

# Substituent Influences on the Stability of the Ring and Chain Tautomers in 1,3-*O,N*-Heterocyclic Systems: Characterization by $^{13}\text{C}$ NMR Chemical Shifts, PM3 Charge Densities, and Isodesmic Reactions

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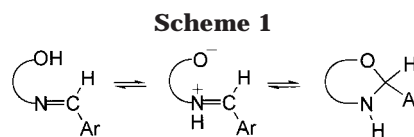
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Substituent effects on the stabilities of the ring and chain forms in a tautomeric equilibrium of five series of 2-phenyloxazolidines or -perhydro-1,3-oxazines possessing nine different substitutions at the phenyl moiety have been studied with the aid of  $^{13}\text{C}$  NMR spectroscopy and PM3 charge density and energy calculations. Reaction energies of the isodesmic reactions, obtained from the calculated energies of formation, show that electron-donating substituents stabilize both the chain and ring tautomers but the effect is stronger on the stability of the chain form than on that of the ring form. The  $^{13}\text{C}$  chemical shift changes induced by the phenyl substituents (SCS) were analyzed by several different single and dual substituent parameter approaches. The best correlations were obtained by equation  $\text{SCS} = \rho_{\text{F}}\sigma_{\text{F}} + \rho_{\text{R}}\sigma_{\text{R}}$ . In all cases the  $\rho_{\text{F}}$  values and in most cases also the  $\rho_{\text{R}}$  values were negative at both the C=N and C-2 carbons, indicating a reverse behavior of the electron density. This concept could be verified by the charge density calculations. The  $^{13}\text{C}$  chemical shifts of the C=N and C-2 carbons show a normal dependence on the charge density ( $q^{\text{tot}}$ ), but the charge density shows a reverse dependence on substitution. Correlation analysis of the  $^{13}\text{C}$  chemical shifts, solvent effect ( $\text{CDCl}_3$  vs  $\text{DMSO}-d_6$ ) on the NMR behavior as well as the effect of substituents on the electron densities and on the stabilities of the ring and chain tautomers show that the substituent dependence of the relative stability of the ring and chain tautomers in equilibrium is governed by several different electronic effects. At least intramolecular hydrogen bonding between the imine nitrogen and the hydroxyl group as well as polarization of the C=N bond seem to contribute in the chain form. Stereoelectronic and electrostatic effects are possible to explain the increase in stability of the ring form by electron-donating substituents.

## Introduction

1,3-*O,N*-heterocycles are known to be capable of ring–chain tautomerism in solution (see Scheme 1).<sup>1–6</sup> For the derivatives carrying a substituted phenyl group at C-2, the tautomeric equilibrium exhibits a clear aromatic substituent dependence. Electron acceptors increase the



relative contribution of the ring form but electron donors increase that of the chain form.<sup>1,4–6</sup> So, for eq 1 where  $K_X$  is [ring]/[chain] ratio with phenyl substituent X,

$$\log K_X = \rho\sigma \text{ (or } \rho\sigma^+) + c \quad (1)$$

$\sigma(\sigma^+)$  is the substituent constant and  $c$  is a constant characteristic of the ring system in question and the solvent used, positive  $\rho$  values are always observed.<sup>1,4–6</sup> In  $\text{CDCl}_3$  solution at ambient temperature,  $\rho$  is, on average,  $0.57 \pm 0.03$  for oxazolidines and  $0.76 \pm 0.04$  for 1,3-oxazines when  $\sigma^+$  constants are used.<sup>1b,e</sup>

The ring–chain ratio is clearly governed by electronic effects of the substituents at the aromatic ring. However, the mechanisms by which the substituents affect the mutual stabilities of the two tautomers are still poorly understood. The only topics considered in some detail concern the stability of the chain tautomer.<sup>4–6</sup> For the chain tautomer of the condensation products of *o*-hy-

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droxybenzylamine with substituted benzaldehydes, McDonagh and Smith<sup>4</sup> verified a linear correlation between the <sup>1</sup>H NMR chemical shift of the hydroxyl proton in CDCl<sub>3</sub> and the  $\sigma$  values (with the exception of *p*-dimethylamino substituent). If an intramolecular hydrogen bond between the phenolic hydroxyl group and the azomethine nitrogen is assumed, this suggests a variation in the strength of this bond along substitution. The concept of the significance of the hydrogen bond is supported by the solvent dependence of the equilibrium constants ( $K = 1.9\text{--}0.10$  when eight common solvents were used) in the case of 4,4-dimethyl-2-phenyloxazolidine studied by Paukstelis and Hammaker.<sup>3</sup> Equation 1 usually gives a better correlation with  $\sigma^+$  constants than with  $\sigma$  constants. Therefore, Paukstelis and Lambing<sup>5</sup> and later Alva Astudillo et al.<sup>6</sup> have suggested that resonance stabilization of the chain tautomer by electron donation through conjugation is involved, but no mechanism has been proposed. The substituent effects influencing on the stability of the ring tautomer have not been discussed at all.

The transmission of electronic substituent effects in aromatic compounds can be studied by <sup>13</sup>C NMR spectroscopy.<sup>7</sup> Correlation analysis of the C=N <sup>13</sup>C chemical shifts vs the Hammett or modified substituent constants has been performed in the cases of imines<sup>8,9c</sup> and hydrazones,<sup>9</sup> but until now the <sup>13</sup>C NMR spectroscopy is neglected in the case of imines capable of ring-chain tautomerism. The present tautomeric equilibrium is slow enough on the NMR time-scale that the signals of both tautomers can be clearly observed. Substituent induced changes in <sup>13</sup>C NMR chemical shifts (SCS) depend on the electronic states of the carbons in question. We consider that they can be useful in interpretation of the detailed mechanisms by which the substituents on the aromatic ring affect the tautomeric equilibrium. So, the relevant <sup>13</sup>C chemical shifts were detected for five different series, and the SCS's were analyzed with the aid of different substituent constants using both single and dual parameter treatments. In addition, electron densities, bond-orders, and heats of formation were calculated on PM3 level. The heat of formation values were used to evaluate the effect of substituents on the stabilities of the chain and ring forms with the aid of the relevant isodesmic reactions.

## Results

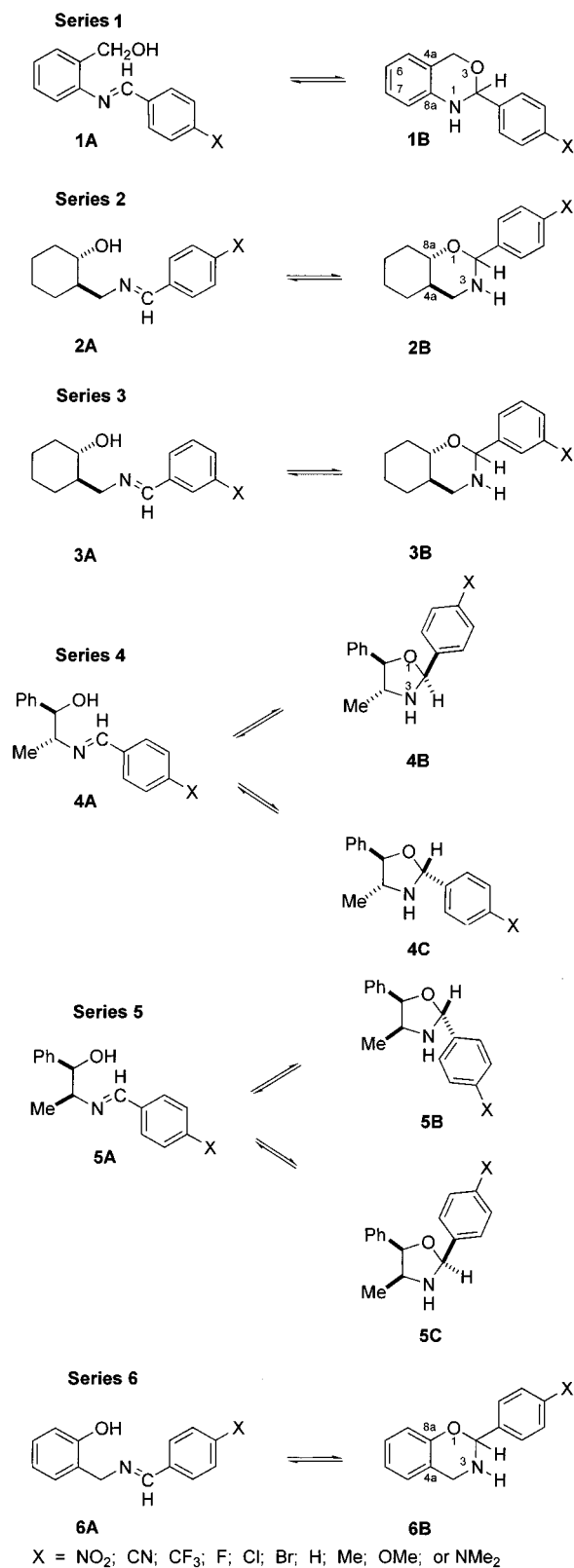
The different equilibrium sets investigated are specified in Scheme 2. To facilitate comparison, some of the carbons of the chain forms are indicated analogously with those of the ring forms and located in quotation marks.

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## Scheme 2. Specification of the Different Series of the Compounds Studied



For instance, "C-4a" in series 1A corresponds to C-4a in series 1B. The range values ( $\Delta\delta$ ) for the C=N carbon <sup>13</sup>C NMR chemical shifts, from 1.8 to 2.7 ppm, are similar to or somewhat smaller than those observed previously for other imines.<sup>8</sup> For the other side-chain carbons the shift variations are usually small, often under 1 ppm. However, the C-2 carbon chemical shifts of the ring forms are

**Table 1. DSP Analysis of Side-Chain SCS Data of C=N, Hydroxymethyl, and C-2 Carbons for Series 1–5 and 7 According to Eq 2<sup>a</sup>**

series	C=N					CH <sub>2</sub> OH <sup>b</sup>			C-2							
	1A	1A <sup>c</sup>	2A	3A	4A	5A	1A	1B	1B <sup>c</sup>	2B	3B	4B	4C	5B	5C	7 <sup>g</sup>
$\rho_F$	-3.7	-2.7	-3.0	-3.2	-3.6	-3.2	-0.9	-2.0	-1.9	-1.8	-2.1	-1.8	-1.6	-1.4	-1.3	-2.6
$\rho_R$	-0.1	0.6	0.2	-1.3	-0.5	-0.1	-1.1	-0.5	-0.5	-0.4	-0.6	-0.6	-0.5	-0.5	-0.3	-0.7
SD <sup>d</sup>	0.17	0.15	0.09	0.13	0.07	0.08	0.06	0.04	0.08	0.04	0.07	0.05	0.04	0.06	0.05	0.16
f <sup>e</sup>	0.11	0.11	0.07	0.11	0.05	0.07	0.14	0.05	0.11	0.06	0.09	0.07	0.07	0.11	0.09	0.16
r <sup>f</sup>	0.9859	0.9819	0.9938	0.9906	0.9980	0.9954	0.9923	0.9978	0.9910	0.9967	0.9926	0.9968	0.9967	0.9914	0.9928	0.9799

<sup>a</sup> In CDCl<sub>3</sub> if not otherwise stated. <sup>b</sup> In DMSO-*d*<sub>6</sub> the shift range was only 0.24 ppm while it was 1.36 ppm in CDCl<sub>3</sub>. <sup>c</sup> In DMSO-*d*<sub>6</sub>. <sup>d</sup> Standard deviation of the correlation. <sup>e</sup>  $f = \text{SD}/\text{RMS}$ , where RMS = root-mean-square of the data. <sup>f</sup> Correlation coefficient. <sup>g</sup> <sup>13</sup>C NMR chemical shift data from ref 10.

**Table 2. DSP Analysis of Side-Chain SCS Data for Series 1–5 According to Eq 2<sup>a</sup>**

series	"C-4a"		"C-8a"				"C-6"		CH <sub>2</sub> N		"C-4"		"C-5"
	1A	1A <sup>b</sup>	1A	1A <sup>b</sup>	2A	3A	1A	1A <sup>b</sup>	2A	3A	4A	5A	4A
$\rho_F$	0.4	0.7	-1.2	-1.0	-0.5	-0.7	1.2	1.0	-0.3	-0.7	0.4	0.5	-0.3
$\rho_R$	0.6	0.6	-1.5	-1.3	-0.7	-0.3	1.9	1.7	-0.3	-0.2	0.4	0.6	-0.3
SD <sup>c</sup>	0.05	0.06	0.05	0.05	0.06	0.04	0.03	0.04	0.02	0.04	0.07	0.09	0.04
f <sup>d</sup>	0.25	0.20	0.09	0.11	0.21	0.14	0.04	0.07	0.14	0.17	0.34	0.33	0.28
r <sup>e</sup>	0.9745	0.9783	0.9969	0.9952	0.9810	0.9818	0.9993	0.9980	0.9903	0.9718	0.9456	0.9541	0.9635

series	C-4		C-4a		C-8a		C-5		C-6			
	1B	4C	5C	1B	1B	1B <sup>b</sup>	2B	4B	4C	5B	1B	1B <sup>b</sup>
$\rho_F$	-0.7	-0.5	-0.5	0.3	-1.1	-0.7	0.2	0.1	0.9	0.6	1.0	0.5
$\rho_R$	-0.4	-0.3	-0.4	0.5	-1.0	-0.7	0.3	0.4	0.9	0.3	1.1	0.6
SD <sup>c</sup>	0.05	0.03	0.06	0.05	0.04	0.03	0.01	0.03	0.04	0.05	0.07	0.03
f <sup>d</sup>	0.16	0.14	0.28	0.29	0.08	0.10	0.13	0.26	0.09	0.21	0.14	0.12
r <sup>e</sup>	0.9846	0.9871	0.9603	0.9658	0.9965	0.9949	0.9930	0.9734	0.9967	0.9736	0.9908	0.9939

<sup>a</sup> In CDCl<sub>3</sub> if not otherwise stated. <sup>b</sup> In DMSO-*d*<sub>6</sub>. <sup>c</sup> Standard deviation of the correlation. <sup>d</sup>  $f = \text{SD}/\text{RMS}$ , where RMS = root-mean-square of the data. <sup>e</sup> Correlation coefficient.

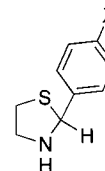
more sensitive to substitution ( $\Delta\delta = 1-1.5$  ppm). Also, for the hydroxymethyl carbon of series 1A, is  $\Delta\delta$  in CDCl<sub>3</sub> 1.4 ppm although in DMSO-*d*<sub>6</sub> it is only 0.24 ppm. For series 1A the <sup>13</sup>C chemical shifts of "C-6" or "C-8a" and for series 1B those of C-6 or C-8a also display large shift variations, from 1.4 to 2.2 ppm. Substituent effects on the <sup>13</sup>C chemical shifts of the benzylic ring carbons C-1' and C-4' are very large, of course, but these effects are not discussed in this connection. The detailed <sup>13</sup>C chemical shifts of the tautomers for series 1–5 are available in the Supporting Information (Tables S1–S4).

The C=N and C-2 <sup>13</sup>C NMR chemical shift data were analyzed according to the various single and dual parameter treatments. The correlations with  $\sigma$ ,  $\sigma^+$ , or  $\sigma^-$  constants alone are totally inadequate to explain the behavior of the C=N and C-2 <sup>13</sup>C chemical shifts (usually  $r < 0.90$ ). With  $\sigma_I$  or  $\sigma_F$  clearly better results are obtained, but in almost all cases even a better correlation is observed with a dual substituent parameter (DSP) treatment ( $\text{SCS} = \rho_I\sigma_i + \rho_j\sigma_j$ ). The best results in 13 cases of the total 15 are obtained with a combination of  $\sigma_F$  and  $\sigma_R$  parameters (eq 2)

$$\text{SCS} = \rho_F\sigma_F + \rho_R\sigma_R \quad (2)$$

In all cases is  $r \geq 0.98$  (cf. Table S5, Supporting Information). The dual parameter eq 2 dissects the effect of substituent into inductive (field effect) ( $\rho_F\sigma_F$ ) and resonance ( $\rho_R\sigma_R$ ) contributions. We use the term inductive for that part of the substituent effect which does not include resonance. It then can be a through-space or a through-bond effect.<sup>11</sup> Table 1 shows the correlation parameters  $\rho_F$  and  $\rho_R$  for the C=N and C-2 carbons for series 1–5, as well as for the hydroxymethyl carbon for series 1A. The  $\rho$  values calculated for the C-2 carbon in

series 7 from the literature shift data<sup>10</sup> are also included.

**Series 7**

X = NO<sub>2</sub>; CN; F; Cl; Br; H; Me; OMe; or NMe<sub>2</sub>

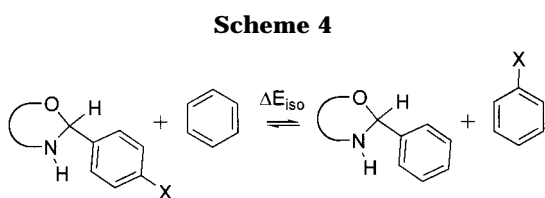
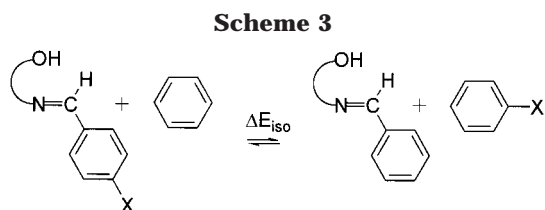
The variations in the  $\rho$  values obtained with different inductive ( $\sigma_I$  or  $\sigma_F$ ) and resonance ( $\sigma_R^+$ ,  $\sigma_R^0$ ,  $\sigma_R^{\text{BA}}$ ,  $\sigma_R^-$ ,  $\sigma_R$ ) parameter combinations were usually small. Because the best results for the <sup>13</sup>C chemical shift data of the C=N and C-2 carbons were obtained by eq 2, it was also used for other carbon shifts (Table 2). The good fits of the correlations prevailing in most cases indicate the electronic origin of the substituent dependence of the chemical shifts.

The calculated PM3 charge densities for series 1 and 6 (Tables S6–S9) as well as the heat of formation values for the same series (Table S10) are given in the Supporting Information. Statistical data for the different correlations of the SCS values, PM3 charge densities or bond-orders for series 1 and 6 are given in Tables S11 and S12. In Table S13 are collected the statistical data of the different correlations of the  $\Delta E$  (chain  $\rightleftharpoons$  ring) values for the same series. The  $\Delta E$  values are obtained as the difference of the heat of formation values (PM3) of the chain and ring forms. The isodesmic reactions shown in Schemes 3 and 4 were designed to determine on PM3 level of calculations the substituent influence on

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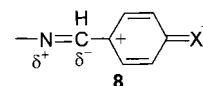
the stabilities of the chain and ring forms, respectively. The  $\Delta E_{180}$  values for series 1 and 6 are shown in Table 3.

### Discussion

**Isodesmic Reactions.** In the case of the both chain forms 1A and 6A,  $\Delta E_{180}$  values for the isodesmic reaction shown in Scheme 3 are negative for the electron-withdrawing substituents, and the reaction energy decreases as the electron-withdrawing ability of the substituent increases (cf. Table 3). With the electron-donating substituents  $\Delta E_{180}$  is positive. For the plot of  $\Delta E_{180}$  vs  $\sigma$  the slope is  $-0.93$  ( $r = 0.9533$ ; *p*-OMe derivative excluded) for series 1A and  $-1.11$  ( $r = 0.9472$ ) for series 6A. In light of these results electron-donating substituents stabilize the chain form while the electron-withdrawing substituents destabilize it. As regards the substituent influence on the stability of the ring form, the interpretation of the  $\Delta E_{180}$  values is somewhat more difficult. The electron-withdrawing substituents clearly destabilize the ring tautomer, except for 1B with  $\text{NH}_{\text{ax}}\text{Ph}_{\text{ax}}$  orientation where variation of the reaction energy is smaller and less systematic than for the other conformations of 1B or 6B. However, mainly negative  $\Delta E_{180}$  values are observed for electron-withdrawing substituents also in this case. With electron-donating substituents both positive and negative  $\Delta E_{180}$  values are observed. To obtain a better understanding of the influence of substituents we made cross-correlations of the  $\Delta E_{180}(\text{ring})$  values vs  $\Delta E_{180}(\text{chain})$  values for all the four conformations and for both series 1 and 6. The statistical data can be found in the Supporting Information (Table S14). The positive slopes of the correlations show that, with the exception of 1B  $\text{NH}_{\text{ax}}\text{Ph}_{\text{ax}}$ , the substituent influence is in the same direction for both the chain and ring forms. However, the effect is stronger on the stability of the chain forms than on that of the ring forms (slopes  $< 1$ ). Our results from the isodesmic calculations are in agreement with the experimental observations (cf. eq 1)<sup>1,4-6</sup>

**C=N Shifts and PM3 Calculations. Manifestation of C=N Polarization.** The SCS's for the C=N carbons of the open chain forms show highly negative values of the inductive correlation coefficient  $\rho_F$  in all cases (Table 1). The present  $\rho_F$  values (from  $-2.7$  to  $-3.7$ ) are, however, less negative than the corresponding values ( $-3.9$  and  $-4.1$ ) calculated earlier by the DSP method for the C=N carbon of *para*-substituted *N*-benzylideneanilines or those observed for *para*- or *meta*-substituted benzaldehyde (2-hydroxycyclohexyl)hydrazones (from  $-5.8$  to  $-6.2$ ).<sup>9c</sup> The value of  $-3.6$  has been previously detected

for *N*-benzylidenebenzylamines.<sup>9c</sup> The systematic effect of substituents on the C=N carbon shift and the "reverse" direction ( $\rho < 0$ ) of the inductive effect indicate that the electron-withdrawing substituents at the imine carbon, i.e., the shielding of the imine carbon is increased, while the electron-donating substituents decrease the electron density. This can be explained by the so-called  $\pi$ -polarization behavior.<sup>7b,e,12,13</sup> Accordingly, the substituent dipole polarizes each  $\pi$ -unit of the side-chain as a localized system (Scheme 5, 1A) affecting the inverse behavior of electron density. The  $\rho_F$  value for the *meta* series (series 3A) is somewhat more negative ( $-3.2$ ) than that for the respective *para* series (series 2A;  $-3.0$ ), which indicates that the substituent effect is at least mainly mediated through space. The  $\rho_R$  values are also negative in four cases of the total six (Table 1), but the contributions of the resonance effects are small. This is typical for imines, while for hydrazones large negative  $\rho_R$  values have been observed.<sup>7b,9c,d,13</sup> Negative  $\rho_R$ 's can be interpreted as a consequence of a secondary resonance effect, the so-called field-transmitted resonance-polar effect (cf. formula 8). The extent of the dipole set in the ring is



proportional to  $\sigma_R$ .<sup>9c,d,13,14</sup> The concept of  $\pi$ -polarization is generally accepted. However, it has also been criticized.<sup>15</sup> In any case, no alternative explanation for the *reverse* trend of the <sup>13</sup>C NMR chemical shifts has been given. Therefore we performed PM3 charge density calculations for series 1 and 6.

Probing the chain tautomers 1A and 6A helps to define the extent of propagation of the substituent effects in molecular framework. *First*, a linear correlation with a positive slope between  $\delta_{\text{C}(\text{C}=\text{N})}$  and the corresponding  $q_{\text{C}^{\text{tot}}}$  value (Table S11; line 1) supports the above interpretation: the low-frequency C=N carbon signal shift, i.e., smaller shift values in  $\delta$  scale, detected with the electron-withdrawing substituents are caused by the increased electron density, i.e., more negative  $q$  values, at the imine carbon. *Second*, the linear plots of  $q_{\text{C}^{\text{tot}}}$  vs  $\sigma$  or  $\sigma^+$  with negative slopes (Table S11; lines 2–9) prove the reverse trend of the variation of  $q_{\text{C}^{\text{tot}}}$ . (For the charge vs substituent constant correlations we have in this work used only single parameter correlations). Correlation with  $\sigma$  is somewhat better than with  $\sigma^+$ . *Third*, for the azomethine group, the plot of  $q_{\text{C}^{\text{tot}}}$  vs  $q_{\text{N}^{\text{tot}}}$  (Table S11, lines 10 and 11) shows an excellent linearity with a slope of ca.  $-1$  again for both of the systems studied ( $-1.06 \pm 0.02$  for 1A;  $-0.99 \pm 0.02$  for 6A).

The SCS behavior reflects variation of the electron density at the C=N carbon. The results attest the dipolar trend of the electron density at the C=N side-chain in harmony with the concept of  $\pi$ -polarization. However, as a concurrent/alternative explanation, we consider the resonance of the imine group as shown in Scheme 6.

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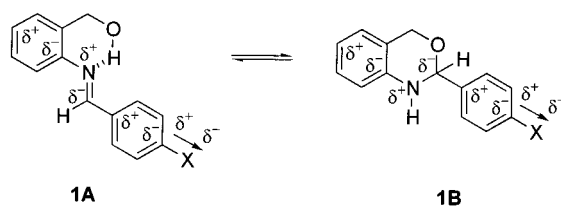
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**Table 3. Calculated  $\Delta E_{\text{iso}}$  (kcal mol<sup>-1</sup>) Values for the Isodesmic Reactions Shown in Scheme 3 for Series 1A and 6A and in Scheme 4 for Series 1B and 6B<sup>a</sup>**

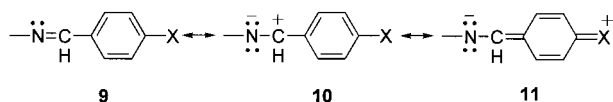
X	1A	1B/NH <sub>ax</sub> Ph <sub>eq</sub>	1B/NH <sub>ax</sub> Ph <sub>ax</sub>	1B/NH <sub>eq</sub> Ph <sub>eq</sub>	1B/NH <sub>eq</sub> Ph <sub>ax</sub>	6A	6B/NH <sub>ax</sub> Ph <sub>eq</sub>	6B/NH <sub>ax</sub> Ph <sub>ax</sub>	6B/NH <sub>eq</sub> Ph <sub>eq</sub>	6B/NH <sub>eq</sub> Ph <sub>ax</sub>
<i>p</i> -NO <sub>2</sub>	-1.04	-0.68	-0.03	-0.53	-0.84	-1.30	-0.64	0.17	-0.59	-0.88
<i>p</i> -CN	-0.57	-0.39	0.10	-0.32	-0.46	-0.72	-0.32	-0.47	-0.32	-0.49
<i>p</i> -CF <sub>3</sub>	-0.78	-0.46	-0.07	-0.48	-0.55	-0.87	-0.46	-0.64	-0.43	-0.56
<i>p</i> -F	-0.21	-0.16	-0.14	0.05	-0.20	-0.28	-0.21	-0.28	-0.15	-0.17
<i>p</i> -Cl	-0.18	-0.11	0.01	0.05	-0.12	-0.15	-0.16	-0.35	-0.07	-0.11
<i>p</i> -Br	-0.37	-0.21	-0.17	-0.04	-0.18	-0.42	-0.25	-0.48	-0.28	-0.28
H	0	0	0	0	0	0	0	0	0	0
<i>p</i> -Me	0.17	0.10	-0.08	0.17	0.17	0.18	-0.10	0.05	-0.08	0.08
<i>p</i> -OMe	0.84	0.67	-0.53	0.93	0.82	0.83	-1.09	0.49	-1.57	0.92
<i>p</i> -NMe <sub>2</sub>	0.51	-0.62	0.39	0.25	0.58	0.58	0.14	-0.06	0.32	-2.64

<sup>a</sup> Heat of formation values for compounds of series 1 and 6 are given in Table S10. Heat of formation values (PM3) for substituted benzenes (in kcal mol<sup>-1</sup>) are as follows with different substituents X: 14.54 (NO<sub>2</sub>); 58.48 (CN); -134.97 (CF<sub>3</sub>); -20.23 (F); 16.67 (Cl); 31.05 (Br); 23.45 (H); 14.10 (Me); -13.99 (OMe); 20.04 (NMe<sub>2</sub>).

**Scheme 5. Schematic Representation of Electronic Effects Based on <sup>13</sup>C Chemical Shift Variations and Charge Density Calculations along Substitution for Series 1**



**Scheme 6**



Electron-withdrawing substituents decrease the contribution of the resonance form **10** by inductively destabilizing the positive charge at the imine carbon. Consequently, electron shielding of the imine carbon is increased. In contrast, electron donation inductively stabilizes the structure **10**, and due to the increased contribution of **10**, electron density at the imine carbon is decreased. The small  $\rho_R$  values (Table 1) suggest that electron donation through conjugation (**11**) does not significantly contribute. The C=N bond-orders obtained by PM3 calculations for series 1 and 6 were also correlated with  $\sigma$  (Table S11; lines 13 and 14). The positive slopes support the concept of polarization of the C=N unit (cf. Scheme 6). The C=N bond-order increases with increasing electron-withdrawal, reflecting a decreased contribution of the resonance forms **10** and **11**.

**Hydroxymethyl Carbon Shift Variation in Series**

**1.** Solvent effect, CDCl<sub>3</sub> vs DMSO-*d*<sub>6</sub>, on the C=N, “C-4a”, “C-6”, “C-8a”, C-2, C-4, C-4a, C-6, or C-8a resonances is small,  $\leq 2.3$  ppm. However, the CH<sub>2</sub>OH carbon signal of series 1A is 4.6–5.7 ppm to a lower frequency in DMSO-*d*<sub>6</sub> as compared to its resonance signal in CDCl<sub>3</sub>. Further, although in CDCl<sub>3</sub> a clear substituent dependence is observed for that carbon ( $\Delta\delta = 1.36$  ppm; Table 1:  $\rho_F = -0.9$ ,  $\rho_R = -1.1$ ), in DMSO-*d*<sub>6</sub> the substituent dependence is very slight ( $\Delta\delta = 0.24$  ppm). Obviously the intramolecular hydrogen bond prevailing in CDCl<sub>3</sub>, and mediating substituent effects, is replaced by an intermolecular hydrogen bond with the solvent DMSO-*d*<sub>6</sub>. This decreases the sensitivity of the hydroxymethyl carbon to the phenyl substituent effects in DMSO-*d*<sub>6</sub>. With oxazolidines the open-chain form is strongly favored in solvents where hydrogen bonding of the hydroxy group

to the solvent is possible.<sup>3</sup> Further, the dependence of  $\rho$  on solvent (eq 1) for substituted 4,4-dimethyl-2-phenyl-oxazolidines supports the above conclusion.<sup>1e</sup>

**Stability of the Chain-Tautomer in the Light of the Polarization of the C=N Moiety.** The positive Hammett  $\rho$  values in eq 1 mean that the electron-withdrawing substituents stabilize the ring form relative to the chain form. The  $\Delta E$  values (in kcal mol<sup>-1</sup>) for the ring-chain equilibrium for series 1 and 6 were obtained as the difference of heat of formation values of the corresponding ring and chain tautomers. Significant correlations of  $\Delta E$  vs  $\sigma$  or  $\sigma^+$  are observed with NH<sub>ax</sub>Ph<sub>eq</sub> or NH<sub>ax</sub>Ph<sub>ax</sub> orientations of the ring forms (Table S13). Interestingly, a good correlation is observed between the logarithm of the experimental equilibrium constant  $K^{1b,4}$  and the  $\Delta E$  value for series 1 and 6 ( $r = 0.9692$  and  $0.9625$ , respectively; Table S13). These results support the model of substituent influences on ring–chain tautomerism proposed.

The isodesmic calculations for series 1 and 6 showed that increase in electron-donation ability of the phenyl substituent stabilizes the chain form. McDonagh and Smith<sup>4</sup> observed a linear correlation between the <sup>1</sup>H NMR chemical shift of the hydroxyl proton and  $\sigma$  substituent constant for series 6A in CDCl<sub>3</sub>. Electron-donating substituents caused a high-frequency shift of the phenolic proton *intramolecularly* hydrogen bonded to the azomethine nitrogen indicating an increase in electron density at the acceptor. The present results give an explanation for this behavior. Although electron-donating substituents decrease the electron density at the imine carbon they increase it at the donor imine nitrogen (cf. discussion above and Scheme 5) and the intramolecular hydrogen bond is strengthened. The presence of an intramolecular hydrogen bond is also manifested as a smaller numerical value of  $\rho_F$  (cf. above) when compared with imines without an intramolecular hydrogen bond. Obviously, with compounds capable of hydrogen bonding the double bond nature of the C=N unit is diminished.

For series 6A, an excellent correlation between the <sup>1</sup>H NMR chemical shifts of the hydroxyl proton<sup>4</sup> and  $q_H^{\text{tot}}$  values (Table S11, line 12,  $r = 0.9989$ ) was found. This indicates a systematic variation in the strength of the intramolecular hydrogen bond. However, we consider that the hydrogen bond cannot play a major role in the effect of substitution on the ring–chain tautomeric equilibrium. There are several contradictory points. First, although the equilibrium is markedly solvent dependent both for oxazolidines and for 1,3-oxazines, obviously

because of the varying contribution of the *intermolecular* hydrogen bond between the solvent and the chain tautomer, the  $\rho$  values vary only slightly from one solvent to the other. For instance, closely similar  $\rho$  values (eq 1 with  $\sigma^+$ ) are observed for substituted 4,4-dimethyl-2-phenyloxazolidines (*p*-NO<sub>2</sub>, *m*-NO<sub>2</sub>, *m*-Cl, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe<sub>2</sub> as phenyl substituents) in CDCl<sub>3</sub>, CD<sub>3</sub>OD, and DMSO-*d*<sub>6</sub>:  $0.55 \pm 0.02$ ,  $0.41 \pm 0.02$ , and  $0.45 \pm 0.01$ , respectively. However, the equilibrium constant *K* for the 2-phenyl derivative is 2.30 in CDCl<sub>3</sub>, but the ones in CD<sub>3</sub>OD and DMSO-*d*<sub>6</sub> only 0.040 and 0.092, respectively.<sup>16</sup> It is even questionable if any intramolecular hydrogen bond prevails in DMSO because of potential intermolecular hydrogen bonding (cf. discussion above).

Further, the correlation coefficient  $\rho$  (eq 1 with  $\sigma^+$ ) is very similar for instance for substituted 2-phenyl-1,3-oxazines (series 12, as to the structure see ref 1b), -1,3-benzoxazines (series 6), or -3,1-benzoxazines (series 1) despite very different position of the tautomeric equilibrium. In CDCl<sub>3</sub> at ambient temperature the  $\rho$  values (eq 1)  $0.74 \pm 0.06$ ,  $0.82 \pm 0.04$ , and  $0.78 \pm 0.03$ , respectively, are observed for series 12 (*p*-NO<sub>2</sub>, *m*-NO<sub>2</sub>, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe<sub>2</sub>), series 6 (*p*-NO<sub>2</sub>, *m*-NO<sub>2</sub>, *p*-Br, H, *p*-*i*Pr, *p*-NMe<sub>2</sub>), and series 1 (*p*-NO<sub>2</sub>, *m*-NO<sub>2</sub>, *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe<sub>2</sub>).<sup>1b</sup> At the same time, the equilibrium constant *K* for the 2-phenyl derivatives of series 12, 6, and 1 are 0.56, 0.19, and 11.5, respectively,<sup>1b</sup> reflecting the significantly higher relative stability of the chain tautomer with respect of the corresponding ring tautomer in the case of series 12 and 6 as compared with series 1. The strength of the intramolecular hydrogen bond should differ considerably for the above molecules due to the different acceptor/donor functions, viz. an aliphatic, a benzylic or a phenolic hydroxyl group as the donor and imine nitrogen with aliphatic, benzylic, or aromatic *N*-substitution as the acceptor. The sensitivity to substitution at the phenyl moiety remains, however, practically constant. This fact contradicts the idea that variation in the strength of the hydrogen bond is the reason for the common  $\rho$  values observed.

Obviously, other effects inherent for the -N=CH-Ar system also affect the stability of the chain form. We proposed above two possible mechanisms to explain the substituent dependence of the C=N carbon <sup>13</sup>C NMR shift, viz.  $\pi$ -polarization and the balance between different resonance structures of the -N=CH-Ar moiety operating either alternatively or concurrently. The substituent effect on the stability of the chain form can be nicely explained by the latter mechanism (cf. Scheme 6). Electron-withdrawing substituents decrease the contribution of the resonance form **10** by destabilizing the positive charge at the imine carbon, and neglect the resonance form **11**, thereby increasing the contribution of the form **9**. As a consequence, the overall resonance stabilization of the chain form is diminished. In contrast, when electron-donating substituents stabilize the structure **10**, and also allow the contribution of form **11**, the overall resonance stabilization of the chain form is increased. This interpretation is in harmony with the shift/charge and bond-order data obtained. Increase in the contribution of structures **10** or **11** of course also leads to an increase in the strength of the hydrogen bond, but as discussed above it seems not to be a dominating effect. The somewhat better correlation of the equilibrium constant (eq 1) with  $\sigma^+$  than with  $\sigma$  has previously been explained by the increased stabilization of the chain form

by electron donation through conjugation although a direct resonance of a positive charge with the aromatic ring was neglected because of the low values of  $\rho$ .<sup>6</sup> In light of <sup>13</sup>C chemical shift data (small  $\rho_R$  values), conjugation (structure **11**), however, is not significant. So the balance is mainly between structures **9** and **10**.

**C-2 Carbon Shift of Ring Tautomers: An Unexpectedly Sensitive Probe.** One would expect that the inductive effects dominate the substituent dependence of the <sup>13</sup>C chemical shifts of C-2 in a 1,3-*O,N*-heterocyclic system giving small *positive*  $\rho_F$  values. However, there are no systematic studies in the literature. To our surprise low-frequency signal shifts were observed by electron-withdrawing substituents and quite high *negative*  $\rho_F$  values (-1.3 to -2.1, Table 1) were detected for series 1-5. This suggests that an electron-withdrawing substituent increases electron density at C-2. For every orientational combination of series 1B, a linear correlation with a positive slope between the  $\delta_C$ (C-2) and  $q_{C-2}^{tot}$  (Table S12, lines 1-4) is found. This proves the above assumption that electron-withdrawing substituents increase electron density at C-2. To the contrary, electron-donating substituents decrease the electron density. In every case the correlation is significant exhibiting slightly higher values for NH<sub>ax</sub>Ph<sub>eq</sub> and NH<sub>eq</sub>Ph<sub>ax</sub> than for NH<sub>ax</sub>Ph<sub>ax</sub> or NH<sub>eq</sub>Ph<sub>eq</sub> orientations. This suggests that conformational reasons are not the origin of the substituent effect at C-2. The  $\pi$ -polarization or varying resonance contributions cannot be used to explain the negative  $\rho_F$  values due to the lack of a  $\pi$ -bond at C-2. However, they can be explained by considering the substituent sensitive polarization of the N-C-O system (cf. Scheme 5, 1B). This concept of substituent interaction with a polar bond in a ring system has not been described earlier. The  $\rho_F$  value for the one *meta* series, 3B, is more negative than that for the respective *para* series, 2B, apparently indicating the through-space effect of the substituent. That the variation of the C-2 carbon chemical shifts as a function of substitution at the phenyl ring is of electronic origin, is further revealed by the fact that significant linear correlations between the  $q_{C-2}^{tot}$  and  $\sigma$  or  $\sigma^+$  with negative slopes are found (Table S12, lines 5-12). Again the slopes in the case of the four different orientational combinations are practically the same. The best correlation, however, is detected for NH<sub>ax</sub>Ph<sub>eq</sub> orientation, which is, as discussed below, the most stable conformation according to the anomeric effect. Correlation with  $\sigma$  is somewhat better than with  $\sigma^+$ . Results obtained for series 6 (Table S12, lines 13-20) are in accordance with those calculated for series 1.

A systematic aromatic substituent effect on the electronic state of the saturated C-2 carbon is observed and the question of the site of polarization is intriguing. In principle, the following units can be considered: (i) the heterocyclic ring, (ii) C-N and/or C-O bonds, and (iii) (C-2)-(C-1') bond. Correlations of the PM3 charge densities  $q_{N-1}^{tot}$  or  $q_{O-3}^{tot}$  vs  $q_{C-2}^{tot}$  for the NH<sub>ax</sub>Ph<sub>eq</sub> orientation showed that the charge of N-1 is more sensitive to substitution than that of O-3 (Table S12; lines 21 and 22). A reverse behavior between  $q_{N-1}^{tot}$  and  $q_{C-2}^{tot}$  is observed. The variation of  $q_{O-3}^{tot}$  is only one-fourth of that of  $q_{N-1}^{tot}$ , and it is in the same direction as that of  $q_{C-2}^{tot}$ . So, the polarization of the C-N bond seems to be sensitive to phenyl substitution (cf. Scheme 5, 1B). The positive slope for the correlation of  $q_{N-1}^{tot}$  with  $\sigma$  (Table S12, line 23) is in harmony with this interpretation. To



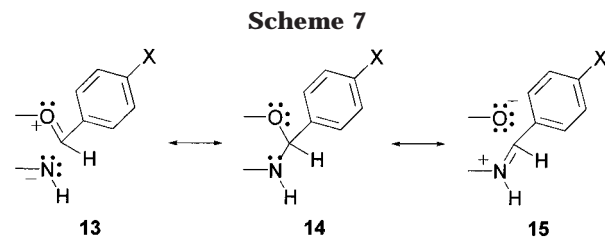
the contrary, for the  $q_{0-3}^{\text{tot}}$  values no correlation was revealed. The (C-2)–(C-1') bond as the polarizable unit can be neglected. The C-1' shifts show a significant variation and a normal trend as a function of substitution (the shifts are not shown). This behavior can be attributed to polarization of the phenyl ring according to  $\pi$ -polarization mechanism with the positive end of the dipole in question at C-1' with electron-withdrawing substituents.<sup>7b</sup> As a consequence, a positive charge should be inductively induced at C-2. Because this is contrary to the experimental findings, the polarization of the phenyl ring cannot explain the reverse trend detected for C-2. To be short, in light of the present results the C–N bond of the ring is the polarized unit. The resonance effects on the <sup>13</sup>C chemical shifts of C-2 carbons are again much smaller than the inductive effects (Table 1). The analogous effect as the secondary resonance effect<sup>9c,d,13,14</sup> discussed in the connection of the C=N unit polarization could explain the slightly negative  $\rho_R$  values observed.

The concept of the substituent sensitive polarization of the carbon-heteroatom bond is supported by the fact that the five- and six-membered rings behave analogously. One series exhibiting enough substituted derivatives for a systematic study was found in the literature (series 7).<sup>10</sup> A  $\rho_F$  value of  $-2.6$  is obtained for C-2, while  $\rho_R$  is  $-0.7$  (Table 1). The numerical value of  $\rho_F$  for this set is even higher than for our compounds. The analogous behavior of the ring systems possessing 1,3-*O,N*- or 1,3-*S,N*-heteroatoms further supports the generality of the saturated bond polarization discussed.

**Other Carbon Chemical Shifts of Ring and Chain Tautomers.** To see the extent of the propagation of substituent effects, we extended the <sup>13</sup>C chemical shift analysis by DSP calculation (eq 2) besides the C=N and C-2 carbons to some other carbons. Although the  $\Delta\text{SCS}$ 's and the calculated  $\rho$  values are small,  $f$  and  $r$  values show that the correlations are good or at least satisfactory (Table 2) showing that the shift variations are systematic. They give a good approximation about propagation of the substituent effects on the carbons quite far away from the substitution site. This interesting fact has been underestimated until now. The significant substituent dependence of the <sup>13</sup>C NMR chemical shifts for the hydroxymethyl carbon of series 1A in CDCl<sub>3</sub> (Table 1) in contrast to a very slight substituent dependence in DMSO-*d*<sub>6</sub> as discussed above is also prominent. Further, in accordance with the contribution of the  $\pi$ -polarization behavior (cf. Scheme 3), C-8a/"C-8a" and C-6/"C-6" for series 1, respectively, exhibit the reverse and the normal trend of the substituent dependence (Table 1).

The above-discussed substituent effects on the polarizable electronic system of the heterocyclic ring are supported by the normal substituent dependence ( $\rho_F, \rho_R > 0$ ) of the carbon adjacent to the ring oxygen, C-4a for series 1B, C-8a for series 2B and C-5 for series 4B, 4C and 5B (cf. Table 2), in contrast to the reverse substituent effect experienced by C-2. For series 3B and 5C the  $\Delta\text{SCS}$ 's of C-8a and C-5, respectively, were relatively small and  $\rho$  values are not given.

The  $\Delta\text{SCS}$ 's of C-4 and C-5 of diastereomeric B and C in series 4 and 5 are indicative. For instance, for series 4C and 5B, for which the two phenyl rings are in anti orientation, the substituent effect on the C-5 shift is higher than that for series 4B and 5C, for which the phenyl rings in question are in syn orientation, indicating the through-space propagation of the substituent effects.



**Stability of the Ring Tautomer in the Light of the <sup>13</sup>C NMR Chemical Shifts and the PM3 Calculations.** The electronic substituent effects on the ring-chain equilibrium via the ring tautomers has not been discussed earlier. However, the <sup>13</sup>C NMR chemical shifts as well as the calculated PM3 charges reveal the fact that the influence of substitution is propagated not only in the chain form but also in the ring tautomer. Further, the isodesmic calculations discussed above show that although the stability of the ring form is less sensitive to the electronic character of the phenyl substituent than that of the chain form, electron-donating substituents stabilize and electron-withdrawing substituents destabilize the both tautomeric forms. So, consideration of the mechanisms by which the phenyl substituents contribute to the shift and charge variations and the stability of the ring form have been neglected without good reasons until now.

1,3-*O,N*-Heterocycles are prone to the known *anomeric effect*.<sup>16,17</sup> This stereoelectronic effect has been effectively used to explain the conformational equilibria of, for example 1,3-oxazines, where the N–H axial orientation is preferred instead of the expected equatorial one. In this axial orientation, there is the possibility for the lone pair of the donor atom ring-nitrogen to situate anti to the  $\sigma_{\text{C-O}}^*$  antibonding orbital acting as the electron acceptor. This is the favorable geometry for the  $n_{\text{N}} \rightarrow \sigma_{\text{C-O}}^*$  two electron–two orbital stabilizing interaction known as the anomeric effect. For our system the valence bond representation of the molecular orbital mixing, the well-known double bond–no bond resonance, is given in Scheme 7. In principle two stereoelectronic effects are possible in the –O–CH(Ar)–NH– moiety.<sup>16</sup> The contribution of the effect represented by structure 15, which is equivalent with the molecular orbital view according to which the lone pair orbital of nitrogen donates electron density into the  $\sigma^*$  orbital of the C2–O bond, is preferred over the one represented by 13, because it is generally thought that nitrogen is the better electron donor but oxygen the better electron acceptor.<sup>16,17</sup> Interestingly, Star and Fuchs<sup>18</sup> point out that the thermodynamic counterpart of the double bond–no bond resonance is the ring–chain tautomerism prevailing in the 1,3-*O,N*-heterocycles (cf. Scheme 1). The large variations of the C-2/N-1 charge densities could reflect, in addition to the degree of the polarization of the C–N bond, that the stereoelectronic effects control not only the conformational equilibrium ( $\text{NH}_{\text{ax}}$  vs  $\text{NH}_{\text{eq}}$ ) but also the ring–chain equilibrium. According to the correlations including the SCS's and PM3 charges, the electron-donating substituents seem to decrease electron density at C-2 and

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increase it at N-1. In terms of the resonance structures shown in Scheme 7, the observed change of charge density at nitrogen indicates a decreased contribution of **15**. Taking into account the suggestion of Star and Fuchs<sup>18</sup> mentioned above (cf. also Scheme 1), this explains the stabilization of the ring form by electron donors in accordance with the isodesmic results.

The stereoelectronic effects are thought to affect the geometry of the O–C–N system: shortening of the C–N bond and elongation of the C–O bond, as examples.<sup>16,17</sup> We tried to probe the geometry of our rings with correlations of C–N and C–O bond-orders but the variations were too small to allow any reliable interpretations. However, the preliminary calculations<sup>19</sup> probing the occupancy of  $\sigma^*(\text{C2}-\text{O3})$  orbital support our conclusions.

An alternative explanation is based on the electrostatic stabilization model presented by Wiberg for carbonyl compounds.<sup>20</sup> In a polarized C–N bond of the heterocyclic ring, the negative end of the dipole situates at the more electronegative N-1 and the positive end at C-2. Electron-donating substituents at the phenyl ring can be considered inductively to stabilize the partial positive charge developed at C-2 and so to strengthen the polarization while electron-withdrawing substituents affect inversely. Increased polarization results in stronger electrostatic stabilization of the ring.<sup>20</sup> This model elegantly explains both the shift/charge variations observed and the variation in the stability of the ring form indicated by the isodesmic calculations.

The results obtained in this work clearly show that the phenyl substituents affect the stability of the ring form, too. We hope that the systematic occupancy calculations of  $\sigma^*(\text{C2}-\text{O3})$  and  $\sigma^*(\text{C2}-\text{N1})$  orbitals in progress allow the differentiation between the above mechanisms.

### Conclusions

The PM3 energies for the isodesmic reactions designed indicate that *electron-donating substituents* at the C-2 phenyl ring *stabilize both the chain and the ring forms*. However, the effect is stronger on the stability of the chain tautomer. Correlation analysis of the <sup>13</sup>C NMR chemical shifts (SCS values) with different substituent parameters allowed evaluation of the mechanisms of the transmission of electronic substituent effects for the ring and chain tautomers. The negative  $\rho_F$  and  $\rho_R$  values observed for the C=N carbons of the chain tautomers together with the charge calculations attest the dipolar trend in the electron density at the C=N moiety induced

by substituents. This is in harmony with the concept of  $\pi$ -polarization, but inductive effects on the inherent polarization of the C=N unit are also considered to be significant. The small  $\rho_R$  values suggest that electron donation through conjugation does not significantly contribute. Surprisingly, negative  $\rho_F$  and  $\rho_R$  values are also observed for the C-2 carbons. The substituent sensitive C–N bond polarization not used until now explains the behavior of the <sup>13</sup>C chemical shift and charge variations. On similar grounds the stability of the ring tautomer can be understood. As a summary, the present results suggest that the substituent dependence of the relative stability of the ring and chain tautomers and consequently that of the ring–chain equilibrium constant can be attributed to different competitive factors. Electron-donating substituents stabilize the chain tautomer by increasing its resonance stabilization via polarization of the C=N unit and by strengthening the intramolecular hydrogen bond. On the other hand, the increase of the stability of the ring tautomer by electron donors is attributed to stereoelectronic and/or electrostatic effects.

### Experimental Section

**General Procedures.** Melting points were determined on an Electrothermal Digital melting point apparatus and are uncorrected. All new compounds (see Table S15) gave satisfactory microanalyses (C, H, N).

**Materials.** *o*-Aminobenzyl alcohol, (1*R*,2*R*)-norpseudoephedrine, ( $\pm$ )-norephedrine, and aromatic aldehydes were commercial products. *trans*-2-Aminomethylcyclohexanol was prepared according to a literature method.<sup>21</sup> The condensation products **1a**, **1e–i**,<sup>1b</sup> **2a**, **2e–i**,<sup>1b</sup> **3a**,<sup>1b</sup> **4a**, **4b**, **4e–i**,<sup>1c</sup> **5a**, **5b**,<sup>1c</sup> and **5e–i**<sup>1c</sup> were prepared as described earlier. For the preparation of new derivatives, the general procedure reported earlier<sup>21</sup> was used.

**NMR Measurements.** <sup>13</sup>C NMR spectra were recorded at 27 °C on a JEOL JNM-A500 FT NMR spectrometer operating at 125.78 MHz on 0.2 M solutions in CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub>. Chemical shift values refer to internal tetramethylsilane (0 ppm). The signal of the deuterium of the solvent was used as a lock signal. <sup>13</sup>C NMR spectra were measured with <sup>1</sup>H broadband decoupling and NOE <sup>1</sup>H nondecoupling techniques. The other conditions were as follows: spectral width 30030 Hz, 32 K data points (<sup>1</sup>H decoupled)/64 K data points (<sup>1</sup>H coupled), digital resolution 0.92 Hz/point (<sup>1</sup>H decoupled)/0.46 Hz/point (<sup>1</sup>H coupled), pulse width 4.35  $\mu$ s (45°), acquisition time 1.09 s (<sup>1</sup>H decoupled)/2.18 s (<sup>1</sup>H coupled), number of transients 1000–12000, pulse delay 3 s (<sup>1</sup>H decoupled)/5 s (<sup>1</sup>H coupled), pulse sequence (by JEOL Ltd) SGBCM (<sup>1</sup>H decoupled)/SGNOE (<sup>1</sup>H coupled). Exponential windowing with line-broadening term 2 Hz (<sup>1</sup>H decoupled)/1 Hz (<sup>1</sup>H coupled) was used.

**Statistical Calculations.** The SCS values [SCS = <sup>13</sup>C chemical shift (in ppm) for a substituted compound relative to the unsubstituted one] were correlated with  $\sigma$ ,  $\sigma^+$ ,  $\sigma^-$ ,  $\sigma_I$ , or  $\sigma_F$  parameters (a single parameter treatment) and with different dual-substituent parameter (DSP) combinations of  $\sigma_I$  or  $\sigma_F$  with  $\sigma_R^+$ ,  $\sigma_R^0$ ,  $\sigma_R^{BA}$ ,  $\sigma_R^-$  or  $\sigma_R$ . Sources of the substituent constants are as follows:  $\sigma$ ,  $\sigma^+$ ,  $\sigma^-$ , ref 22;  $\sigma_I$ ,  $\sigma_R^+$ ,  $\sigma_R^0$ ,  $\sigma_R^{BA}$ ,  $\sigma_R^-$ , ref 7a;  $\sigma_F$  or  $\sigma_R$ , ref 23 (except  $\sigma_F$  and  $\sigma_R$  for Br, ref 22).

**PM3 Calculations.** The 3D structures of the compounds were composed employing the program SYBYL,<sup>24</sup> and the structures thus obtained optimized with the Tripos force field. The resulting conformations were used as starting structures for the semiempirical calculations of conformations, heats of

(19) Ab initio calculations at the Becke3LYP/6-31G\* level with the aid of localized bond orbitals have been carried out to get more detailed information about the activity of stereoelectronic effects in the title compounds. For example, with **1Bb** the occupancy of the  $\sigma^*(\text{C2}-\text{N1})$  orbital as the function of orientation is relatively constant. These values include probably the contribution of an anomeric effect where oxygen functions as a donor. In the case of the  $\sigma^*(\text{C2}-\text{O3})$  orbital the same level of occupancy is observed with NH<sub>eq</sub> conformations. However, with the NH<sub>ax</sub> orientations the occupancy is essentially on a higher level. These are conformations where nitrogen can affect as a donor. The results, obviously, support the influence of the anomeric effect on the stability of the ring tautomers as discussed in the text.

	$\sigma^*(\text{C2}-\text{O3})$	$\sigma^*(\text{C2}-\text{N1})$
NH <sub>ax</sub> Ph <sub>ax</sub>	0.04544	0.02867
NH <sub>ax</sub> Ph <sub>eq</sub>	0.04426	0.03377
NH <sub>eq</sub> Ph <sub>ax</sub>	0.02912	0.02811
NH <sub>eq</sub> Ph <sub>eq</sub>	0.03352	0.03498

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formation, and atomic charges. These calculations were performed using the semiempirical quantum mechanical method PM3<sup>25</sup> of the program MOPAC 7.0.<sup>26</sup> All structures were optimized without any restriction. The quantum chemical calculations were processed on the SGI "Octane" (2 x R 12000) computer of University of Potsdam.

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**Supporting Information Available:** Detailed <sup>13</sup>C NMR chemical shift data for compounds included in series 1–5 (Tables S1–S4). Correlation coefficients *r* for correlations of SCS's of the C=N and C-2 carbons using different substituent constants (Table S5). PM3 charge densities for compounds included in series 1 and 6 (Tables S6–S9). The heat of formation values for series 1 and 6 (Table S10). Statistical data for the different correlations of the SCS values, PM3 charges or bond-orders for series 1 and 6 (Tables S11 and S12) and statistical data of the different correlations and cross-correlations of the  $\Delta E(\text{chain} \rightleftharpoons \text{ring})$  or  $\Delta E_{\text{iso}}$  values for the same series (Tables S13 and S14, respectively). Analytical data on new compounds of series 1–5 (Table S15). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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