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Stereoelectronic Effects in Ring-Chain Tautomerism of 1,3-Diarylnaphth[1,2-*e*][1,3]oxazines and 3-Alkyl-1-arylnaphth[1,2-*e*][1,3]oxazines†

István Szatmári,‡ Tamás A. Martinek,‡ László Lázár,‡ Andreas Koch,§ Erich Kleinpeter,§ Kari Neuvonen,|| and Ferenc Fülöp*,‡

Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary, Department of Chemistry, University of Potsdam, POB 691553, Germany, and Department of Chemistry, University of Turku, FIN 20014 Turku, Finland

fulop@pharma.szote.u-szeged.hu

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The disubstitution effects of X and Y in 1-(Y-phenyl)-3-(X-phenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*]-[1,3]oxazines on the ring-chain tautomerism, the delocalization of the nitrogen lone pair (anomeric effect), and the ^{13}C NMR chemical shifts were analyzed by using multiple linear regression analysis. Study of the three-component equilibrium **B** ⇌ **A** ⇌ **C** revealed that the chain ⇌ trans (**A** ⇌ **B**) equilibrium constants are significantly influenced by the inductive effect (σ_F) of substituent Y on the 1-phenyl ring. In contrast, no significant substituent dependence on Y was observed for the chain ⇌ cis (**A** ⇌ **C**) equilibrium. There was an analogous dependence for the epimerization (**C** ⇌ **B**) constants of 1-(Y-phenyl)-3-alkyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. With these model compounds, significant overlapping energies of the nitrogen lone pair was observed by NBO analysis in the trans forms **B** (to $\sigma^*_{C1-C1'}$, $\sigma^*_{C1-C10b}$, and σ^*_{C3-O4}) and in the cis forms **C** (to σ^*_{C1-H}, $\sigma^*_{C1-C10b}$, and σ^*_{C3-O4}). The effects of disubstitution revealed some characteristic differences between the cis and trans isomers. However, the results do not suggest that the anomeric effect predominates in the preponderance of the trans over the cis isomer. When the ^{13}C chemical shift changes induced by substituents X and Y (SCS) were subjected to multiple linear regression analysis, negative ρ_F^Y and ρ_F^X values were observed at C-1 and C-3 for both the cis and trans isomers. In contrast, the positive ρ_R^Y values at C-1 and the negative ρ_R^X values at C-3 observed indicated the contribution of resonance structures ***f*** ($\rho_R > 0$) and ***g*** ($\rho_R < 0$), respectively. The classical double bond−no-bond resonance structures proved useful in explaining the substituent sensitivities of the donation energies and the behavior of the SCS values.

Introduction

The ring-chain tautomeric interconversion of *N*-unsubstituted 1,3-*O*,*N*-heterocycles and the corresponding hydroxyalkylimines can often be exploited advantageously in different areas of organic synthesis and also in physical, medicinal, and peptide chemistry.[1] From quantitative studies on such equilibria, it has been concluded that the tautomeric ratios for oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2 can be characterized by an aromatic substituent dependence:

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

where K_X is the [ring]/[chain] ratio and σ^+ is the Hammett−Brown parameter of substituent X on the 2-phenyl group. The scope and limitations of eq 1 have been thoroughly studied from the aspects of the applicability of this equation in the case of complex tautomeric mixtures containing several types of open and/or cyclic forms, and the influence of the steric and/or electronic effects of the substituents at positions other than 2 on the parameters in eq 1.[1,2] Previous quantitative investigations on the ring-chain tautomeric equilibria of some 1,3-Y,*N*-heterocyclic model compounds (Y = O, NR) did not result in precise mathematical formulas with which to characterize the effects of substituents at positions other than 2 or were restricted to the recording of the substituent-induced changes in the parameters in eq 1.[3]

A recent study on the ring-chain tautomeric equilibria of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines

* To whom correspondence should be addressed. Tel.: +36-62-545564. Fax: +36-62-545705.

† Dedicated to Professor Istvan Hermecz on the occasion of his 60th birthday.

‡ University of Szeged.

§ University of Potsdam.

|| University of Turku.

(1) (a) Valters, R. E.; Fülöp, F.; Korbonits, D. *Adv. Heterocycl. Chem.* **1996**, *66*, 1−71. (b) Lázár, L.; Fülöp, F. *Eur. J. Org. Chem.* **2003**, 3025−3042.

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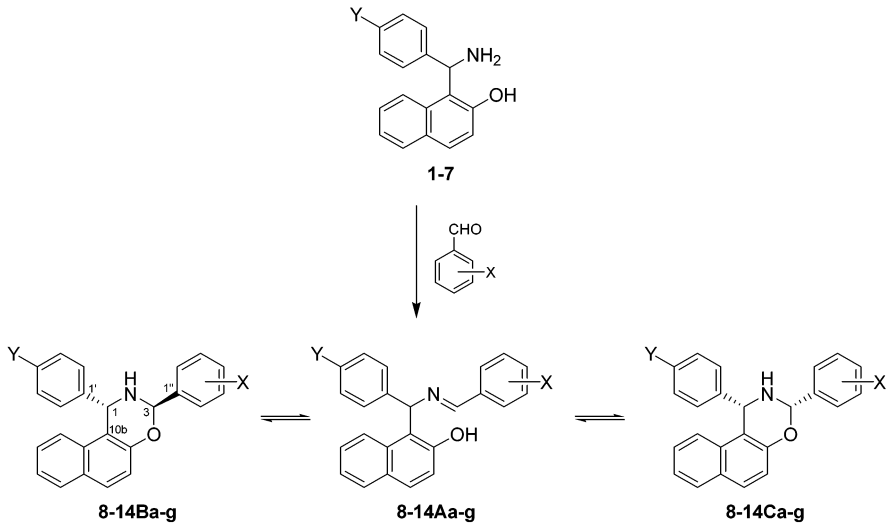
SCHEME 1



Y = NO_2: **1**,**8**; Br: **2**,**9**; Cl: **3**,**10**; H: **4**,**11**; F: **5**,**12**; Me: **6**,**13**; OMe: **7**,**14**
X = *p*NO_2: **a**; *m*Br: **b**; *p*Br: **c**; *p*Cl: **d**; H: **e**; *p*Me: **f**; *p*OMe: **g**

demonstrated that the tautomeric ratios were strongly influenced not only by the aryl group at position 3 but also by that at position 1.[4] As a continuation of that work, our present aim was to clarify the influence of the substituents and to attempt to find a generalized multivariate extension of eq 1 describing double substituent effects (e.g., a double aromatic substituent dependence and the alkyl/aryl substituent effects) in the ring-chain tautomeric equilibria of 1,3-disubstituted 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. For a better understanding of the ring-chain tautomeric process a further aim was a characterization of the propagation of the substituent effect in the naphthoxazine model compounds by quantum chemical calculations and correlation analysis of the ^{13}C chemical shifts. Special emphasis was put on the question of the potential influence of the delocalization of the nitrogen lone pair (i.e., anomeric effect) on the ring-chain equilibria or on the propagation of the effects of the phenyl substituents.

Results and Discussion

1,3-Diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. Synthesis. 1,3-Diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **10**, **11**, **13** and **14** were prepared according to a known procedure,[4] involving the ring-closure reactions of the Betti base (**4**) and its Y-substituted analogues (**3**, **6**, and **7**) with equivalent amounts of aromatic aldehydes. To extend the electronic characteristics and increase the diversity of the substituents Y in the model compounds, three new α-aminonaphthols (**1**, **2**, and **5**) were synthesized and converted in an analogous manner to the corresponding naphthoxazine derivatives (**8**, **9**, and **12**) (Scheme 1).

The ^1H NMR spectra of **8**, **9**, and **12** revealed that, in $CDCl_3$ solution at 300 K, the members **a**−**g** of each set of compounds **8**, **9**, and **12** participated in three-component ring-chain tautomeric equilibria involving C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**). The relative configurations of the cyclic tautomers were determined by NOE measurements.[4] The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) in the tautomeric equilibria of **8**, **9**, and **12** were determined by integration of the well-separated O−C*H*Ar−N (ring) and N=C*H*Ar (chain) proton singlets or doublets (some cases in the ring forms) in the ^1H NMR spectra (Tables S1 and S2, Supporting Information).

Hansch Analysis of Equilibrium Constants. The three-component equilibrium (**B** ⇌ **A** ⇌ **C**) offers an interesting system on which to study the properties of the cis (**C**) and trans (**B**) isomers, because they are in thermodynamic equilibrium in solution via the chain form.

The influence of the 3-aryl group on the tautomeric equilibria of 1,3-naphthoxazines **8**−**14** could be described by using eq 1.[4] The Hammett−Brown parameter σ^+ was found to be inadequate to describe the influence of aryl substituents at position 1.[4] The effect of substituent Y was therefore divided into two parts: σ_F (inductive effect) and σ_R (resonance effect). Since the Hammett−Brown parameter σ^+ has proved to be a convenient substituent parameter with which to characterize the influence of substituent X on tautomeric equilibria,[4] it was used to set up the following Hansch quantitative structure−properties relationship (QSPR) model:

$$DV = k + \rho_F^Y\sigma_F^Y + \rho_R^Y\sigma_R^Y + \rho^X\sigma^{+X} \qquad (2)$$

where DV is the dependent variable (log *K* or donation energies). However, analogously with that of substituent Y, the influence of substituent X can also be divided into two parts (σ_F and σ_R), as represented by eq 3. Multiple linear regression analysis of eqs 2 and 3 was performed by using the SPSS statistical software. A value of 0.05 was chosen as the significance level.[5]

$$DV = k + \rho_F^Y\sigma_F^Y + \rho_R^Y\sigma_R^Y + \rho_F^X\sigma_F^X + \rho_R^X\sigma_R^X \qquad (3)$$

(4) Szatmári, I.; Martinek, T. A.; Lázár, L.; Fülöp, F. *Tetrahedron* **2003**, *59*, 2877−2884.
(5) SPSS Advanced Models 9.0; SPSS Inc.: Chicago, IL.

TABLE 1. Multiple Linear Regression Analysis of log *K* Values for 8−21

		k	ρ_F^Y	ρ_R^Y	ρ^X,ρ_F^X and ρ_R^X,ρ^R	*r*
by eq 2	**8−14A ⇌ 8−14B**	0.32(0.03)[a]	0.33(0.06)	*b*	1.44(0.04)	0.980
	8−14A ⇌ 8−14C	−0.53(0.03)	*b*	*b*	1.30(0.05)	0.971
by eq 3	**8−14A ⇌ 8−14B**	0.34(0.03)	0.30(0.05)	*b*	1.17(0.04) 1.87(0.06)	0.992
	8−14A ⇌ 8−14C	−0.53(0.04)	*b*	*b*	1.08(0.06) 1.66(0.08)	0.981
by eq 5	**15−21C ⇌ 15−21B**	0.48(0.04)	0.22(0.05)	*b*	7.99(0.68)	0.921

[a] Standard deviations. [b] Insignificant (significance value > 0.05).

Multiple linear regression analysis of eqs 2 and 3 with DV as log *K* values led to the results listed in Table 1. As regards substituent X, both inductive and resonance effects seem to be significant for the equilibria **A** ⇌ **B** and **A** ⇌ **C**. On the other hand, substituent Y does not affect the equilibrium **A** ⇌ **C** at all, and only inductive effects are significant for the equilibrium **A** ⇌ **B**.

There is a relatively large difference in the values of the equilibrium constants for **A** ⇌ **B** and **A** ⇌ **C** (on the average, K_B:K_C ≈ 11:1; Tables S1 and S2, Supporting Information). The sensitivities of K_B and K_C to substituent X within both isomeric series are marked (Table 1). The observed values of both ρ_F^X (inductive) and ρ_R^X (resonance) are positive. Positive values mean that the electron-withdrawing (EW) substituents increase the relative proportion of the ring form both inductively and by resonance. Interestingly, somewhat more positive ρ values are observed for the equilibrium **A** ⇌ **B**, indicating that the sensitivity of the equilibrium in question to substituent X depends on the orientation of the phenyl ring at position 1 (a disubstitution effect). Extensive previous data demonstrate that for 1,3-*O*,*N*-heterocycles EW substituents on the phenyl ring situated between the two heteroatoms (i.e., substituent X) increase the relative proportion of the ring tautomers as compared with the parent compound (X = H).[1−4,6] Good correlations of log *K* with σ^+ have shown that both inductive and resonance effects are usually significant. For excellent reasons, this can be stated to be *normal behavior of the substituent dependence of the ring-chain equilibria*.[1−4,6] The origin of this effect is now understood.[6] As regards substituents X, the present results are in harmony with the above concept. In contrast with the above behavior, in the case of a phenyl substituent on C-1, the sensitivities of the log *K* values for the cis and trans isomers differ. For the equilibrium **A** ⇌ **C**, no significant dependence on substituent Y was observed. For the equilibrium **A** ⇌ **B**, a positive value of ρ_F^Y (0.30) was found, but there was no significant dependence on resonance parameter ρ_R. The present results show for the first time that aromatic ring substituents that are not attached to a phenyl ring situated between two heteroatoms can have a systematic effect on the relative proportions of the ring tautomers. The diminished inductive sensitivity, as compared with that of substituent X (0.30 vs 1.17), reflects the fact that the substituent in question is situated farther away from the reaction center. In summary, the equilibrium **A** ⇌ **B** seems to be somewhat more sensitive to both substituent X and substituent Y than the equilibrium **A** ⇌ **C**.

Hansch Analysis of Donation Energies for Rigid Model Structures. Donation energy calculations were performed with conformationally rigid models in order to clarify the potential connections between the electron donation of the nitrogen lone pair (anomeric effects)[7] and the relative stabilities of the cis and trans isomers or the substituent sensitivity of the ^{13}C NMR chemical shifts.

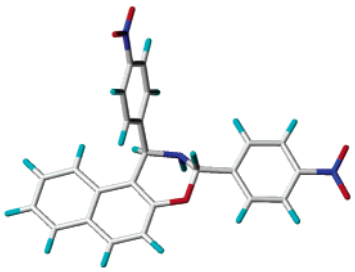


FIGURE 1. Final predominant minimum energy molecular structure for **8aB**, obtained by using ab initio HF/6-31G* calculations.

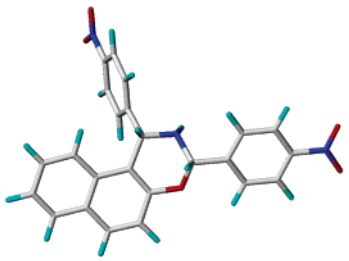


FIGURE 2. Final predominant minimum energy molecular structure for **8aC**, obtained by using ab initio HF/6-31G* calculations.

The conformational search protocol involved PM3 geometry minimization, followed by optimization at the ab initio level, using the HF/6-31G* base set for all of the compounds. The final conformations, with **8aB** and **8aC** as examples, are shown in Figures 1 and 2, respectively. Ab initio calculations were performed by second-order perturbative analysis of the Fock matrix in the NBO base,[8−11] where the energy of donation (kcal/mol) of a lone pair to a given antibonding orbital could be calculated.

In principle, the nitrogen lone pair can overlap with six different vicinal antibonding orbitals associated with C1 (σ^*_{C1-H}, $\sigma^*_{C1-C1'}$, and $\sigma^*_{C1-C10b}$) or with C3 (σ^*_{C3-H}, $\sigma^*_{C3-C1''}$, and σ^*_{C3-O4}). The overlapping energy values are

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TABLE 2. Multiple Linear Regression Analysis of Overlapping Energy Values According to eq 2 for 8−14

	overlapping	*k*	ρ_F^Y	ρ_R^Y	ρ^X	*r*
B	$n_N \rightarrow \sigma^*_{C1-C1'}$	3.13(0.01)[a]	0.34(0.01)	0.37(0.02)	−0.13(0.01)	0.983
	$n_N \rightarrow \sigma^*_{C1-C10b}$	8.94(0.01)	*b*	*b*	−0.25(0.02)	0.915
	$n_N \rightarrow \sigma^*_{C3-O4}$	20.31(0.01)	−0.36(0.02)	−0.24(0.03)	−0.16(0.01)	0.956
	$n_N \rightarrow \sigma^*_{C3-C1''}$	1.10(0.01)	−0.11(0.01)	−0.07(0.02)	0.12(0.01)	0.909
	$n_N \rightarrow \sigma^*_{C3-H}$	1.42(0.01)	0.09(0.01)	0.09(0.02)	−0.05(0.01)	0.865
C	$n_N \rightarrow \sigma^*_{C1-H}$	4.49(0.01)	*b*	*b*	−0.13(0.01)	0.799
	$n_N \rightarrow \sigma^*_{C1-C10b}$	8.70(0.01)	0.09(0.02)	0.15(0.03)	−0.25(0.01)	0.942
	$n_N \rightarrow \sigma^*_{C3-O4}$	20.82(0.01)	−0.72(0.02)	−0.61(0.03)	−0.10(0.02)	0.984
	$n_N \rightarrow \sigma^*_{C3-C1''}$	1.07(0.01)	*b*	*b*	−0.08(0.01)	0.819
	$n_N \rightarrow \sigma^*_{C3-H}$	1.62(0.01)	−0.08(0.02)	*b*	*b*	0.642

[a] Standard deviations. [b] Insignificant (significance value > 0.05).

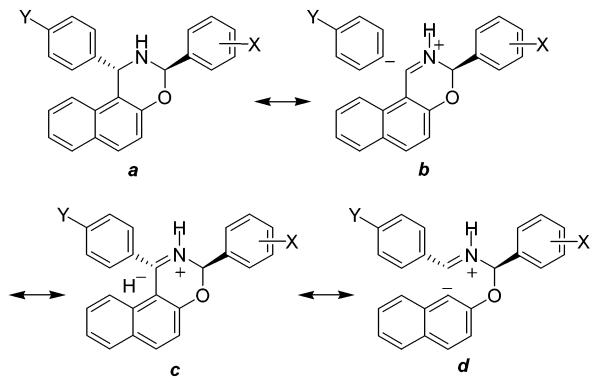
listed in Table S3 of Supporting Information. The results of Hansch analysis of the energy values as DV according to eq 2 are given in Table 2.

The three most significant overlappings of the nitrogen lone pair were observed in the trans forms **B** to $\sigma^*_{C1-C1'}$, $\sigma^*_{C1-C10b}$, and σ^*_{C3-O4} and in the cis forms **C** to σ^*_{C1-H}, $\sigma^*_{C1-C10b}$, and σ^*_{C3-O4}. The noteworthy difference between the cis and trans forms is that for the trans form there is no significant $n_N \rightarrow \sigma^*_{C1-H}$ donation but there is a significant $n_N \rightarrow \sigma^*_{C1-C1'}$ donation, whereas for the cis form there is no $n_N \rightarrow \sigma^*_{C1-C1'}$ donation but there is a significant $n_N \rightarrow \sigma^*_{C1-H}$ donation. Further, although the $n_N \rightarrow \sigma^*_{C1-H}$ donation energy detected for the cis form does not depend on the substituent Y, the $n_N \rightarrow \sigma^*_{C1-C1'}$ donation energy detected for the trans form exhibits a clear substituent dependence on Y, both inductive and resonance effects being important. As for the $n_N \rightarrow \sigma^*_{C1-C10b}$ donation, for the cis form there is a slight dependence on substituent Y, but for the trans isomer no analogous dependence was observed.

From a comparison of Figures 1 and 2, it can be supposed that the destabilizing steric interactions mainly explain the greater stability of the trans versus the cis isomers. An anomeric effect is also a stabilizing effect and, in principle, can play a role in stabilization of the trans over the cis isomers. However, the sums of the different significant donation energies are relatively close to each other: for X = Y = H, they are 34.90 and 36.70 kcal/mol (in other words, the sum of the *k* values in Table 2) for the trans and cis isomers, respectively, but the total is always somewhat larger for the cis isomers (Table S3, Supporting Information). Obviously, the anomeric effects stabilize the cis isomers more than the trans isomers. This excludes the idea that the anomeric effect controls the marked stability difference between the cis and trans series.

For the trans forms (**B**), the overlapping energy for $n_N \rightarrow \sigma^*_{C1-C1'}$ was clearly dependent on substituent Y (ρ_F^Y = 0.34 and ρ_R^Y = 0.37; Table 2). On the other hand, for the cis forms (**C**), the overlapping energy for $n_N \rightarrow \sigma^*_{C1-C10b}$ was substituent-dependent, but to an essentially smaller extent (ρ_F^Y = 0.09 and ρ_R^Y = 0.15; Table 2). Thus, the extent of the effect of substituent Y on the donation energies seems to depend on the configuration. In both cases, electron donation/withdrawal by both inductive and resonance mechanisms is to be seen, but the sensitivity to the resonance effect is slightly higher. The positive values of both ρ_F^Y and ρ_R^Y mean that EW substituents increase the value of the DV. It is generally thought that the mechanism of the anomeric effect is the overlapping between an occupied lone pair orbital and an antibonding orbital of an adjacent polar bond, and its valence bond representation is a double bond−no-bond resonance structure (cf. Scheme 2). For example, electron density is transferred from N-2 to the C1−C1′ antibonding orbital. In the case of $n_N \rightarrow \sigma^*_{C1-C1'}$ overlapping, the positive ρ_F^Y and ρ_R^Y values can be understood in terms of the contribution of the corresponding double bond−no-bond resonance structure ***b*** (Scheme 2). The stabilization of resonance structure ***b*** by EW substituents results in an increase in the donation energy in question as compared with that of the parent compound, and consequently positive ρ values are observed.

SCHEME 2



Both **B** and **C** possess a half-chair structure. Scheme 3 gives the relevant conformations due to nitrogen/ring inversions. It is generally thought that in 1,3-oxazine systems the equatorial orientation of the substituent attached to the O-*C*-N carbon is favored.[12] The 1,3-axial-pseudoaxial orientations (cis II and IV) of the cis forms are highly unfavored as a result of the severe steric interaction, and their presence can be neglected. Hence, the equatorial-pseudoequatorial orientations (cis I and III) preponderate in the cis forms. As a result of the equatorial preponderance of 3-phenyl substituents (trans I and III), the trans forms exhibit 1-phenyl pseudoaxial orientations.[12] Thus, the minimum energy conformations used in the NBO analysis (trans I and cis I, cf. Figures 1 and 2) are relevant model structures. In the orientation trans I (see Scheme 3), overlap between the nitrogen lone pair and the σ antibonding orbital of the C1−C1′ bond is possible, even if it is not as favored as it could be in the

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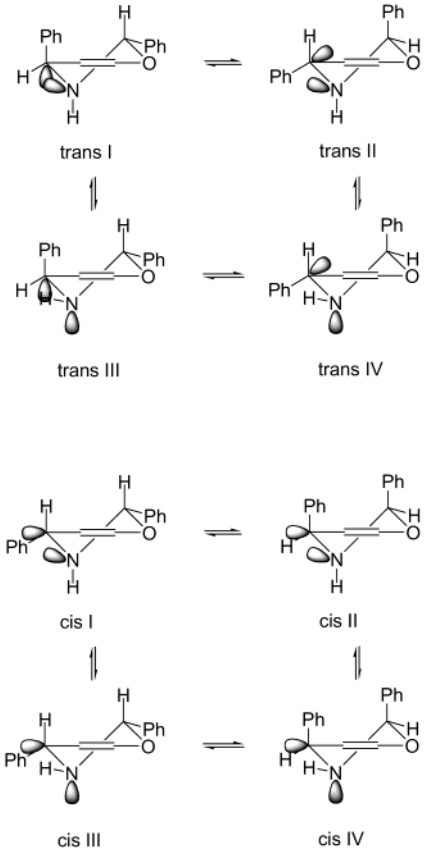
SCHEME 3



orientation trans III. In cis I, the spatial orientations of the nitrogen lone pair and the C1−C1′ antibonding orbital do not allow overlap. Accordingly, the calculations did not indicate any significant $n_N \rightarrow \sigma^*_{C1-C1'}$ donation for the cis isomers. Interestingly, for trans I the dependence of the overlapping energy of $n_N \rightarrow \sigma^*_{C1-C1'}$ on substituent Y is clearly significant ($\rho_F^Y = 0.34$ and $\rho_R^Y = 0.37$; Table 2), the overlapping increasing with increasingly EW substituents. As concerns the $\sigma^*_{C1-C10b}$ orbital, the favorable overlapping of the nitrogen lone pair is possible in orientations I, which possess an equatorial nitrogen lone pair orientation for both the cis and the trans isomers. The calculated donation energies are about three times greater than those for $n_N \rightarrow \sigma^*_{C1-C1'}$ donation in the case of the trans isomers. However, in contrast with the above, the dependence on substituent Y is small for the cis isomers and insignificant for the trans isomers. In summary, the differences between the calculated substituent-dependent stereoelectronic effects (anomeric effects) at C-1 can be understood on a conformational basis.

The largest of the overlapping energies observed for our compounds are connected with $n_N \rightarrow \sigma^*_{C3-O4}$ transmission. However, the donation energies in question for the cis and trans series are very close to each other. Hence, this anomeric effect cannot explain the stability differences between the isomers. For both the trans (**B**) and the cis (**C**) forms, the overlapping energy for $n_N \rightarrow \sigma^*_{C3-O4}$ was clearly dependent on substituent Y (**B**, $\rho_F^Y = -0.36$ and $\rho_R^Y = -0.24$; **C**, $\rho_F^Y = -0.72$ and $\rho_R^Y = -0.61$, Table 2). Because both the inductive and resonance parameters (ρ_F and ρ_R) in question are <0, the value of the donation energy is increased by electron-donating (ED) substituents. The different magnitudes of the ρ values indicate that the substituent dependence in question is dependent on the orientation of the substituted phenyl ring at C-1, the eq′-Ph-N-C-O pathway being able to transmit the effect of substituent Y more efficiently than the ax′-Ph-N-C-O pathway. The substituent dependence of the $n_N \rightarrow \sigma^*_{C3-O4}$ donation can be explained by comparison with $n_N \rightarrow \sigma^*_{C1-C1'}$ (**B**, $\rho_F^Y = 0.34$ and $\rho_R^Y = 0.37$; **C**, ρ_F^Y and ρ_R^Y, not significant), because the contributions of the $n_N \rightarrow \sigma^*_{C3-C1''}$ and $n_N \rightarrow \sigma^*_{C3-H}$ donations are small and can be neglected. It may be considered that the donation ability of one nitrogen lone pair is limited as regards the number and extent of different donations and the routes giving the maximal stabilization of the molecular structure prevail. Hence, for the trans isomers $n_N \rightarrow \sigma^*_{C1-C1'}$ and $n_N \rightarrow \sigma^*_{C3-O4}$ compete. For the trans isomers, both the ρ_F^Y and ρ_R^Y values are positive for $n_N \rightarrow \sigma^*_{C1-C1'}$. This means that EW substituents increase the value of the donation energy. In contrast, for $n_N \rightarrow \sigma^*_{C3-O4}$ both ρ_F^Y and ρ_R^Y are <0. This means that EW substituents decrease the value of the donation energy. This decrease is compensated by the increase in $n_N \rightarrow \sigma^*_{C1-C1'}$. The $n_N \rightarrow \sigma^*_{C3-O4}$ transmission also seems to be sensitive to substituent X but to an essentially smaller extent than above. It has been shown by Neuvonen et al. that an increase in the contribution of $n_N \rightarrow \sigma^*_{C3-O4}$ donation facilitates the ring opening in ring-chain tautomerism.[6]

3-Alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]-oxazines. The ring-chain tautomeric ratio is determined by the free energy difference between the tautomeric forms. Therefore, the observed systematic change in log K cannot be simply related to the energetic changes either in the ring form or in the chain form. To find evidence of the substituent effect in the ring form, the tautomeric system of 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **15**−**21** was analyzed. Condensations of aminonaphthols **1**−**7** with equivalent amounts of aliphatic aldehydes resulted in the naphthoxazine model compounds **15**−**21** (Scheme 4).

The ^{1}H NMR spectra of **15**−**21** showed that, in $CDCl_3$ solution at 300 K, the members **a**−**e** of each set of compounds **15**−**21** participated in two-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** and **C**). The relative configurations of **B** and **C** were proved by using NOE measurements (see Experimental Section). In any set of compounds, chain forms (**A**) could not be detected. This is in accordance with the results of earlier studies on the condensation products of 2- or 3-aminoalkanols and aliphatic carbonyl compounds, in which branching of the chain in 2-alkyl substituents proved to stabilize the cyclic tautomers.[13] The proportions (%) of the ring forms are given in Table S4, Supporting Information.

The epimerization constants were calculated from the ratio of the ring forms, log K_R = [**B**]/[**C**]. To find a linear equation to describe the influence of the alkyl substituents on log K_R, three different alkyl substituent param-

(13) Bergmann, E. D.; Gil-Av, E.; Pinchas, S. *J. Am. Chem. Soc.* **1953**, *75*, 358−361.

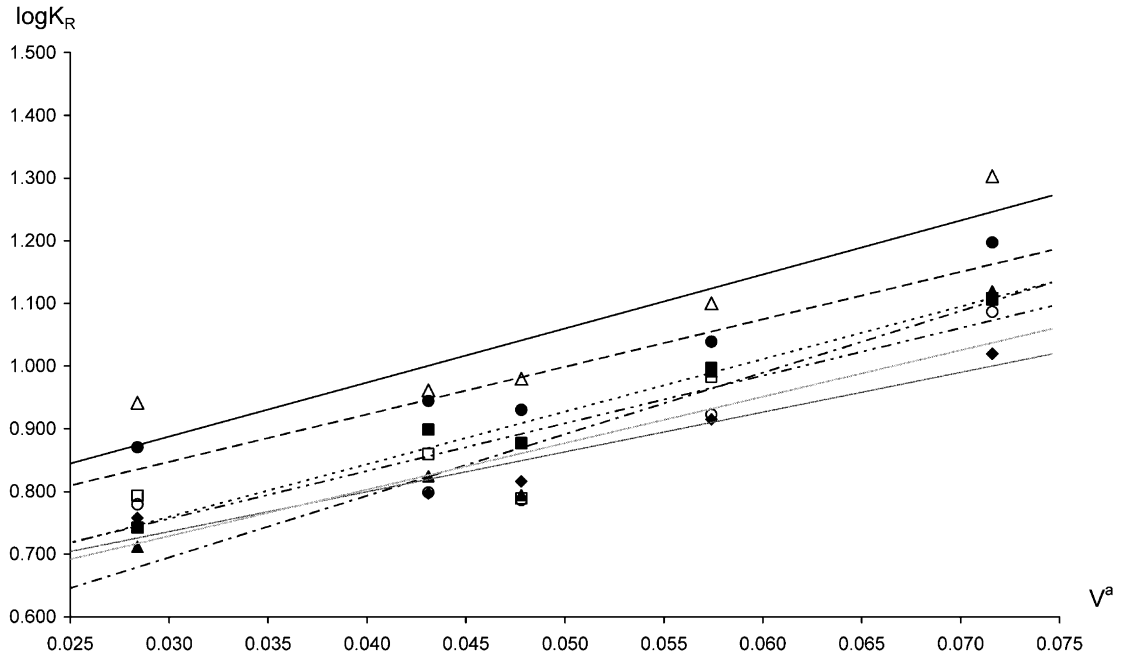
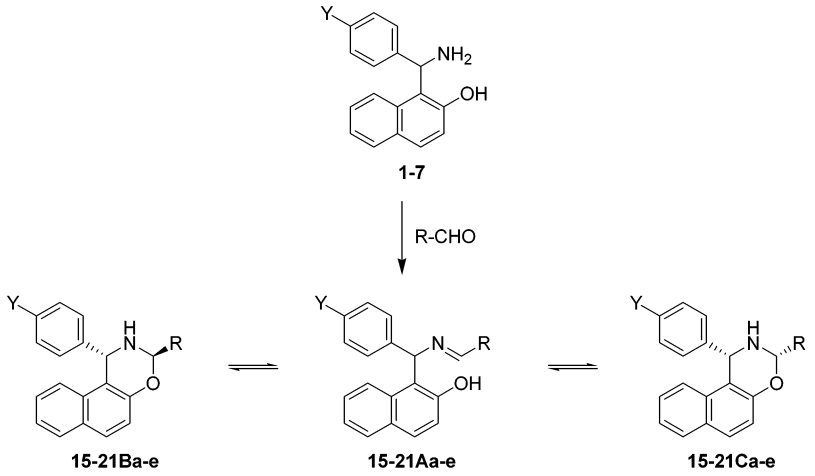


FIGURE 3. Plots of log K_R (in $CDCl_3$) for **15a**−**e** (△), **16a**−**e** (▲), **17a**−**e** (●), **18a**−**e** (◆), **19a**−**e** (■), **20a**−**e** (○) and **21a**−**e** (□) versus Meyer parameter V^a.

SCHEME 4



Y = NO_2: **1,15**; Br: **2,16**; Cl: **3,17**; H: **4,18**; F: **5,19**; Me: **6,20**; OMe: **7,21**
R = Me: **a**; Et: **b**; Pr: **c**; *i*Pr: **d**; *t*Bu: **e**

eters were studied: E_s (calculated from the hydrolysis or aminolysis[14] of esters) and two other steric parameters independent of any kinetic data, ν (derived from the van der Waals radii[15]) and V^a (the volume of the portion of the substituent that is within 0.3 nm of the reaction center[16]). Good correlations were found with all three alkyl substituent parameters. The linear regression analysis data for series **15**−**21** are given in Table S5, Supporting Information. As the best correlations were observed versus the Meyer parameters (V^a, eq 4), this was used for the further examinations (Figure 3).

$$\log K_R = 0.55 + 7.88V^a \quad (4)$$

To study the common influence of the aryl substituents at position 1 and the alkyl substituents at position 3, multiple linear regression analysis of log K_R as dependent variable was performed according to eq 5. The analysis results are listed in Table 1.

$$\log K_R = k + \rho_F^Y\sigma_F^Y + \rho_R^Y\sigma_R^Y + \rho^R V^a \quad (5)$$

The significant dependence of log K_R on the inductive effect (σ_F) of substituent Y for **15**−**21**, together with the

(14) De Tar, D. F.; Delahunty, C. *J. Am. Chem. Soc.* **1983**, *105*, 2734−2739.
(15) (a) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552−1556. (b) Charton, M. *J. Org. Chem.* **1976**, *41*, 2217−2220.
(16) Meyer, A. Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1567−1572.

TABLE 3. Multiple Linear Regression Analysis of Chemical Shifts for 8−14 According to eq 6

		ρ_F^Y	ρ_R^Y	ρ_F^X	ρ_R^X	r
for	**A**	−1.81(0.11)[a]	*b*	*b*	0.45(0.16)	0.967
C-1	**B**	−1.12(0.06)	0.75(0.09)	*b*	*b*	0.982
	C	−1.51(0.08)	0.60(0.13)	−0.49(0.08)	*b*	0.983
for	**A**	1.74(0.14)	2.31(0.21)	−2.96(0.14)	*b*	0.977
C-3	**B**	*b*	0.44(0.15)	−1.56(0.09)	−0.56(0.15)	0.968
	C	−0.53(0.07)	−0.30(0.11)	−1.88(0.07)	−0.44(0.11)	0.987

[a] Standard deviations. [b] Insignificant (significance value > 0.05).

σ_F dependence of log K for **8**−**14**, led us to conclude that only the free energies of the trans forms are influenced by the inductive effect of substituent Y, which can be explained by the anomeric effect influenced quantitatively by Y. The ρ_F^Y value obtained via eq 5 is relatively close to that obtained according to eq 3 for the equilibrium chain ⇌ trans (**A** ⇌ **B**). This supports the validity of the ρ_F^Y values, indicating that these parameters reflect the pure contribution of Y.

Influences of Substituents on ^{13}C NMR Chemical Shifts of Compounds 8−14. The ^{13}C NMR chemical shift changes induced by phenyl substituents (SCS) on C-2 have been analyzed by several different dual substituent parameter approaches.[6,17f,g] The best correlation was obtained with the equation SCS = $\rho_F\sigma_F + \rho_R\sigma_R$.[6] For all of the studied 1,3-heterocyclic systems, negative ρ_F values were observed, indicating reverse behavior of the electron density on C-2.[6]

To check the previous hypothesis, the chemical shifts of C-1 and C-3 were measured in $CDCl_3$ and are listed in Table S6, Supporting Information. To facilitate comparison, some of the carbons of the chain forms are indicated analogously with those of the ring forms and given in quotation marks. For example, "C-3" in the series **8**−**14A** corresponds to C-3 in the series **8**−**14B** and **8**−**14C**.

Chemical shift changes induced by an aryl substituent (SCS) for a given compound were calculated as the differences in the ^{13}C chemical shift for the substituted relative to the unsubstituted (X = Y = H) compound.

$$\mathrm{SCS} = \rho_F^Y\sigma_F^Y + \rho_R^Y\sigma_R^Y + \rho_F^X\sigma_F^X + \rho_R^X\sigma_R^X \qquad (6)$$

The multiple regression analysis data obtained via eq 6 for C-1 and C-3 are presented in Table 3.

The cis isomers **C** exhibit low-field (i.e., high-frequency) C-1 ^{13}C NMR chemical shifts as compared with those of the trans isomers **B**, ΔSCS being about 3 ppm. The values of ρ_F^Y and ρ_R^Y for C-1 seem to depend on the configuration. The trans isomers exhibit somewhat less negative ρ_F^Y values but slightly more positive ρ_R^Y values. Thus, the sensitivity to the inductive effect is somewhat stronger within the cis series.

(17) (a) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1−80. (b) Craik, D. J.; Brownlee, R. T. C. *Prog. Phys. Org. Chem.* **1983**, *14*, 1−73. (c) Reynolds, W. F. *Prog. Phys. Org. Chem.* **1983**, *14*, 165−203. (d) Kawasaki, A. *J. Chem. Soc., Perkin Trans. 2* **1990**, 223−228. (e) Gordon, M. S.; Sojka, S. A.; Krause, J. G. *J. Org. Chem.* **1984**, *49*, 97−100. (f) Neuvonen, K.; Fülöp, F.; Neuvonen, H.; Pihlaja, K. *J. Org. Chem.* **1994**, *59*, 5895−5900. (g) Neuvonen, K.; Fülöp, F.; Neuvonen, H.; Simeonov, M.; Pihlaja, K. *J. Phys. Org. Chem.* **1997**, *10*, 55−66.

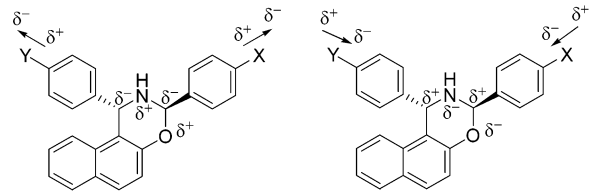
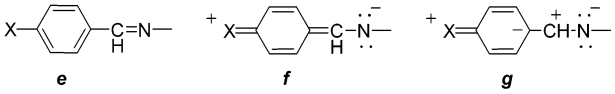


FIGURE 4. Polar substituent interactions in the trans form.

Table 3 reveals a reverse trend of the inductive substituent effects for both the cis and the trans series. This behavior means that the EW substituents induce upfield ^{13}C NMR chemical shifts as compared with those of the corresponding nonsubstituted derivative. This behavior is contrary to the well-established idea of the inductive effect, but its appearance is nowadays well documented for many different series of unsaturated side-chain derivatives of substituted benzene.[17] The origin of the reverse trend of the substituent effect for unsaturated carbon is qualitatively satisfactorily understood. On the other hand, the appearance of the analogous effect with saturated carbon centers such as those situated between the two heteroatoms in 1,3-*O*,*N*-heterocycles has been much less studied.[6] The trans and cis series in the present work offer an interesting opportunity to study this type of reversed trend of substituent effect. The negative ρ_F values have been explained by Neuvonen et al. by the concept of the substituent-sensitive polarization of the N−C−O system.[6] The substituent interaction with the polar C−O and/or C−N bond results in dipolar induction, as depicted in Figure 4. In consequence, with EW substituents the electron density at the carbon joined to a heteroatom is increased, whereas with ED substituents it is decreased. The idea of substituent interaction with the polar bond is, like that of π-polarization,[17] in conflict with the concept of the generalized inductive effect. Interestingly, the concept of polar bond interactions now seems to hold in connection with the polar (C-1)−N bonds in the title compounds.[6]

Both the cis and the trans isomers exhibit negative ρ_R^X values, in harmony with the operation of a resonance-induced polar mechanism (***g***).[6]



e ***f*** ***g***

The anomeric effect can explain the differences in sensitivity of the ^{13}C NMR chemical shifts of C-1 to substituent Y between the trans and the cis series. A significant substituent-dependent $n_N \rightarrow \sigma^*_{C1-C1'}$ donation (Table 2, 3.13 kcal/mol if X = Y = H) was observed in the trans series but not in the cis series. On the other hand, a significant $n_N \rightarrow \sigma^*_{C1-H}$ donation (4.49 kcal/mol if X = Y = H) was observed in the cis series. In the latter case the donation in question was not significantly dependent on substituent Y. This fact can be understood on the basis that the C1−H bond is more remote from the site of the substituent Y than the C1−C1′ bond. The valence bond representation of the anomeric effect is the double bond−no-bond resonance structure (Scheme 2). According to the donation energies, the resonance structure ***c*** is possible for the cis isomers, as is the resonance

structure ***b*** for the trans isomers. In addition, for both isomers the $n_N \rightarrow \sigma^*_{C1-C10b}$ donation corresponding to the resonance structure ***d*** occurs. The significance of ***d*** is closely similar in the cis and trans series (cf. Table 2). According to the magnitudes of these energies, the contribution of ***c*** (cis isomer) is stronger than that of ***b*** (trans isomer). A stronger donation means increased contribution of the resonance structure exhibiting an sp^2 hybridized carbon. Usually the sp^2 hybridized carbons exhibit lower-field ^{13}C NMR chemical shifts as compared with those of the sp^3 hybridized carbons. This explains the low-field C-1 shifts observed for the cis series. The substituent-dependent stereoelectronic effect $n_N \rightarrow \sigma^*_{C1-C1'}$ (***b***) is present in the trans form. Since EW substituents stabilize resonance form ***b***, the sp^2 character of C-1 is increased. As a consequence, a less negative ρ_F^Y value is observed for the trans isomers. Unexpectedly, both the trans and cis isomers exhibit positive ρ_R^Y values. ρ_R values are measures of the prevailing resonance interactions. In principle, there are two possible mechanisms for the resonance interaction of a side-chain-substituted benzene derivative (a C=N double bond as an example). A ρ value > 0 is based on an interaction of type ***f***. A resonance-induced polar effect is based on an interaction of type ***g***.

By contribution of the resonance structure ***f***, ED substituents increase the electron density at the probe site (C-1), resulting in upfield ^{13}C NMR chemical shifts (i.e., smaller shift values) and consequently in $\rho_R > 0$. In contrast, by contribution of the resonance structure ***g***, ED substituents decrease the electron density at the probe site (C-1), resulting in $\rho_R < 0$. The observed positive ρ_R^Y values can be understood by the appearance of the double bond−no-bond structure ***d*** corresponding to $n_N \rightarrow \sigma^*_{C1-C10b}$ donation (see above), which is sensitive to substituent Y by resonance depicted as ***f***. In summary, the behavior of the ^{13}C NMR chemical shifts of C-1 can be nicely explained on the basis of the anomeric effect directed on C-1.

The values of ρ_F^X and ρ_R^X for C-3 also seem to depend on the configuration. The trans isomers exhibit somewhat less negative ρ_F^X values but slightly more negative ρ_R^X values. The sensitivity to the inductive effect is again somewhat stronger for the cis series. For C-1, positive ρ_R^Y values were observed for both the trans and the cis forms (Table 3), whereas for C-3 negative ρ_R^X values were found for both series.

Conclusions

The influence of aryl substituents at positions 1 and 3 on the ring-chain equilibria of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines could be described by using Hansch equations. Multiple linear regression analysis via eqs 2, 3, 5, and 6 allowed determination of the influences of substituents Y and X situated on the 1- or 3-phenyl ring, respectively. Previous systematic quantitative investigations on the ring-chain tautomeric equilibria of 1,3-*O*,*N*-heterocyclic compounds) have shown that EW substituents X on the phenyl ring attached to the carbon situated between the heteroatoms increase the relative proportion of the ring tautomer inductively and by resonance. It has now been proved for the first time that EW substituents on the 1-phenyl ring have an analogous inductive influence on the chain ⇌ trans (**A** ⇌ **B**) tautomeric equilibria. By means of the model structures, the overlapping of the nitrogen lone pair with six different vicinal antibonding orbitals (anomeric effect) associated with C-1 (σ^*_{C1-H}, $\sigma^*_{C1-C1'}$, and $\sigma^*_{C1-C10b}$) or with C-3 (σ^*_{C3-H}, $\sigma^*_{C3-C1''}$, and σ^*_{C3-O4}) was studied. The anomeric effects associated with C-1 turned out to be dependent on the configurations of the isomers. The stereoelectronic effect was also studied in the case of 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. The influence of alkyl substituents on the values of the epimerization constant (K_R) could be described in terms of their Meyer parameters *V* [a]. The results of multiple linear regression analysis of the log K_R values reveal a significant dependence on the inductive effect of substituent Y (σ_F), which is comparable with that found for the equilibrium chain ⇌ trans (**A** ⇌ **B**).

Significant dependences on the inductive effect for both ring forms with negative ρ values were observed. On the other hand, both the cis and the trans isomers gave positive ρ_R^Y values at C-1, but negative ρ_R^X values at C-3, indicating the contribution of the resonance structures depicted as ***f*** and ***g***, respectively. The chemical shift changes induced by substituents Y (SCS) could be explained with the aid of the double bond−no-bond resonance structures ***b*** and ***c***. Our conclusions were supported by the calculated energies of donation of the nitrogen lone pair to the C1−C1′, C1−H, and C1−C10b antibonding orbitals.

Experimental Section

1-[Amino-(4-nitrophenyl)methyl]-2-naphthol Hydrochloride (1·HCl). To a solution of 2-naphthol (14.42 g, 0.10 mol) and 4-nitrobenzaldehyde (30.22 g, 0.20 mol) in absolute MeOH (100 mL) was added 25% methanolic ammonia solution (8 mL). The mixture was left to stand at ambient temperature for 24 h, and the crystalline product that separated out was filtered off, washed with MeOH (2 × 50 mL), dried, and suspended in 20% HCl (200 mL). The mixture was stirred at 50−60 °C for 4 h. The solvent was then evaporated off and the oily residue crystallized on treatment with EtOAc. The pale-yellow crystals were filtered off, washed with EtOAc (2 × 30 mL), and recrystallized from MeOH−Et_2O (20 mL:200 mL). Yield: 8.27 g (25%), mp 190−192 °C. Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.77; H, 4.53; N, 8.51. ^1H NMR (DMSO): δ 6.46 (s, 1H, C*H*NH_2), 7.32−7.42 (m, 2H, H-3, H-6), 7.54 (t, 1H, J = 7.8 Hz, H-7), 7.72 (d, 2H, J = 8.6 Hz, H-2′), 7.88 (d, 1H, J = 5.6 Hz, H-5), 7.91 (d, 1H, J = 6.0 Hz, H-4), 8.14 (d, 1H, J = 8.3 Hz, H-8), 8.24 (d, 2H, J = 8.6 Hz, H-3′). ^{13}C NMR (DMSO): δ 50.0, 113.3, 118.8, 121.9, 123.2, 123.5, 128.1, 128.1, 128.8, 128.8, 131.2, 131.8, 145.1, 146.9, 153.9.

1-[Amino-(4-bromophenyl)methyl]-2-naphthol (2) and 1-[Amino-(4-fluorophenyl)methyl]-2-naphthol (5). Compounds **2** and **5** were prepared from 2-naphthol (14.42 g, 0.10 mol) and 4-bromobenzaldehyde (37.00 g, 0.20 mol) or 4-fluorobenzaldehyde (24.82 g, 0.20 mol) according to ref 4. **Data for 2:** yield 5.25 g (16%), mp 115−116 °C (*i*Pr_2O). Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.20; H, 4.32; N, 4.25. ^1H NMR ($CDCl_3$): δ 6.10 (s, 1H, C*H*NH_2), 7.14 (d, 1H, J = 8.8 Hz, H-3), 7.25 (t, 1H, J = 8.1 Hz, H-6), 7.31−7.36 (m, 3H, H-2′, H-7), 7.41 (d, 2H, J = 8.6 Hz, H-3′), 7.65 (d, 1H, J = 8.8 Hz, H-8), 7.70 (d, 1H, J = 8.8 Hz, H-4), 7.72 (d, 1H, J = 8.1 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 55.2, 114.8, 120.6, 121.2, 121.9, 122.5, 127.3, 128.5, 129.2, 129.4, 130.2, 131.9, 131.9, 141.5, 156.8. **Data for 5:** yield 6.15 g (23%), mp

115−117 °C (*i*Pr_2O). Anal. Calcd for $C_{17}H_{14}FNO$: C, 76.39; H, 5.28; N, 5.24. Found: C, 76.42; H, 5.31; N, 5.22. ^{1}H NMR ($CDCl_3$): δ 6.12 (s, 1H, C*H*NH_2), 6.97 (t, 2H, J = 8.6 Hz, H-3′), 7.15 (d, 1H, J = 8.8 Hz, H-3), 7.24 (t, 1H, J = 7.6 Hz, H-6), 7.33 (t, 1H, J = 7.3 Hz, H-7), 7.42 (dd, 2H, J = 5.5, 8.56 Hz, H-2′), 7.65 (d, 1H, J = 8.6 Hz, H-8), 7.70 (d, 1H, J = 8.8 Hz, H-4), 7.72 (d, 1H, J = 8.1 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 55.2, 115.1, 115.7, 120.9, 121.2, 122.5, 126.6, 128.6, 128.8, 129.5, 129.6, 131.9, 138.3, 156.9, d (161.2, 163.7).

General Method for the Synthesis of 3-Aryl- or Alkyl-Substituted 1-Aryl-2,3-Dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (8−21). To a solution of the appropriate aminonaphthol (1 mmol) or aminonaphthol hydrochloride (**1**·HCl) in absolute MeOH (20 mL) was added an equivalent amount of aromatic or aliphatic aldehyde (for liquid aldehydes, a freshly distilled sample was used) and (in the case of **1**·HCl) Et_3N (0.11 g. 1.1 mmol), and the mixture was left to stand at ambient temperature for 24 h. The crystalline products (**8a**−**g**, **9a**−**g**, **12a**−**g**, **10c**, **11c**, **13c**, **14c**, **15a**, **15d**, **15e**, **16a**−**e**, **17a**, **17c**−**e**, **18a**−**e**, **19a**−**e**, **20a**−**e**, **21a**, **21d**, and **21e**) were filtered off and recrystallized. When no crystals separated out, the solvent was evaporated off. For **15b**, **15c**, **17b**, **21b**, and **21c**, the oily residue was partitioned between H_2O (10 mL) and $CHCl_3$ (10 mL), and the organic layer was separated, dried, and evaporated. All of the oily products (**15b**, **15c**, **17b**, **21b**, and **21c**) were dried in a vacuum desiccator for 24 h. The NMR spectra proved that the purities of these compounds were greater than 95%.

All of the new naphthoxazines gave satisfactory data on elemental analysis (C, H, N ±0.3%). The physical data on compounds **15**−**21a**−**e** are listed in Table S7, Supporting Information.

In consequence of the very similar NMR spectroscopic characters of 2-alkyl-1-aryl-2,3-dihydro-2*H*-naphth[1,2-*e*][1,3]-oxazines **15**−**21a**−**e**, determination of the relative configurations of the major and minor ring-closed tautomers was performed only for **20a**. Its data were chosen to illustrate the ^{1}H NMR spectra of the prepared tautomeric compounds. 3-Alkyl-1-aryl substituents did not change the sequence of the chemical shifts of the characteristic O−C*H*R−N protons. The NOESY spectra of **20a** unequivocally showed that the *major* ring forms in all tautomeric equilibria (**15**−**21a**−**e**) contain the 3-alkyl-1-aryl substituents in the trans position (**B**). **Data for 20a:** 1:6 cis−trans mixture δ 1.44 (d, 3H, J = 5.8 Hz, Me-3trans), 1.52 (d, 3H, J = 5.8 Hz, Me-3cis), 4.83 (q, 1H, J = 5.8 Hz, H-3cis), 4.90 (q, 1H, J = 5.8 Hz, H-3trans), 5.45 (s, 1H, H-1trans), 5.72 (s, 1H, H-1, cis), 7.02−7.11 (Ar), 7.12−7.18 (Ar), 7.21−7.28 (Ar), 7.29−7.35 (Ar). ^{13}C NMR ($CDCl_3$): overlaping signals in the aromatic region.

Statistical Calculations. The sources of the substituent constants were as follows: σ^+, ref 18b; σ_F, σ_R, ref 18a (except σ_F and σ_R for Br, ref 18b); V^a, ref 16. Statistical calculations were performed with the aid of the SPSS statistical program, version 9.0.

Quantum Chemical Calculations. Hartree−Fock energies were calculated and NBO analysis was performed by using the ab initio GAUSSIAN 98 program package.[19] All structures were optimized without any restriction. The optimized structures obtained were analyzed and the results were visualized with the modeling program SYBYL 6.7.[20]

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Supporting Information Available: Measured log K values. Donor−acceptor stabilization energies obtained from the second-order perturbation theory analysis of the Fock matrix in the NBO base. Linear regression analysis data for **15**−**21**. ^{13}C chemical shifts for oxazines **8**−**14**. Physical data on **8**−**21**. Cartesian coordinates and HF energies for **8a**−**g**. Coordinates of the other compounds studied are available on request. This material is available free of charge via the Internet at http://pubs.acs.org.

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