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Linear Free-Energy Relationships Applied to the ^{13}C NMR Chemical Shifts in 4-Substituted *N*-[1-(Pyridine-3- and -4-yl)ethylidene]anilines

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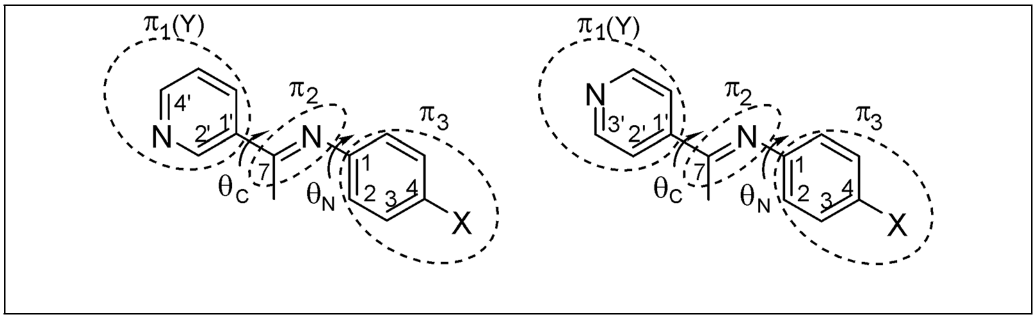

Two series of 4-substituted *N*-[1-(pyridine-3- and -4-yl)ethylidene]anilines have been synthesized using different methods of conventional and microwave-assisted synthesis, and linear free-energy relationships have been applied to the ^{13}C NMR chemical shifts of the carbon atoms of interest. The substituent-induced chemical shifts have been analyzed using single substituent parameter and dual substituent parameter methods. The presented correlations describe satisfactorily the field and resonance substituent effects having similar contributions for C1 and the azomethine carbon, with exception of the carbon atom in *para* position to the substituent X. In both series, negative ρ values have been found for C1′ atom (reverse substituent effect). Quantum chemical calculations of the optimized geometries at MP2/6-31G++(d,p) level, together with ^{13}C NMR chemical shifts, give a better insight into the influence of the molecular conformation on the transmission of electronic substituent effects. The comparison of correlation results for different series of imines with phenyl, 4-nitrophenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl group attached at the azomethine carbon with the results for 4-substituted *N*-[1-(pyridine-3- and -4-yl)ethylidene]anilines for the same substituent set (X) indicates that a combination of the influences of electronic effects of the substituent X and the π_1-unit can be described as a sensitive balance of different resonance structures.

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INTRODUCTION

Azomethines have emerged in the past two decades as promising materials for applications in photonics and optoelectronics. Low molecular weight compounds and polymers with the C=N unit are investigated as bent-core and rod-shaped liquid crystals [1–3], and depending on the chemical structure, they exhibit one mesophase or rich polymorphism [4,5]. The favorable properties of azomethines are mostly governed by extended π-conjugated system, in which the C=N unit is contained, and are sensitive even to subtle changes in it. In this context, investigations of molecular structures of benzylidene anilines have indicated that changes in substituents in both aniline and benzylidene rings largely affect the overall electronic distribution and conformation of the molecules [6–8]. The molecular structures of *N*-(phenyl substituted)pyridine-2-, -3-, and -4-aldimines have been studied in detail [9,10]. On the other side, ketimines, in which hydrogen atom of the azomethine group is replaced by an aliphatic or aryl group, have not been widely investigated. 4-Substituted *N*-[1-(pyridine-3- and -4-yl) ethylidene]anilines are important intermediates in the synthesis of pharmacologically active triazoles [11], triazolines [12], and aminoalkylpyridine derivatives that are useful as anticonvulsants, excitatory amino acid inhibitors, and *N*-methyl-D-aspartate (NMDA) sigma receptor antagonists [13]. The investigation of the similarities and differences between structurally related aldimines and ketimines may contribute to a better understanding of the charge generation at a molecular level and design of new materials for optical purposes.

The present investigation has been focused on the study of cross-interaction effects of the benzylidene and aniline substituents (Fig. 1). Two series of 4-substituted *N*-[1-(pyridine-3- and -4-yl)ethylidene]anilines have been synthesized using different methods of conventional and microwave-assisted synthesis (Fig. 1), and linear free-energy relationships (LFERs) have been applied to the ^{13}C NMR chemical shifts of the carbon atom of interest with the aim to obtain an insight into the factors, which influence charge distribution in the molecules.

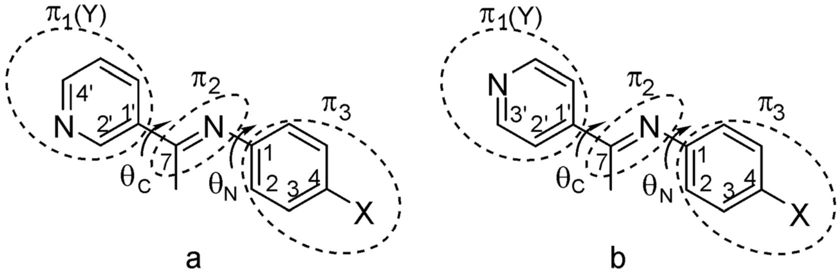

Figure 1. Structures of the 4-substituted *N*-[1-(pyridine-3-yl)ethylidene]anilines (series **6**; X=H, $N(CH_3)_2$, OH, OCH_3, CH_3, Cl, Br, and $COCH_3$) and 4-substituted *N*-[1-(pyridine-4-yl)ethylidene]anilines (series **7**; X=H, $N(CH_3)_2$, OH, OCH_3, CH_3, F, Cl, Br, $COOCH_3$, and $COCH_3$) with labels of the carbon atoms and π-resonance units.

Substituent effects on the ^{13}C NMR shifts of the carbon atoms of interest in the synthesized compounds have been compared with the correlation results obtained for different imines: *N*-benzylideneanilines [14] (series **1**), *N*-[(4-nitrophenyl)-methylene] anilines (series **2**) [14], *N*-(substituted phenyl)pyridine-2-, -3-, and -4-aldimines (series **3**, **4**, and **5**, respectively) [9,10].

The ^{13}C NMR chemical shifts are frequently used for the study of the transmission of electronic effects of substituents in organic molecules [8–10,14–16]. Analysis of ^{13}C NMR substituent-induced chemical shifts (SCS) is based on the principles of LFERs using the single substituent parameter (SSP) (eq. 1) and dual substituent parameter (DSP) (eq. 2) equations in the following form:

$$s = \rho\sigma + h \qquad (1)$$

$$s = \rho_F F + \rho_R R + h \qquad (2)$$

where s is substituent-dependent value SCS, ρ is the proportionality constant reflecting the sensitivity of the ^{13}C NMR chemical shifts to the substituent effects, σ is the corresponding substituent constant, and h is the intercept describing unsubstituted member of the series.

Equation 1 attributes the observed substituent effect to an additive blend of polar and resonance effects given as corresponding σ values. In the DSP (eq. 2), SCS are correlated by a linear combination of field (F) and resonance scales (R) depending on the electronic demand of the atom under examination. The calculated values of ρ, ρ_F, and ρ_R are relative measures of the transmission of overall, polar (inductive/field), and resonance effects, respectively, through the investigated system.

The transmission of polar and resonance electronic effects from the substituent X on the aniline ring of both series to the carbon atoms of interest has been studied by using eqs. 1 and 2. The contributions from both electronic substituent effects and the other factors determining chemical shifts have been discussed. MP2/6-31G++(d,p) theoretical calculations indicated nonplanar *E* configuration around the C=N bond in the investigated compounds. The most stable conformations of *N*-[1-(pyridine-3-yl)ethylidene]aniline and *N*-[1-(pyridine-4-yl)ethylidene]aniline are presented in Figure 2.

RESULTS AND DISCUSSION

The investigation of the effect of the aniline substituent X on the sensitivity of the polarization of the C=N group to the benzylidene substituent Y has been the main goal of the presented study. The contributions of both substituent effects have been investigated separately. To obtain a better insight into the transmission of electronic effects of the substituent X on the aniline ring, an extensive analysis of ^{13}C NMR chemical shifts of the carbon atoms of interest has been performed. The chemical shifts of the corresponding carbon atoms are given in Table 1 in terms of the SCS relative to the parent compounds.

The general conclusion derived from the data in Table 1 is that all substituents on the aniline ring of the ketimine molecule influence via their electronic effects (polar/inductive and resonance) the value of the SCS of C1, C7, and C1′ atoms. Electron-donor substituents induce downfield shifts, whereas electron acceptors induce upfield shifts of

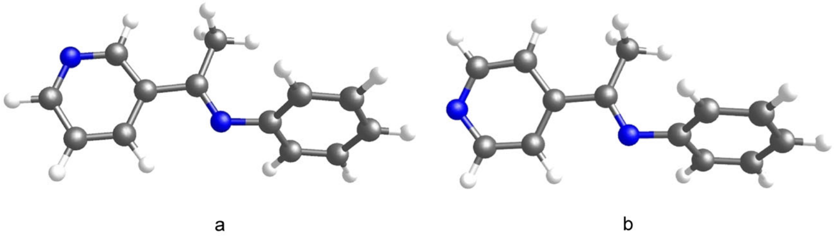

Figure 2. Optimized structures of the *N*-[1-(pyridine-3-yl)ethylidene]anilines (**a**) and *N*-[1-(pyridine-4-yl)ethylidene]anilines (**b**) obtained by the use of MP2 method.

Table 1

SCS values of carbon atoms in substituted *N*-[1-(pyridine-3-yl)ethylidene]anilines (**6**) and *N*-[1-(pyridine-4-yl)ethylidene]anilines (**7**).

	N-[1-(pyridine-3-yl)ethylidene]anilines			*N*-[1-(pyridine-4-yl)ethylidene]anilines		
X	SCS^{a}_{C7}	SCS_{C1}	$SCS_{C1'}$	SCS_{C7}	SCS_{C1}	$SCS_{C1'}$
H	164.005	151.059	134.417	164.515	150.877	145.617
$N(CH_3)_2$	−1.475	−7.411	0.874	−1.839	−11.614	0.783
OH	−0.655	−2.512	0.547	−0.819	−8.667	0.601
OCH_3	−0.447	−1.256	0.292	−0.237	−7.174	0.383
CH_3	−0.054	−1.274	0.310	−0.115	4.533	0.328
F	—	—	—	0.856	−3.787	0.005
Cl	0.933	2.622	− 0.109	1.056	−1.201	−0.163
Br	1.002	2.622	− 0.109	1.020	−1.578	−0.163
$COOCH_3$	—	—	—	2.185	−0.334	−0.362
$COCH_3$	1.368	4.941	− 0.315	2.185	−0.414	−0.398

[a] ^{13}C NMR chemical shifts (in ppm) expressed relative to the unsubstituted compound; downfield shifts are positive.

C1 and C7 atoms. The chemical shift of C1′ atom exhibits the opposite behavior. Among factors contributing to the differences in SCS values, the molecular geometry might play an important role, which arises from an out-of-plane rotation of both pyridyl and phenyl rings for the torsion angles θ_C and θ_N (Fig. 1), respectively, and this task has been studied on the basis of the results obtained from theoretical calculation at MP2/6-31G++(d,p) level. The definite molecular geometry has been defined and discussed as a consequence of the particular transmission modes of the substituent electronic effects.

To analyze substituent influence on SCS of the carbon atoms of interest, the LFER in the form of SSP equation with the σ substituent constant [17] has been applied to ketimines, and the correlation results are presented in Table 2.

Additionally, results of the correlations for series of structurally similar imines and the ones for ketimines that include the following common set of substituents: $COOCH_3$, Cl, Br, H, CH_3, OCH_3, and $N(CH_3)_2$ are presented in Table 3.

From the observed ρ values for all carbons, it is obvious that the chemical shifts of C1, C7, and C1′ atoms show different susceptibility to electronic substituent effects. The chemical shift of C1 shows increased susceptibility to substituent effects, and somewhat lower sensitivity of C7 atom is observed. This phenomenon undoubtedly indicates a considerable contribution of extended resonance interaction of electron-donor substituents from the aniline ring to C1 atom. Reverse substituent effects are observed for C1′ atom in all imines and ketimines studied. The negative sign of the proportionality constant means reverse behavior, that is, the SCS values of C1′ decrease, although the electron-accepting ability of the substituent X, given by σ, increases.

Although SSP analysis (eq. 1) uses σ parameter as an additive blend of inductive and resonance substituent effect, it provides a satisfactory description of transmission of substituent effects. To measure the separate contributions of polar (inductive/field) and resonance effects of the substituent X, the regression analysis according to eq. 2, DSP analysis, with the F and R substituent constants [17], has been performed, and the results of the best fits for two series of ketimines are presented in Table 4, and together for common series of substituents for former and imine series (**1–5**) are given in Table 5. The correlation results obtained with various combinations of σ_I and σ_R^o, σ_R, σ_R^+, using the equation $s = \rho_I\sigma_I + \rho_R\sigma_R + h$, are of lower statistical values and are not presented. The principal deficiency of correlations with σ_R arises from the hybrid natures of this substituent constant, that is, field is included

Table 2

Correlations of the SCS values for investigated ketimines (**6** and **7**) with SSP eq. 1.

Series	Atom	ρ	*h*	*r*	*F*	*s*	*n*
6	C1	9.29(±0.40)	0.56(±0.16)	0.995	545	0.43	8
	C7	2.32(±0.16)	0.30(±0.06)	0.986	214	0.17	
	C1′	−0.95(±0.06)	0.10(±0.02)	0.988	244	0.07	
7	C1	9.13(±0.68)	0.80(±0.26)	0.979	183	0.82	10
	C7	3.09(±0.21)	0.44(±0.09)	0.981	209	0.26	
	C1′	−0.98(±0.07)	0.08(±0.02)	0.980	216	0.08	

r, correlation coefficient; *F*, Fisher test of significance; *s*, standard deviation; *n*, number of data included in the correlation.

Table 3

Correlations of the SCS values for investigated imines (**1–5**) and ketimines (**6** and **7**) with SSP eq. 1.

Series	Atom	ρ	*h*	*r*	*F*	*s*	*n*	Ref.
1	C1	10.77(±1.41)	2.09(±068)	0.960	59	1.80	7	[8]
	C7	4.50(±0.26)	0.63(±0.13)	0.992	293	0.34		
	C1′	−1.13(±0.11)	0.26(±0.05)	0.977	103	0.14		
2	C1	10.75(±1.50)	2.31(±0.73)	0.954	51	1.93	7	[8]
	C7	6.79(±0.73)	0.61(±0.36)	0.972	86	0.94		
	C1′	−1.32(±0.06)	0.10(±0.03)	0.995	521	0.07		
3	C1	13.78(±1.49)	0.64(±0.63)	0.972	86	1.55	7	[10]
	C7	5.35(±0.41)	0.44(±0.16)	0.986	166	0.43		
	C1′	−1.02(±0.10)	0.18(±0.04)	0.978	108	0.10		
4	C1	11.74(±1.42)	1.81(±0.56)	0.965	68	1.47	7	[10]
	C7	5.23(±0.33)	0.37(±0.13)	0.990	246	0.35		
	C1′	−1.01(±0.09)	0.18(±0.04)	0.980	119	0.10		
5	C1	13.06(±1.53)	1.93(±0.62)	0.968	73	1.62	7	[9]
	C7	5.80(±0.45)	0.67(±0.18)	0.985	163	0.48		
	C1′	−1.25(±0.09)	0.04(±0.04)	0.988	198	0.09		
6	C1	9.39(±0.42)	0.52(±0.17)	0.995	502	0.44	7	This work
	C7	2.30(±0.18)	0.31(±0.07)	0.986	128	0.18		
	C1′	−0.93(±0.05)	0.09(±0.02)	0.992	308	0.05		
7	C1	9.598(±0.71)	4.33(±0.30)	0.986	181	0.77	7	This work
	C7	2.98(±0.28)	0.43(±0.12)	0.979	114	0.30		
	C1′	−0.97(±0.09)	0.08(±0.04)	0.980	120	0.10		

Table 4

Correlations of the SCS values for investigated ketimines (**6** and **7**) with DSP eq. 2.

Series	Atom	ρ_F	ρ_R	*h*	*r*	*F*	*s*	λ[a]
6	C1	10.56(±0.80)	9.01(±0.38)	0.15(±0.27)	0.997	370	0.37	0.85
	C7	2.74(±0.35)	2.24(±0.17)	0.16(±0.12)	0.992	121	0.16	0.82
	C1′	−0.84(±0.14)	−0.98(±0.07)	0.06(±0.05)	0.992	118	0.07	1.17
7	C1	9.02(±1.75)	9.16(±0.80)	4.24(±0.61)	0.980	80	0.88	1.02
	C7	3.59(±0.51)	2.98(±0.23)	0.31(±0.18)	0.987	107	0.26	0.83
	C1′	−0.928(±0.17)	−0.99(±0.08)	0.07(±0.06)	0.985	96	0.09	1.08

[a] $\lambda = \rho_R/\rho_F$.

in σ_R value. To obtain resonance values, which present satisfactory measures of the substituent resonance potential, pure field contributions may be obtained by the use of Swain–Lupton constants F and R. From that point of view, better correlations have been obtained with these constants, which indicate that pure resonance effect is included in correlations.

The investigation of SCS values in the benzylidene ring (side chain group) is of interest, because it may further help the understanding of polarization effects in compounds having the C=N bridging group. In general, the introduction of different groups Y (Fig. 1) at the azomethine carbon significantly changes contribution of the particular substituent effect, field and resonance, in the investigated series of imines and ketimines (Table 5), although their resonance/field ratio might be similar.

The obtained ρ_F and ρ_R values for the C1 atom indicate a significantly higher contribution of the resonance effect for series **1** and **2**. Significant (series **1**) and somewhat lower (series **3–7**) contributions of resonance effect at C1′ indicate that the π-resonance units can effectively transfer electron density from the substituent to a distant carbon. Field effects are important at C1 and C7 atoms in the compounds of series **6** and **7**, which is due to the presence of the methyl group at the azomethine carbon. Steric repulsion causes a higher deviation of the aniline ring from the planarity reducing the extent of resonance interaction. Regarding the particular carbon position in the molecular structure, the noticeable alternation of ρ_F is observed. The extent of this alternation bears an evidence of the transfer of substituent effects by the bond polarization mechanism. Despite the dependence of the transmission of

Table 5

Correlation of the SCS values for investigated imines (**1–5**) and ketimines (**6** and **7**) with DSP eq. 2.

Series	Atom	ρ_F	ρ_R	*h*	*r*	*F*	*s*	λ
1	C1	2.91(±2.37)	12.69(±1.19)	0.11(±0.79)	0.983	59	1.08	4.36
	C7	3.38(±0.43)	4.95(±0.22)	0.23(±0.14)	0.997	304	0.20	1.46
	C1′	−0.66(±0.25)	−1.26(±0.13)	0.12(±0.08)	0.982	55	0.11	1.90
2	C1	2.73(±2.17)	13.23(±1.01)	0.16(±0.72)	0.987	59	0.99	4.85
	C7	3.26(±0.50)	6.27(±0.25)	0.23(±0.17)	0.997	342	0.23	1.92
	C1′	−1.55(±0.07)	−1.20(±0.03)	0.01(±0.02)	0.999	945	0.03	0.77
3	C1	12.62(±3.75)	14.10(±1.89)	0.27(±1.25)	0.973	35	1.70	1.12
	C7	3.57(±0.38)	5.85(±0.19)	0.12(±0.13)	0.998	537	0.17	1.63
	C1′	−0.90(±0.24)	−1.05(±0.12)	0.14(±0.08)	0.979	46	0.11	1.17
4	C1	6.43(±2.11)	13.20(±1.06)	0.13(±0.70)	0.988	84	0.96	2.05
	C7	3.79(±0.29)	5.63(±0.15)	0.08(±0.10)	0.999	856	0.13	1.49
	C1′	−0.81(±0.25)	− 1.03(±0.12)	0.13(±0.08)	0.978	44	0.11	1.27
5	C1	6.86(±2.14)	15.12(±1.07)	0.23(±0.71)	0.990	107	0.97	2.20
	C7	4.02(±0.34)	6.48(±0.17)	0.01(±0.11)	0.999	798	0.16	1.61
	C1′	−1.03(±0.24)	− 1.34(±0.12)	0.05(±0.08)	0.987	77	0.11	1.30
6	C1	10.48(±0.89)	9.09(±0.45)	0.17(±0.30)	0.997	294	0.40	0.87
	C7	2.82(±0.34)	2.15(±0.17)	0.14(±0.11)	0.992	118	0.16	0.76
	C1′	−0.88(±0.13)	− 0.94(±0.07)	0.07(±0.04)	0.992	129	0.06	1.07
7	C1	9.82(±2.02)	9.02(±1.02)	0.85(±0.67)	0.981	54	0.92	0.92
	C7	3.54(±0.64)	2.77(±0.32)	0.26(±0.21)	0.987	57	0.29	0.78
	C1′	−0.96(±0.17)	−0.92(±0.08)	0.08(±0.06)	0.995	82	0.08	0.96

substituent effects on the molecular geometry (Fig. 1), it can be seen that the π-polarization mechanism is operative within the distant π_3-unit, considering the negative ρ_F for C1′. The negative sign of ρ_F is indicative of the reverse SCS effect, that is, electron-acceptor substituents cause an upfield shift, which has been explained to be due to the π-polarization [18]. Similar effects have been observed in other systems: *N*-1-*p*-substituted phenyl-5-methyl-4-carboxyuracils [19], 3-aryl 2-cyanoacrylamides [20], *N*-benzylidenanilines [14], and 2-substituted 5-*N*′,*N*′-dimethylaminophenyl-*N,N*-dimethyl carbamates [21].

π-Polarization of a distant π-system induced by substituent dipole is not necessarily transmitted via a conjugated π-system [18], and theoretical results have confirmed that a substituent dipole mainly polarizes individual π-units [22]. This phenomenon is defined as "localized polarization" (direct π-polarization). On the other side, additional polarization of the whole π-network can be induced at terminal atoms of a conjugated π-system, which is termed as "extended polarization." The satisfactory DSP long-range correlation found for $SCS_{C1'}$ indicated significant contribution of π-polarization to the overall electron density transmission in series **6** and **7**. The decreased contribution of resonance effects in series of ketimines, considering λ values for C1 and C7 atoms, is undoubtedly influenced by the nonplanarity of π_2- and π_3-units, which indicates that direct π-polarization is of high significance. Similarly, long-range correlations have been found in series of insulated systems of *N*-benzylidenbenzylamines [23–25] and diaryloxadiazolines [26].

The contributions of polar (inductive/field) and resonance effects of the substituent X on the SCS of the azomethine carbon indicate a significant attenuation effect of this group on the overall transmission of substituent effects. The correlation results for the azomethine carbon demonstrate higher contribution (series **1–5**; Table 5) of π,π-conjugation for the electron-donor substituted compounds in comparison with series **6** and **7** and increased *n*,π-conjugation in the aniline part of molecule for the electron-acceptor substituted compounds [9,10]. From this point of view, in the investigated compounds, two opposite effects are operative: the electron-accepting character of the substituent Y (π_1-unit) and the contribution of *n*,π-conjugation in the aniline part depending on the substituent X. When the C=N group and the aniline ring strive toward coplanarity, the π,π-conjugation is the prevalent mode of interaction. On the other side, in the orthogonal orientation, the interaction of the nitrogen lone pair and the π_3-unit is strong. In other words, when *n*,π-conjugation in the aniline part is increased, the higher deviation of this ring influences the transmission mode of substituent effects.

According to previous discussion, the transmission of substituent electronic effects can be presented by mesomeric structures (Fig. 3; structures **a–e**) of the electron-acceptor substituted derivatives with contribution of π-polarization (Fig. 3; structure **f**).

If X is an electron-acceptor substituent, a dipole on X (or near the C-X bond) is induced (Fig. 3; structure **f**), and interaction of this dipole through the molecular structure results in a definite polarization of the individual

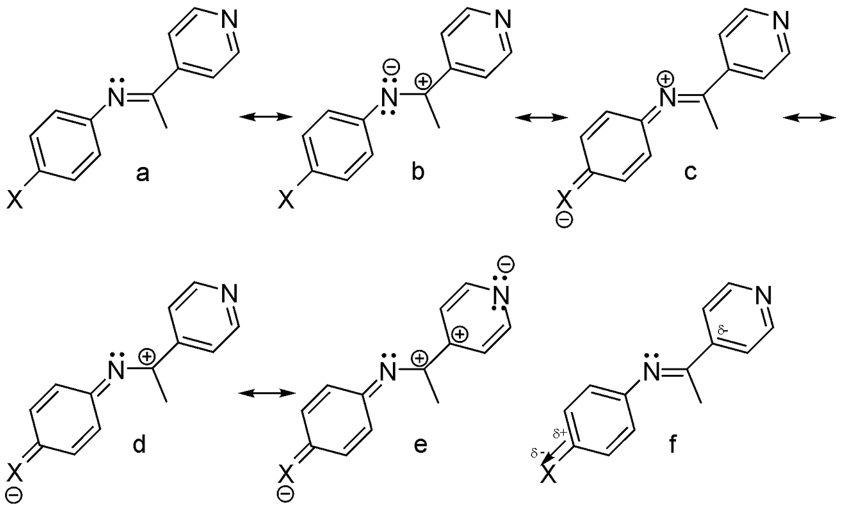

Figure 3. Mesomeric structures of the electron-acceptor substituted ketimines (**a–e**) with contribution of π-polarization (**f**).

π-units, as well as polarization of the entire conjugated system. Resonance interaction in an extended conjugated system of π_2- and π_3-units (Fig. 3; structures **c** and **d**) has an opposite effect to the electron-accepting character of π_1-unit, that is, "aza" substituent in series **6** and **7**. The net result of the electron density change at C1′ atom is reflected in a somewhat lower contribution of resonance effect in comparison with imine series **1** and **3–5**; the lowest contribution is observed for series **2**. Resonance interaction strongly depends on the spatial arrangement (*E* configuration around the C═N bond) of the investigated molecules (Table 6; θ_{C} and θ_{N}) and can be effectively transmitted through π_2- and π_3-units by resonance (Fig. 3; structures **c** and **d**). These effects influence large differences in the ρ_{F} values for the carbon atoms within series **6** and **7** and are higher in comparison with the series of the investigated imines.

In similar systems [8], with imine side chain functionalities, it has been discussed that the substituent-sensitive inherent polarization of the C═N bond can be proposed as an alternative/competitive explanation of π-polarization. Conjugative effects in these systems are negligible and can be explained as the contribution of resonance-induced polar effect. According to this concept, electron-withdrawing substituents increase polarization of the C═N bond, increasing contribution of the wave function presented by structure **b** in Figure 3. Electron-accepting substituents cause a decrease of electron density at the azomethine carbon, whereas electron-donating substituents have the opposite effect.

Electron donors induce the charge separation at the aniline ring increasing electron density in π_3-unit. The increased electron density on C7 atom (shielding effect caused by electron donors) is indeed a type of a "push effect" of the electron-rich aniline ring, which is manifested as higher

Table 6

Elements of optimized geometry of *N*-[1-(pyridine-3- and -4-yl)ethylidene]anilines obtained by the use of MP2 method.

	N-[1-(pyridine-3-yl)ethylidene]anilines						*N*-[1-(pyridine-4-yl)ethylidene]anilines					
	Angle		Atomic charge				Angle		Atomic charge			
X	θ_{C}[a]	θ_{N}[b]	q_{C}	q_{N}	$q_{\mathrm{C1'}}$	q_{C1}	θ_{C}	θ_{N}	q_{C}	q_{N}	$q_{\mathrm{C1'}}$	q_{C1}
H	13.9	57.5	0.176	−0.276	−0.146	0.061	11.9	57.1	0.140	−0.269	0.011	0.058
$N(CH_3)_2$	14.2	56.8	0.163	−0.273	−0.135	0.032	12.0	56.3	0.137	−0.265	0.013	0.028
OH	14.3	55.9	0.160	−0.272	−0.133	0.036	12.5	55.3	0.135	−0.262	0.014	0.030
OCH_3	14.4	55.9	0.160	−0.271	−0.139	0.041	12.4	55.4	0.133	−0.261	0.013	0.031
CH_3	14.3	57.4	0.158	−0.277	−0.138	0.048	12.0	56.5	0.138	−0.267	0.013	0.044
F	—	—	—	—	—	—	11.8	57.4	0.143	−0.266	0.009	0.023
Cl	12.7	58	0.163	−0.282	−0.139	0.063	11.8	57.4	0.149	−0.271	0.007	0.059
Br	12.7	58.2	0.175	−0.285	−0.147	0.069	11.8	57.6	0.149	−0.272	0.007	0.065
$COOCH_3$	—	—	—	—	—	—	11.5	58.8	0.157	−0.278	0.005	0.110
$COCH_3$	12.7	59.5	0.178	−0.286	−0.147	0.100	11.8	58.1	0.152	−0.276	0.004	0.098

[a] The dihedral angle is defined by the atoms C2′-C1′-C═N (Fig. 1).

[b] The dihedral angle is defined by the atoms C═N-C1-C2.

contribution of extended conjugative interaction (Fig. 4; structure **h**). A more implicit view in assessing the substituent effects on the polarization of the C═N group has been obtained from the calculation of atomic charges (q_{C}, q_{N}, q_{C1}, and $q_{\mathrm{C1'}}$) and elements of the optimized geometries (angles θ_{C} and θ_{N}) of 4-substituted *N*-[1-(pyridine-3- and -4-yl)ethylidene]anilines obtained by the use of MP2 calculation methods (Table 6).

Theoretical calculation showed that *E* configuration with respect to the C═N bond of the optimized structure is a far more stable isomer for both series of ketimines. The optimized conformations are in a very good concordance with results obtained from NOESY spectra. The established atom connectivity between H proton of the methyl group at the azomethine carbon and *ortho* protons (C2′-H and C2-H), in both series **6** and **7**, unambiguously confirms *E* configuration of the C═N bond.

As mentioned previously, the major structural characteristics are reflected in deviation of the aniline ring from the plane of the C═N group (Table 6; θ_{N}). The 3- and 4-pyridyl rings have a tendency to be coplanar with the C═N bond, whereas the aniline ring behaves oppositely. Moreover, the opposite trend of the changes of the dihedral angles θ_{N} and θ_{C} can be observed, which means that a deviation from planarity of one side of the molecule produces a small conformational adaptation of the opposite side. The values of θ_{N} vary from 55.9° (X═OH, OCH_3) to 59.5° (X═$COOCH_3$, $COCH_3$) and are clearly dependent on substitution on the aniline ring. The dihedral angle θ_{N} increases with increasing electron-accepting character of the substituent X because of *n*,π-conjugation of the nitroaniline type [9,10]. Namely, this conjugation, which involves the nitrogen lone pair and π-electrons from the aniline ring (π_3-unit), is possible only if the aniline ring takes such conformational arrangement, that is, it is deflected for a certain angle θ_{N} (Fig. 3; structures **c** and **d**). In that way, the electron density shifts toward the π_3-unit causing the deshielding of the azomethine carbon (Fig. 3; structure **d**), and, consequently, the electron density shifts from the benzylidene part of the molecule. Furthermore, the calculated atomic charges indicate somewhat higher polarization of the C═N bond, when the electron-accepting character of the substituent X increases, and generally higher polarization in series **6** is observed. It has been pointed out in our previous works [9,10] that electron-donor substituents support π,π-conjugation and, together with the steric interference of the methyl group and lower electron-accepting character of the 3-pyridyl group, cause somewhat higher deviation of the benzylidene ring in series **6**, and thus influence higher polarization of the C═N bond (Table 6).

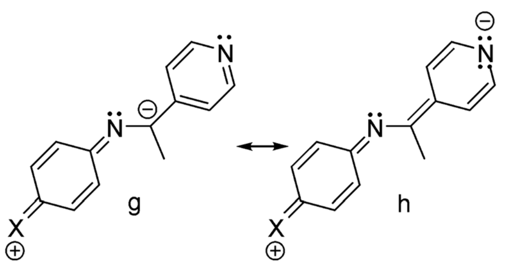

Figure 4. Mesomeric structures of the electron-donor substituted compounds.

Electron-donor substituents cause an increase of the electronic density at the azomethine carbon via their $^{+}$R effect (Fig. 4; structure **g**) resulting in the shift of the corresponding signal toward higher magnetic field. Such electron density shift causes considerably lower polarization of the C═N group (Table 6), which in turn causes somewhat higher deviation of π_1-unit with respect to π_2-unit for series **6** of ketimine (Table 6; θ_{C}).

A study of the cross-interaction effect of the benzylidene and aniline substituents on the polarization of the C═N bond has been additionally performed. DSP model (eq. 3) has been applied to $\mathrm{SCS_{C7}}$ of the investigated imines and ketimines with the F and $\mathrm{R^-}$ constants of the Y substituents [27]. Because of the pronounced electron-accepting character of the Y substituent, the $\mathrm{R^-}$ constant has been chosen (values for "aza" substituents are not available in the literature).

$$\mathrm{SCS_{C7}} = \rho_{\mathrm{F}}(\mathrm{Y})\mathrm{F} + \rho_{\mathrm{R^-}}(\mathrm{Y})\mathrm{R^-} + h \qquad (3)$$

However, correlation results, obtained by eq. 3, are of low statistical validity ($r = 0.48$–0.62, $F < 5$). Because of that, a three-parameter equation (eq. 4), which includes the steric parameter ($Es(\mathrm{CH_3}) = -1.24$ for the series of ketimines [28]), has been applied, and the corresponding $\rho_{\mathrm{F}}(\mathrm{Y})$, $\rho_{\mathrm{R}}^{-}(\mathrm{Y})$, and $\rho_{\mathrm{Es}}(\mathrm{Y})$ values are presented in Table 7.

$$\mathrm{SCS_{C7}} = \rho_{\mathrm{F}}(\mathrm{Y})\mathrm{F} + \rho_{\mathrm{R^-}}(\mathrm{Y})\mathrm{R^-} + \rho_{\mathrm{Es}}(\mathrm{Y})\mathrm{Es} + h \qquad (4)$$

The sensitivity of the azomethine carbon to the electron-accepting character of the benzylidene group Y strongly depends on the substituent X. The contribution of the steric effect has been found high for all of the substituents X (Table 7) and higher for those with larger electron-donating capabilities. The positive value of the proportionality constant $\rho_{\mathrm{F}}(\mathrm{Y})$ implies that the field-induced electron density change at the azomethine carbon increases with increasing electron-accepting character of the benzylidene substituent Y, whereas resonance and steric effects act in the opposite direction. Steric effect has the highest contribution in the electron-donor substituted series of imines, and in that way, more planar molecular conformations are achieved. A higher extent of planarity is induced by the substituent X having larger $^{+}$R, and contribution of the wave function ***h*** (Fig. 4.) is increased, as is observed for the series with $N(CH_3)_2$ substituent (Table 7). These observations can be explained in relation to the electron-accepting character of the substituent Y and the balanced contribution of extended and localized π-units polarization to the overall transmission of electronic substituent effect. The higher contribution of

Table 7

Correlation of the SCS values for the investigated imines (**1–5**) and ketimines (**6** and **7**) with eq. 4.

Substituent (X)	ρ_F(Y)	ρ_R^-(Y)	ρ_{Es}(Y)	*r*	*F*	*s*
H	3.19	−2.76	−5.33	0.931	59	1.08
$N(CH_3)_2$	1.93	−3.72	−8.32	0.959	88	0.45
OCH_3	2.76	−2.97	−7.00	0.949	76	0.56
CH_3	2.80	−2.75	−5.84	0.937	65	0.97
Cl	3.18	−2.31	−5.70	0.935	62	0.85
$COOCH_3$	3.98	−1.59	−5.20	0.917	39	1.10

extended resonance and π-polarization interaction through the molecule as a whole, with the electron-donor substituent X, and higher localized interaction within defined π-units (Fig. 1) for electron-acceptor substituted molecules can be supposed.

The obtained values ρ_F(Y), ρ_R^-(Y), and ρ_{Es}(Y) reflect the sensitivity of the azomethine carbon to the electronic effects of the benzylidene substituent Y for the appropriate substituent X. The cross-correlation of the constants ρ_F(Y), ρ_R^-(Y), and ρ_{Es}(Y) versus σ_p/σ_p^+ constants [17] of the substituent X has been performed according to eq. 1, and results are presented by eqs. 5–7.

$$\begin{gathered}\rho_F(Y) = 3.12(\pm 0.08) + 1.47(\pm 0.18)\sigma_p \\ r = 0.981, F = 72, s = 0.18, n = 6\end{gathered} \tag{5}$$

$$\begin{gathered}\rho_{R^-}(Y) = -2.53(\pm 0.08) + 1.55(\pm 0.19)\sigma_p \\ r = 0.971, F = 66, s = 0.19, n = 6\end{gathered} \tag{6}$$

$$\begin{gathered}\rho_{Es}(Y) = -5.68(\pm 0.13) + 1.51(\pm 0.17)\sigma_{p+} \\ r = 0.976, F = 80, s = 0.29, n = 6\end{gathered} \tag{7}$$

Equations 5–7 indicate similar influences of electronic effects of the substituent X on the sensitivity of the regression coefficients ρ_F(Y), ρ_R^-(Y), and ρ_{Es}(Y). The results of the cross-correlations of the constants ρ_F(Y), ρ_R^-(Y), and ρ_{Es}(Y) with respect to aniline substituents (X) are manifested in their similar slopes when the electron-accepting character of the substituent X increases. This leads to a conclusion that the higher sensitivity is achieved when two opposite electron-accepting characters of substituents X and Y operate simultaneously. Although no significant conformational adaptation has been observed in series **6** and **7** as a consequence of the effect of the substituent X (Table 6; θ_N), the high values of torsional angle of the aniline part of molecules significantly affect the transmission of electronic substituent effects. The significant and positive value of the proportionality constant for ρ_{Es}(Y) (eq. 7) indicates that the steric hindrance results mainly from the presence of the methyl group in the ketimine series. Steric effect increases as electron-donating character of the substituent X increases, which indicates the importance of π,π-conjugation on molecular geometry and steric repulsion on the transmission of the overall substituent effects.

CONCLUSION

Two series of 4-substituted *N*-[1-(pyridine-3-and-4-yl) ethylidene]anilines have been synthesized using two conventional and one microwave-assisted method. The developed solvent-free microwave-assisted method has given higher yields of the products within shorter reaction time. The applied LFER analysis appears to be a straightforward method for correlations of SCS values data of the investigated molecules with the appropriate substituent constants. Polar (inductive/field) and resonance effects have similar contributions at all carbons, except C1 for imine series **1**, **2**, and **6**, but the actual values of ρ_F and ρ_R, which correspond to these effects, are significantly different depending on the carbon position. Considerable deviation of the aniline and benzylidene rings, with respect to the C=N group, causes a decrease in the transmission of both polar and resonance substituent effects. Polar effect is slightly higher at C1 and C7 carbons in series **6** and **7** of ketimines and is transmitted mainly by inductive and π-polarization modes. Reverse polarization is operative at C1′ carbon, regarding contribution of the field effect of the substituent X, as a consequence of π-polarization effect. Optimized geometries of the investigated compounds and transmission of the individual substituent electronic effects through well-defined π-resonance units indicate that these units behave both as isolated and as conjugated fragments, depending on the substituent present in the corresponding molecules.

EXPERIMENTAL

Materials, methods, and instrumentation. Two series of the investigated compounds have been synthesized using different methods of conventional syntheses according to the literature procedure. However, these methods still have more limitations such as long reaction times, moderate yields, use of toxic reagents or solvents, and demand of extensive purification of the products. To obtain higher yields and more pure products and to shorten reaction time, we have developed an additional solvent-free microwave-assisted method for efficient condensation of acetylpyridines with anilines. The yields of the investigated compounds obtained using methods A, B, and C are collected in Table S1 (Supporting Information).

Fourier-transform infrared spectra have been recorded in transmission mode using a Bomem (Hartmann & Braun) spectrometer (Québec City, Québec, Canada). Elemental analysis has been performed using a Vario EL III elemental analyzer (Hanau, Germany).

The ^{1}H and ^{13}C NMR spectral measurements have been performed on a Varian Gemini 2000 (Palo Alto, California). The spectra have been recorded at room temperature in DMSO-d_6. The chemical shifts are expressed in parts per million (ppm) values referenced to TMS ($\delta_H = 0$ ppm) in ^{1}H NMR spectra and the residual solvent signal ($\delta_C = 39.5$ ppm) in ^{13}C NMR spectra. The chemical shifts have been assigned by the complementary use of DEPT, 2D ^{1}H–^{13}C correlation HETCOR, and by selective INEPT long-range experiments. All spectra have been recorded at ambient temperature. 2D NOESY spectra have been recorded on a Bruker Avance III 500 spectrometer (Rheinstetten, Germany) (500.26 MHz for ^{1}H; 125.80 MHz for ^{13}C) equipped with broadband 5-mm probe. Microwave synthesis has been performed in Milestone MycroSYNTH reactor (Sorisole, Italy). The characterization of the investigated compounds is given in the Supporting Information.

General procedure for the preparation of imines

Method A [29]. Molecular sieves (5 Å; 6.25 g) were added to a solution of equimolar amounts of the corresponding 3- and 4-acetylpyridine (5.00 mmol) and 4-substituted anilines in anhydrous toluene (25 mL), and the reaction mixture was heated under reflux for 8 h. The mixture was then cooled, the sieves were filtered off, the filtrate was evaporated, and the residue was purified by column chromatography on a silica gel column (pretreated overnight with 10% triethylamine in petroleum ether) with a petroleum ether–ethyl acetate mixture (100:0 to 60:40).

Method B [12]. A stirred solution of acetylpyridine (50 mmol) and 4-substituted aniline (60 mmol) in 20 mL of glacial acetic acid was cooled in ice bath. Solid potassium cyanide (3.9 g) was added slowly at such a rate that the temperature did not exceed 10°C. The reaction mixture was kept at this temperature for 5 h and then overnight at room temperature. After adding ice water (50 mL), the obtained product was filtered off and washed with ice water and petrolether successively. The obtained 2-substituted 2-arylaminopropionitrile (20 mmol) was dissolved in methanol (25 mL) and added to the boiling solution of potassium hydroxide (50 mmol) in methanol (20 mL). Reaction mixture was refluxed for 1 h and poured into ice water (50 mL), and the obtained imine was filtered off.

Method C. Condensation of acetylpyridines (1.5 mmol) with corresponding 4-substituted anilines (1 mmol) was carried out under solvent-free conditions using montmorillonite K-10 clay as a catalyst under microwave irradiation (300 W) at temperature ranging from 100 to 150°C during 10 min. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature, the product was extracted with dichloromethane, and the solvent was removed under reduced pressure to give the crude product, which was further purified by recrystallization from benzen–petrolether mixture until the constant melting point has been achieved.

Geometry optimization. The geometry optimizations have been carried out by MP2 method with standard basis set, 6-31G ++(d,p). Harmonic vibrational frequencies have been evaluated at the same level to confirm the nature of the stationary points found (to confirm an optimized geometry corresponding to local minimum that has only real frequencies) and to account for the zero-point vibrational energy correction. Global minima have been found for every molecule. The solvent (DMSO) has been simulated with standard static isodensity surface polarized continuum model. Theoretical calculations of chemical shifts at MP2/6-31G++(d,p) level provide good basis for estimation of experimental data. All calculations have been performed with Gaussian03 software (Gaussian, Inc., Wallingford, CT) [30].

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