Ring–Chain Tautomerism in Oxazolidines

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Ring–chain tautomerism involving the reversible addition of a heteroatom to a heteropolar double bond[1] is a well-established process for 1,3-O,N-heterocycles.[2,3] Particular attention has been paid to the tautomerism of 1,3-oxazolidines,[4-7] which contrasts to Baldwin's rules.[8] In spite of the interest in this ring system, few papers[5] describe the quantitative determination of the ring–chain equilibria. The pioneering work by Paukstelis and Lambing[5b] reported that the tautomerism of 2-aryl-substituted 4,4-dimethyloxazolidines in CCl_4 can be described by eq 1, where $\rho = 0.54$, and σ^+ is the Hammett constant:

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

Alva Astudillo et al.[5d] reinvestigated this series in $CDCl_3$ and found that $\rho = 0.47$. It was recently stated[3] that the tautomerism of different 1,3-oxazine derivatives in $CDCl_3$ can practically always be described by eq 1 with $\rho = 0.76$-(4).

The aim of our study is a comparative quantitative study of the ring–chain tautomerism of four different series of 2-aryl-substituted oxazolidines: the parent compounds **1**, the 4,4-dimethyl-substituted derivatives **2**, and cyclohexane-fused trans (**4**) and cis (**6**) derivatives. Until now the correlation between Hammett σ^+ and $\log K_X$ only was investigated for 2-monosubstituted oxazines and oxazolidines, so a further aim of this study was to extend the treatment to 2,2-disubstituted derivatives of the latter.

Results and Discussion

The aryl-substituted compounds **1** and their 4,4-dimethyl-substituted derivatives **2** were prepared earlier.[4a,5d,9] The ring–chain tautomerism of **2** has been studied quantitatively[5b,d] whereas only qualitative observations are available on compounds **1**[4a] (Scheme I). The earlier syntheses were carried out under conditions of reflux or water separation[5d] from the corresponding amino alcohol and aldehyde. We have found that the reaction takes place quantitatively within 2 h in ethanol even at room temperature.

Only the phenyl and *p*-nitrophenyl derivatives were previously prepared from *trans*- (**3**) and *cis*-2-aminocyclohexanols (**5**).[10] Their condensation proceeds as readily as mentioned above[11] (Schemes II and III). The 2,2-disubstituted oxazolidines **7a–c** and tetrahydro-1,3-oxazines **8a–c** were prepared from 2-aminoethanol and 3-aminopropanol, respectively, with differently substituted acetophenones in toluene by azeotropic removal of water (Scheme IV).

The tautomeric ratio determination of compounds **1**, **2**, and **6** was based on the integrals of well-separated protons—the ring H-2 (ca 5.5 ppm) and the corresponding proton in the open-chain form (ca 8.3 ppm)—in the 400-MHz ^1H NMR spectra. Similarly, in the case of the ketone derivatives **7** and **8** the determination of the tautomeric ratios is based on the integration of well-separated methyl signals at 2.3 ppm for the chain and at ca. 1.6 ppm for the ring form. The experimental error in the integration was minimized by using identical concentrations and by following the equilibrations as a function of time. For compounds **1** and **2**, both components of the ring–chain tautomeric mixture were readily detectable. The products **4** did not exhibit a detectable amount of the ring form in $CDCl_3$; i.e., <0.01% of the ring form can be present, even for the *p*-nitrophenyl derivative **4a**.

The corresponding *cis*-amino alcohol **5**, however, gave products **6** which were mixtures of the open-chain and two ring C-2 epimers, the predominant form always being the *E* form of the open-chain tautomer.

Earlier observations showed the tautomerism process to be complete within a few seconds. However, for the crystalline products **6a** and **6g** the C-2 epimerization requires a few days in $CDCl_3$. The spectra taken immediately after dissolution of the starting material revealed only the kinetically controlled product **6C** besides the prevailing open-chain tautomer. Thereafter, a slow C-2 epimerization takes place, and the thermodynamically controlled product **6A** is always obtained in somewhat higher concentration than the **6C** epimer. In the solid state, it is likely that only the open-chain form (**6B**) is present, which in solution rapidly gives the kinetically controlled product **6A**. The second step is the slow C-2 epimerization. The oily products **6b–6f** gave the C-2 epimers in equilibrium amounts immediately after dissolution of the sample. The ratio of the two ring forms was always nearly 1:1, though with a slight excess of the **A** form.

The plots of eq 1 for compounds **1**, **2**, and **6** in $CDCl_3$ were a set of parallel lines with an average slope of 0.57

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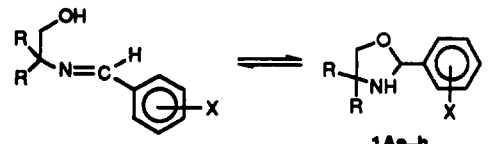
(11) Compounds 3–10 are racemates. In the formulas, only one of the enantiomers is shown.

0022-3263/93/1958-1967$04.00/0

Scheme I

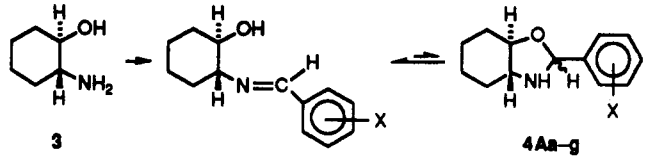


R = H: **1Ba–h**
R = Me: **2Ba–h**

1Aa–h
2Aa–h

X = *p*-NO_2, **a**; *m*-NO_2, **b**; *m*-Cl, **c**; *p*-Cl, **d**; H, **e**; *p*-Me, **f**; *p*-OMe, **g**; *p*-$N(Me)_2$, **h**.

Scheme II



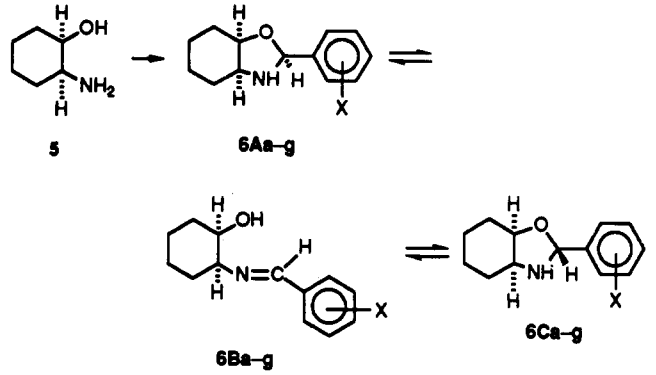
3

4Ba–g

4Aa–g

X = *p*-NO_2, **a**; *m*-Cl, **b**; *p*-Cl, **c**; H, **d**; *p*-Me, **e**; *p*-OMe, **f**; *p*-$N(Me)_2$, **g**.

Scheme III



5

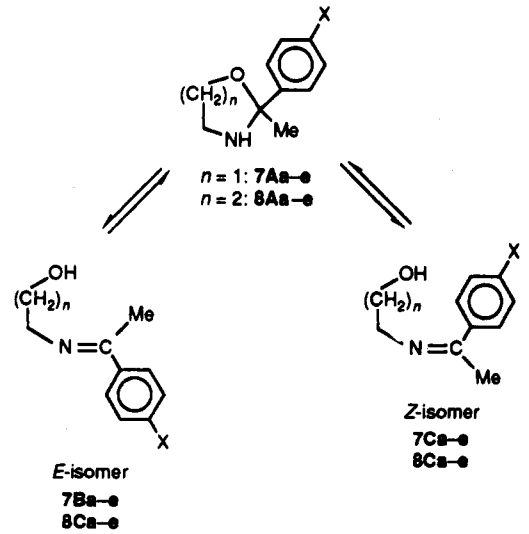
6Aa–g

6Ba–g

6Ca–g

X = *p*-NO_2, **a**; *m*-Cl, **b**; *p*-Cl, **c**; H, **d**; *p*-Me, **e**; *p*-OMe, **f**; *p*-$N(Me)_2$, **g**.

Scheme IV



n = 1: **7Aa–e**
n = 2: **8Aa–e**

E-isomer
7Ba–e
8Ca–e

Z-isomer
7Ca–e
8Ca–e

X = *p*-NO_2, **a**; *p*-Br, **b**; H, **c**; *p*-Me, **d**; *p*-OMe, **e**.

± 0.03 (Table I). Since the slope for compounds **2** differed somewhat from that given by Alva Astudillo et al.[5d] we remeasured the ring–chain ratios for these derivatives in DMSO-d_6 and CD_3OD. The solvent had only a small (but significant) effect on the slope (see Table I) whereas the intercept changed dramatically. For example, the ring/chain ratios for **2b** were as follows: $CDCl_3$ 79/21; CD_3OD 35/65; DMSO-d_6 13/87. The latter differences were due to the different hydrogen-bonding abilities of the solvents, as pointed out earlier.[5d]

Table I. Linear Regression Analysis Data for Compounds 1, 2, 6, 7, and 8

compd	no. of points	slope[a]	intercept[a]	*r*	solvent
1	7	0.60(4)	−1.10(2)	0.989	$CDCl_3$
2[b]	7	0.55(2)	0.35(1)	0.998	$CDCl_3$
		(0.47(2))	(0.20)	(0.993)	
2[b]	7	0.41(2)	−0.43(1)	0.996	CD_3OD
		(0.41(2))	(−0.41)	(0.989)	
2[b]	8	0.45(1)	−1.00(1)	0.998	DMSO-d_6
		(0.48(9))	(−0.96)	(0.877)	
6	7	0.56(0)	−1.34(0)	0.9999	$CDCl_3$
7[c]	5	0.57(4)	0.27(2)	0.994	$CDCl_3$
	5	0.47(3)	0.19(2)	0.993	$CDCl_3$
8[d]	5	0.73(7)	−0.01(3)	0.988	$CDCl_3$

[a] Standard deviations in parentheses. [b] The data in parentheses refer to the literature results[5d] measured at 60 MHz. [c] The first line refers to K = [ring]/[chain-(*E*)] and the second line to K = [ring]/[chain-(*E*+*Z*)]. [d] For the condensation products of 3-aminopropanol with aromatic aldehydes in $CDCl_3$: slope = 0.74(6) and intercept = 0.15(5).[3]

According to the linear regression analysis the slope values for compounds **7** and **8** are practically equal to those for the 2-monosubstituted derivatives (Table I). This indicates that a replacement of the 2-hydrogen with a methyl substituent does not change the physical meaning of the ring–chain equilibrium.

It is worth mentioning that the stabilization of the ring form due to the 2-methyl group (difference in the intercepts) is positive but not of the same magnitude for the two sets of compounds. This difference for oxazolidines is 1.37 but only 0.16 for 1,3-oxazines (for a comparison the stabilization effect due to the 4,4-dimethyl substitution in oxazolidines is 1.45).

Although the content of the ring form of the trans derivatives **4** in $CDCl_3$ is less than 0.01% their *N*-methyl derivatives should be stable. From *trans*- and *cis*-2-(methylamino)cyclohexanols with *p*-nitrobenzaldehyde, oxazolidines **9** and **10** were prepared. Their crystal structures were determined by means of X-ray diffraction (Figure 1).

The Gibbs standard free energy difference between *cis*- and *trans*-hydrindan is very small (ca. 1.3 kJ/mol) in favor of the trans isomer.[12] In spite of this there is a considerable difference between the rates of formation and the reactivities of the *cis*- and *trans*-fused 1,3-heteroanalogues of hydrindan. Several papers on 1,3-oxazolidines fused with the cyclohexane ring[13] and on tetrahydro-1,3-oxazines fused with the cyclopentane ring[14] describe large differences in the rates of formation and the reactivities of the cis- and trans-fused derivatives.

The differences in stability of the ring forms can be estimated from the ring–chain tautomeric results as follows. A constant *c*, the difference between the intercept for the parent compounds and that for the series of

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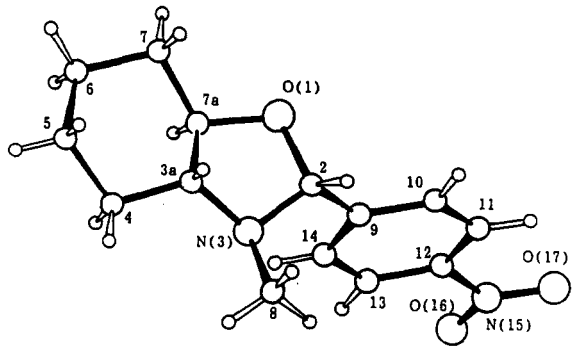
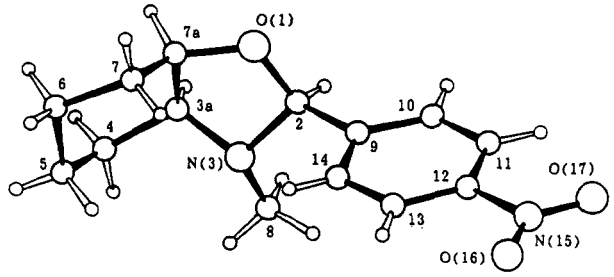


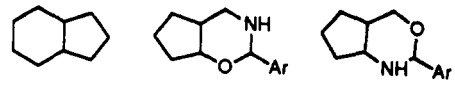
9



10

Figure 1. Perspective view of molecules **9** and **10** showing atom numbering. The bare numbers are for carbon atoms unless indicated otherwise. The H atoms are shown but not labeled.

compounds in question, is indicative of the sum of the steric and electronic effects of the substituents.[3] A positive value denotes stabilization and a negative one destabilization of the ring form due to the substituents. The *c* values for compounds **11**–**14** are 0.61, −1.5, 0.37, and −3.1, respectively.[15]



cis: **11** *trans*: **12** *cis*: **13** *trans*: **14**

Although the alkyl substituents increase the ring stability, the fusion strain is so high that *c* becomes negative (−0.23) even in the cis derivatives **6**. In the trans series **4** the amount of the ring form is always less than 0.01%, which means, if the slope value in the σ^+ correlation is assumed to be the same as for the other oxazolidines studied, that *c* must be less than −5.

Experimental Section

For general experimental details see ref 3.

Materials. The 2-aminoethanol, 2-amino-2-methylpropanol, 3-aminopropanol, aromatic aldehydes, and acetophenones were commercial products. *trans*-2-Aminocyclohexanol (**3**) and *trans*-2-(methylamino)-cyclohexanol (**9**) were prepared from cyclohexene oxide by ammonia or methylamine treatment. *cis*-2-Aminocyclohexanol (**5**) and *cis*-2-(methylamino)cyclohexanol were prepared from the trans counterparts via their *N*-acetyl derivatives, followed by thionyl chloride inversion to oxazoline and acidic hydrolysis.[16]

General Method To React 1,2-Amino Alcohols with Aromatic Aldehydes. Freshly distilled or crystallized 1,2-amino alcohol (1 mmol) was dissolved in 10 mL of ethanol, and an equivalent amount of freshly distilled or crystallized aldehyde was added. After the mixture had been left to stand for 2 h at ambient temperature, the solvent was evaporated off and the products were recrystallized. In the case of oily products, the evaporation was repeated after the addition of benzene. The oily products were dried in a vacuum desiccator for 24 h. The yields were over 85%. All new products gave satisfactory microanalyses (C, H, N).

Melting points and solvents for recrystallization (H, n-hexane; E, ethyl acetate) are as follows.

1a: 83–84 °C, H (lit.[9b] mp 82–83 °C). **1b**: 72–74 °C, E (lit.[4a] mp 73 °C). **1c**: oil. **1d**: 72–73 °C, H (lit.[9b] mp 71–73 °C). **1e**: oil (lit.[9b] bp 92 °C/0.7 mmHg). **1f**: 69–71 °C, H (lit.[9b] mp 67–69 °C). **1g**: oil (lit.[9b] bp 139 °C/1.2 mmHg). **1h**: 102–103 °C, E (lit.[9c] mp 103–104 °C).

2a: 64–65 °C, H (lit.[5d] mp 60 °C). **2b**: 124–125 °C, E (lit.[5d] mp 126 °C). **2c**: 77–78 °C, H (lit.[5d] mp 65 °C). **2d**: 64–65 °C, H (lit.[5d] mp 66 °C). **2e**: 64–65 °C, H (lit.[5d] mp 65 °C). **2f**: 54–55 °C, H (lit.[5d] mp 55 °C). **2g**: 52–53 °C, H (lit.[5d] mp 49 °C). **2h**: 105–106 °C, E (lit.[5d] mp 111 °C).

4a: 127–128 °C, H (lit.[10a] mp 127 °C). **4b**: 89–90 °C, H. **4c**: 132–133 °C, H. **4d**: 84–85 °C, H (lit.[10b] mp 90–92 °C). **4e**: 89–90 °C, H. **4g**: 99–100 °C, H.

6a: 71–72 °C, H (lit.[10a] mp 73–73.5 °C). **6b**: oil. **6c**: oil. **6d**: oil (lit.[10b] bp 122–123 °C/1 mmHg). **6e**: oil. **6f**: oil. **6g**: 85–86 °C, H.

Reaction of 2-Aminoethanol and 3-Aminopropanol with Acetophenones. 2-Aminoethanol or 3-aminopropanol (3 mmol) and an equivalent amount of the appropriately substituted acetophenone were refluxed in 25 mL of toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid for 8–10 h. Evaporation of the solvent left a viscous, pale yellow oil which was distilled (except **7a** and **8a**) on a Hickman still at 100–200 Pa (on an oil bath at 120–160 °C). The *p*-nitro derivatives **7a** and **8a** were crystalline products (**7a**: 88–89 °C, ether; **8a**: 128–129 °C, ethyl acetate).

***r*-7a,*t*-2,*t*-3a-3-Methyl-2-(*p*-nitrophenyl)perhydrobenzoxazolidine (9).** 258 mg (2 mmol) of *trans*-2-(methylamino)-cyclohexanol was refluxed with 302 mg (2 mmol) of *p*-nitrobenzaldehyde in 20 mL of ethanol. After 15 h the solvent was evaporated off. The desired product crystallized from hexane after vigorous scratching. After recrystallization from hexane, the product was obtained, mp 76–78 °C, yield 49%. ^{1}H NMR: H-2 4.69 ppm (s); *H*CO 4.19 ppm (m); *H*CN (2.75 ppm (m); NC*H*$_3$ 2.18 ppm.

***r*-7a,*c*-2,*c*-3a-3-Methyl-2-(*p*-nitrophenyl)perhydrobenzoxazolidine (10)** was prepared similarly to **9**, starting from *cis*-2-(methylamino)cyclohexanol. After recrystallization from hexane, the product was obtained, mp 68–69 °C, yield 64%. ^{1}H NMR: H-2 4.69 ppm (s); *H*CO 4.21 ppm (m); *H*CN 2.76 ppm (m); NC*H*$_3$ 2.19 ppm.

Supplementary Material Available: Analytical data for new oxazolidines **4a–g**, **6a–g**, and **7a–e** and tetrahydro-1,3-oxazines **8a–e**, discussion and relevant data on X-ray data, equilibrium constants, and the relevant ^{1}H NMR chemical shifts for the condensation products of 2-aminoethanol (**1**, Table I), 2-amino-2-methylpropan-1-ol (**2**, Table II), *cis*-2-aminocyclohexanol (**6**, Table III), 2-aminoethanol (**7**, Table IV), and 3-aminopropanol (**8**, Table V), and X-ray data for compounds **9** and **10** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) By mistake, the *c* values of compounds **11**–**14** were increased by 0.3 in an earlier paper.[14d]

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