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Five-Component Equilibria of Ring-Chain Tautomeric Mixtures Derived from 2-Amino-1-phenyl-1,3-propanediol Diastereomers

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Abstract. In the reactions of (1*R**,2*S**)- or (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol with aromatic aldehydes, five-component ring-chain tautomeric mixtures were formed, involving C-2 epimers of structurally isomeric oxazolidines and the corresponding Schiff base. These multicomponent tautomeric equilibria could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$.

Keywords: tautomerism; oxazolidines; amino alcohols; stereochemistry

Ring-chain tautomerism of the products formed from 1,2- and 1,3-amino alcohols with oxo compounds, *i.e.* the reversible addition of a β- or γ-hydroxyl group to a heteropolar C=N bond is a well established process.[1] Qualitative studies on the equilibria of the open-chain (Schiff base) and ring-closed (1,3-*O,N*-heterocycle) forms started in the early 1940s, however exact quantitative data on the tautomeric ratios could only be established more recently by the application of high resolution NMR spectroscopy or mass spectrometry.[2,3]

Studies of the substituent effects on the ring-chain tautomerism of 2-aryl-1,3-*O,N*-heterocycles revealed that tautomeric ratios were strongly influenced by the electonic character of the aryl subtituents. Tautomeric equilibria of 2-(*X*-phenyl)-substituted derivatives could be described by the Hammett-type linear free energy equation (Eq. 1):

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad \text{(Eq. 1)}$$

where K_X = [ring]/[chain], ρ is a characteristic value of the ring system and σ^+ is the Hammett-Brown constant for substituent *X*. Equation (1) describes not only two- or three-component tautomeric equilibria of 2-aryl-1,3-*O,N*-heterocycles, but also was applied recently to the case of a five-component system containing C-2 epimeric oxazolidine and tetrahydro-1,3-oxazine pairs.[4]

Our present aim was to study the condensation reactions of 2-amino-1-phenyl-1,3-propanediol diastereomers with aromatic aldehydes, to compare the ring-chain tautomeric character of the diastereomeric products and to study the scope and limitations of equation (1) in multicomponent tautomeric systems.

The current chemical interest in 2-amino-1-phenyl-1,3-propanediol and its derivatives could be explained by its ready availability and the wide range of synthetic utility of these compounds. (1*S*,2*S*)-2-Amino-1-phenyl-1,3-propanediol has been applied as resolving agent[5] and starting material for the synthesis of many homochiral

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Dedicated to Professor **Gábor Bernáth** on the occasion of his 65th birthday.

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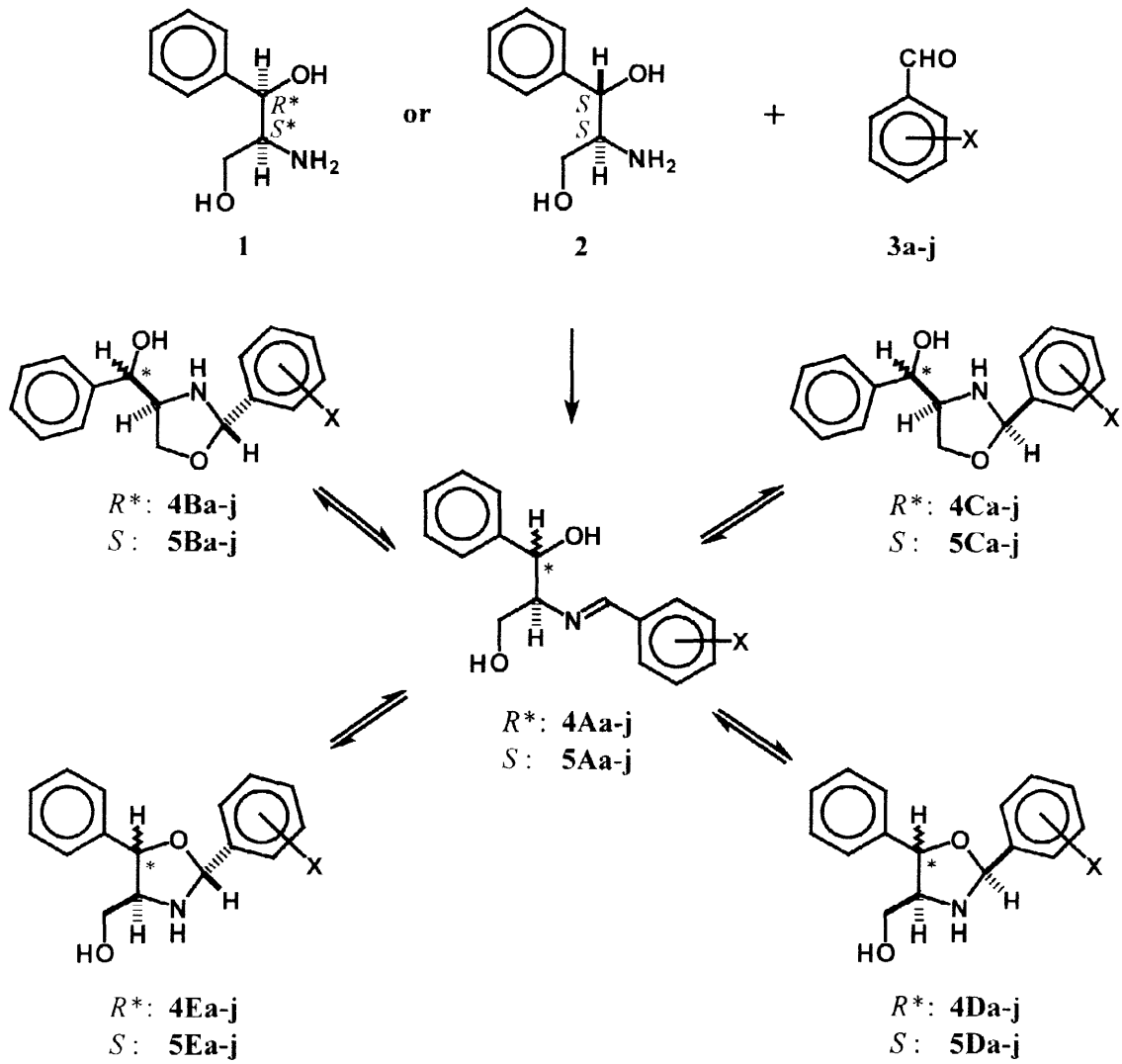
compounds, important from either pharmacological or chemical points of view, *e.g.* dexamphetamine,[6] (*R*)-phenylalaninol,[7] optically pure 2-aziridinemethanols,[8] 1,3-dithiol derivatives,[9] β-lactams,[10] *etc.* Many types of asymmetric transformations, *e.g.* alkylations,[11] conjugate additions to α,β-unsaturated carboxylic acids,[12] cyclopropanations,[13] conversion of sulphides into sulphoxides,[14] organozinc additions,[15] *etc.* are based on chiral auxiliaries (oxazolidin-2-ones, oxazolines or bicyclic lactam derivatives) derived from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol.

RESULTS

When (1*R**,2*S**)- and (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (**1**, **2**) were reacted with ten substituted aromatic aldehydes (**3a-j**) in methanol at ambient temperature, the condensations resulted in well defined crystalline (or in case **4b.c** and **5c** oily) products (**4a-j**, **5a-j**) (Scheme 1). ^{1}H NMR spectra of **4a-j** and **5a-j** unequivocally showed (Fig. 1), that all of these compounds exist in $CDCl_3$ solution as five-component tautomeric mixtures containing a Schiff-base (**A**) and two pairs of C-2 epimeric oxazolidine regioisomers (**B**, **C** and **D**, **E**).



a, X = NO_2(*p*); **b**, NO_2(*m*); **c**, Br(*m*); **d**, Br(*p*); **e**, Cl(*p*); **f**, F(*p*); **g**, H; **h**, Me(*p*); **i**, OMe(*p*); **j**, NMe_2(*p*).

Scheme 1

A similar ring-chain tautomeric equilibrium (in DMSO-d_6) derived from (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (*p*-nitrophenylserinol) and aromatic aldehydes was published recently, however only two ring-closed tautomers could unequivocally be distinguished by NMR analysis and traces of another ring form could be seen only in the case of some strongly electron withdrawing 2-aryl-substituents.[16]

Line assignment of multicomponent (tautomeric) mixtures is often a difficult spectroscopic task.[17] Structural similarity of components causes extended overlap of signals belonging to different tautomers either in 1D or in 2D spectra and, therefore, characteristic scalar couplings remain hidden. A further problem is the very similar topology of COSY and TOCSY patterns due to the same spin connectivity. Therefore, information from these 2D spectra cannot be fully exploited. A further complication is that the NOESY cross signals of minor components may diminish into the noise in case of low relative concentration. Analysis of complex tautomeric mixtures could sometimes be simplified by a combination of spectroscopic and synthetic chemical methods.[4]

The formation of structurally isomeric heterocycles in the ring-closures of 2-amino-1-phenyl-1,3-propanediol isomers is a well known phenomenon.[10a,12,18] In these reactions, the 4,5-disubstituted oxazol(id)ine derivatives of **D**/**E** type are formed as *major* products besides less amounts of 4-monosubstituted oxazol(id)ine derivatives of **B**/**C** type. When the structural isomeric products are not participating in the equilibrium, the ring-closures resulting in them are governed by kinetic rather than thermodynamic control. Therefore, predictions concerning the regioisomeric ratios of tautomeric mixtures **4a-j** and **5a-j** on the basis of the non-equilibrium examples could not be taken into consideration. However, 4,5-disubstituted oxazolidines proved also to be the *major* (or only) ring forms in the above mentioned equilibria of isomeric oxazolidines derived from (1*S*,2*S*)-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol.[16]

The very similar NMR spectroscopic properties (chemical shifts, spin connectivity) of the isomeric ring-closed tautomers **B**-**E** originate from their close structural similarity. Unfortunately, application of recently developed PFG techniques[17] to distinguish them was not possible due to their similar diffusion coefficients. The methods of the line assignment of tautomeric mixtures **4a-j** and **5a-j** are discussed for the examples of the *p*-nitrophenyl derivatives **4a** and **5a** (Table 1).

NMR analysis on compound 4a

The spectrum recorded immediately after dissolution of **4a** contained only the lines of the open form (**A**) which could be easily assigned. The well separated peaks of O-C*H*Ar-N and the O-C*H*Ph protons in the spectra, recorded after attaining ring-chain equilibrium, could be arranged into the corresponding pairs according to their integral values. From COSY and TOCSY spectra the lines of O-C*H*Ph, N-C*H*-C and O-CH_2 belonging to the same component were identified.

NOE crosspeaks were found between two O-C*H*Ar-N, O-C*H*Ph pairs (5.62, 4.99 and 5.77, 5.25 ppm), so they belong to structures having these hydrogens in *cis* positions that are structures **B** and **D**.

TOCSY and COSY connectivities from the O-C*H*Ph doublets were followed. These showed that the peaks of O-CH_2 goups of two of the isomers were at much lower frequency than usual. This can only be explained if they are in the shielding region of the phenyl group, which is possible only for structures **B** and **C**. The 5.24 ppm O-C*H*Ph resonance is associated with the O-CH_2 protons at 3.24 and 3.36 ppm and the 5.25 ppm O-C*H*Ph doublet is associated with the O-CH_2 protons at 3.21 and 3.39 ppm. The proximity of the O-CH_2 protons and the phenyl groups in these structures, that places the O-C*H*Ar-N protons in the shielding region of the phenyl, is supported by molecular mechanics calculations.

An NOE is observed between the singlet at 5.77 ppm and doublet at 5.25 ppm, therefore these resonances arise from isomer **C**. The other NOE observed is between the singlet at 5.62 ppm and the O-C*H*Ph doublet at 4.99 ppm, so these signals arise from isomer **D**. By elimination, and from comparison of the respective integrals, the 6.08 ppm singlet is associated with the 5.24 ppm doublet and must arise from isomer **B**. The 5.55 ppm singlet is associated with the 4.91 ppm doublet and arises from isomer **E**.

The crosspeak between O-C*H*Ph and N=C*H*Ar protons in the NOESY spectrum unequivocally proves their spatial proximity and, therefore, the *E* configuration of the C=N bond in the Schiff-base **A**.

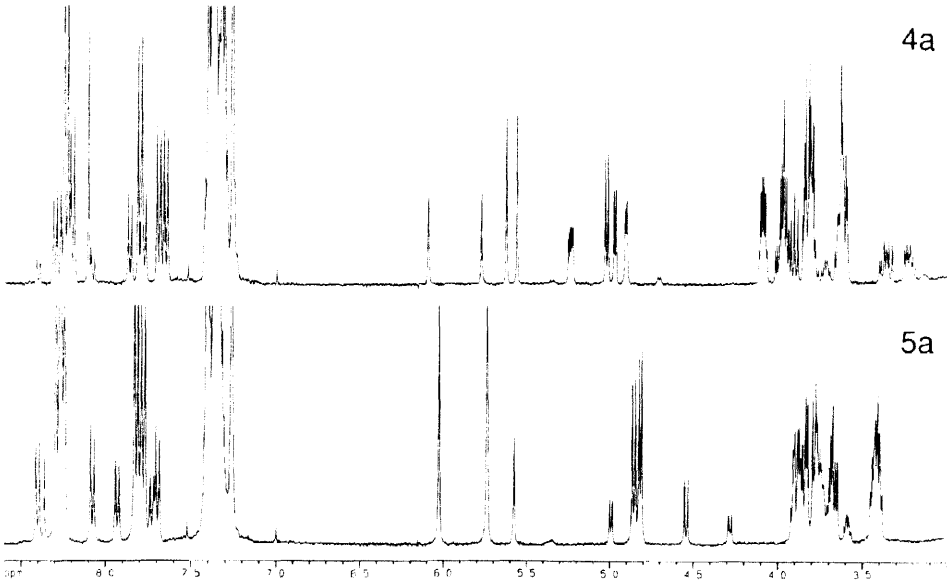


Figure 1. Parts of ^{1}H NMR spectra of compounds **4a** and **5a**

NMR analysis on compound 5a

Similarly to the line assignment of **4aA**, resonances from the open form **5aA** were also identified from a spectrum taken immediately after dissolution, containing only the lines of the open form. Surprisingly, in the spectrum recorded on the equilibrium mixture there were only three peaks in the region 5.5-6.2 ppm instead of the four expected singlets of O-C*H*Ar-N ring protons. According to the integral values of O-C*H*Ph protons, two signals of O-C*H*Ar-N protons could be arranged into corresponding pairs and the peak at 5.72 ppm proved to be a superposition of two O-C*H*Ar-N proton resonances. Following TOCSY and COSY connectivities through well separated O-C*H*Ph doublets, the peaks of O-C*H*Ph, N-C*H*-C and O-CH_2 protons belonging to the same compound were assigned.

NOE crosspeaks were found between O-C*H*Ph and O-C*H*Ar-N protons of 4.82, 5.72 ppm and 4.55, 5.57 ppm. This is possible for structures **B** and **E**.

To distinguish the lines of the structural isomers, the method described for the *erythro* counterpart could not be followed. The resonances of the O-CH_2 protons did not exhibit large differences in chemical shift in contrast to the *erythro* isomer, however they showed different crosspeak patterns in homonuclear correlation experiments. The rotation of the CH_2 groups is not so hindered in the compounds **D** and **E** as in the corresponding *erythro* isomers, because the *threo* isomers contain hydroxymethyl and phenyl groups in a *trans* position. Therefore, the chemical shift difference between the protons in both of those CH_2 groups is expected to be about zero or a small value, so that the arising signal does not show clear *ddd* structure. According to this

assumption, the multiplets at 3.83 and 3.87 ppm suggest that those can be assigned to compounds **D** and **E**. The protons in the ring methylenes obviously have greater differences between their chemical shifts. Therefore the two *ddd* multiplets at chemical shifts of 3.82, 3.75 ppm and 3.86, 3.65 ppm belong to **B** and **C** structures.

The 4.55 ppm doublet of O-C*H*Ph proton is associated with the multiplet at 3.87 ppm and has an NOE with the singlet at 5.57 ppm, so it corresponds to isomer **E**. Other NOEs were observed between O-C*H*Ar-N at 5.72 ppm and O-C*H*Ph at 4.82 ppm that are associated with O-CH_2 peaks at 3.82 and 3.75 ppm. These resonances refer to isomer **B**. Without an NOE and having O-CH_2 protons on oxazolidine ring is isomer **C**, with O-C*H*Ph at 4.85 ppm, O-CH_2 at 3.86, 3.65 ppm and O-C*H*Ar-N at 6.02 ppm. By elimination the remaining signals arise from isomer **D**.

The *E* configuration of the C=N bond of the open form **A** was proved as described for **4aA**.

Table 1. Selected chemical shifts (ppm) for compounds **4a** and **5a**

Compd.	O-C*H*-Ph *(d)*	N-C*H*-C *(m)*	O-CH_2 *(m)*	O-C*H*Ar-N *(s)*
4Aa	5.02	3.62	3.95, 3.99	8.10*
4Ba	4.99	3.64	3.85, 3.92	5.62
4Ca	4.91	3.80	3.88, 3.98	5.55
4Da	5.25	3.83	3.21, 3.39	5.77
4Ea	5.24	3.73	3.24, 3.36	6.08
5Aa	4.97	3.57	3.75	8.36*
5Ba	4.82	3.39	3.82, 3.75	5.72
5Ca	4.85	3.43	3.86, 3.65	6.02
5Da	4.27	3.73	3.83	5.72
5Ea	4.55	3.69	3.87	5.57

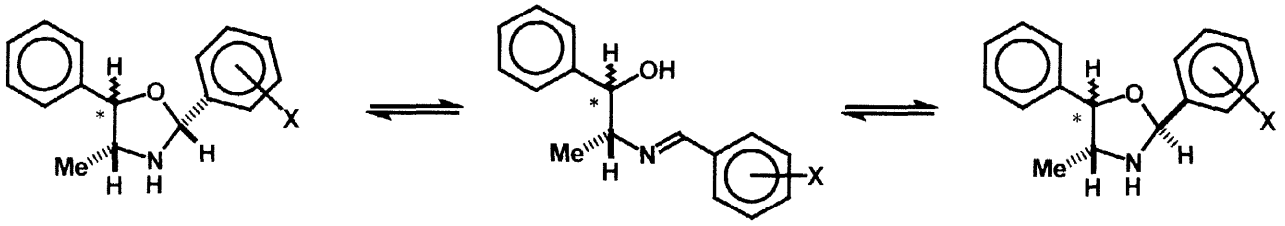
*N=C*H*Ar (*s*)

Characterization of tautomeric sets 4a-j and 5a-j

The assignment procedures described above were applied to the remaining members of both the *erythro* (**4a-j**) and *threo* (**5a-j**) series. 2-Aryl-substituents did not change the sequence of the chemical shifts of O-C*H*Ph, N-C*H*-C, O-CH_2 and O-C*H*Ar-N or N=C*H*Ar protons. The relative arrangements of O-C*H*-Ph and O-C*H*Ar-N lines of the structures **5D** and **5E** were in accordance with the literature data on the analogous oxazolidines derived from *p*-nitrophenylserinol.[16]

Ratios of the tautomeric equilibria were determined by integration of the well separated signals from the O-C*H*Ph and O-C*H*Ar-N or N=C*H*Ar protons (Table 2). The time required for attaining equilibria was a crucial point in these measurements,[1,2,19] because studies on non-equilibrium state mixtures would produce inconsistent results. When $CDCl_3$ solutions of compounds **4a-j** and **5a-j** were allowed to stand at 300 K, all tautomeric mixtures, except the *threo p*-nitrophenyl derivative (**5a**), reached equilibrium within 48 hours. For **5a**, tautomeric ratios were changing even after standing for two weeks. However, on adding traces of hydrochloric acid to the solution of **5a** constant tautomeric ratios were immediately attained, which can be rationalized by the fact that addition of hydroxyl group to the C=N bond is a proton catalysed process. A similar phenomenon was observed in the case of the structurally analogous tautomeric mixtures (**6a-k**, **7a-k**) derived from (±)-norephedrine and (1*R*,2*R*)-norpseudoephedrine with aromatic aldehydes (Scheme 2). While *erythro p*-nitrophenyl derivative **6a** reached equilibrium in $CDCl_3$ within 4 hours, equilibrium was established for the *threo* counterpart **7a** only after 48 hours.[19a]

Data on the tautomeric equilibria (Table 2) show that addition of hydroxy groups to the C=N bond of the open forms (**A**) occurred regio- and stereo-selectively. These ring-closures are unfavoured (*5-endo-trig*) according to Baldwin's rules.[20] Increasing the value of constant σ^+ of substituent *X* caused higher ratios of ring-closed forms. The coefficients of Hammett-Brown equation (1) were evaluated by means of linear regression analysis (Table 3). Contrary to the generally applied previous methods,[1] for exact thermodynamical comparison of the oxazolidine forms (**B-E**), regression analysis was performed for each ring-closed isomer separately, instead of their sums. By using this concept, literature data[20a] on the tautomeric mixtures (**6** and **7**) derived from norephedrine and norpseudoephedrine were recalculated (separately for **6B**, **6C**, **7B** and **7C**) for the proper comparison to the values of the corresponding oxazolidines **4D, 4E** and **5D, 5E**.



4*R**,5*S**: **6Ba-k**	1*S**,2*R**: **6Aa-k**	4*R**,5*S**: **6Ca-k**
4*R*,5*R*: **7Ba-k**	1*R*,2*R*: **7Aa-k**	4*R*,5*R*: **7Ca-k**

a, X = NO_2(*p*); **b**, CN(*p*); **c**, CF_3(*m*); **d**, Br(*m*); **e**, Cl(*m*); **f**, Cl(*p*); **g**, H; **h**, Me(*m*); **i**, Me(*p*); **j**, OMe(*p*); **k**, NMe_2(*p*)

Scheme 2

The differences between the slopes of the regression lines for 2-aryloxazolidines (**4-6**) derived from both aminophenylpropanediol diastereomers and from norephedrine were not significant, and the slopes are very similar to the value for the unsubstituted 2-aryloxazoline (0.60).[3c] Slopes for the norpseudoephedrine-derived oxazolidines (**7**) are slightly smaller. The greater differences in intercept values of these compounds could be explained by the effects and interactions of the substituents of the oxazolidine ring.

The sum of steric and electronic effects of the substituents in positions 4 and 5 on the stability of the 2-aryloxazolidine tautomers (**B-E**) could be described by a constant c,[1,3a,c] introduced earlier, which means the intercept difference of the given 4- or/and 5-substituted 2-aryloxazolidine (log $K_{X=H}$) and the parent 2-aryloxazolidine (**8**) unsubstituted at other positions (log K_0 = -1.10).

On comparison of c values for compounds **4B-E, 5B-E, 6B,C** and **7B,C**, it can be concluded that each of the isomeric ring forms has a positive c value, which means the greater stability of these rings compared to the 4,5-unsubstituted oxazolidine. Generally, for **4B-E** and **5B-E**, the c values for oxazolidines (**5**) derived from *threo* aminodiol are greater than those for their *erythro* counterparts (**4**), except compounds **4D-5D**. For *erythro* compounds **4**, oxazolidines of type **B** and **D** are the most stable, in contrast to the *threo* isomers **5**, where oxazolidines **C** and **D** are the preferred cyclic forms. This fact could be explained by the different steric arrangement of phenyl and hydroxymethyl groups in the diastereomers. For oxazolidines of type **D** and **E**, *cis* arrangements of 2-aryl and/or 4-hydroxymethyl and/or 5-phenyl groups (in the case of *erythro* isomers) causing a destabilizing effect on the ring forms by a remarkable steric hindrance. It is surprising, that all-*cis* oxazolidine **4D** is not the least stable ring form among oxazolidines of aminophenylpropanediol-type, while the analogous all-*cis* **6B** is the least stable cyclic tautomer of norephedrine/norpseudoephedrine-type. This difference could be explained by the possible stabilizing intramolecular hydrogen bond in **4D** between CH_2OH group and the nitrogen atom, which is supported by molecular mechanics calculations (Fig. 2).

Table 2. Tautomeric ratios for compounds **4a-j** and **5a-j**

Compd.	X	σ^+	**A** (%)	**B** (%)	**C** (%)	**D** (%)	**E** (%)	log K_B*	log K_C*	log K_D*	log K_E*
4a	*p*NO_2	0.79	29.4	21.8	13.8	21.4	13.5	-0.130	-0.330	-0.138	-0.338
4b	*m*NO_2	0.73	37.8	20.6	10.4	23.6	7.6	-0.264	-0.561	-0.204	-0.606
4c	*m*Br	0.405	46.5	16.9	8.9	17.8	9.9	-0.439	-0.716	-0.416	-0.673
4d	*p*Br	0.15	49.9	13.7	10.4	15.6	10.4	-0.561	-0.682	-0.505	-0.681
4e	*p*Cl	0.114	52.3	14.4	9.6	14.6	9.3	-0.561	-0.738	-0.555	-0.751
4f	H	0	57.8	12.3	8.0	13.6	8.3	-0.673	-0.860	-0.628	-0.846
4g	*p*F	-0.073	55.7	13.6	7.9	14.7	8.1	-0.613	-0.850	-0.578	-0.838
4h	*p*Me	-0.311	67.4	9.6	6.4	10.6	6.0	-0.847	-1.021	-0.803	-1.054
4i	*p*OMe	-0.778	77.9	6.8	4.5	6.9	4.0	-1.061	-1.234	-1.054	-1.292
4j	*p*NMe_2	-1.7	90.6	2.6	2.2	2.7	1.9	-1.548	-1.623	-1.523	-1.672
5a	*p*NO_2	0.79	12.7	13.6	30.8	9.3	33.6	0.029	0.384	-0.136	0.422
5b	*m*NO_2	0.73	10.3	12.9	33.7	6.7	36.4	0.096	0.514	-0.188	0.546
5c	*m*Br	0.405	18.4	10.6	30.5	5.2	35.4	-0.238	0.220	-0.550	0.285
5d	*p*Br	0.15	22.2	10.5	27.2	6.4	33.7	-0.324	0.089	-0.539	0.181
5e	*p*Cl	0.114	20.2	11.9	23.8	4.7	39.4	-0.228	0.072	-0.631	0.291
5f	H	0	23.2	11.6	23.3	4.1	37.7	-0.301	0.002	-0.752	0.211
5g	*p*F	-0.073	24.5	12.9	22.7	5.7	34.2	-0.279	-0.034	-0.636	0.144
5h	*p*Me	-0.311	30.9	11.8	19.6	3.4	34.2	-0.418	-0.197	-0.955	0.044
5i	*p*OMe	-0.778	45.4	8.2	16.0	2.9	27.6	-0.743	-0.454	-1.193	-0.217
5j	*p*NMe_2	-1.7	75.2	4.5	6.4	1.3	12.6	-1.225	-1.067	-1.757	-0.776

* K_B = **[B]** / **[A]**; K_C = **[C]** / **[A]**; K_D = **[D]** / **[A]**; K_E = **[E]** / **[A]**

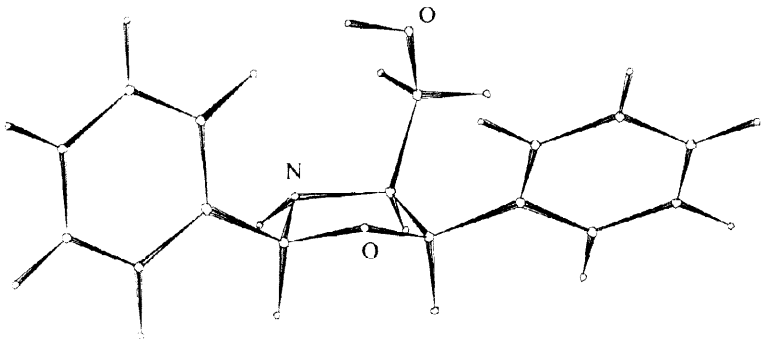


Fig. 2
The resulting conformation of **4Df** after a 100 ps molecular dynamics simulation at 300 K and a subsequent minimisation using cff91 force field implemented in Discover program (all other parameters were set as default).

Table 3. Linear regression analysis data on compounds **4**, **5**, **6**, **7** and the parent 2-aryl-substituted oxazolidines (**8**)[3c]

Compd.	No. of points	Slope[a] (ρ)	Intercept[a] (log $K_{X=H}$)	Correlation coefficient	c[b]
4B	10	0.55(2)	-0.63(1)	0.995	0.47
4C	10	0.48(3)	-0.83(2)	0.983	0.27
4D	10	0.55(2)	-0.60(1)	0.997	0.50
4E	10	0.50(3)	-0.84(2)	0.982	0.26
5B	10	0.51(3)	-0.33(2)	0.985	0.77
5C	10	0.61(2)	-0.01(1)	0.996	1.09
5D	10	0.64(3)	-0.69(2)	0.990	0.41
5E	10	0.50(3)	0.15(2)	0.983	1.25
6B	11	0.65(3)	-0.79(2)	0.993	0.31
6C	11	0.47(3)	-0.57(2)	0.985	0.53
7B	11	0.43(3)	-0.54(2)	0.980	0.56
7C	11	0.33(2)	-0.17(1)	0.990	0.93
8	7	0.60(4)	-1.10(2)	0.989	0

[a]Standard deviations are in parentheses. [b]For the meaning of c see text.

In accordance with the literature data, oxazolidines derived from (1*R*,2*R*)-norpseudoephedrine (*threo* amino alcohol) proved to be more stable than oxazolidines derived from the (±)-*erythro* counterpart norephedrine, even by the regression analysis based on the ratios of individual ring forms. In comparison with the c values for the analogous methyl- or hydroxymethyl-substituted oxazolidines **4D**,**E**, **5D**,**E**, **6B**,**C** and **7B**,**C**, the hydroxy substitution increased the difference in stability for the *threo* C-2 epimers, and produced a reversal in stability for the *erythro* C-2 epimers (see above).

It can be concluded that ring-chain tautomeric equilibria of **4a-j** and **5a-j** could be characterized by the electronic effects of the substituents *X* on the 2-phenyl group, which could be described by Hammett-type equations (1). The regio- and stereo-selectivities of the intramolecular ring-closures involved in the tautomeric process proved to be strongly determined by the relative configurations of the hydroxymethyl- and phenyl-substituted carbon atoms and the steric interactions of the substituents in the formed cyclic tautomers.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ solution at 300 K on a Bruker MSL 500 in high resolution mode and on a Bruker AVANCE DRX 400 spectrometers, with TMS as internal standard. For the equilibria to be established,[2] the compounds **4a-j** and **5b-j** were left to stand in $CDCl_3$ at room temperature for 48 h before the ^{1}H NMR spectra were run. To the $CDCl_3$ solution of **5a**, 1 drop of $CDCl_3$ containing *ca.* 1% hydrochloric acid was added. The TOCSY and the NOESY experiments were performed in phase sensitive mode with TPPI and the mixing time was 80 ms and 700 ms respectively. For the COSY experiment gradient coherence selection was applied. For all heteronuclear spectra shifted sinebell was used as window function and zero filling was applied in both dimensions.

Melting points were determined on a Kofler micro melting point apparatus and are not corrected.

General procedure for the preparation of **4a-j** *and* **5a-j**

To a solution of 3 mmol (1*R**,2*S**)- or (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (**1** or **2**) in absolute methanol (30 ml), 3 mmol of an appropriate aromatic aldehyde was added (liquid aldehydes were distilled before used) and the mixture was left to stand at room temperature for 1 h. The solvent was evaporated off and the evaporation was repeated after the addition of 10 ml benzene. The oily products, formed in nearly quantitative yields, were dried in a vacuum desiccator for 24 h. NMR spectra proved >95% purity of these compounds. Crystalline products were filtered off and recrystallized. Yields: 55-85%. The physical and analytical data on **4a-j** and **5a-j** are given in Table 4.

Table 4. Physical and analytical data on **4a-j** and **5a-j**

Compd.	M.p. (°C)	Found			Formula (M.W.)	Requires		
		C	H	N		C	H	N
4a	86-92[a]	63.65	5.14	9.08	$C_{16}H_{16}N_2O_4$ (300.32)	63.99	5.37	9.33
4b	oil[b]	–	–	–	$C_{16}H_{16}N_2O_4$ (300.32)	63.99	5.37	9.33
4c	oil[b]	–	–	–	$C_{16}H_{16}BrNO_2$ (334.22)	57.50	4.83	4.19
4d	128-130[a]	57.30	4.67	4.09	$C_{16}H_{16}BrNO_2$ (334.22)	57.50	4.83	4.19
4e	125-128[a]	66.45	5.27	4.70	$C_{16}H_{16}ClNO_2$ (289.77)	66.32	5.57	4.83
4f	89-100[a]	74.99	6.12	5.33	$C_{16}H_{17}NO_2$ (255.32)	75.27	6.31	5.49
4g	74-76[c]	70.43	5.74	5.11	$C_{16}H_{16}FNO_2$ (273.31)	70.32	5.90	5.12
4h	86-88[c]	75.66	6.89	4.95	$C_{17}H_{19}NO_2$ (269.35)	75.81	7.11	5.20
4i	124-125[a]	71.14	6.38	4.07	$C_{17}H_{19}NO_3$ (285.35)	71.56	6.71	4.19
4j	111-114[a]	72.19	7.16	9.22	$C_{18}H_{22}N_2O_2$ (298.39)	72.46	7.43	9.39
5a	135-138[a]	64.10	5.08	9.15	$C_{16}H_{16}N_2O_4$ (300.32)	63.99	5.37	9.33
5b	80-83[d]	63.76	5.14	9.34	$C_{16}H_{16}N_2O_4$ (300.32)	63.99	5.37	9.33
5c	oil[b]	–	–	–	$C_{16}H_{16}BrNO_2$ (334.22)	57.50	4.83	4.19
5d	153-155[e]	57.24	4.64	4.03	$C_{16}H_{16}BrNO_2$ (334.22)	57.50	4.83	4.19
5e	147-154[e]	66.28	5.37	4.91	$C_{16}H_{16}ClNO_2$ (289.77)	66.32	5.57	4.83
5f	149-154[f,g]	75.06	6.19	5.36	$C_{16}H_{17}NO_2$ (255.32)	75.27	6.31	5.49
5g	150-152[e]	70.15	5.77	5.03	$C_{16}H_{16}FNO_2$ (273.31)	70.32	5.90	5.12
5h	122-126[f]	76.17	7.08	4.99	$C_{17}H_{19}NO_2$ (269.35)	75.81	7.11	5.20
5i	138-142[f]	71.23	6.67	4.14	$C_{17}H_{19}NO_3$ (285.35)	71.56	6.71	4.19
5j	166-169[e]	72.35	7.21	9.28	$C_{18}H_{22}N_2O_2$ (298.39)	72.46	7.43	9.39

[a]Recrystallized from iPr_2O–EtOAc. [b]Elemental analyses were performed only for the purified crystalline compounds. [c]Recrystallized from iPr_2O. [d]Recrystallized from *n*-hexane. [e]Recrystallized from EtOH. [f]Recrystallized from EtOAc. [g]Lit[21] mp. 151 °C.

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