DOI: 10.1002/ejoc.200600563

# Study of the Substituent-Influenced Anomeric Effect in the Ring-Chain Tautomerism of 1-Alkyl-3-aryl-naphth[1,2-*e*][1,3]oxazines

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**Keywords:** Naphthoxazines / Conformational analysis / Ab initio calculations / NBO analysis / Anomeric effect / Ring-chain tautomerism.

The stabilities of the *trans* (**B**) and *cis* (**C**) tautomeric ring forms that are experimentally observed in the ring-chain tautomeric interconversion of 1-alkyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines has been investigated. Stability differences are explained by the analysis of the natural bond orbital results for the lone pairs of electrons that are on the heteroatoms in the oxazine ring system and by regression analysis of the calculated $^{13}C$ NMR chemical shift values.

## Introduction

The general rules relating to the interactions of electronic orbitals in space (stereoelectronic effects) are important for the comprehension of molecular properties and general chemical reactivity.[1] In many cases, hyperconjugation influences conformational equilibria,[2–5] modifies reactivity,[6–8] determines the selectivity of reactions,[9] and is enhanced dramatically in excited, radical, and ionic species.[10]

Lone pairs of electrons on oxygen, nitrogen, sulfur, and other heteroatoms are particularly well-suited for the role of donor in hyperconjugative interactions and stereoelectronic effects, and their participation is well-documented in the scientific literature. Arguably, among these interactions, the most intensively studied effect is the anomeric effect.[2,11]

Recent studies indicate that the substituent-dependent anomeric effect plays an important role in the observed stabilities of two specific geometries of the same molecule. In particular, the anomeric effect is instrumental in two-electron, two-orbital hyperconjugative interactions that results in an excess of stabilization energy.[12,13]

The hyperconjugative interactions of the nitrogen lone pair of electrons with the C2-associated antibonding orbital have been experimentally observed to be substituent-dependent.[14] The epimerization reactions of conformationally inflexible 2-aryl-1,3-*N*,*N*-heterocycles could be used as model systems for the determination of the role of the nitrogen lone pair of electrons in relation to the anomeric effect.

We pointed out earlier that in the ring-chain tautomeric interconversion of 1-(Y-phenyl)-3-(X-phenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines and 1-(Y-phenyl)-3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines, the experimentally observed differences between the stabilities of the two ring forms could be explained by the substituent-dependent anomeric effect caused by the aryl substituent in the 1-position.[15]

In the present work, we set out to extend the application of the concept of the anomeric effect by the exploitation of the tautomeric equilibrium that exists for 1-alkyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**1**–**5**, Scheme 1). We also hoped to demonstrate from the regression analysis of the $\log K$ values, with $V^a$ (the Meyer parameter, which characterizes the volume of the alkyl substituent at the 1-position)[16] and $\sigma^+$ (the Hammett-Brown parameter, which characterizes the electronic behavior of the aryl substituent at the 3-position) as independent variables, that the significant difference between the slopes of the $V^a$ values for the ring$_{trans}$-chain [Equation (1)] and ring$_{cis}$-chain [Equation (2)] equilibria (–0.32 versus –0.46) can be explained by substituent-dependent stereoelectronic stabilization effects.[17] The synthesis of model compounds 1-alkyl-3-aryl-naphth[1,2-*e*][1,3]oxazines **1**–**5** (Scheme 1) was previously described.[17]

$$\log K_B = 0.61 – 0.32 V^a + 0.85\sigma^+ \quad (1)$$

$$\log K_C = 0.41 – 0.46 V^a + 0.98\sigma^+ \quad (2)$$

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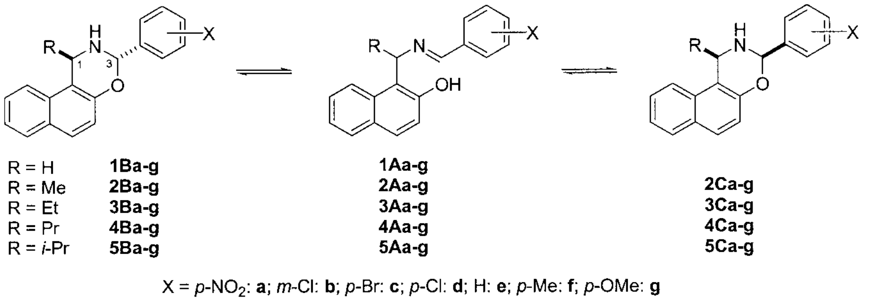


Scheme 1.

## Results and Discussion

### Computational Methods

The conformational search protocol involved PM3 geometry minimization, followed by geometry optimization without restrictions. All calculations were carried out with the Gaussian 03 program package.[18] The density functional theory (DFT) calculations include electron correlation effects. This is important for the analysis of electron delocalizations. The B3LYP[19] DFT hybrid method and the 6-31G*[20] double zeta split valence basis set were used for all calculations.

The natural bond orbital population analysis and all of the properties – the coupling constants and the chemical shifts – were calculated at this level of theory.

Calculated $^1$H- and $^{13}$C NMR chemical shift values were measured as the difference in the magnetic shielding of tetramethylsilane relative to the studied compounds.

The molecular modeling software package SYBYL 7.1 was used to display results and geometries [SYBYL 7.1, Tripos Inc. 1699 South Hanley Rd. St. Louis, MO 2005].

### Conformational Analysis

Because stereoelectronic interactions are highly dependent on the geometry of the studied molecules, a thorough conformational analysis was performed. Our goal was to determine the predominant geometry for all of the models.

The relevant calculated conformations that can be attributed to nitrogen–ring inversions of **2aB** and **2aC**, as examples, are shown in Figure 1. Chemical shift values and coupling constants were calculated at the same level of theory; selected bond lengths (for comparison with NOE measurements) and NMR parameters are given in Table 1.

In the analysis of **2a**, the strong NOE interaction between the C1-*Me* protons and C3-*H* (for **B**) or between C1-*H* and C3-*H* (for **C**) predicted the presence of $\mathbf{B_1}$ and $\mathbf{B_3}$, or $\mathbf{C_1}$ and $\mathbf{C_3}$ geometries, respectively (Table 1, Entries 1 and 2). The only difference between $\mathbf{B_1}$ and $\mathbf{B_3}$, or $\mathbf{C_1}$ and $\mathbf{C_3}$ is a nitrogen inversion. To decide between the $\mathbf{B_1}$ and $\mathbf{C_1}$ or the $\mathbf{B_3}$ and $\mathbf{C_3}$ geometries, the $^3J$ coupling constants between N-*H* and C1–3-*H* of **2a** that are observed with low temperature $^1$H NMR techniques ($CD_2Cl_2$, 173 K) should be taken into account. These values (Table 1, Entries 3 and 4) were in very good agreement with the coupling constants calculated for conformers $\mathbf{B_1}$ and $\mathbf{C_1}$. This finding, together with the comparison of the energy values (the data were calculated for the full set of compounds, but are only shown for **2a**; Figure 1) allows for the conclusion that, for all of our model compounds, $\mathbf{B_1}$ and $\mathbf{C_1}$ are the global minimum conformers.

The NMR calculations were performed at the B3LYP/6-31G* level, with geometries optimized at the same level. Table 1 (Entries 5–8) summarizes the measured and calcu-

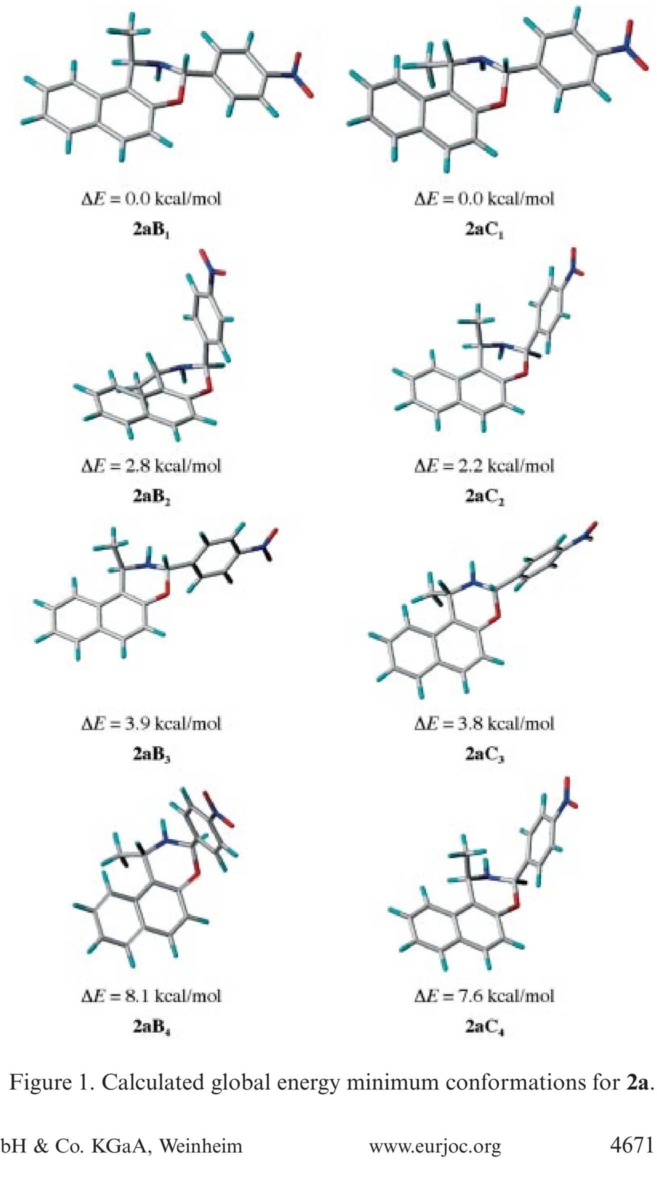


Figure 1. Calculated global energy minimum conformations for **2a**.

Table 1. Some measured and calculated NMR parameters for **2a**.

| Entry | Parameter | 2aB[a] | $2aB_1$[b] | $2aB_2$[b] | $2aB_3$[b] | $2aB_4$[b] | 2aC[a] | $2aC_1$[b] | $2aC_2$[b] | $2aC_3$[b] | $2aC_4$[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $d_{C1\text{-}\mathit{Me}–C3\text{-}\mathit{H}}$[c] | yes | 2.78 | 4.39 | 2.83 | 4.43 | – | – | – | – | – |
| 2 | $d_{C1–\mathit{H}–C3\text{-}\mathit{H}}$[c] | – | – | – | – | – | yes | 2.77 | 4.04 | 2.81 | 4.07 |
| 3 | $J_{C1\text{-}\mathit{H}–N\text{-}\mathit{H}}$ | 4.6[d] | 4.80 | 7.77 | 1.01 | 3.42 | 8.8[d] | 7.37 | 4.98 | 5.13 | 1.22 |
| 4 | $J_{C3\text{-}\mathit{H}–N\text{-}\mathit{H}}$ | 14.2[d] | 12.84 | 4.84 | 0.58 | 2.53 | 14.0[d] | 12.85 | 6.53 | 0.83 | 1.24 |
| 5 | $\delta_{C1\text{-}\mathit{H}}$ | 4.65 | 4.51 | 4.53 | 4.71 | 4.66 | 5.01 | 5.02 | 4.33 | 4.98 | 4.58 |
| 6 | $\delta_{C3\text{-}\mathit{H}}$ | 6.06 | 6.15 | 5.85 | 5.93 | 5.81 | 5.66 | 5.60 | 6.04 | 5.43 | 6.09 |
| 7 | $\delta_{C1}$ | 45.8 | 48.3 | 44.0 | 48.9 | 44.7 | 47.9 | 48.9 | 46.8 | 50.8 | 46.6 |
| 8 | $\delta_{C3}$ | 80.7 | 78.5 | 83.7 | 81.6 | 82.2 | 85.5 | 84.1 | 82.9 | 85.7 | 81.8 |

[a] Measured NMR parameters. [b] Calculated NMR parameters. [c] Observed NOE interaction/calculated distances. [d] The coupling constants were measured in $CD_2Cl_2$ at 173 K.

lated $^1H$ NMR (C1-*H* and C3-*H*) and $^{13}C$ NMR (C1 and C3) chemical shift values for **2a**.

### Natural Bond Orbital (NBO) Analysis

The extra stabilization of the conformers that is observed with alkyl substituents in the 1-position of the *trans* ring form, indicated by the slope values (–0.32 versus –0.46),[17] may originate from a substituent-dependent stereoelectronic effect. Analysis of the delocalization energy contributions to this effect is a complex problem that can be tackled through a second-order perturbative analysis of the elements of the Fock matrix elements in the frame of the DFT hybrid method in the NBO basis.

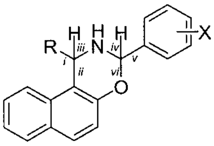
The NBO[21] calculations were performed at the B3LYP/6-31G* level, with geometries optimized at the same level. The solvent effect can be taken into account with a self-consistent reaction field method. The self-consistent isodensity polarized continuum model (SCIPCM)[22] used the isodensity surface of the electron density, which was influenced consistently by a dielectric continuum outside the molecule. The solvent effect was checked for series of compounds **12** (data not included). A dielectric constant $\varepsilon$ = 4.81 (chloroform) and a value of 0.0004 a.u. for the isodensity surface were used in the calculations. The difference between the epimerization energy without a solvent effect ($\Delta E_{\mathbf{B}–\mathbf{C}}$ = 1.12 kcal/mol) and that including a solvent effect ($\Delta E_{\mathbf{B}–\mathbf{C}}$ = 1.21 kcal/mol) was found to be 0.09 kcal/mol for the most polar compound **12a**; in further calculations, the effect of the solvent was neglected.

We were interested in the substituent dependence of the calculated NBO parameters. The calculated occupancy values (Table S1) and the energies for the overlap (Tables S2–S4) of the lone pairs of electrons on the nitrogen and oxygen atoms are given in the Supporting Information. Accordingly, multiple linear regression analysis of these values as dependent variables (DV), with $V^a$ and $\sigma^+$ as independent variables, was performed with SPSS statistical software according to Equation (3). A value of 0.05 was chosen to denote the level of significance.[23]

$$DV = k + \rho^1 V^a + \rho^2 \sigma^+ \qquad (3)$$

The calculated occupancy values indicate the level of overlap (%) with different antibonding orbitals. Comparison of the results of the regression analysis for the level of overlap of the lone pair of electrons (*n*) on the nitrogen atom (Table 2, Entry 1) for the *trans* (**B**) and *cis* (**C**) ring forms revealed a somewhat higher slope for the **B** form (0.12 versus 0.04) compared to that of **C**. This was in accordance with our experimental findings.[17] It was also concluded that the extra stabilization energy could result from a complex stereoelectronic interaction between $n_N$ and the vicinal antibonding orbitals. Hence, regression analysis of the overlapping energies (kcal/mol) was performed for the

Table 2. Multiple linear regression analysis of the occupancy and overlapping energy values for the lone pair of electrons on the nitrogen atom as dependent variables according to Equation (3) for **1**–**5**.



| Entry | Dependent variable (DV) | B k | B $\rho^1$ | B $\rho^2$ | B r | C k | C $\rho^1$ | C $\rho^2$ | C r |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Occupancy[a] | 10.47 | 0.12 | –0.12 | 0.906 | 10.51 | 0.04 | –0.11 | 0.774 |
| 2 | $n_N \rightarrow \sigma^*_i$ | 2.57 | –0.13 | –[b] | 0.702 | – | – | – | – |
| 3 | $n_N \rightarrow \sigma^*_{ii}$ | 6.92 | –0.13 | –0.11 | 0.949 | 6.75 | –0.20 | –[b] | 0.953 |
| 4 | $n_N \rightarrow \sigma^*_{iii}$ | – | – | – | – | 2.60 | 0.15 | –[b] | 0.905 |
| 5 | $n_N \rightarrow \sigma^*_{iv}$ | 0.79 | 0.09 | –[b] | 0.746 | 0.79 | –0.01 | 0.05 | 0.751 |
| 6 | $n_N \rightarrow \sigma^*_{v}$ | 0.78 | –0.03 | 0.05 | 0.946 | 0.87 | 0.03 | –[b] | 0.764 |
| 7 | $n_N \rightarrow \sigma^*_{vi}$ | 15.93 | 0.10 | –0.18 | 0.781 | 16.00 | 0.07 | –0.19 | 0.795 |

[a] For regression analysis, the ratios of the occupancy values in % were used. [b] Insignificant (significance value > 0.05).

six possible vicinal antibonding orbitals (three around C1 and three around C3). The results showed that the overlap of $n_N$ with the antibonding orbital of the C1–R bond ($\sigma^*_i$) in **B** or the C1–H bond ($\sigma^*_{iii}$) in **C** had relatively similar intensities (around 2.6 kcal/mol; Table 2, Entry 2). The opposite slope can be explained by the change in the relative configuration of C1 and is in accordance with the experimental findings.[17] The overlap of $n_N$ with $\sigma^*_{ii}$ in **B** and the corresponding overlap in **C** (Table 2, Entry 3) showed similar intensities and similar tendencies.

The low intercept values of **C** (0.79 and 0.87, respectively; Table 2, Entries 5 and 6) and the slope (around 0) indicate that, around C3, the most important and the strongest overlap occurs in the direction of the most polar C–O (*vi*) bond (Table 2, Entry 7). No comparable difference was observed between ring forms **B** and **C** either in the slope of $V^a$ or in the slope of $\sigma^+$. The value of 0.1 for $V^a$ can be explained by the small inductive influence of the alkyl substituents. The slope of $\sigma^+$, which is double the expected value, can be the result of the polarization of bond *vi*, induced by substituent X.

From the analysis of the overlapping behavior of $n_N$, the additional stabilization of the conformers that is observed when alkyl substituents are in the 1-position can be nicely explained, but in order to map the summed influence of the alkyl and aryl substituents, an analysis of the overlapping behaviour of the oxygen lone pairs of electrons ($n_{O1}$ and $n_{O2}$) was also necessary.

A comparison of the overlapping levels of $n_{O1}$ and $n_{O2}$ (Table 3, Entries 1 and 7, respectively) leads to the conclusion that $n_{O2}$ (π-like lone pair) participates in overlapping interactions to a greater extent than $n_{O1}$ does (see intercepts, Table 3, Entries 1 and 7), and because of the low slope values (Table 3, Entry 1) the substituent dependence on the overlapping level of $n_{O1}$ can be neglected. The occupancy level of $n_{O2}$ is strongly influenced by the aryl substituent in the 3-position (–0.38 and –0.34, respectively, Table 3, Entry 7). The comparison of the slopes of $V^a$ for the ring forms yielded low values, but the different tendencies (0.08 versus –0.07, Table 3, Entry 7) indicates that there is some influence of the alkyl substituent in the 1-position. Because of the large difference between the interaction of the alkyl substituent with $n_{O2}$ and the pure electronic character of an alkyl substituent alone, this dependence can be explained only in terms of an alkyl substituent-controlled quantitative change in the torsion angle between $n_{O2}$ and the corresponding antibonding orbital (e.g. by an alkyl substituent-dependent conformational change).

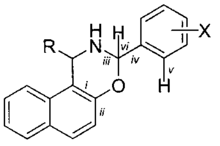
The NBO analyses demonstrated that negative hyperconjugation (n→σ*) and conjugation (n→π*) play important roles in the ring-chain tautomeric interconversions of **1**–**5**. The results also indicate that these conjugative interactions, which result from substituent-dependent conformational changes, explain the relative stability differences between ring forms **B** and **C**.

## Shifted Carbon Chemical Shift (SCS) Analysis

The changes in the $^{13}$C NMR chemical shift values that are induced by phenyl substituents (SCS) on C2 have been analyzed by various dual substituent parameter approaches.[24–26] The best correlation was obtained with the equation SCS = $\rho_F\sigma_F + \rho_R\sigma_R$, where $\sigma_F$ characterizes the inductive effect, and $\sigma_R$ the resonance effect, of the aryl substituent. In a previous study on the ring-chain tautomerism of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines, by means of a dual substituent parameter treatment of SCS, the difference in the stabilities of ring forms **B** and **C** was explained by the changes in the *sp*$^2$ and *sp*$^3$ hybridized character of the carbon atom, which is influenced by the aryl substituents on C1 and C3.[15]

The low concentrations of the minor forms of **B** and **C** in the tautomeric mixtures did not allow for the measure-

Table 3. Multiple linear regression analysis of the occupancy and overlapping energy values for the lone pairs of electrons on the oxygen atom as dependent variables according to Equation (3) for **1**–**5**.



| Entry | Dependent variable (DV) | B | | | | C | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | k | $\rho^1$ | $\rho^2$ | r | k | $\rho^1$ | $\rho^2$ | r |
| 1 | Occupancy ($n_{O1}$)[a] | 4.05 | 0.03 | –[b] | 0.897 | 4.04 | –0.01 | 0.02 | 0.834 |
| 2 | $n_{O1}\to\sigma^*_i$ | 6.58 | 0.07 | –0.16 | 0.880 | 6.55 | –0.05 | –0.15 | 0.937 |
| 3 | $n_{O1}\to\sigma^*_{ii}$ | 0.50 | 0.02 | –[b] | 0.857 | – | – | – | – |
| 4 | $n_{O1}\to\sigma^*_{iii}$ | 2.62 | 0.21 | –[b] | 0.785 | 2.66 | –0.12 | –[b] | 0.914 |
| 5 | $n_{O1}\to\sigma^*_{iv}$ | 1.09 | –0.03 | –[b] | 0.645 | 1.05 | –0.01 | 0.06 | 0.940 |
| 6 | $n_{O1}\to\sigma^*_v$ | 0.58 | 0.01 | 0.01 | 0.799 | 0.57 | –0.01 | 0.03 | 0.681 |
| 7 | Occupancy ($n_{O2}$)[a] | 15.21 | 0.08 | –0.38 | 0.907 | 15.15 | –0.07 | –0.34 | 0.928 |
| 8 | $n_{O2}\to\pi^*_i$ | 28.17 | 0.28 | –0.93 | 0.896 | 27.79 | –0.46 | –0.82 | 0.935 |
| 9 | $n_{O2}\to\sigma^*_{iii}$ | 5.13 | –0.41 | –[b] | 0.720 | 4.93 | 0.15 | 0.20 | 0.904 |
| 10 | $n_{O2}\to\sigma^*_{vi}$ | 5.51 | –0.08 | 0.21 | 0.599 | 5.34 | –0.06 | 0.20 | 0.945 |

[a] For regression analysis, the ratios of the occupancy values in % were used. [b] Insignificant (significance value > 0.05).

ment of the $^{13}$C NMR chemical shift values of C1 and C3. They were therefore calculated for all compounds at the B3LYP/6-31G* level with geometries optimized at the same level, and they are listed in Table S5. The chemical shift changes induced by the alkyl substituent in the 1-position and by the aryl substituent in the 3-position (SCS) for a given compound were calculated as the differences in the calculated $^{13}$C NMR chemical shift values for the substituted relative to the unsubstituted (R = H, X = H) compound. The multiple regression analysis[23] data obtained from Equation (4) for C1 and C3 are presented in Table 4.

$$DV = \rho^1 V^a + \rho^2 \sigma_F + \rho^3 \sigma_R \qquad (4)$$

Table 4. Multiple linear regression analysis of the calculated SCS values for C1 and C3 according to Equation (4) for **1**–**5**.

| Dependent variable (DV) | B | | | | C | | | |
|---|---|---|---|---|---|---|---|---|
| | $\rho^1$ | $\rho^2$ | $\rho^3$ | r | $\rho^1$ | $\rho^2$ | $\rho^3$ | r |
| $SCS_{C1}$ | 2.22 | –[a] | –[a] | 0.996 | 2.34 | –[a] | –[a] | 0.997 |
| $SCS_{C3}$ | –0.98 | –1.79 | –[a] | 0.967 | 0.09 | –1.02 | –[a] | 0.931 |

[a] Insignificant (significance value > 0.05).

Table 4 shows that the calculated $^{13}$C NMR chemical shift values for C1 are influenced only by the alkyl substituents in the 1-position. The small difference in slope between ring forms **B** and **C** indicates that the behavior of the alkyl substituent in the 1-position in relation to the conformational changes around C1 is similar in the two ring forms.

The calculated $^{13}$C NMR chemical shift values for C3 seem to depend much more on the changes in the relative configurations. In comparison, the influence of an alkyl substituent in the 1-position (–0.98 versus 0.09; Table 4) on the SCS values for C3 was found to be strongly dependent on the relative configurations of C1 and C3. This provides further evidence for the theory that alkyl substituents stabilize the *trans* (**B**) ring form, which can be explained in terms of an alkyl substituent-induced stereoelectronic effect. This results in small alkyl substituent-induced conformational changes in **B**.

The reverse trend in the inductive substituent effect ($\sigma_F$) for unsaturated carbon is well-documented.[25–30] The negative slope of $\sigma_F$ for saturated carbon centers such as those situated between the two heteroatoms in 1,3-*O*,*N*-heterocycles was explained by Neuvonen et al. to be due to the substituent-sensitive polarization of the N–C–O system.[24] The *trans* and *cis* series in the present work offered an interesting opportunity for the study of this type of reverse trend in the substituent effect ($\sigma_F$) on the calculated SCS values. Table 4 shows that negative slopes of $\sigma_F$ (–1.79 versus –1.02) were obtained for both series **B** and **C**, which is in accordance with the concept found for similar carbon centers.[15,24] The difference between the slopes is a further consequence of the stronger substituent-induced stereoelectronic effect in the *trans* (**B**) ring form.

## Conclusions

This analysis of the disubstitution effects of R (alkyl) and X in 1-alkyl-3-(X-phenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines on ring-chain tautomerism, the delocalization of the nitrogen and oxygen lone pairs of electrons (anomeric effect), and the calculated $^{13}$C NMR chemical shifts permitted an explanation for the experimentally observed stabilization difference between the *trans* (**B**) and *cis* (**C**) ring forms.

The multiple linear regression analysis of the calculated overlapping energies for the lone pairs of electrons on the nitrogen and oxygen atoms showed that the relative stability difference between the two ring forms is the result of an alkyl substituent-induced quantitative conformational change in the naphthoxazine ring system. The analysis of the $^{13}$C NMR chemical shift changes induced by the substituents (SCS) for C1 and C3 revealed that, by the alkyl substituent-dependent small conformational changes, the substituent-dependent anomeric effect predominates in the preponderance of the *trans* over the *cis* isomer.

**Supporting Information** (see footnote on the first page of this article): Calculated occupancy values (Table S1), calculated overlapping energies (kcal/mol) of *lpN* (Table S2), calculated overlapping energies (kcal/mol) of *lpO1* (Table S3), calculated overlapping energies (kcal/mol) of *lpO2* (Table S4) and calculated $^{13}$C NMR chemical shifts (Table S5) of naphthoxazines **1**–**5.**

## Acknowledgments

The author's thanks are due to the Deutsche Forschungsgemeinschaft (DFG 436 UNG 113/161) and the Hungarian Research Foundation (OTKA No. D48669) for financial support.

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Received: June 30, 2006