).[15b]

Because of their ring-chain tautomeric character, oxazolidines and tetrahydro-1,3-oxazines can be used as aldehyde sources in acid-catalysed condensation reactions. This approach is especially advantageous in those cases in which the aldehydes required for the condensations are unstable or difficult to access. Carbon-transfer reactions of tetrahydro-1,3-oxazines **115** or oxazolidines **116** have been utilized in recent years for the synthesis of fused pyran and pyridine derivatives **118**, **119**, **121** and **122**. Depending on the imine-enamine tautomerism of the open forms and the presence of an additional electrophilic or nucleophilic reactive site in the C-2 substituent, the starting 1,3-O,N-heterocycles were found to react with nucleophiles either in 1:2 or in 1:1 stoichiometric ratios (Scheme 36).[48]

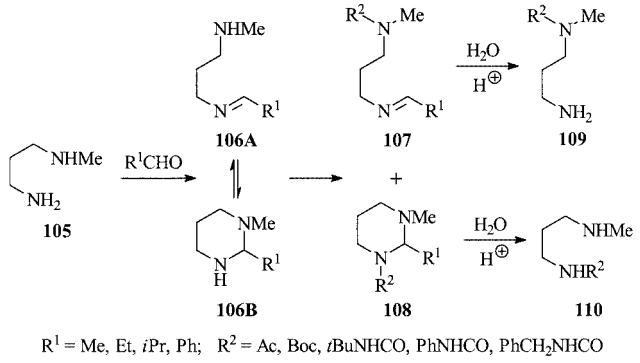
2-Substituted 1,3-O,N-heterocycles **115** and **116** were applied in modified Pictet−Spengler reactions to yield tetrahydro-β-carbolines **124** and **125**. Condensations with tryptophan esters (**123**: R^6 = COOMe, COO*i*Pr) took place with low to excellent diastereoselectivity, resulting in the *trans*-1,3-disubstituted derivatives (**a**) as the main products. The diastereoselectivities of the reactions were found to be influenced strongly both by the *N*-substituent (R^7) of the tryptophan ester and by the C-2 substituents (R^1 and CH_2R^4) in the starting 1,3-O,N-heterocycles (Scheme 36).[49]

An asymmetric carbon-transfer reaction was also performed through the use of 2-(*p*-tolyl)sulfinylmethyltetrahydro-1,3-oxazine (**126**) as a chiral aldehyde equivalent, but only moderate diastereomeric excesses (ca. 40%) could be achieved in the case of tryptamine-derived tetrahydro-β-carbolines (**127**: R^6 = H) (Scheme 37).[50]

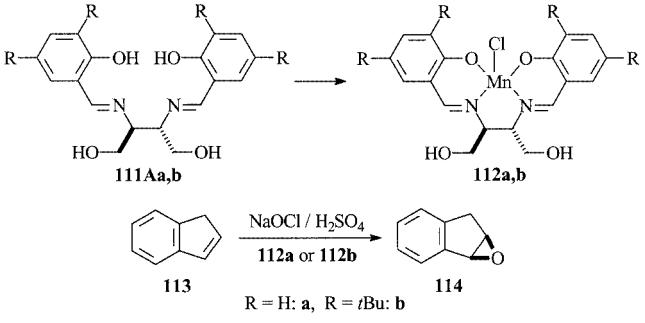
Serine-, threonine- and cysteine (**128**)-derived ring-chain tautomeric 1,3-X,N-heterocycles (**129**: pseudo-prolines) proved not only to be reversible protecting groups for these



Scheme 33



Scheme 34



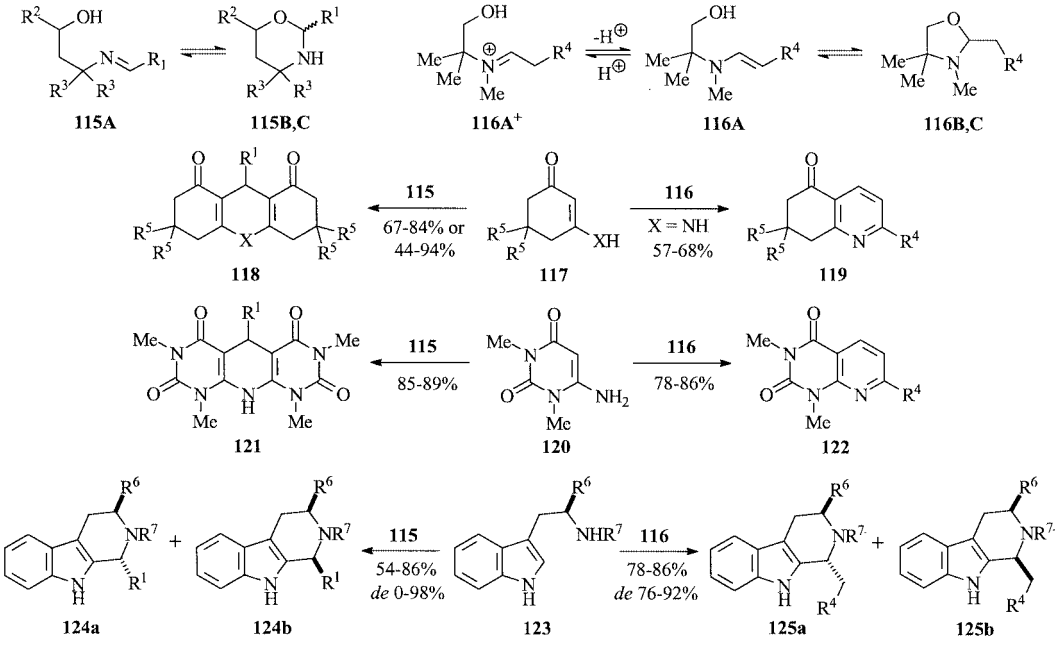
Scheme 35

amino acids, but also to be versatile tools with which to overcome some intrinsic problems in peptide synthesis (Scheme 38). Thanks to the induction of a kink conformation in the peptide backbone, pseudo-prolines prevent peptide aggregation, self-association and β-structure formation, thereby improving the solvation and coupling kinetics of the growing peptide chain.[51] A perfluoroalkyl-substituted pseudo-proline analogue of bis(trifluoromethyl)serine (**133**) was recently prepared by condensation-addition of glycine (**130**) with hexafluoroacetone in DMSO (Scheme 39).[52]

The formation and subsequent rearrangement of a pseudo-proline ring could also be exploited in the coupling of peptide segments. Condensations of peptidyl glycoaldehyde esters **135** with an *N*-terminal serine, threonine or cysteine peptide moiety **134** resulted in ring-chain tautomeric pseudo-proline derivatives **136**, in which the new peptide bond was formed by *O*- → *N*-acyl migration. Pseudoprolines of thiazolidine type **136** (X = S) could be prepared both under aqueous and under non-aqueous conditions by use of unprotected peptides, while couplings via the oxazolidine derivatives **136** (X = O) were best performed in a non-aqueous pyridine/acetic acid mixture. This concept was also applied in the synthesis of cyclic peptides (Scheme 40).[53]

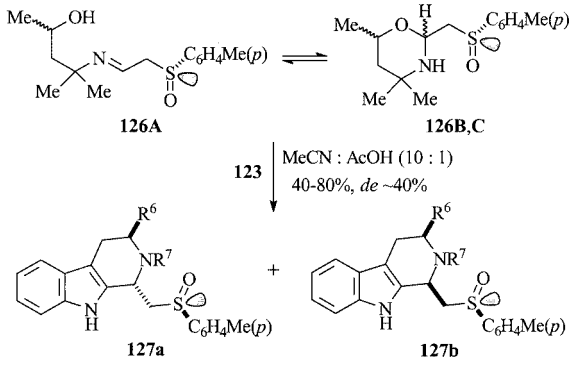
Many unfavourable pharmacological and physicochemical properties of drugs can be improved by the application of prodrugs. Ring-chain tautomeric prodrugs include 1,3-X,N-heterocycles prepared from difunctional compounds with aldehydes or ketones. From the ring-chain equilibria of these derivatives, the open form undergoes hydrolysis to give the bioactive molecule, which can be either the original difunctional compound or an oxo compound (Scheme 41). This concept was applied in cases of oxazolidine and thiazolidine prodrugs derived from (−)-ephedrine, L-cysteine and hydrocortisone.[1−3,54] Among 1,2,4-heterocycles, 2-substituted 1,2,4-oxadiazines can serve as prodrugs of anti-inflammatory 1,2-hydrazinoalcohol derivatives.[55]

Oxazolidine derivatives **139** obtained by condensations between (−)-ephedrine (**138**) and oxo compounds were found to have abilities similar to or somewhat poorer than that of ephedrine to increase locomotor activity in rats. Hydrolysis of oxazolidines **139** via the open iminium intermediates **140** is the key step in the liberation of the active substance, and substituent effects were investigated in detail. The hydrolysis half-lives for **139** were strongly influenced by the C-2 substituents.[56,57] Complexation with hydroxypropyl-β-cyclodextrin caused increases both in the stability of the oxazolidine prodrugs **139** towards hydrolysis and in their effects on the central nervous system.[58]



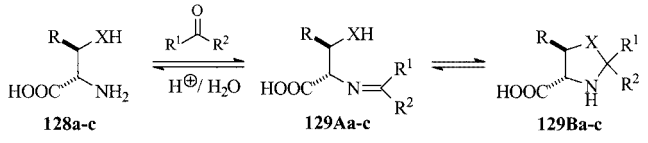
R^1 = H, alkyl, aryl; R^2, R^3, R^5 = H, Me; R^4 = Me, CH_2COOEt, CN, COMe, COPh, COOEt, $COCH_2COMe$, $COCH_2COOEt$;
R^6 = H, COOMe, COO*i*Pr; R^7 = H, CH_2Ph, $C_6H_4OMe(p)$; X = O, NH

Scheme 36



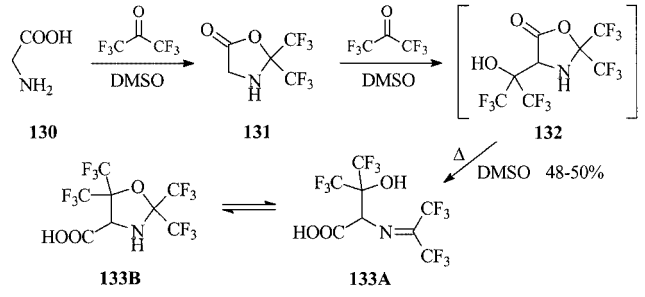
R^1 = H, COOMe, COO*i*Pr; R^2 = H, $C_6H_4OMe(p)$

Scheme 37

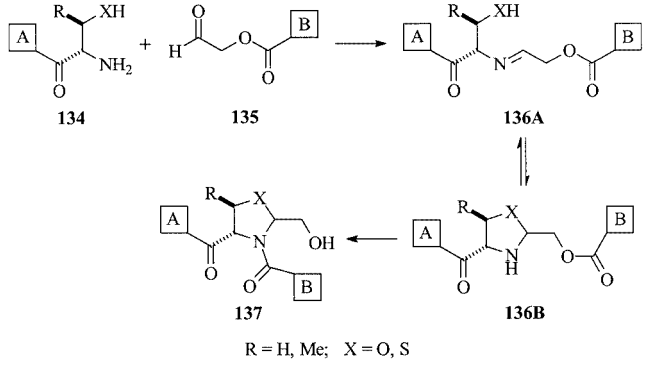


R = H, X = O: **a**, R = Me, X = O: **b**, R = H, X = S: **c**
R^1, R^2 = H, alkyl

Scheme 38



Scheme 39



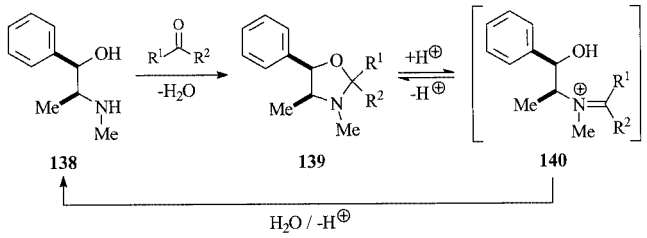
R = H, Me; X = O, S

Scheme 40

Conclusions and Prospects

Ring-chain tautomerism is to be expected in 1,3-X,N-heterocycles in which C-2 has an sp^3 character. With progress in spectroscopic methods, increasingly more complex tautomeric systems have been suitably characterized, and ever more is becoming known on the effects of substituents, heteroatoms, etc. Most of these effects can be described by simple mathematical equations.

Many qualitative and quantitative data with which to describe the tautomeric process are available, but on the other hand more investigations are still necessary in order to



Scheme 41

understand the fine-tuned stereoelectronic effects on the process. Full mapping theoretical calculations to describe the process in general will most probably appear in the near future. Besides investigations of the quantitative substituent effect and theoretical calculations, exponential progress is to be expected in the synthetic use of the process, primarily in enantioselective transformations, and especially in dynamic kinetic resolution processes. Dynamic progress is also being made in the synthesis of self-organized macromolecules and in medicinal chemistry use.

Acknowledgments

The authors' thanks are due to the Hungarian Research Foundation (OTKA no. TS04888) for financial support.

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