RING-CHAIN TAUTOMERISM AND CRYSTAL STRUCTURE OF SOME 1,3-OXAZACYCLANES, AND THE ELECTROPHILIC SUBSTITUENT CONSTANTS FOR SOME HETEROARYL GROUPS IN SOLUTION AND IN THE GAS-PHASE

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Abstract – In principle, the ring-chain tautomeric ratios of a number of 2-heteroaryl-substituted oxazolidines and tetrahydro-1,3-oxazines are well suited for determination of the Hammett-Brown σ^+ constants of heteroaryl substituents such as 2-furyl, 3-furyl, 3-thienyl and 2-pyrrolyl in $CDCl_3$ solution and in the gas phase. However, a number of factors, and especially hydrogen-bonding, can change the monomeric character of either the ring or the chain form (or both), leading to deviations from the ideal σ^+ values. X-Ray analysis has demonstrated the chain structures of the products of the reactions of L-(-)-norpseudoephedrine and (±)-*trans*-2-aminomethylcyclohexanol with pyrrole-2-carboxaldehyde.

Determination of various substituent constants of heterocycles is of current interest.[1-3] Traditionally, determination of the Hammett-Brown σ^+ values of simple heteroaromatic systems is based on classical methods[4] such as solvolysis, pyrolysis and substitution reactions. Spectroscopic methods, including infrared (ir)[5,6] and ^{1}H and/or ^{13}C nmr[2,3] spectroscopy, are also used.

Dedicated to **Professor Alan R. Katritzky** on the occasion of his 65th birthday.

A new approach[7] was recently applied for determination of the σ^+ values of 2-, 3- and 4-pyridyl substituents.[8] The method is based on the observation[8-10] that the ring-chain tautomeric equilibria of oxazolidines and tetrahydro-1,3-oxazines can be described by the equation:

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

where K = [ring]/[chain] and ρ is a constant characteristic of the ring system. This equation and the ring-chain equilibria therefore offer a good means of calculating σ^+ values. The above approach gave good agreement with the literature values for 3- and 4-pyridyl derivatives. For the 2-pyridyl substituent, the σ^+ value determined *via* the ring-chain tautomeric method was about twice the earlier results. The difference is due to the extra stabilization of the ring form that results from intramolecular hydrogen-bonding.[8]

The purpose of the present work was to establish whether eqn (1) can be utilized for determination of the σ^+ values of electron-rich five-membered heteroaromatic systems including 2- and 3-furyl, 3-thienyl and 2-pyrrolyl substituents in solution and in the gas phase, and to determine the solid-state structure of some of the compounds studied.

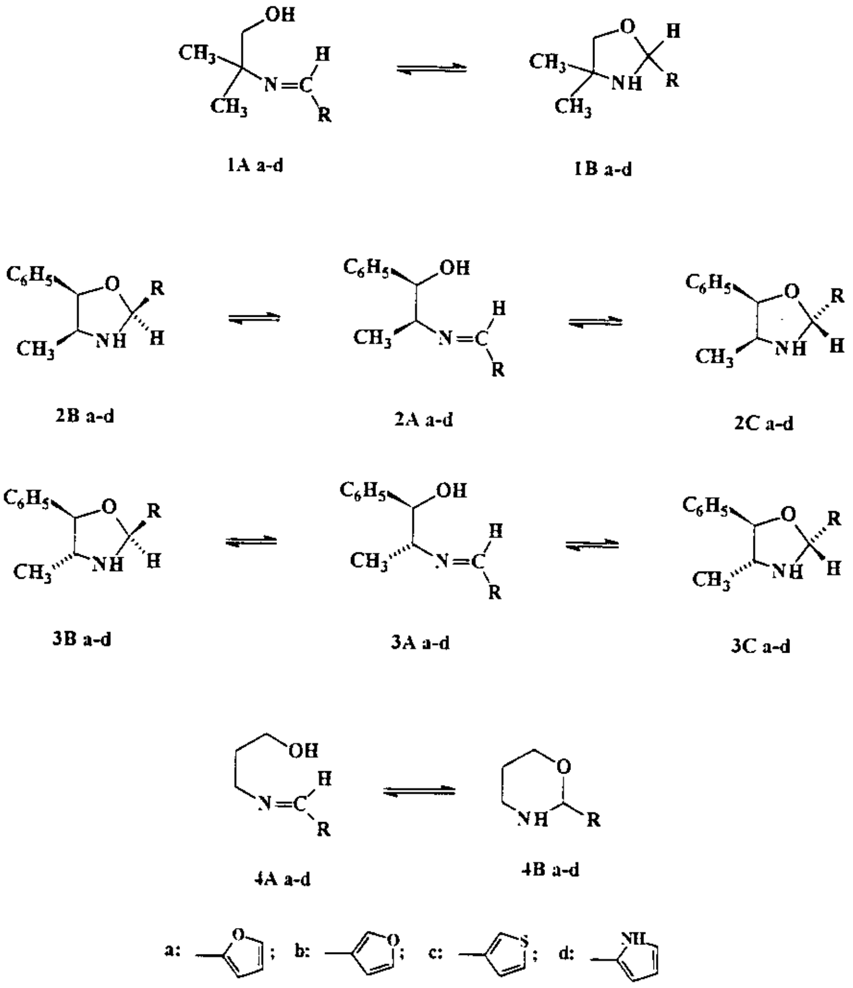
As a consequence of intra- and/or intermolecular interactions, many 2-pyrrolyl derivatives can be expected to display exceptional behaviour as compared with that observed earlier for 2-pyridyl compounds.[8] Since these interactions in the gas phase might differ from those observed in non-polar solvents, "electrophilic substituent constants" for the above-mentioned heteroaromatic systems were also measured in the gas phase. In principle, mass spectrometry can be used to study gas-phase ring-chain tautomerism *via* observations of the ratio of the relative abundances of ions connected with one or other tautomeric form.[10,11] The method has been successfully applied to oxazolidines, which usually give rise to only a few fragment ions, especially when low ionization energies are used.[10] For this reason, compounds derived from (±)-norephedrine and L(-)-norpseudoephedrine were also used here for gas-phase studies.

RESULTS AND DISCUSSION

For calculation of the σ^+ values of the 2- and 3-furyl, 3-thienyl and 2-pyrrolyl substituents, the aminoalcohols 2-amino-2-methylpropanol, (±)-norephedrine, L-(-)-norpseudoephedrine and 3-aminopropanol were reacted in ethanol with 2- or 3-furfural, thiophen-3-aldehyde or pyrrole-2-aldehyde. At room temperature, condensations took place nearly quantitatively within a few hours.

SOLUTION RESULTS

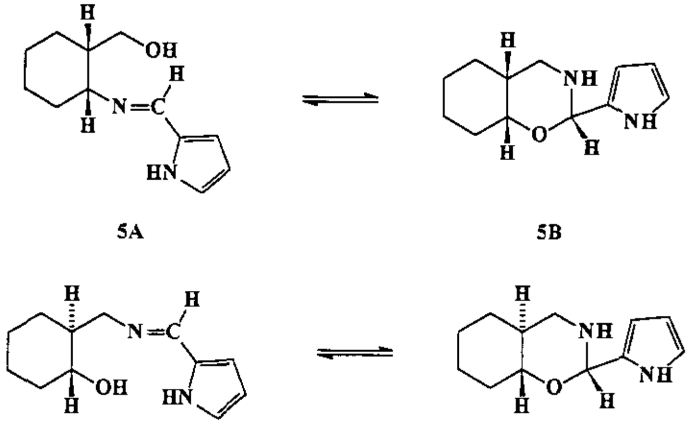
In $CDCl_3$ solution, products (**1-4**) exist as mixtures of ring-chain tautomers (Scheme 1), with the exception of 2-pyrrolyl derivatives, which exhibited only open-chain forms in their ^1H nmr spectra.



Scheme 1

Since it was earlier found[7,9] that the introduction of alkyl substituents increases the contribution of the ring form, *cis*-2-hydroxymethylcyclohexylamine and *trans*-2-aminomethylcyclohexanol were also reacted with pyrrole-2-aldehyde, which resulted in **5** and **6** (Scheme 2). As expected, these showed the presence of the ring forms.

Determination of the ring-chain ratios is based on the integrals of the corresponding lines in the 400 MHz ^1H nmr spectra. Mainly the 2H (ring form, at *ca* 5.6 ppm) and the corresponding CH=N (open-chain form, at *ca* 8.3 ppm) lines were used for integration. The percentage contributions of the ring forms are listed in Table 1.



5A **5B**

6A **6B**

Scheme 2

The present approach[8] applies the conventional eqn (1) for calculation of the σ^+ values. The actual ρ and log K_0 (= c) values (**1**: 0.55 and 0.35; **2**: 0.54 and -0.36; **3**: 0.53 and 0.34; **4**: 0.74 and -0.15; **5**: 0.75 and 0.79; **6**: 0.75 and 0.50) were taken from our previous work.[7,9] Table 2 gives the σ^+ values found earlier, together with those determined in this work.

FT-IR SPECTRA

The ^{1}H nmr results indicate that in $CDCl_3$ **3d** exists as the open-chain tautomer only, whereas **3a-c** involve 38, 65 and 62%, respectively, of the open-chain form. The presence of the open-chain tautomer is also well established from the ir spectra, where a strong C=N stretching band appears within the region 1635-1649 cm^{-1} (Table 3), both in the solid phase and in $CDCl_3$ solution. In consequence of the comparable amounts of the two tautomers for **3a-c** in $CDCl_3$ solution, no firm conclusions can be drawn about the existence of intramolecular hydrogen-bonds, since the OH stretching bands of the open-chain tautomers appear at about the same ir frequency as the NH stretching band of the ring tautomer. In the open-chain tautomer of **3d**, there is no possibility for an intramolecular hydrogen-bond, as confirmed by comparison with its crystal structure. The intermolecular hydrogen-bonds of especially **3b-c** seem to be weak, because no broad bands due to associated molecules appeared in the ir spectra of 0.1 mol dm^{-3} solutions of these compounds.

Table 1. Physical data on **1a-d** – **4a-d**, **5** and **6**, together with the calculated σ^+ values

No	mp (°C)	Solvent	Formula	Ring (%)	$\delta_{\text{N-CH-O}}$(s) (ring)	$\delta_{\text{CH=N}}$(s) (chain)	σ^+
1a	77-79[a]	hexane	$C_9H_{13}NO_2$	39	5.56	8.13	-0.99
2a[b]	105-106	hexane	$C_{14}H_{15}NO_2$	16[c]	5.59, 6.06	8.03	-0.67
3a[b]	68-71	hexane	$C_{14}H_{15}NO_2$	38[c]	5.72, 5.85	8.16	-1.04
4a	oil		$C_8H_{11}NO_2$	23	5.24	8.09	-0.51
						av.	**-0.80**
1b	oil		$C_9H_{13}NO_2$	65	5.50	8.27	-0.15
2b	99-101	hexane	$C_{14}H_{15}NO_2$	25[c]	5.57, 6.05	8.21	-0.22
3b	109-110	hexane	$C_{14}H_{15}NO_2$	65[c]	5.75, 5.85	8.25	-0.13
4b	oil		$C_8H_{11}NO_2$	30	5.15	8.20	-0.29
						av.	**-0.20**
1c	76-77	hexane	$C_9H_{13}NOS$	58	5.59	8.34	-0.38
2c	oil		$C_{14}H_{15}NOS$	27[c]	5.66, 6.12	8.29	-0.13
3c	106-107	hexane	$C_{14}H_{15}NOS$	62[c]	5.84, 5.94	8.33	-0.24
4c	oil		$C_8H_{11}NOS$	40	5.22	8.26	-0.04
						av.	**-0.20**
1d	120-122	hexane	$C_9H_{14}N_2O$	d	–	7.93	–
2d	106-107	hexane	$C_{14}H_{16}N_2O$	d	–	8.07	–
3d	147-148	ether	$C_{14}H_{16}N_2O$	d	–	7.92	–
4d	59-60	ether	$C_8H_{12}N_2O$	<1	5.27	8.03	–
5	135-137	hexane	$C_{12}H_{18}N_2O$	13	5.27	8.05	-2.15
6	119-121	hexane	$C_{12}H_{18}N_2O$	7	5.31	7.97	-2.22
						av.	**-2.2**

[a] lit.,[23] mp 73 °C. [b] lit., data[10]. [c] Sum of the ring forms. [d] Ring form not detected.

CRYSTAL STRUCTURES OF 3d AND 6.

Both of these compounds crystallize as chain tautomers (Figures 1 and 2). Fractional atomic coordinates for **3d** and **6** are listed in Table 5. Bond distances, and bond and selected torsion angles are given for **3d** in Table 6 and for **6** in Table 7. The bonding parameters are quite normal for both compounds, except for one bond angle [C(9)-C(10)-C(13) in **3d** and C(8)-C(9)-C(12) in **6**], which is quite large for an sp^2 hybridized carbon atom. The values are 128.1 (7)° and 129.3(4)°, respectively. However, in the copper(II) complex of the condensation product of 3-aminopropanol and pyrrole-2-carboxaldehyde, the relevant angle is 131.3(11)°.[12] The pyrrole and benzene rings are planar within experimental error. The cyclohexane ring has an almost ideal chair conformation, with absolute torsion angles of from 53.6(4)° to 55.9(5)°.

Table 2. Hammett-Brown σ^+ constants for electron-rich aromatic heterocyclic substituents

Method	Lit.	2-Furyl	3-Furyl	3-Thienyl	2-Pyrrolyl
Solvolysis	13	-0.85	-0.44	-0.44	-1.61
	14, 15a	-0.94	-0.49	-0.47	
Pyrolysis	16a	-0.89	-0.41	-0.38	
Protodesilylation	16b	-0.91	-0.45	-0.43	
Substitution	18	-1.03	(-0.88)	-0.50	
	19	-0.93	-0.44	-0.52	
C≡N stretching vibration[a]	6	(-0.13)	(0)	(-0.10)	-1.33
Ring-chain tautomerism	this work				
Solution		-0.80[b]	-0.20[b]	-0.20[b]	-2.2
Gas phase[c]		0.46	-0.10	-0.21	-0.70

Method	Lit.	2-Pyridyl	3-Pyridyl	4-Pyridyl
Pyrolysis	17a,b	0.80	0.30	0.87
	17c	0.76-0.89	0.28-0.30	0.85-0.87
Solvolysis	15b	0.75	0.54	1.16
	20	0.72-0.73	0.45-0.57	1.13-1.20
Rate of deuteration	21	–	–	0.67
Nitration	22	–	0.60-0.71	–
Ring-chain tautomerism				
Solution[d]	8	1.5±0.2	0.49±0.15	1.29±0.06
Gas phase[d]	this work	0.48±0.17	0.63±0.03	1.08±0.10

[a] Values in parentheses not included in averages. [b] Standard deviations 0.22, 0.07 and 0.13, respectively. [c] At 14 eV. [d] Standard deviations shown.

Table 3. Tentative assignments of the ν_{NH}, ν_{OH} and $\nu_{C=N}$ ir bands (cm^{-1}) in the solid phase and in $CDCl_3$ solution

Compound	Phase	ν_{NH}	ν_{OH}	$\nu_{C=N}$
3a	solid	3345	3252	1647
	$CDCl_3$	3308	3204	1645
3b	solid	3302	3194	1645
	$CDCl_3$	3293	3204	1649
3c	solid	3320	3212	1640
	$CDCl_3$	3295	3189	1640
3d	solid	3395	3315	1635

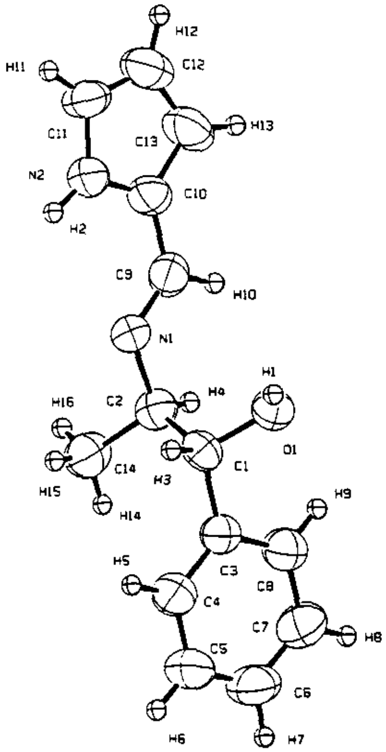


Figure 1. ORTEP drawing of **3d**

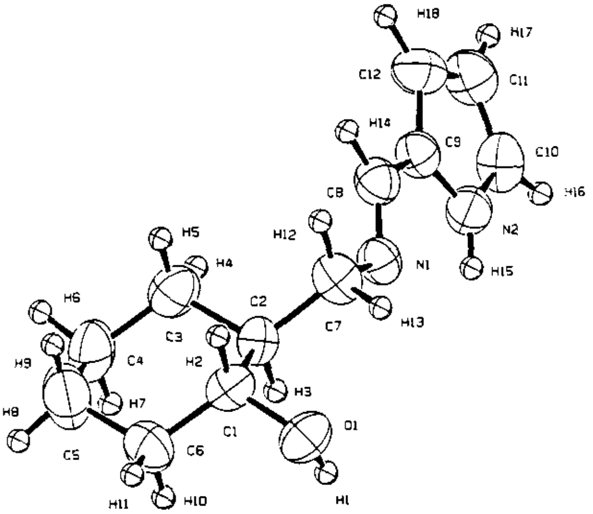


Figure 2. ORTEP drawing of **6**

3d is formed of layers of linear molecules. Intermolecular hydrogen-bonds (Table 8) in a layer bind the molecules into a polymer in which every second molecule is upside down. Between layers, there are only weak van der Waals contacts.

6 is likewise formed of layers of linear molecules, but the "basic structural" unit is a hydrogen-bonded dimer, which contains a (-)-(**6**) and a (+)-(**6**) molecule (Table 8). Between dimers and layers, there are only weak van der Waals contacts. Otherwise, the crystal structures of **3d** and **6** are as expected.

In $CDCl_3$ solution, the possibility of strong intermolecular hydrogen-bonding is reflected in the ring-chain equilibria as an increased stability of the chain tautomer, which explains the very negative σ^+ value for the 2-pyrrolyl group (Tables 1 and 2).

GAS-PHASE RESULTS

We recently found[10] that eqn (1) is also valid for the gas-phase tautomeric equilibria of oxazolidines derived from norephedrine and norpseudoephedrine. Since inter- and/or intramolecular interactions between the ring nitrogen and the heteroatom at position 2 of the heteroaromatic ring might be totally absent, in the gas phase or at least weaker in the gas phase than in solution, the mass spectrometric behaviour of oxazolidines was studied. Besides **2a-d** (norephedrine series) and **3a-d** (norpseudoephedrine series), the 2- (**2e**, **3e**), 3- (**2f**, **3f**) and 4-pyridyl (**2g**, **3g**) substituted norephedrine and norpseudoephedrine derivatives[8] were also examined.

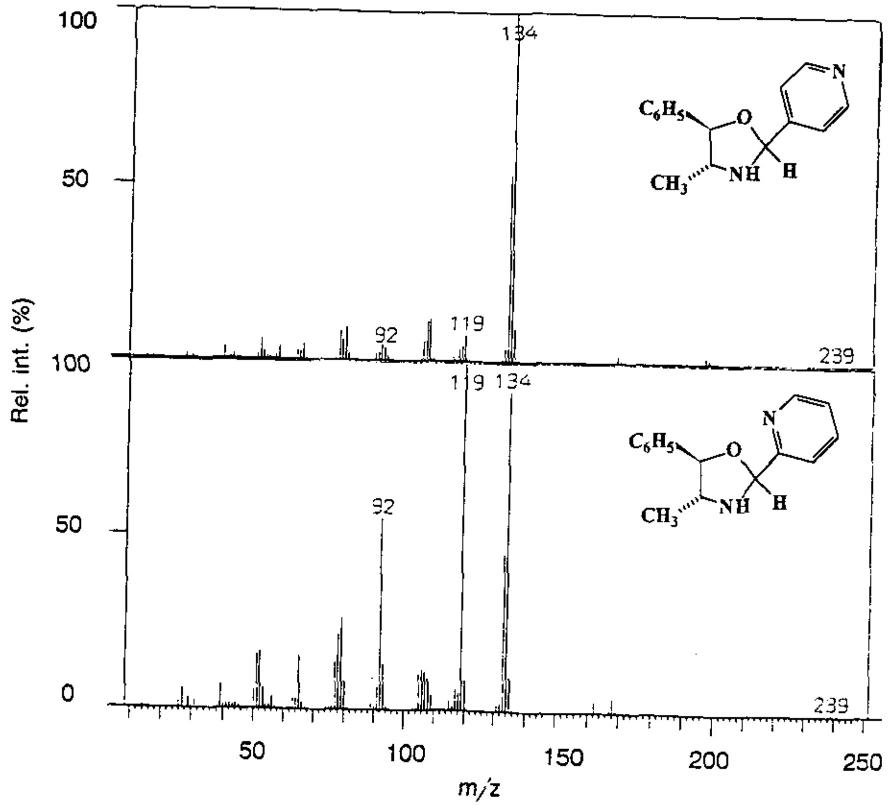


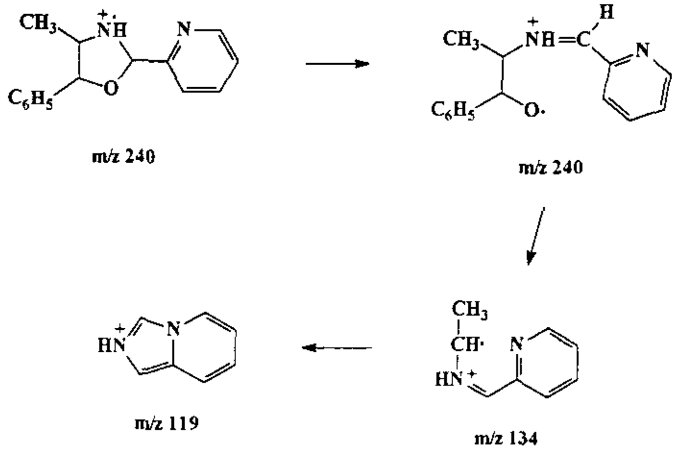
Figure 3. 3.70 eV mass spectra of **3g** and **3e**

Except for the 2-pyridyl derivatives, the fragmentations of these compounds were simple and closely resembled those of the related 2-aryl-substituted derivatives.[10] None of the compounds gave rise to the molecular ion peak. There were practically only two primary fragment ions: $[M-106]^{+\cdot}$ and $[M-107]^{+}$, produced by loss of C_7H_6O and $C_7H_7O^{\cdot}$, respectively, from the molecular ion. $[M-106]^{+\cdot}$ can be connected with the ring forms and rationalized as produced through two consecutive cleavages initiated by the radical site, whereas formation of $[M-107]^{+}$ must occur from the open-chain form through a simple α-cleavage reaction. Secondary fragmentations were rare, even when 70 eV ionization energy was used, and they were practically absent with 14 eV electrons.

Instead, both of the 2-pyridyl derivatives (**2e**, **3e**) gave rise to several abundant fragment ions (Figure 3), especially those at m/z 119 and 92. When 14 eV electrons were used, only the ions $[M\text{-}106]^{+\cdot}$, $[M\text{-}107]^{+}$ and m/z 119 yielded moderate fragment ion peaks. The ion $[C_7H_7N_2]^{+}$ at m/z 119 was most probably formed from $[M\text{-}106]^{+\cdot}$ by loss of the methyl radical and is therefore connected with the ring form. The easy elimination of $CH_3^{\cdot}$ can be explained by the formation of a stable bicyclic cation, as presented in Scheme 3. This kind of replacement reaction is not possible with the other 2-substituted heteroaromatic systems studied.

Analogously as in our previous work,[10] the ratio of the abundances of $[M\text{-}106]^{+\cdot}$ and $[M\text{-}107]^{+}$ was taken as a measure of the [ring]/[chain] equilibrium, except for the 2-pyridyl derivatives, where the abundance of the ion m/z 119 was added to that of $[M\text{-}106]^{+\cdot}$ (14 eV). The σ^{+} values were calculated from eqn (1), where the actual ρ and c values are as follows at 14 eV:[10] 0.58 and 0.15 for norephedrine derivatives (**2**), and 0.55 and 0.30 for norpseudoephedrine derivatives (**3**), respectively. The results obtained are listed in Table 4.

It is interesting that the σ^{+} values obtained for the pyridyl substituents in the gas phase do not differ essentially from those determined earlier by various methods (Table 2), including those obtained by the Fülöp-Pihlaja approach in $CDCl_3$ solution, with the exception of the σ^{+} value for the 2-pyridyl substituent determined with the latter approach. This supports the view that no complications due to strong hydrogen-bonding occur in the gas phase.



Scheme 3

Table 4. σ^+ Values determined mass spectrometrically in the gas phase at 14 eV, based on K = [ring]/[chain] = [B]/[A] = $[M\text{-}106]^+/[M\text{-}107]^+$, except for the 2-pyridyl derivatives (**2e**, **3e**), which are based on K = $([M\text{-}106]^+ + [m/z\ 119])/[M\text{-}107]^+$

No	[A]	[B]	log K	σ^+	No	[A]	[B]	log K	σ^+
2a	34.3	94.6	0.440	0.52	**2e**	62.7	114.5	0.319	0.31
3a	28.8	95.4	0.520	0.40	**3e**	27.9	126.2	0.656	0.65
2b	75.0	88.1	0.070	-0.12	**2f**	28.7	95.0	0.520	0.66
3b	51.7	91.8	0.250	-0.09	**3f**	22.2	96.2	0.638	0.61
2c	86.6	85.6	-0.005	-0.25	**2g**	18.8	96.8	0.712	0.99
3c	56.7	90.6	0.204	-0.17	**3g**	11.0	98.1	0.951	1.18
2d	100	58.4	-0.233	-0.64					
3d	100	67.7	-0.169	-0.85					

For the five-membered heteroaromatic substituents the situation is more complicated, since especially the gas-phase results differ clearly from most of the literature data (Table 2) and even from those determined *via* the ring-chain tautomeric equilibria for the 2-furyl and 2-pyrrolyl groups in $CDCl_3$ solution (Tables 1 and 2). The latter values also differ somewhat, but not so clearly, from the averages of the various values given in the literature (Table 2).

CONCLUDING REMARKS

The difference in the gas-phase and solution results can be explained as follows. The chain form is obviously stabilized by intermolecular hydrogen-bonds relative to the ring form (cf. the crystal structures above), especially for the 2-furyl and 2-pyrrolyl substituents. This stabilization disappears in the gas phase, making the ring form relatively more favoured. In the light of our earlier results, solute-solvent hydrogen-bonding is not of great importance in $CDCl_3$. It should also be emphasized that the literature data based on the C=N stretching vibrations are closest to our gas-phase values (Table 2).

In addition to the above, the following factors should be taken into account: (i) The $\sigma I/\sigma R^+$ balance, which determines the value of σ^+, is known to be medium dependent. The values (Table 2) for aqueous and chloroform solution, and for the gas phase, are therefore all likely to differ to some extent; (ii) for the substituents containing *ortho* heteroatom(s), the $\sigma I/\sigma R^+$ balance depends on the reaction system, which renders measurement of a true *ortho* σ-value of any sort difficult.[24]

EXPERIMENTAL

The ^1H nmr spectra were recorded on a Jeol GX-400 FT nmr spectrometer in $CDCl_3$, at ambient temperature, with TMS as internal standard. The experimental details were given earlier.[7]

The ir spectra of **3a-d** were recorded on a Mattson Galaxy 6020 FT-IR spectrophotometer. The KBr disk technique was applied to record the ir spectra of the solid samples. The spectra of **3a**, **3b** and **3c** in 0.1, 0.05 and 0.025 mol dm^{-3} $CDCl_3$ solution were also recorded by using a variable path-length cell with KBr windows.

Mass spectrometric measurements were made on a Jeol 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 313-368 K. Typical source conditions were: temperature 443 K, electron energy 70 or 14 eV, accelerating voltage 3 kV and ionization current 300 μA.

X-RAY CRYSTALLOGRAPHIC ANALYSES

Crystal data for **3d**. - $C_{14}H_{16}N_2O$, Mr = 228.29, orthorhombic, space group $P2_12_12_1$ (No. 14), a = 7.996(4), b = 25.995(5), c = 6.156(6) Å, V = 1280(2) Å^3 (by least-squares refinement on diffractometer angles for 18 automatically centred reflections, λ = 0.71069 Å), Z = 4, D_x = 1.185 g/cm^3, $\mu(MoK_\alpha)$ = 0.71 cm^{-1}, T = 296(1) K; colourless bars, crystal dimensions 0.12 x 0.18 x 0.22 mm.

Crystal data for **6**. - $C_{12}H_{18}N_2O$, Mr = 206.29, monoclinic, space group $P2_1/c$ (No. 14), a = 8.150(2), b = 17.155(6), c = 8.442(3) Å, β = 94.34(3), V = 1177(1) Å^3 (by least-squares refinement on diffractometer angles for 20 automatically centred reflections, λ = 0.71069 Å), Z = 4, D_x = 1.164 g/cm^3, $\mu(MoK_\alpha)$ = 0.70 cm^{-1}, T = 296(1) K; colourless bars, crystal dimensions 0.20 x 0.35 x 0.35 mm.

Data collection, analysis and refinement. - A Rigaku AFC5S diffractometer was used, with graphite-monochromated MoK_α radiation, and the ω-2θ-scan mode with an ω-scan rate of 8.0° min^{-1} and an ω scan width of (1.13 + 0.30 tanθ) for **3d**, and an ω scan rate of 4.0° min^{-1} and an ω scan width (1.15 + 0.30 tanθ) for **6**. The weak reflections [$I < 10\sigma(I)$] were rescanned once or twice.

For **3d**, 1374 unique reflections were obtained ($2\theta_{max}$ = 50°). Direct methods and difference Fourier syntheses; full matrix least-squares refinement; non-hydrogen atoms anisotropic; hydrogen atoms were calculated (H1 was refined) and were included with fixed isotropic temperature parameters (1.2 times B_{eq} of the carrying atom). The data were corrected for Lorentz and polarization effects. In the final

Table 5. Final fractional atomic coordinates for **3d** and **6**

	3d				**6**		
atom	x	y	z	atom	x	y	z
O(1)	0.6330(6)	0.2164(2)	0.7314(7)	O(1)	-0.0538(3)	-0.1350(1)	1.1035(3)
N(1)	0.9304(6)	0.2781(2)	0.6454(8)	N(1)	0.1243(4)	-0.0049(2)	0.7462(4)
N(2)	0.9215(7)	0.3765(2)	0.419(1)	N(2)	0.1870(4)	0.1398(2)	0.5787(4)
C(1)	0.7933(8)	0.1941(2)	0.693(1)	C(1)	0.1148(5)	-0.1507(2)	1.0792(5)
C(2)	0.9301(8)	0.2307(2)	0.775(1)	C(2)	0.1877(4)	-0.0890(2)	0.9764(4)
C(3)	0.8041(8)	0.1417(2)	0.801(1)	C(3)	0.3699(5)	-0.1079(3)	0.9570(5)
C(4)	0.8863(9)	0.1009(2)	0.705(1)	C(4)	0.4701(5)	-0.1191(3)	1.1142(6)
C(5)	0.902(1)	0.0547(3)	0.811(2)	C(5)	0.3953(6)	-0.1798(3)	1.2139(7)
C(6)	0.831(1)	0.0473(3)	1.009(2)	C(6)	0.2154(5)	-0.1607(3)	1.2356(5)
C(7)	0.745(1)	0.0871(3)	1.106(1)	C(7)	0.0910(5)	-0.0803(2)	0.8157(5)
C(8)	0.7340(9)	0.1346(2)	1.002(1)	C(8)	0.1993(5)	-0.0030(2)	0.6192(5)
C(9)	0.8586(8)	0.3174(2)	0.723(1)	C(9)	0.2372(4)	0.0674(2)	0.5349(4)
C(10)	0.8517(8)	0.3672(2)	0.616(1)	C(10)	0.2353(5)	0.1932(3)	0.4706(6)
C(11)	0.894(1)	0.4266(3)	0.367(1)	C(11)	0.3160(5)	0.1545(3)	0.3605(5)
C(12)	0.803(1)	0.4483(2)	0.526(2)	C(12)	0.3166(5)	0.0759(3)	0.3992(5)
C(13)	0.775(1)	0.4112(3)	0.687(1)				
C(14)	1.1018(8)	0.2068(2)	0.760(1)				

Table 6. Bond lengths (Å), and bond and torsion angles (°) with esds in parentheses for **3d**

bond	bond length (Å)	bonds	bond angle (°)	bonds	torsion angle (°)
O(1) - C(1)	1.426(7)	C(2) - N(1) - C(9)	118.1(5)	O(1) - C(1) - C(3) - C(8)	-39.5(8)
C(3) - C(8)	1.374(9)	C(10)- N(2) - C(11)	108.4(6)	O(1) - C(1) - C(3) - C(4)	142.2(6)
N(1) - C(2)	1.467(7)	O(1) - C(1) - C(2)	109.5(4)	O(1) - C(1) - C(2) - C(14)	174.1(6)
C(4) - C(5)	1.374(8)	O(1) - C(1) - C(3)	110.0(5)	O(1) - C(1) - C(2) - N(1)	-39.5(8)
N(1) - C(9)	1.267(7)	C(2) - C(1) - C(3)	111.8(5)	C(1) - C(2) - N(1) - C(9)	99.8(7)
C(5) - C(6)	1.35(1)	N(1) - C(2) - C(1)	110.0(5)	C(2) - N(1) - C(9) - C(10)	178.7(6)
N(2) - C(10)	1.355(8)	N(1) - C(2) - C(14)	108.0(5)	N(1) - C(9) - C(10)- N(2)	0(1)
C(6) - C(7)	1.38(1)	C(1) - C(2) - C(14)	111.9(5)	N(1) - C(9) - C(10)- C(13)	179.1(7)
N(2) - C(11)	1.360(7)	C(1) - C(3) - C(4)	122.0(6)		
C(7) - C(8)	1.392(8)	C(1) - C(3) - C(8)	119.6(6)		
C(1) - C(2)	1.535(8)	C(4) - C(3) - C(8)	118.4(6)		
C(9) - C(10)	1.455(8)	C(3) - C(4) - C(5)	120.9(7)		
C(1) - C(3)	1.519(7)	C(4) - C(5) - C(6)	120.9(8)		
C(10) - C(13)	1.368(8)	C(5) - C(6) - C(7)	119.5(7)		
C(2) - C(14)	1.510(9)	C(6) - C(7) - C(8)	119.8(7)		
C(11) - C(12)	1.344(9)	C(3) - C(8) - C(7)	120.6(6)		
C(3) - C(4)	1.379(8)	N(1) - C(9) - C(10)	124.3(6)		
C(12) - C(13)	1.399(9)	N(2) - C(10) - C(9)	123.2(6)		
		N(2) - C(10) - C(13)	108.7(6)		
		C(9) - C(10) - C(13)	128.1(7)		
		N(2) - C(11) - C(12)	108.5(7)		
		C(11) - C(12) - C(13)	108.2(6)		
		C(10) - C(13) - C(12)	106.3(7)		

cycles, 766 data with $I > 1\sigma(I)$ yielded an R value of 0.053 (Rw = 0.052, sigma weights) for 153 parameters; maximum/minimum residual electron density = 0.17/-0.16 e/Å^3.

For **6**, 2163 unique reflections were obtained ($2\theta_{max}$ = 50°). Direct methods and difference Fourier syntheses; full matrix least-squares refinement; non-hydrogen atoms anisotropic; hydrogen atoms with fixed isotropic temperature parameters (1.2 times B_{eq} of the carrying atom). The data were corrected for Lorentz and polarization effects. In the final cycles, 882 data with $I > 1\sigma(I)$ yielded an R value of 0.059 (Rw = 0.052, sigma weights) for 190 parameters; maximum/minimum residual electron density = 0.19/-0.17 e/Å^3.

All calculations were performed with TEXSAN-89 software[25] on a VAXSTATION 3520 computer. Neutral atomic scattering factors were taken from the literature.[26] Figures were drawn with PLUTO[27a] and ORTEP[27b].

Table 7. Bond distances (Å) and bond and torsion angles (°) with esds in parentheses for **6**

bond	bond distance (Å)	bonds	bond angle (°)	bonds	torsion angle (°)
O(1) - C(1)	1.431(4)	C(7) - N(1) - C(8)	118.6(3)	O(1) - C(1) - C(6) - C(5)	178.4(4)
C(2) - C(7)	1.523(5)	C(4) - C(5) - C(6)	110.8(4)	O(1) - C(1) - C(2) - C(3)	178.8(3)
N(1) - C(7)	1.454(4)	C(9) - N(2) - C(10)	108.7(3)	O(1) - C(1) - C(2) - C(7)	-56.8(4)
C(3) - C(4)	1.517(6)	C(1) - C(6) - C(5)	112.5(4)	C(1) - C(2) - C(7) - N(1)	159.4(3)
N(1) - C(8)	1.274(4)	O(1) - C(1) - C(2)	111.9(3)	C(2) - C(7) - N(1) - C(8)	114.1(2)
C(4) - C(5)	1.497(6)	N(1) - C(7) - C(2)	110.3(3)	C(7) - N(1) - C(8) - C(9)	178.5(4)
N(2) - C(9)	1.368(4)	O(1) - C(1) - C(6)	111.1(3)	N(1) - C(8) - C(9) - N(2)	-4.0(6)
C(5) - C(6)	1.526(6)	N(1) - C(8) - C(9)	124.7(4)	N(1) - C(8) - C(9) - C(12)	179.9(4)
N(2) - C(10)	1.372(5)	C(2) - C(1) - C(6)	111.6(3)		
C(8) - C(9)	1.448(5)	N(2) - C(9) - C(8)	123.1(3)		
C(1) - C(2)	1.518(5)	C(1) - C(2) - C(3)	109.7(3)		
C(9) - C(12)	1.365(5)	N(2) - C(9) - C(12)	107.5(4)		
C(1) - C(6)	1.510(5)	C(1) - C(2) - C(7)	112.3(3)		
C(10) - C(11)	1.352(6)	C(8) - C(9) - C(12)	129.3(4)		
C(2) - C(3)	1.541(5)	C(3) - C(2) - C(7)	111.3(3)		
C(11) - C(12)	1.389(6)	N(2) - C(10) - C(11)	108.0(4)		
		C(2) - C(3) - C(4)	113.1(3)		
		C(10)- C(11) - C(12)	108.0(4)		
		C(3) - C(4) - C(5)	111.4(4)		
		C(9) - C(12) - C(11)	107.9(4)		

The starting 2-amino-2-methylpropanol, (±)-norephedrine, L-(-)-norpseudoephedrine, 3-aminopropanol and aldehydes were commercial products. *cis*-2-Hydroxymethylcyclohexylamine was prepared by lithium aluminium hydride reduction of the corresponding amino acid as described earlier;[28] *trans*-2-

aminomethylcyclohexanol was prepared from *trans*-2-cyanocyclohexanol by catalytic reduction.[29] Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

Table 8. Distances (Å) and angles (°) involving hydrogen atoms of hydroxy and amino groups (X, Y = O or N) in **3d** and **6** with esds in parentheses

No		X-H/Å	H···Y/Å	X···Y/Å	<X-H···Y/°
3d	O(1)-H(1)···N(1^{i})	0.82(4)	2.02(4)	2.833(7)	170(7)
	N(2)-H(2)···O(1^{ii})	0.95	2.20	3.091	156
6	O(1)-H(1)···N(1^{iii})	0.93(4)	1.91(4)	2.795(4)	159(3)
	N(2)-H(15)···O(1^{iii})	0.87(3)	2.14(3)	2.970(4)	158(3)

Symmetry codes: i = x-½, ½-y, 1-z; ii = x+½, ½-y, 1-z; iii = -x,1-y,1-z

GENERAL PROCEDURE FOR THE REACTIONS OF 1,2- OR 1,3-AMINOALCOHOLS WITH HETEROAROMATIC ALDEHYDES

Amino alcohol (1 mmol) was dissolved in ethanol (10 ml), and aldehyde (1 mmol) was added. After standing for 3-4 h at room temperature, the solvent was evaporated off, and the products were crystallized by hexane/ether treatment, and recrystallized from an appropriate solvent (Table 1). When the products were oily, they were dried in a vacuum desiccator for 24 h.

* * *

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REFERENCES

1. R. August, C. Davis, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1265.
2. C. N. Robinson, L. J. Wiseman, Jr., and C. D. Slater, *Tetrahedron*, 1989, **45**, 4103.
3. V. P. Karavai, P. N. Gaponik, and O. A. Ivashkevich, *Magn. Reson. Chem.*, 1989, **27**, 611.
4. G. Marino, *Adv. Heterocycl. Chem.*, 1971, **13**, 235.
5. J. M. Angelelli, A. R. Katritzky, R. F. Pinzelli, and R. D. Topsom, *Tetrahedron*, 1972, **28**, 2037.
6. L. W. Deady, R. A. Shants, and R. D. Topsom, *Tetrahedron Lett.*, 1973, 1881.
7. F. Fülöp, K. Pihlaja, J. Mattinen, and G. Bernáth, *J. Org. Chem.*, 1987, **52**, 3821.
8. F. Fülöp, M. Dahlqvist, and K. Pihlaja, *Acta Chem. Scand.*, 1991, **45**, 273.

9. a) F. Fülöp, K. Neuvonen, Gy. Argay, A. Kálmán, G. Bernáth, and K. Pihlaja, *J. Org. Chem.*, 1993, **58**, 1967; b) F. Fülöp, G. Bernáth, J. Mattinen, and K. Pihlaja, *Tetrahedron*, 1989, **45**, 4317.
10. P. Vainiotalo, S. Ronkanen, F. Fülöp, and K. Pihlaja, *Tetrahedron*, 1990, **46**, 3683.
11. P. Vainiotalo, F. Fülöp, and K. Pihlaja, *Org. Mass Spectrom.*, 1991, **26**, 438.
12. J. A. Bertrand and C. E. Kirkwood, *Inorg. Chim. Acta*, 1971, **6**, 248.
13. G. T. Bruce, A. R. Cooksey, and K. J. Morgan, *J. Chem. Soc., Perkin Trans. 2*, 1975, 551.
14. E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Am. Chem. Soc.*, 1969, **91**, 7381.
15. a) D. S. Noyce, C. A. Lipinski, and G. M. Loudon, *J. Org. Chem.*, 1970, **35**, 1718; b) D. S. Noyce, J. A. Virgilio, and B. Bartman, *J. Org. Chem.*, 1973, **38**, 2657.
16. a) R. Taylor, *J. Chem. Soc. (B)*, 1968, 1397; b) R. Taylor, *J. Chem. Soc. (B)*, 1970, 1364.
17. a) R. Taylor, *J. Chem. Soc., (B)*, 1962, 4881; b) R. Taylor, *J. Chem. Soc. (B)*, 1971, 2382; c) H. B. Amin and R. Taylor, *J. Chem. Soc.,Perkin Trans. 2*, 1979, 228.
18. E. Maccarone, G. Musumarra, and G. A. Tomaselli, *J. Chem. Soc., Perkin Trans. 2*, 1976, 906.
19. S. Clementi, P. Linda, and G. Marino, *Tetrahedron Lett.*, 1970, 1389; *J. Chem. Soc. (B)*, 1970, 1153; G. Ciranni, and S. Clementi, *Tetrahedron Lett.*, 1971, 3833.
20. T. J. Broxton, G. L. Butt, L. W. Deady, S. H. Toh, R. D. Topsom, A. Fischer, and M. W. Morgan, *Can. J. Chem.*, 1973, **51**, 1620.
21. A. R. Katritzky, and I. Pojarlieff, *J. Chem. Soc. (B)*, 1968, 873.
22. a) P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc. (B)*, 1970, 117; b) C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and M. Viney, *J. Chem. Soc. (B)*, 1967, 1204.
23. M. Senkus, *J. Am. Chem. Soc.*, 1945, **67**, 1515.
24. M. Charton, *Prog. Phys. Org. Chem.*, 1971, **8**, 235.
25. TEXSAN: Single Crystal Structure Analysis Software, Version 5.0, Molecular Structure Corporation, The Woodlands, Texas, 1989.
26. International Tables for X-Ray Crystallography, Kynoch Press, Birmingham 1974, Vol. IV.
27. a) W. D. S. Motherwell, W. Clegg PLUTO78. A Program for Plotting Crystal and Molecular Structures. Univ. of Cambridge, England, 1978; b) Johnson, C. K. ORTEP-II. A Fortran Thermal-ellipsoid Plot Program for Crystal Structure Illustrations. Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, 1976.
28. G. Bernáth, K. Kovács, and K. L. Láng, *Acta Chim. Acad. Sci. Hung.*, 1970, **64**, 183.
29. F. Fülöp, I. Huber, G. Bernáth, H. Hönig, and P. Seufer-Wasserthal, *Synthesis*, 1991, 43.

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