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GAS-PHASE RING-CHAIN TAUTOMERISM IN 1,3-OXAZOLIDINES

Pirjo Vainiotalo[a,*] Sari Ronkanen[a], Ferenc Fülöp[b,§], and Kalevi Pihlaja[b,*]

[a]Department of Chemistry, University of Joensuu, P.O. Box 111, SF-80101 Joensuu, Finland; [b]Department of Chemistry, University of Turku, SF-20500 Turku, Finland.

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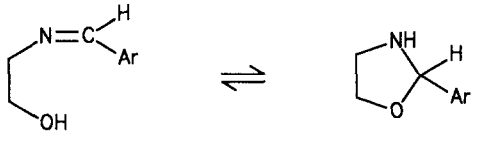
Abstract: Gas-phase ring-chain tautomeric equilibria with fourteen 1,3-oxazolidines derived from norephedrine and norpseudoephedrine were studied by means of mass spectrometry. Using 14 eV ionizing electrons these equilibria were comparable to those in non-polar solvent and obeyed the simple equation: $\log K_X = \rho\,\sigma^+ + c$, where ρ = 0.58±0.06 and 0.55±0.03 and c = 0.14±0.05 and 0.30±0.03 for norephedrine and norpseudoephedrine derivatives, respectively. Approximate values of enthalpy differences were also observed.

Ring-chain tautomerism is much studied and well understood in the liquid phase, especially with 1,3-O,N-heterocycles.[1-3] Special attention has been paid to the 1,3-oxazolidine ring system,[4-7] because according to Baldwins rules[8] the ring closure is formally disallowed 5-endo-trig process. In spite of this, a rapid equilibrium has observed to exist between the open chain Schiff's base (IA) and the ring form (IB).



IA **IB**

This equilibrium can be described with a simple equation,

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

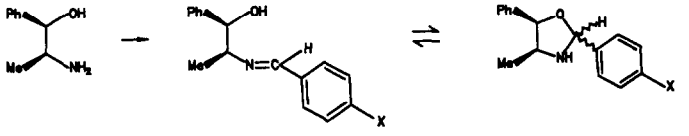
where K_X = [ring]/[chain] (X ≠ H) and ρ has value 0.47 - 0.57.[5b,5d,9,10] Slope (ρ) measures the sensitivity of the reaction to electronic effects of the substituent X. It depends on temperature and solvent but has found to be

§ Permanent Address: Institute of Pharmaceutical Chemistry, Albert-Szent-Györgyi Medical University, H-6720 Szeged, Hungary

relatively insensitive to the nature and stereochemistry of the substituents in the 1,3-oxazolidine ring. Instead, intercept log $K_{X=H}$ shows remarkable dependence on these factors.

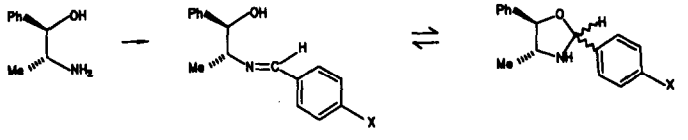
During the recent decades tautomeric equilibria have been much studied by means of mass spectrometry,[11] still there exist only one paper concerning ring-chain tautomerism in the gas phase.[12] The authors measured the changes in the relative abundances of peaks connected to one or another tautomeric form as a function of temperature. Although they were not able to determine the exact equilibrium constants from the mass spectrometric data, their data show that at least in case of 4,4-dimethyl-2-phenyl-1,3-oxazolidine and some aryl-substituted derivatives the tautomerism in the gas phase resembles that in non-polar solvent. To the advantage of gas-phase studies has to be counted the possibility to separate structural influences from solvation effects, which cannot be completely ruled out in the liquid phase.

The aim of our study was to compare gas-phase ring-chain tautomeric equilibria in the 1,3-oxazolidines derived from norephedrine, compounds **1 a - g** in Scheme 1, and norpseudoephedrine compounds **2 a - g** in Scheme 2,



1A a - g **1B a - g**

Scheme 1.



2A a - g **2B a - g**

Scheme 2.

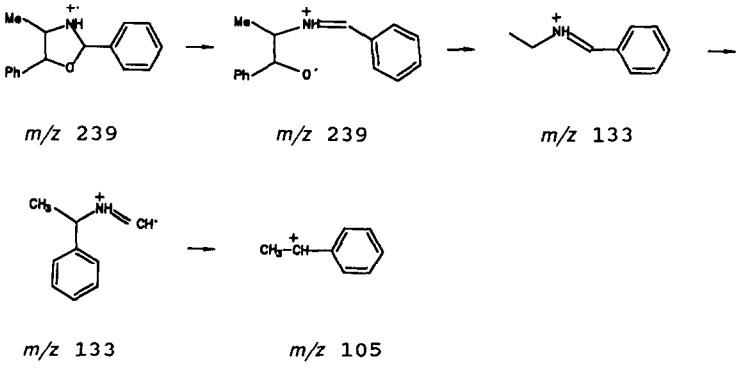
with those observed in the liquid phase. In this purpose their mass spectra were recorded as a function of ion source temperature and ionization energy. Because very little is known about the mass spectrometry of 1,3-oxazolidines[12,13] in general their basic fragmentation behaviour under electron ionization was studied using metastable ion analysis and exact mass measurement as well. The isobutane chemical ionization spectra were also

measured. In comparison, the 70 eV mass spectra of 3-methyl-2-phenyl- and 3-methyl-2-(p-NO_2-phenyl)-1,3-oxazolidines, compounds **3** - **4**, were also recorded.

RESULTS AND DISCUSSION

The 70 eV mass spectra of compounds **1 a - g** and **2 a - g** were very simple.[14] Only compounds **1 g** and **2 g** gave rise to a small molecular ion peak. With every compound there were practically only two primary fragment ions, namely $(M-106)^{+\cdot}$ and $(M-107)^{+}$ representing the loss of C_7H_6O and $C_7H_7O^{\cdot}$ from the molecular ions, respectively. According to basic fragmentation rules in mass spectrometry the formation of both of these fragment ions can be rationalized as a simple α-cleavage reaction with respect to nitrogen atom. In this case, the first mentioned ion can be connected to the ring form (IB) and the second to the open form (IA). This assumption was tested with compounds **3** and **4** where the formation of the open chain form is prohibited by the N-methyl substitution. They gave rise to a small amount of the $(M-107)^{+}$ ions,[14] which must have formed through a rearrangement reaction. This also means that part of the $(M-107)^{+}$ ions formed from compounds **1 a - g** and **2 a - g** may also originate from the ring forms through a hydrogen atom transfer.

Secondary fragmentations common to all of the compounds **1 a - g** and **2 a - g** were scant. The B/E spectra showed clearly that the primary fragments resulting from the open forms were more resistant towards the electron ionization than those from the ring forms. The most important secondary decomposition was the loss of CH_2N from the $(M-106)^{+\cdot}$ ions, which required a phenyl group migration to take place as presented in Scheme 3.



Scheme 3.

Table 1. The relative intensities of the $(M-107)^+$ [A] and $(M-106)^{+\cdot}$ [B] ions generated from norephedrine (**1 a - g**) and norpseudoephedrine (**2 a - g**) derivatives under 70 and 14 eV at constant source temperature (443 K).[14] Intensities are corrected for isotopic contributions.

			Norephedrine derivatives					
			70 eV			14 eV		
		σ^+	[A]	[B]	log [B]/[A]	[A]	[B]	log [B]/[A]
1a	p-NO_2	0.79	44.5	95.6	0.332	8.7	99.1	1.059
1b	p-CN	0.659	76.0	91.6	0.082	22.5	97.5	0.637
1c	p-Cl	0.114	100	51.3	-0.290	53.9	94.7	0.244
1d	H	0	100	36.3	-0.441	84.8	91.6	0.033
1e	p-CH_3	-0.311	100	29.8	-0.527	100	78.2	-0.107
1f	p-OCH_3	-0.778	100	17.6	-0.753	100	41.5	-0.382
1g	p-$N(CH_3)_2$	-1.7	100	5.3	-1.270	100	18.0	-0.745
			Norpseudoephedrine derivatives					
2a	p-NO_2	0.79	31.9	96.8	0.482	5.6	99.4	1.248
2b	p-CN	0.659	75.2	91.7	0.086	18.2	98.0	0.731
2c	p-Cl	0.114	100	71.4	-0.146	40.9	96.5	0.372
2d	H	0	100	54.1	-0.267	54.1	94.6	0.243
2e	p-CH_3	-0.311	100	43.8	-0.359	79.8	91.2	0.058
2f	p-OCH_3	-0.778	100	28.1	-0.551	100	71.7	-0.145
2g	p-$N(CH_3)_2$	-1.7	100	10.7	-0.971	100	25.3	-0.598

Especially intense fragmentations typical to the substituents X were observed in connection of the nitro group. Both of the primary fragment ions, $(M-106)^{+\cdot}$ and $(M-107)^{+}$, lost NO_2. In addition, $(M-106)^{+\cdot}$ eliminated consequently $OH^{\cdot}$ and $NO^{\cdot}$.

The ratio of the abundances of the $(M-106)^{+\cdot}$ and $(M-107)^{+}$ ions ([B]/[A]) was taken as a measure of [ring]/[chain] equilibrium (Table 1). Because much of the ion current were carried by these two ions, 23-55% under 70 eV, we believe that this ratio describes well the equilibrium process, although it is not possible to determine the exact equilibrium constant from these data. Supposing ionization cross-sections were the same for the tautomers, the ring form became still underrated in this ratio mainly for two reasons. It is possible, as mentioned above, that a small amount of the $(M-107)^{+}$ ions formed from compounds **1 a - g** and **2 a - g** might also originate from the ring forms through a hydrogen atom transfer. The larger decomposition cross-section of the $(M-106)^{+\cdot}$ ions compared to that of the $(M-107)^{+}$ ions also decreased the relative amount of the ring forms. Instead, when 14 eV electrons were used the much more reliable measure for the real equilibrium constant was available because now 80-90% from the total ion current was carried by the $(M-106)^{+\cdot}$ and $(M-107)^{+}$ ions, except in case of the nitro compounds 57% and 74%.

The tautomeric process in the gas phase resembled much that in the non-polar solvent. An electron-withdrawing substituent of the benzene ring at position 2 of the 1,3-oxazolidine ring shifted the equilibrium in favour to the ring form while an electron donating substituent favoured the open form. In general, the equilibrium was well described with Equation (1) (Table 2). The nitro compounds (**1 a** and **2 a**), however, systematically gave values too large to fit the line. For this reason, they were left out from the final calculations of the lines. The slopes of the calculated lines at normal source temperature under 14 eV, 0.58±0.03 for norephedrine derivatives and 0.55±0.02 for norpseudoephedrine derivatives, were strikingly close to the related values in the $CDCl_3$ solution at room temparature, 0.54±0.02 and 0.53±0.02, respectively.[9] As can be seen from Table 2, with norephedrine derivatives neither the source temperature nor the ionization energy had any great influence to the sensitivity of the tautomerism towards the electronic effects of the substituent X. Instead, with norpseudoephedrine derivatives the slope values at 70 eV were systematically smaller than those at lower ionization energies in all temperatures used. Although the differences were not large, they still seemed to be significant. This was verified by carrying out parallel measurements after several weeks. In comparison to the results in the solution this is quite an exceptional behaviour. This could be an

Table 2. The dependence of the slope and intercept values in equation log K_x = ρ σ^+ + log K_{x-H} on the ion source temperature and ionization energy.

Norephedrine derivatives

	14 eV			70 eV		
T (K)	slope	intercept	corr. coeff.	slope	intercept	corr.coeff.
443	0.58 ± 0.06	0.14 ± 0.05	0.980	0.55 ± 0.03	-0.35 ± 0.03	0.993
453	0.57 ± 0.06	0.12 ± 0.05	0.977	0.55 ± 0.03	-0.36 ± 0.03	0.993
468	0.58 ± 0.07	0.07 ± 0.05	0.973	0.54 ± 0.03	-0.39 ± 0.03	0.992
483	0.58 ± 0.06	0.00 ± 0.05	0.981	0.53 ± 0.04	-0.42 ± 0.03	0.990
498	0.64 ± 0.07	0.01 ± 0.06	0.975	0.54 ± 0.04	-0.45 ± 0.03	0.988
518	0.62 ± 0.08	-0.07 ± 0.06	0.969	0.55 ± 0.04	-0.48 ± 0.04	0.987
538	0.61 ± 0.06	-0.12 ± 0.06	0.974	0.54 ± 0.05	-0.50 ± 0.04	0.986
578	0.61 ± 0.08	-0.21 ± 0.06	0.970	0.52 ± 0.05	-0.55 ± 0.04	0.981
		16 eV			18 eV	
443	0.61 ± 0.04	-0.05 ± 0.03	0.992	0.60 ± 0.04	-0.14 ± 0.03	0.993
			Norpseudoephedrine derivatives			
443	0.55 ± 0.03	0.30 ± 0.03	0.993	0.44 ± 0.02	-0.21 ± 0.01	0.998
453	0.53 ± 0.04	0.27 ± 0.03	0.990	0.45 ± 0.02	-0.23 ± 0.02	0.996
468	0.56 ± 0.05	0.23 ± 0.04	0.986	0.44 ± 0.02	-0.27 ± 0.01	0.997
483	0.56 ± 0.05	0.16 ± 0.04	0.984	0.45 ± 0.02	-0.30 ± 0.02	0.996
498	0.60 ± 0.06	0.16 ± 0.05	0.980	0.44 ± 0.03	-0.33 ± 0.02	0.994
518	0.60 ± 0.06	0.08 ± 0.05	0.979	0.45 ± 0.03	-0.36 ± 0.02	0.992
538	0.55 ± 0.06	0.02 ± 0.05	0.975	0.49 ± 0.05	-0.39 ± 0.02	0.987
578	0.56 ± 0.07	-0.08 ± 0.07	0.972	0.44 ± 0.04	-0.45 ± 0.03	0.986
		16 eV			18 eV	
443	0.53 ± 0.03	0.11 ± 0.02	0.995	0.52 ± 0.02	0.03 ± 0.01	0.998

indication that the extra energy introduced to the system in the ionization increases the significance of the steric factors at the expense of the electronic effects. This phenomenon is reflected to the slope value and seems to occur easier with compounds **2**.

The [B]/[A] ratio varied considerably with the measurement conditions, as can be seen from Table 1 and the values of log K_{X-H} term in Table 2. The more energy was available the more favourable was the formation of the open chain forms. The amount of the open chain forms was increased with increasing temperature and decreased with decreasing energy of ionizing electrons. These changes in the [B]/[A] ratio as a function of measurement conditions imply that the tautomeric equilibria attained must mostly be a unimolecular process. Some attempts were also made to record the spectra as a function of probe temperature under constant source conditions. These, however, were not very successful but indicated that also the probe temperature might have some effect to the equilibria. At normal source conditions (70 eV) the [B]/[A] ratios agreed well with those in the $CDCl_3$ solution[9] with norephedrine derivatives (**1 a - g**). Instead, with norpseudoephedrine derivatives (**2 a - g**) the ring forms were at least nominally overwhelmingly more favourable in the solution than in the gas phase. Here, however, one has to keep in mind that under 70 eV the [B]/[A] does not reflect the real equilibrium as mentioned above. When 14 eV ionizing electrons were used the equilibrium corresponded to that in the solution with norpseudoephedrine derivatives, but favoured ring forms in case of norephedrine derivatives. In every case the difference between the intercept values with both group of compounds was much smaller than those in the solution implying that stereochemical effects caused by the substituent in the 1,3-oxazolidine ring did not play as large role in tautomeric equilibria as they do in the non-polar solution.

Reaction enthalpy ΔH for the chain $\rightleftharpoons$ ring tautomerism was also estimated using van't Hoff equation both under 70 and 14 eV for comparison (Table 3), although only the last mentioned results are significant. The stereochemistry of the substituents in the 1,3-oxazolidine ring had no effect to these values. According to our results the formation of the ring forms is a little more favourable with compounds **1 a - g** and **2 a - g** than with 4,4-dimethyl-2-phenyl-1,3-oxazolidine.[5a,12]

The mass spectral behaviour of the compounds studied was not very sensitive for the stereochemical orientation of the substituents in the 1,3-oxazolidine ring. The difference in the [B]/[A] ratio observed with the norephedrine and norpseudoephedrine derivatives made it possible to differentiate between

Table 3. The estimated - ΔH values (kJ/mol) for norephedrine (**1 a - g**) and norpseudoephedrine (**2 a - g**) derivatives under 14 and 70 eV.

Norephedrine derivatives

		14 eV		70 eV	
1a	p-NO_2	21.6 ± 0.8	0.996	11.1 ± 0.3	0.998
1b	p-CN	8.9 ± 1.8	0.897	5.5 ± 0.2	0.997
1c	p-Cl	15.4 ± 0.4	0.998	8.9 ± 0.3	0.997
1d	H	13.6 ± 0.4	0.997	7.2 ± 0.3	0.994
1e	p-CH_3	14.3 ± 0.4	0.998	9.2 ± 0.2	0.999
1f	p-OCH_3	13.6 ± 0.5	0.995	8.9 ± 0.3	0.997
1g	p-$N(CH_3)_2$	15.2 ± 0.9	0.990	4.0 ± 0.7	0.924

Norpseudoephedrine derivatives

		14 eV		70 eV	
2a	p-NO_2	20.5 ± 1.0	0.993	11.5 ± 0.3	0.997
2b	p-CN	8.8 ± 2.1	0.872	5.6 ± 0.3	0.993
2c	p-Cl	16.3 ± 0.9	0.992	10.0 ± 0.3	0.997
2d	H	16.0 ± 0.6	0.995	9.5 ± 0.2	0.998
2e	p-CH_3	15.3 ± 0.5	0.996	10.4 ± 0.4	0.996
2f	p-OCH_3	14.6 ± 0.4	0.998	9.9 ± 0.3	0.996
2g	p-$N(CH_3)_2$	13.7 ± 1.2	0.977	6.6 ± 0.3	0.997

these two groups of compounds, although no other differences were present. Earlier NMR results[9] show that when (±)-norephedrine and (1R,2R)-norpseudoephedrine are allowed to react with aromatic aldehydes a three-component equilibrium is attained in every case. In this equilibrium the ring form, where the 2-phenyl and 4-methyl groups are trans to each other, is always dominant over the related cis form. This information was unattainable with mass spectrometry because if both forms were present they gave rise to similar spectra. The isobutane chemical ionization spectra of the compounds offered another mean to differentiate between norephedrine and norpseudoephedrine derivatives. Namely, the first mentioned compounds always clearly eliminated water when with norpseudoephedrine derivatives this was a minor process or totally absent. The proton affinity of the CN-derivatives, compounds **1 b** and **2 b**, were considerably lower than those of the other compounds. This was indicated with a strong $(M+57)^+$ adduct ion peak, 51-55% relative abundance, when it with all the other compounds was a minor peak.

EXPERIMENTAL

Measurements were made with a Jeol JMS D300 mass spectrometer equipped with a combined EI/CI ion source and connected to a Jeol JMA 2000H data system. Samples were introduced through a direct inlet probe at temperatures 323 - 383 K. Typical source conditions were: temperature 443 K, electron energy 70 eV, accelerating voltage 3 kV and ionization current 300 μA, if not stated otherwise. Accurate mass measurements were made at resolution 5000 using the data system. Fragmentation pathways were verified with metastable ion analysis and/or CID spectra using linked scans at constant B/E.

The preparation and stereochemical assignments of the compounds examined have been described elsewhere.[9]

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14. The complete spectra are available from the authors.