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Five-Component Equilibria of Ring-Chain Tautomeric Mixtures Derived from 3-Amino-1,2-propanediol and Aromatic Aldehydes

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Abstract. In the reactions of 3-amino-1,2-propanediol with aromatic aldehydes, five-component ring-chain tautomeric mixtures were formed, involving oxazolidine and oxazine C-2 epimers and the corresponding Schiff base. These multicomponent tautomeric equilibria could be described by the equation $\log K = \rho\sigma^+ + \log K_0$, used earlier for the two- and three-component equilibria relating to only oxazine or oxazolidine rings. Copyright © 1996 Elsevier Science Ltd

The reactions of 1,2- and 1,3-aminoalcohols containing primary amino groups with oxo compounds result in products that exist as ring-chain tautomeric mixtures of 1,3-*O,N*-heterocycles and the corresponding Schiff bases.[1] In these equilibria, Baldwin's rules[2] postulate that the ring-closure reactions of *endo-trig* type should be favoured for tetrahydro-1,3-oxazines (*6-endo-trig*), but disfavoured for oxazolidines (*5-endo-trig*).

For the 2-aryl-substituted saturated 1,3-*O,N*-heterocycles, the ring-chain tautomeric process can be described by equation (1), where K = [ring]/[chain], σ^+ is the Hammett-Brown constant of the 2-aryl substituent and ρ is a constant characteristic of the ring system. Its value is 0.76±0.04 for 1,3-oxazines and 0.60±0.04 for oxazolidines in $CDCl_3$ solution at room temperature.[3]

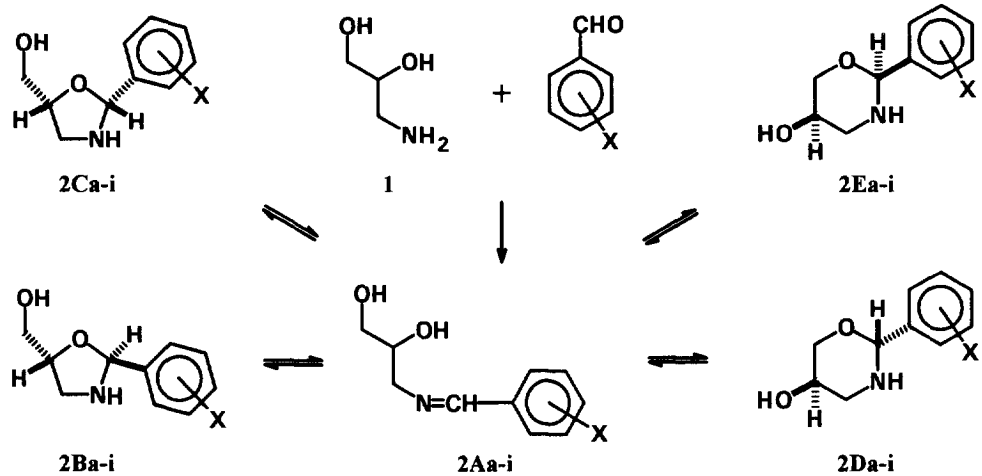
$$\log K = \rho\sigma^+ + \log K_0 \qquad (1)$$

The tautomeric character of the 1,3-*O,N*-heterocycles offers a great number of synthetic possibilities, *e.g.* they can be used for the addition of organometallics, in enantioselective syntheses of chiral amines,[4] or as aldehyde or ketone sources in the Hantzsch and Pictet-Spengler reactions.[5]

Aminodiols comprise a very interesting class of compounds because of their chemical and pharmacological importance. This structural moiety is present in numerous biologically active compounds, *e.g.* aminosugar derivatives,[6] chloromycetine,[7] and the diaminodiol core units of HIV protease inhibitors.[8] 1,2,3-Aminodiols are convenient synthons for the preparation of potentially useful compounds, *e.g.* 1,3,3-trinitroazetidine,[9] chiral 2-oxazolidones[10] and α-hydroxy-β-amino acids.[11] Despite the current chemical and pharmacological interest in compouds of this type, their reactions with oxo compounds have not been studied. Our aim was to investigate the ring closures of 3-amino-1,2-propanediol, the simplest model of this type, with aromatic aldehydes and to study the scope and limitations of equation (1) in these cases.

When 3-amino-1,2-propanediol (**1**) was reacted with nine different aromatic aldehydes in methanol at room temperature, the condensations took place in good to excellent yields. The ^1H NMR spectra unequivocally revealed that in $CDCl_3$ solution at room temperature all products (**2a-i**) participated in a five-component

equilibrium involving five- (**B**, **C**) and six-membered (**D**, **E**) heterorings and the corresponding Schiff bases (**A**). Equilibria of two to four components (the possible C-2 epimers of the ring forms and the *syn-anti* isomers of the Schiff bases) are known in the literature, all of them involving compounds prepared from difunctional 1,2- or 1,3-aminoalcohols.[1] To the best of our knowledge, the present paper describes the first example of a five-component ring-chain equilibrium of 1,3-*O,N*-heterocycles and also the first example of the preparation of favoured and unfavoured ring-closed forms in the same ring-chain tautomeric equilibrium of this type. Tice and Ganem described a three-component equilibrium involving oxazolidine and tetrahydro-1,3-oxazine rings with the Schiff base forms for the products obtained from hydroxyputrescine and benzaldehyde or *p*-nitrobenzaldehyde, but the exact tautomeric ratios and the relative configurations of the ring-closed components were not determined.[12] Similar competitions of unfavoured and favoured ring closures were observed in the ring-chain tautomeric processes of β-hydroxyimino ketones in which intramolecular cyclizations by attack of a hydroxy group to a C=O bond (*6-exo-trig*) or C=N bond (*5-endo-trig*) resulted in oxazolidines or 1,4-oxazines.[13]



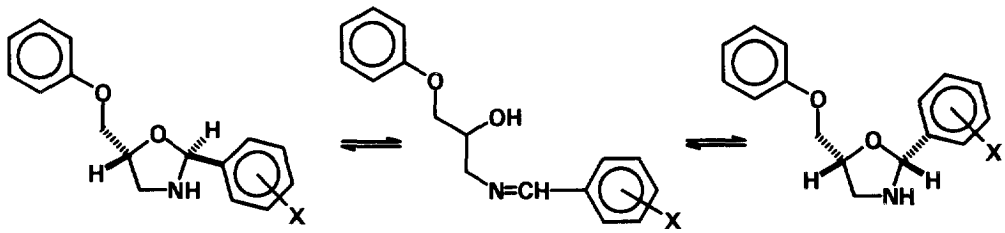
X = NO_2(*p*): **a**, CN(*p*): **b**, Br(*m*): **c**, Br(*p*): **d**, Cl(*p*): **e**, H: **f**, CH_3(*p*): **g**, OCH_3(*p*): **h**, $N(CH_3)_2$: **i**

Scheme 1

Figure 1 shows the 500 MHz ^{1}H NMR spectrum of the product (**2a**) of the reaction of 3-amino-1,2-propanediol and *p*-nitrobenzaldehyde. The four singlets in the region 5.15-5.75 ppm are those of H-2 of the four ring-closed tautomers, while the azomethine singlet is at 8.42 ppm. For the other aryl-substituted analogues, these singlets are in the same regions: 4.93-5.74 ppm for the ring H-2 and 8.14-8.42 ppm for the azomethine protons (Tables 1 and 2).

The formation of regioisomeric products in the ring closures of 3-amino-1,2-propanediol is well documented and the differentiation of the components is often a difficult spectroscopic task.[14] To help with the line assignment of H-2 in the oxazolidine and oxazine forms, 3-amino-1-phenoxy-2-propanol (**3**), the *O*-phenyl derivative of **1**, was reacted with the same nine aromatic aldehydes to give products **4a-i** (Scheme 2). Their ^{1}H NMR spectra showed that these compounds exist in $CDCl_3$ solution at room temperature as three-component equilibria involving the diastereomeric oxazolidine ring forms (**B**, **C**). The H-2 singlets of **4a-i** in the region 5.36-5.78 ppm correspond to the two lowest-field singlets of H-2 in the five-component equilibria of **2a-i**. If the chemical shifts of the derivatives bearing the same 2-aryl substituents are compared, the differences between the lowest-field H-2 signals for **2a-i** and those of the corresponding protons in **4a-i** are seen to be less than 0.1 ppm, which suggests that these lines arise from the oxazolidine rings (**B**, **C**).

Because of the small influence of the different 2-aryl substituents on the chemical shifts and couplings in the two series of compounds (**2a-i** and **4a-i**), a complete line assignment extending to the distinction of the H-2 lines of the diastereomeric ring forms was performed only in the case of the 2-(*p*-nitrophenyl) derivatives **2a** and **4a** (Table 1).



4Ba-i **4Aa-i** **4Ca-i**

For the meanings of letters **a-i**, see Scheme 1.

Scheme 2

From the spectra recorded immediately after the dissolution of **2a** and **4a** in $CDCl_3$, the lines of the imine forms (**A**) were assigned. The solutions were allowed to attain equilibrium. At this point, identification of the resonances from each distinct molecular species of the equilibrium mixture was possible by means of the COSY spectra. nOe difference spectra then allowed establishment of the relative stereochemistry of each component.

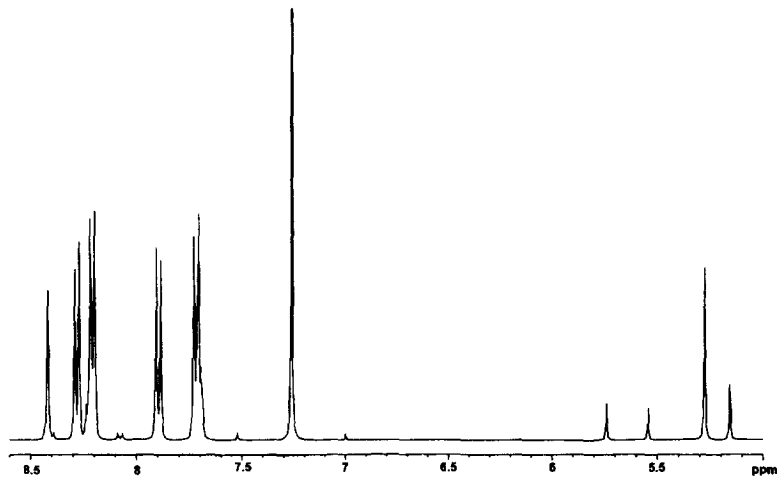


Figure 1. Part of ^{1}H NMR spectrum of compound **2a** (the small doublets at 8.08 and 8.40 ppm correspond to *p*-nitrobenzaldehyde which was formed by partial hydrolysis of **2a** on standing in $CDCl_3$)

From the COSY spectrum recorded after **4a** had attained equilibrium, the lines of the N-C*H*$_2$, O-C*H*$_2$ and O-C*H* protons in the same molecule were identified. The O-C*H* line at 4.41 ppm exhibited an nOe to the O-C*H*Ar-N line at 5.56 ppm (4.5%), indicating that they are *cis* and therefore relate to structure **C** (the other O-C*H* and O-C*H*Ar-N lines displayed no nOe at all). Structure **C** is in accordance with the observed nOe-s of its NC*H*$_2$ and O-C*H*Ar-N (4.6%) or O-C*H* (7.3% and 5.9% in the reverse direction) lines.

Because of the low abundance of the oxazolidine forms in the tautomeric equilibrium, only the lines from N-C*H*$_2$, O-C*H*$_2$ and O-C*H* relating to each of the six-membered ring components could be identified from

the COSY spectrum of **2a**. The predominance of chair conformations for differently substituted 1,3-oxazines was established earlier.[15]

Table 1. Selected chemical shifts (ppm) for compounds **2a** and **4a**

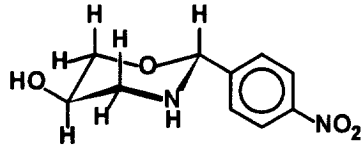
Compd.	O-C*H* *(m)*	OCH_2 *(m)*	N-CH_2 *(m)*	O-C*H*Ar-N *(s)*
2aA	4.05	3.83	3.76, 3.83	8.42[a]
2aB	b	b	b	5.74
2aC	b	b	b	5.54
2aD	3.71	3.56 *(ax)* 4.28 *(eq)*	2.85 *(ax)* 3.40 *(eq)*	5.16
2aE	3.64	4.09 *(ax)* 4.18 *(eq)*	3.18 *(eq)* 3.27 *(ax)*	5.28
4aA	4.31	4.06	3.92	8.43[a]
4aB	4.36[b]	4.04	3.17[b], 3.27[b]	5.79
4aC	4.41[b]	4.01[b], 4.08[b]	3.34[b]	5.56

[a]N=C*H*. [b]Overlapping multiplets.

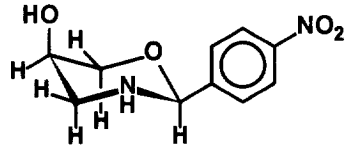
From the nOe-s observed between the *axial* O-C*H*Ar-N hydrogens and the *axial* hydrogens in the O-CH_2 and N-CH_2 methylenes, the structures can be assigned. The line at 5.28 ppm displays nOe-s and therefore a *syn diaxial* relationship with the resonances at 3.27 and 4.09 ppm. These resonances are seen to be parts of AB systems (3.73/3.18 and 4.09/4.18 ppm) in which there are only small additional couplings. These resonances must be from **E** in which H-5 is *equatorial* (Fig. 2).

The line at 5.16 ppm exhibits nOe-s to the resonances at 3.56 ppm and 2.85 ppm, both of which contain two large couplings. The 3.56 ppm resonance is therefore the *axial* O-C*H* and the 2.85 ppm resonance the *axial* N-C*H* resonance in **D**, both of which have a large geminal and a large *axial/axial* coupling. The COSY spectrum allows the assignment of the other resonances in **D**.

Interestingly, the major six-membered ring isomer is **E**, with an *axial* hydroxy group in position 5. The stability of this *axial* group must arise from hydrogen-bonding interactions to the ring nitrogen and oxygen atoms.



2Da



2Ea

Figure 2. Predominant conformations of compounds **2Da** and **2Ea**

As mentioned above, the δ values of the oxazolidines involved in the tautomeric equilibria **2** and **4** are very similar, suggesting that the two smallest of the four O-C*H*Ar-N lines of **2a** arise from the five-membered oxazolidine rings. In accordance with the known spectral data on the diastereomeric components in the ring-

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

Compd.	X	δ N=C*H* (*s*, **A**) and N–C*H*Ar–O (*s*, **B-E**) / (%)[a]					σ^+	log K(5)[b]	log K(6)[c]
		A	**B**	**C**	**D**	**E**			
2a	*p*NO_2	8.42 (39.6)	5.74 (6.3)	5.54 (5.7)	5.16 (14.1)	5.28 (34.3)	0.79	-0.5195	0.0864
2b	*p*CN	8.34 (42.4)	5.69 (6.2)	5.48 (5.7)	5.09 (13.4)	5.22 (32.3)	0.659	-0.5508	0.0344
2c	*m*Br	8.23 (56.1)	5.57 (4.9)	5.39 (4.7)	5.04 (10.0)	5.16 (24.3)	0.405	-0.7652	-0.2152
2d	*p*Br	8.24 (65.3)	5.55 (3.9)	5.39 (3.9)	5.04 (7.6)	5.15 (19.3)	0.15	-0.9225	-0.3830
2e	*p*Cl	8.16 (68.7)	5.52 (3.0)	5.34 (3.1)	4.98 (6.8)	5.12 (18.4)	0.114	-1.0511	-0.4368
2f	H	8.21 (72.0)	5.51 (3.2)	5.36 (3.6)	5.00 (6.2)	5.14 (15.0)	0	-1.0254	-0.5288
2g	*p*CH_3	8.14 (81.6)	5.46 (1.9)	5.30 (2.3)	4.93 (4.3)	5.09 (9.9)	-0.311	-1.2869	-0.7592
2h	*p*OCH_3	8.19 (87.9)	5.49 (1.3)	5.37 (1.5)	5.02 (2.7)	5.15 (6.5)	-0.778	-1.4965	-0.9774
2i	*p*$N(CH_3)_2$	8.15 (96.5)	5.48 (0.3)	5.38 (0.6)	5.00 (0.7)	5.15 (1.9)	-1.7	-2.0561	-1.5662
4a	*p*NO_2	8.43 (72.5)	5.78 (15.3)	5.55 (12.2)	–	–	0.79	-0.4202	–
4b	*p*CN	8.39 (70.0)	5.75 (13.1)	5.51 (16.9)	–	–	0.659	-0.3689	–
4c	*m*Br	8.25 (79.8)	5.63 (8.8)	5.41 (11.4)	–	–	0.405	-0.5978	–
4d	*p*Br	8.26 (84.0)	5.61 (6.6)	5.40 (9.4)	–	–	0.15	-0.7197	–
4e	*p*Cl	8.32 (84.7)	5.65 (6.3)	5.44 (9.0)	–	–	0.114	-0.7425	–
4f	H	8.25 (87.7)	5.59 (5.0)	5.41 (7.3)	–	–	0	-0.8514	–
4g	*p*CH_3	8.33 (89.6)	5.61 (4.2)	5.42 (6.2)	–	–	-0.311	-0.9351	–
4h	*p*OCH_3	8.28 (94.3)	5.59 (2.2)	5.41 (3.5)	–	–	-0.778	-1.2165	–
4i	*p*$N(CH_3)_2$	8.16 (98.2)	5.52 (0.6)	5.36 (1.2)	–	–	-1.7	-1.7433	–

[a] **[A]+[B]+[C]+[D]+[E] = 100%.** [b] **K(5) = ([B]+[C])/[A].** [c] **K(6) = ([D]+[E])/[A].**

chain equilibrium of **4a**, assignment of the line at 5.74 ppm to the O-C*H*Ar-N hydrogen in structure **B** and the line at 5.54 ppm to the corresponding hydrogen in structure **C** is very probable.

The tautomeric ratios were determined by integration of the O-C*H*Ar-N (ring) and N=C*H* (chain) singlets (Table 2). The results of the linear regression analysis according to equation (1) are given in Table 3. The data on the parent 2-aryl-substituted oxazolidines and tetrahydro-1,3-oxazines, taken from the literature,[3] are also given in Table 3.

The electronic effect of the 2-aryl substituent was marked in all four cases; the equilibria of **2** and **4** could be described by equation (1). The sum of the ratios for the five- and six-membered diastereomers were used in the case of **2** in the log K calculations. Within experimental error, the values of the constant ρ of the Hammett equation for the oxazolidine-type equilibria of **2** (0.62±0.02) and **4** (0.55±0.02) were very similar to the usual oxazolidine value (0.60±0.04). The constant ρ for the oxazine-type equilibrium of **2** (0.67±0.02) was slightly smaller than the usual oxazine value (0.76±0.04).

Table 3. Linear regression analysis data on compounds **2** and **4** and the parent 2-aryl-substituted oxazolidines (**5**)[3] and tetrahydro-1,3-oxazines (**6**)[3]

Compd.	No. of points	Slope (ρ)	Intercept	Correlation coefficient	c[a]
2[b]	9	0.62±0.02	-1.03±0.05	0.990	0.07
2[c]	9	0.67±0.02	-0.48±0.05	0.991	-0.33
4	9	0.55±0.02	-0.80±0.04	0.992	0.30
5	7	0.60	-1.10	0.989	0
6	7	0.76	-0.15	0.998	0

[a]See text. [b]For oxazolidine components of the equilibrium. [c]For tetrahydro-1,3-oxazine components of the equilibrium.

The sum (c) of the steric and electronic effects of the substituents at positions 4 and 5 (oxazolidines) or 4, 5 and 6 (1,3-oxazines) was earlier introduced[3] and defined as the difference of the data for the 4/5/6-substituted derivatives and the parent 2-aryltetrahydro-1,3-oxazines (-0.15) or oxazolidines (-1.10). Accordingly, the steric and electronic contributions of the hydroxymethyl (0.07) and phenoxymethyl groups (0.30) are positive, which means that they have stabilizing effects on the ring-closed form. The negative value of c for the oxazine-type equilibrium of **2** expresses a destabilizing effect of the hydroxy group on the ring form.

Baldwin's rules predict that the *5-endo-trig* ring-closures to give the oxazolidines should be disfavoured relative to the *6-endo-trig* closures giving the oxazines. However, Baldwin pointed out[2] that "... a *disfavoured* ring closure is not an impossible reaction, merely a process which may not compete effectively with alternative *favoured* ring closures or other reaction pathways." Baldwin's rules relate to the ease of a ring-closure reaction (*i.e.* kinetics). Our results relate to the stability of the products (thermodynamics), but support the general scope of the Baldwin's rules. The results presented in this paper show that, where equilibria are established in which both ring-closure routes can compete, the favoured *6-endo-trig* route does not exclude ring closures via the *5-endo-trig* route, but that the six-membered rings are the thermodynamically favoured products.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ solution at ambient temperature on Bruker MSL 500 and AM 400 spectrometers, with TMS as internal standard. For the equilibria to be established,[16] the compounds were left to stand in $CDCl_3$ at room temperature for 1 day before the ^{1}H NMR spectra were run.

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

General procedure for the preparation of **2a-i** *and* **4a-i**

Aminoalcohol **1** or **3** (5 mmol) was dissolved in methanol (30 ml) and an appropriate aromatic aldehyde (5 mmol) was added. After standing for 30 min at room temperature, the solvent was evaporated off and the oily product was crystallized by treatment with *n*-hexane–Et_2O (yield: 75-95%). The physical and analytical data on **2a-i** and **4a-i** are given in Table 4.

Table 4. Physical and analytical data on **2a-i** and **4a-i**

Compd.	M.p. (°C)	Found			Formula (M.W.)	Requires		
		C	H	N		C	H	N
2a	86-90[a]	53.38	5.76	12.96	$C_{10}H_{12}N_2O_4$ (224.22)	53.57	5.39	12.49
2b	89-91[a]	64.35	6.24	14.10	$C_{11}H_{12}N_2O_2$ (204.23)	64.69	5.92	13.72
2c	49-52[b]	46.64	4.80	5.31	$C_{10}H_{12}BrNO_2$ (258.12)	46.53	4.69	5.43
2d	73-75[a]	46.78	4.82	5.12	$C_{10}H_{12}BrNO_2$ (258.12)	46.53	4.69	5.43
2e	72-74[b]	56.49	5.38	6.87	$C_{10}H_{12}ClNO_2$ (213.67)	56.21	5.66	6.56
2f	77-80[b]	67.40	6.93	7.40	$C_{10}H_{13}NO_2$ (179.22)	67.02	7.31	7.82
2g	76-80[b]	68.82	7.74	7.17	$C_{11}H_{15}NO_2$ (193.25)	68.37	7.82	7.25
2h	79-83[b]	63.32	6.91	6.72	$C_{11}H_{15}NO_3$ (209.25)	63.14	7.23	6.69
2i	143-148[a]	64.54	7.84	12.12	$C_{12}H_{18}N_2O_2$ (222.29)	64.84	8.16	12.60
4a	107-110[a]	64.10	5.42	9.81	$C_{16}H_{16}N_2O_4$ (300.32)	63.99	5.37	9.33
4b	74-79[a]	73.02	5.66	9.75	$C_{17}H_{16}N_2O_2$ (280.33)	72.84	5.75	9.99
4c	77-78[a]	57.28	4.64	4.01	$C_{16}H_{16}BrNO_2$ (334.22)	57.50	4.83	4.19
4d	115-117[a]	57.94	5.23	4.58	$C_{16}H_{16}BrNO_2$ (334.22)	57.50	4.83	4.19
4e	112-114[a]	66.51	5.38	4.72	$C_{16}H_{16}ClNO_2$ (289.77)	66.32	5.57	4.83
4f	92-95[a]	74.92	6.88	5.30	$C_{16}H_{17}NO_2$ (255.32)	75.27	6.71	5.49
4g	77-79[a]	75.93	6.87	5.14	$C_{17}H_{19}NO_2$ (269.35)	75.81	7.11	5.20
4h	99-101[a]	71.48	6.28	4.65	$C_{17}H_{19}NO_3$ (285.35)	71.56	6.71	4.91
4i	92-94[a]	72.69	7.21	9.18	$C_{18}H_{22}N_2O_2$ (298.39)	72.46	7.43	9.39

[a]Recrystallized from iPr_2O–EtOAc. [b]Recrystallized from iPr_2O.

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