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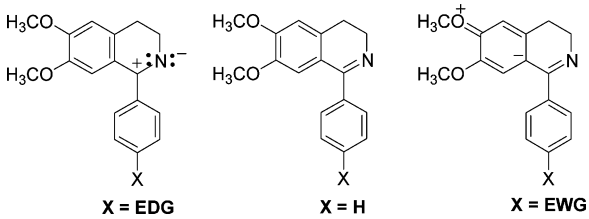
Propagation of Polar Substituent Effects in 1-(Substituted phenyl)-6,7-dimethoxy-3,4-dihydro- and -1,2,3,4-tetrahydroisoquinolines As Explained by Resonance Polarization Concept

Kari Neuvonen,*,† Ferenc Fülöp,‡ Helmi Neuvonen,† Andreas Koch,§ Erich Kleinpeter,§ and Kalevi Pihlaja†

Department of Chemistry, University of Turku, FIN-20014 Turku, Finland, Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary, and Department of Chemistry, University of Potsdam, P.O. Box 691553, D-14415 Potsdam, Germany

kari.neuvonen@utu.fi

Received April 19, 2005



Propagation of inductive and resonance effects of phenyl substituents within 1-(substituted phenyl)-6,7-dimethoxy-3,4-dihydro- and -1,2,3,4-tetrahydroisoquinolines were studied with the aid of ^{13}C and ^{15}N NMR chemical shifts and ab initio calculations. The substituent-induced changes in the chemical shift (SCS) were correlated with a dual substituent parameter equation. The contributions of conjugative (ρ_R) and nonconjugative effects (ρ_F) were analyzed, and mapping of the substituent-induced changes is given over the entire isoquinoline moiety for both series. The experimental results can be rationalized with the aid of the resonance polarization concept. This means the consideration of the substituent-sensitive balance of different resonance structures, i.e., electron delocalization, and the effect of the aromatic ring substituents on their relative contributions. With tetrahydroisoquinolines, the delocalization of the nitrogen lone pair (stereoelectronic effect) particularly contributes. Correlation analysis of the Mulliken atomic charges for the dihydroisoquinoline derivatives was also performed. The results support the concept of the substituent-sensitive polarization of the isoquinoline moiety even if the polarization pattern achieved via the NMR approach is not quite the same as that predicted by the computational charges. Previously the concepts of localized π-polarization and extended polarization have been used to explain polar substituent effects within aromatic side-chain derivatives. We consider that the resonance polarization model effectively contributes to the understanding of the polar substituent effects.

Introduction

When substitution in one part of an organic molecule is varied, reorganization of the electronic framework all through the molecule occurs. This can affect the molecule's reactivity, conformation, solubility, equilibrium between the different potential tautomeric forms, acid−base properties or stacking tendency, and so forth. The analysis of the systematic substituent effects on the ^{13}C NMR chemical shifts propagating all along the molecule is an effective way to study the changes in electronic states promoted by different phenyl substituents.[1−5] The substituent effects can follow the normal pattern, for instance, electron-withdrawing substituents affecting

* To whom correspondence should be addressed. Fax: +358-2-3336700.
† University of Turku.
‡ University of Szeged.
§ University of Potsdam.

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10.1021/jo0507946 CCC: $30.25
Published on Web 11/30/2005

low-field (high-frequency) ^{13}C NMR chemical shifts. The occurrence of the so-called reverse substituent effect (RSE) is, however, well-established at some sites of, for example, styrenes, chalcones, carboxylic acid derivatives, imines, and hydrazones.[1−5] RSE means that EW substituents affect upfield ^{13}C NMR chemical shifts (low-frequency shift values), whereas the ED substituents affect low-field shifts. Extensive data shows that upfield chemical shifts generally mean increase in the electron density at the probe atom.[4c,d,5b,6−10]

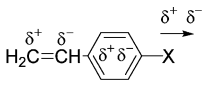
The substituent-induced changes in the chemical shift, SCS, can be correlated with a single parameter equation that uses substituent parameters such as the Hammett σ values (eq 1) or with a dual substituent parameter equation such as eq 2, which allows the blend of the inductive (σ_F or σ_I) and resonance (σ_R) contributions to vary.

$$\mathrm{SCS} = \rho\sigma \quad (1)$$

$$\mathrm{SCS} = \rho_F\sigma_F\,(\text{or } \rho_I\sigma_I) + \rho_R\sigma_R \quad (2)$$

In eq 2, different resonance scales (usually σ_R^+, σ_R^0, σ_R^{BA}, σ_R^-) can be tested, and the one that yields the best fit to the experimental data is selected. SCS is the ^{13}C NMR chemical shift for a substituted compound relative to that for the unsubstituted one. Even in those cases where a good correlation with eq 1 is obtained, the use of eq 2 gives more information because it shows the contributions of conjugative (ρ_R) and nonconjugative effects (ρ_F or ρ_I). An observed positive ρ value in eqs 1 and 2 means a normal substituent effect, and a negative one indicates a reverse substituent effect.

Qualitatively RSE can be understood on the basis of the so-called π-polarization mechanism, first proposed by Reynolds et al.[2,11] and later characterized in a more detailed way by Bromilow et al.[1,12] Each π-unit (a double bond, triple bond, or aromatic ring system) is thought to be polarized separately, the polarization being induced by the substituent dipole in another part of the molecule (see **1**and **2**). This interaction can be transmitted either



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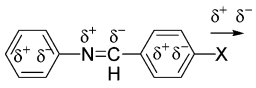

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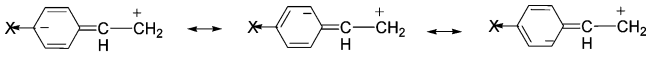
through the molecular framework or through the solvent continuum. The above interaction is exactly called localized or direct polarization because each π-unit in the side chain is polarized separately. Considerable nonsymmetry



3

FIGURE 1.

SCHEME 1

4 **5**

stabilized by ED X
destabilized by EW X

stabilized by EW X
destabilized by ED X

is, however, often observed for the ρ_I values (cf. eq 2) at the two ends of a localized dipole. A typical case (**3**, Figure 1) is discussed by Reynolds et al.[2] The ρ_I and $\Delta\delta$ values for C(α) and C(β) differ in sign (being opposite) and markedly also in magnitude [larger for C(β)]. It was thought by Reynolds et al. that the net polarization observed is a sum of two different contributing mechanisms, the localized π-polarization and the π-polarization due to the resonance structures **3**.[2] Reynolds et al. suggest the use of the term extended π-polarization for the latter phenomenon.[2] As an alternative the term field-induced resonance was suggested by Reynolds et al.,[2] but this term was first used by Topsom et al. in a different meaning.[13] The relationship between the localized and extended polarization has been comprehensively discussed by Craik et al.[12b,14]

Even if convenient in predicting propagation of substituent effects, the π-polarization mechanism exhibits limitations in quantitative treatments. This prompted us to consider the importance of the resonance concept.[4c,d] Both neutral and charged resonance structures contribute to the stability or reactivity of organic molecules. The significance of the charged resonance structures and the polarizability of a site in the molecule seem to be connected. According to our resonance polarization concept the substitutions (EW or ED) can either increase or decrease contributions of charged resonance structures as compared with the situation when X = H (cf. Scheme 1). This alteration is reflected in the observed sensitivity of the measurable property. A decrease in the electron density at the probe atom by the ED substituents can be due to the fact that the ED substituents stabilize those resonance structures where a positive charge is oriented

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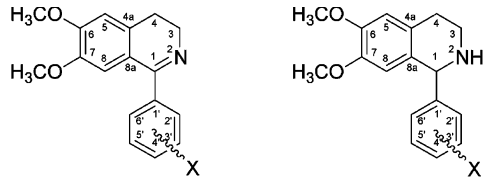
SCHEME 2



X = *p*-NO_2, *p*-CN, *p*-CF_3, *p*-F, *p*-Cl, *p*-Br, H, *p*-Me, *p*-MeO, *p*-$N(Me)_2$
= *m*-NO_2, *m*-CN, *m*-CF_3, *m*-F, *m*-Cl, *m*-Br, *m*-Me, *m*-MeO

toward the ED substituent (C-α in **4**, Scheme 1). On the other hand, the EW substituents can stabilize those resonance structures where a negative charge is oriented toward the EW substituent and therefore increase the electron density at the probe site (C-α in **5**, Scheme 1). In both cases an RSE is observed. The extent of the inductive stabilization/destabilization depends on the distance between X and the charged atom. This resonance polarization model in general predicts correctly the appearance of the local π-polarization. Further, it was possible to evaluate by this model the importance of electronic effects governing the position of the various ring-chain equilibria[4c] and the origin of the large negative ρ_R values (−1.6 to −5.0) observed for hydrazones as compared with the much smaller values for imines (0.2 to −0.7).[4d] Further, by using the resonance polarization concept the substituent interaction between X and Y in $X-C_6H_4-CH=N-Y$ could be explained.[4d]

In this work both the ^{13}C and ^{15}N NMR shifts were recorded for a set of 6,7-dimethoxy-1-(*para*- or *meta*-substituted phenyl)-3,4-dihydroisoquinolines and -1,2,3,4-tetrahydroisoquinolines (DHIQ and THIQ, respectively; Scheme 2) to investigate the substituent effects on their polar character. This structural study is also due to the fact that the isoquinoline system is present in many medicinal compounds and alkaloids.

Results

Tables S3 and S4 (Supporting Information) give the NMR chemical shifts measured for the DHIQ and THIQ sets (Scheme 2), respectively. The measurements were performed in $CDCl_3$ with a low and constant sample concentration (0.1 M) to diminish intermolecular associations. The SCS (substituent-induced chemical shift) data were analyzed by both eq 1 and eq 2. Equation 2 gave a better correlation than the single parameter eq 1, with one exception only (N-2 in *meta* THIQ series). Therefore, the correlation parameters obtained by eq 2 were adopted for the discussion. The resonance parameter scale selected in each case is the one from σ_R^+, σ_R^0, σ_R^{BA}, and σ_R^-, that gave the best fit to the experimental data. The values are given in Tables 1 and 2. For comparison, in Supporting Information in Tables S5 and S6 are also given the ρ_F and ρ_R values obtained by eq 2 when a constant set of substituent parameters (σ_F, σ_R) is used in each case. In addition, in Tables S7 and S8 are given the ρ_F and ρ_R values obtained by eq 2 using an alternative set of substituent parameters (σ_F, σ_R^0). The trends of the substituent effects are similar as those shown in Tables 1 and 2. The excellent to satisfactory fits seen in Tables 1 and 2 indicate that the substituent effects are electronic in origin. The main conclusions discussed below are based on the shift ranges $\Delta\delta$, which are about 0.5−1 ppm or higher for the carbon atoms and about 3 ppm or higher for the nitrogen atoms. This means the substituent effects on C-1, C-6, C-8a, and C-8 of both the DHIQ and THIQ sets and N-2 of the DHIQ sets and the *para* THIQ set. For other carbons the $\Delta\delta$ values are smaller and consequently the ρ values are small, too. It is interesting to see, however, that also in these cases mainly from good to excellent correlations are observed (Tables 1 and 2). This means that systematic electronic effects are experienced over the whole molecule. The patterns of the substituent-sensitive polar character of the compounds studied in terms of ^{13}C and ^{15}N NMR chemical shifts

TABLE 1. Correlation Parameters ρ from Equation 1 and ρ_F and ρ_R and from DSP Equation 2 for NMR Shift Data of 1-(*para*- or *meta*-Substituted phenyl)-6,7-dimethoxy-3,4-dihydroisoquinolines[a]

	$\rho \pm s$	r	$\rho_F \pm s$	$\rho_R \pm s$	scale for σ_R	r	ρ_F/ρ_R
			para-Substituted Series				
C1	−0.70 ± 0.25	0.7008	−2.20 ± 0.07	0.14 ± 0.04	σ_R^+	0.9861	−15.7
N2	10.7 ± 0.5	0.9897	9.5 ± 0.5	11.6 ± 0.6	σ_R^{BA}	0.9943	0.82
C3	0.33 ± 0.03	0.9773	0.27 ± 0.02	0.53 ± 0.03	σ_R^0	0.9927	0.51
C4	−0.26 ± 0.01	0.9888	−0.27 ± 0.01	−0.14 ± 0.01	σ_R^+	0.9965	1.93
C4a	−0.19 ± 0.04	0.8602	−0.02 ± 0.02	−0.17± 0.01	σ_R^+	0.9708	0.12
C5	0.24 ± 0.03	0.9557	0.34 ± 0.01	0.27 ± 0.02	σ_R^0	0.9930	1.26
C6	0.61 ± 0.04	0.9834	0.72 ± 0.04	0.29 ± 0.02	σ_R^+	0.9892	2.48
C7	0.31 ± 0.02	0.9904	0.37 ± 0.02	0.28 ± 0.02	σ_R^{BA}	0.9926	1.32
C8	−0.76 ± 0.07	0.9638	−1.16 ± 0.01	−0.53 ± 0.01	σ_R^{BA}	0.9993	2.19
C8a	−0.82 ± 0.09	0.9542	−1.22 ± 0.04	−0.81 ± 0.05	σ_R^0	0.9955	1.51
			meta-Substituted Series				
C1	−2.90 ± 0.20	0.9830	−2.87 ± 0.10	−0.47 ± 0.09	σ_R^+	0.9914	5.94
N2	10.2 ± 1.1	0.9617	8.7 ± 0.5	2.9 ± 0.5	σ_R^+	0.9781	3.00
C3	0.24 ± 0.04	0.9276	0.19 ± 0.02	0.09 ± 0.02	σ_R^+	0.9664	2.11
C4	−0.24 ± 0.02	0.9751	−0.25 ± 0.01	−0.04 ± 0.01	σ_R^+	0.9923	6.25
C4a	0.18 ± 0.06	0.7646	0.09 ± 0.02	0.14 ± 0.02	σ_R^-	0.9570	0.64
C5	0.48 ± 0.07	0.9254	0.33 ± 0.02	0.24 ± 0.02	σ_R^-	0.9907	1.38
C6	0.83 ± 0.08	0.9657	0.67 ± 0.02	0.30 ± 0.03	σ_R^-	0.9955	2.23
C7	0.45 ± 0.05	0.9637	0.35 ± 0.01	0.18 ± 0.01	σ_R^-	0.9972	1.94
C8	−1.30 ± 0.10	0.9784	−1.21 ± 0.02	−0.33 ± 0.02	σ_R^+	0.9989	3.67
C8a	−1.52 ± 0.11	0.9835	−1.41 ± 0.02	−0.64 ± 0.04	σ_R^0	0.9981	2.20

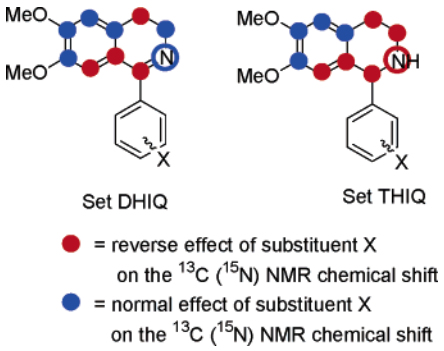
[a] s, standard deviation; r, correlation coefficient; σ_F values are from ref 22a except that for Br, which is from ref 21; σ_R^+, σ_R^0, σ_R^{BA}, σ_R^- are from ref 22b.

TABLE 2. Correlation Parameters ρ from Equation 1 and ρ_F and ρ_R and from DSP Equation 2 for NMR Shift Data of 1-(*para*- or *meta*-Substituted phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines[a]

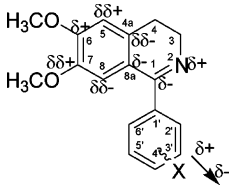
	$\rho \pm s$	r	$\rho_F \pm s$	$\rho_R \pm s$	scale for σ_R	r	ρ_F/ρ_F
			para-Substituted Series				
C1	−0.10 ± 0.16	0.2147	−1.17 ± 0.09	0.31 ± 0.05	σ_R^+	0.8928	−1.67
N2	−1.88 ± 0.23	0.9453	−1.68 ± 0.32	−1.69 ± 0.18	σ_R^{BA}	0.9689	0.55
C3	−0.20 ± 0.07	0.7026	−0.26 ± 0.05	−0.28 ± 0.07	σ_R^-	0.8857	1.43
C4	−0.21 ± 0.02	0.9546	−0.31 ± 0.01	−0.22 ± 0.02	σ_R^0	0.9945	1.50
C4a	0.10 ± 0.02	0.8466	0.19 ± 0.01	0.20 ± 0.01	σ_R^-	0.9969	0.77
C5	0.25 ± 0.03	0.9508	0.34 ± 0.01	0.28 ± 0.02	σ_R^0	0.9924	1.27
C6	0.41 ± 0.04	0.9677	0.56 ± 0.01	0.45 ± 0.01	σ_R^0	0.9995	1.25
C7	0.23 ± 0.02	0.9550	0.32 ± 0.01	0.25 ± 0.02	σ_R^0	0.9948	1.30
C8	−0.31 ± 0.04	0.9256	−0.53 ± 0.01	−0.18 ± 0.02	σ_R^{BA}	0.9953	2.17
C8a	−1.66 ±0.16	0.9664	−2.12 ± 0.08	−2.03 ± 0.08	σ_R^0	0.9972	1.04
			meta-Substituted Series				
C1	−1.26 ± 0.16	0.9465	−1.27 ± 0.08	−0.20 ±0.08	σ_R^+	0.9675	3.24
N2	−1.97 ± 0.24	0.9531	−1.70 ± 0.16	−0.40 ± 0.16	σ_R^+	0.9514	2.01
C3	−0.47± 0.09	0.9029	−0.43 ± 0.05	−0.05 ±0.05	σ_R^+	0.9070	5.25
C4	−0.35 ± 0.03	0.9734	−0.35 ±0.01	−0.05 ±0.01	σ_R^+	0.9883	3.09
C4a	0.29 ± 0.07	0.8581	0.19 ± 0.01	0.20 ±0.01	σ_R^-	0.9969	0.73
C5	0.52 ± 0.07	0.9456	0.39 ± 0.01	0.23 ± 0.02	σ_R^-	0.9944	1.22
C6	0.71 ± 0.06	0.9741	0.65 ± 0.01	0.34 ± 0.02	σ_R^0	0.9979	1.68
C7	0.41 ± 0.04	0.9648	0.37 ± 0.01	0.22 ± 0.01	σ_R^0	0.9992	1.44
C8	−0.51 ± 0.04	0.9837	−0.47 ± 0.02	−0.10 ±0.02	σ_R^+	0.9881	2.05
C8a	−2.47± 0.16	0.9858	−2.37± 0.04	−0.88 ±0.07	σ_R^0	0.9980	2.36

[a] s, standard deviation; r, correlation coefficient; σ_F values are from ref 22a except that for Br which is from ref 21; σ_R^+, σ_R^0, σ_R^{BA}, σ_R^- are from ref 22b.

SCHEME 3



SCHEME 4



are given in Scheme 3. This kind of variation can mean, for instance, different ability to bind to a medicinally important target receptor for one thing for a nitro-substituted derivative and for another for a methoxy-substituted derivative because of different electrostatic interactions. Polarization of the molecules was studied with the aid of ab initio atomic charge calculations too. The atomic charges are given Tables S11 and S12.

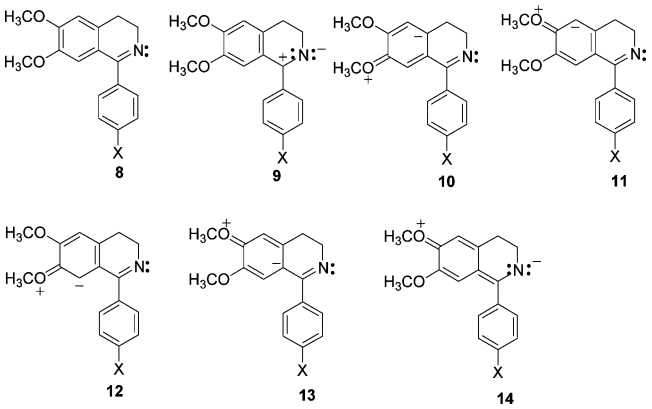
When comparing Schemes 3 and 4 it is seen that the concept of the localized π-polarization (Scheme 4) qualitatively predicts the NMR shift behavior at C-1, C-5, C-6, C-7, C-8, and C-8a for both the DHIQ and THIQ sets and also that at N-2 for the DHIQ set: a marked reverse effect is observed at C-1, C-8, and C-8a while a normal effect is observed at C-5, C-6, C-7, and at N-2 of the DHIQ sets. Surprisingly, at N-2 of the THIQ series a small reverse effect is observed. As regards the other carbons, at C-4a there is practically no effect, and the effects at C-3 and C-4 are also small, the effect at C-4 being reverse in all cases while those at C-3 are normal for the DHIQ sets but reverse for the THIQ sets. According to the localized π-polarization model the extent of the effects at C-6 and C-8a should be equal but of opposite signs. However, the size of the ρ_F and ρ_R values in Tables 1 and 2 reveal (i) a significant unbalance between the magnitude of the ρ values for C-6 and C-8a for both the DHIQ and THIQ sets and (ii) a significant difference in the mutual magnitudes of the ρ values for C-8a and C-8 when compared the DHIQ and THIQ sets. The numerical ρ values at C-8a are about twice as large for the DHIQ sets and about four times as large for the THIQ sets as the corresponding values at their C-6 carbons, with the exception of the *meta* THIQ series for which the numerical value of ρ_R at C-8a is only 2.6 times as large as ρ_R at C-6. For the DHIQ sets the ρ values at C-8 and C-8a are close to each other, whereas for the THIQ sets the ρ values at C-8a are 4−11 times higher than those at C-8.

The polarization pattern depicted with the aid of the signs of the ρ_F and ρ_R values is closely similar with the *para* and *meta* DHIQ sets (Tables 1 and 2; Scheme 3). At C-1, C-8a, and C-8 the *meta* derivatives, however, show slightly larger inductive effects. In that respect the THIQ sets follow closely similar patterns. The surprisingly large reverse inductive effects (−1.17 and −1.27 for the *para* and *meta* sets, respectively) at the sp^3 hybridized C-1 of the THIQ sets are intriguing, as are also the resonance effects at C-1 of the DHIQ (0.14 and −0.47, respectively, for *para* and *meta*) and THIQ (0.31 and −0.20, respectively, for *para* and *meta*) sets.

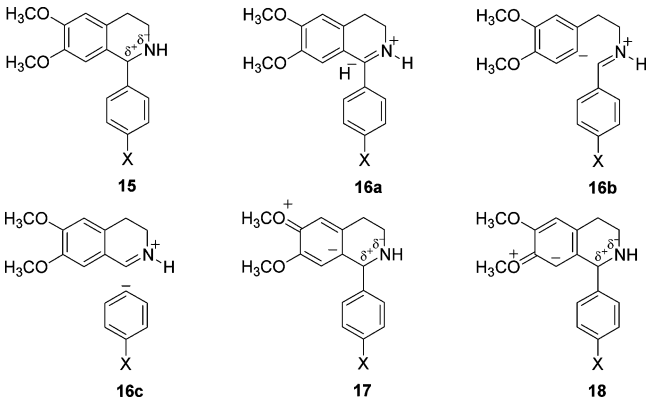
Discussion

Inductive Effects. The signs of the ρ_F values observed for the DHIQ sets (Table 1; Scheme 3) follow a pattern predicted by the π-polarization concept for both π units,

SCHEME 5



SCHEME 6



the C=N bond, and the phenyl ring (cf. **1**, **2**, Scheme 4).[1,4c,d] C-6, C-8, and C-8a exhibit marked effects, but C-4a, C-5, and C-7 show much smaller effects. The magnitude of the ρ_F values at C-6 is 0.67−0.72. Much larger effects are observed at C-8 and C-8a (from −1.16 to −1.41). The former values can be considered as normal for a polarized phenyl unit and are in accordance with π-polarization concept. To the contrary, the marked asymmetry in the ρ_F values at C-6 and C-8a is not explainable by the direct π-polarization concept only. The extended polarization model used by Reynolds et al.[2] does not explain the increased sensitivity to substitution at C-8 and C-8a.

The degree of the (partial) charge development at a certain atom depends on the balance of different resonance structures. Electron-donating resonance from the methoxy group (Scheme 5) can be effective at *ortho*/*para* positions in respect to a methoxy substitution, and negative charge can be induced at C-4a, C-5, C-8, or C-8a (cf. **10**−**13**). The electron donation from the neighboring oxygen atom can be concluded to diminish the significance of those resonance structures where negative charge is situated at C-6 or C-7 (structures not shown). With the DHIQ sets, C-1 carbon exhibits the largest inductive effect, which is reverse for both *para* and *meta* series. To the contrary, N-2 exhibits an extensive normal effect. An ED substituent X inductively stabilizes the resonance structure **9**. According to the resonance polarization concept, the contribution of **9** exhibiting a positive charge at the C-1 carbon and a negative charge at N-2 is increased by ED substituents resulting in diminished electron density and a low-field ^{13}C NMR chemical shift at C-1, an RSE as the consequence ($\rho_F < 0$).[4c,d] To the contrary, a normal substituent effect ($\rho_F > 0$) is observed at N-2 (Table 1). With the EW substituents the situation is opposite. This behavior of the chemical shifts at C-1 and N-2 is in accordance with the π-polarization concept, too. When the phenyl π unit is considered, the opposite behavior of C-8a ($\rho_F < 0$) and C-6 ($\rho_F > 0$) is that predicted by the π-polarization. Further, the positive and closely similar ρ_F values for C-5 and C-7, which are smaller than that for C-6, agree with that model. The reverse inductive effects observed at C-8 and C-8a are, however, exceptionally large, the effect at C-8a being about two times as large as that at C-6. This is not in accordance with the localized π-polarization concept and is not explained by the general extended polarization model either.[2] The enhanced sensitivity at C-8 and at C-8a reflects the fact that not only π-polarization but also polarization resulting from the electron-donating resonance of 7-OMe (**12**) and that of 6-OMe group (**13**) contribute (cf. Scheme 5). The resonance structures **12** and **13** are inductively destabilized by the ED substituents. The decrease in their contribution and the following decrease in electron density at C-8 and C-8a, respectively, result in low-field shift at these carbons when the substituent becomes more electron-donating. Consequently, the reverse substituent effects are observed ($\rho_F < 0$). The value of ρ_F at C-8 or C-8a is higher than expected on the basis of the localized π-polarization because the observed value is a sum of the two effects. The lack of the substituent effect at C-4a and a small effect only at C-5 suggest that substitution does not significantly change the contribution of resonance structures **10** and **11**. Diminished effects have been observed for quaternary aromatic carbons (ring junction) such as C-4a with other condensed aromatic systems, too.[3a] The values of ρ_F for C-1, C-8, and C-8a are with *meta*-substituted series somewhat larger than with *para*-substituted derivatives. This obviously is connected to the through space contribution in the propagation of the substituent effects and to the shorter distance between the *meta*-substituents and the probe site.

The trends of the normal/reverse substituent effects are surprisingly similar with the DHIQ and THIQ sets (Tables 1 and 2). One explanation for the reverse effect at C-1 of the THIQ sets ($\rho_F < 0$) is that ED substituents can inductively stabilize the partial positive charge at that carbon (**15**, Scheme 6) resulting in the high-frequency ^{13}C chemical shifts. C-1 is now less positively charged than the C=N carbon and the magnitude of the reverse inductive effects at C-1 for THIQ [$\rho_F = -1.17$ (*para*), −1.27 (*meta*)] is about half of that observed for the sp^2 hybridized C-1 carbon of DHIQ. Surprisingly, however, a reverse effect is observed at N-2 (Table 2). The ρ_F (−1.17) and ρ_R (0.31) values now observed for the sp^3 hybridized C-1 carbon of THIQ *para* series are close to the ρ_F(Y) (−1.12) and ρ_R(Y) (0.75) values recently observed by Szatmári et al. for the sp^3 hybridized C-1 carbon of the *trans* isomer of 1-(*p*-Y-phenyl)-3-(*p*-X-phenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines and not far from those observed for the *cis* isomer [ρ_F(Y) = −1.51, ρ_R(Y) = 0.60].[16] When the same set of substituent

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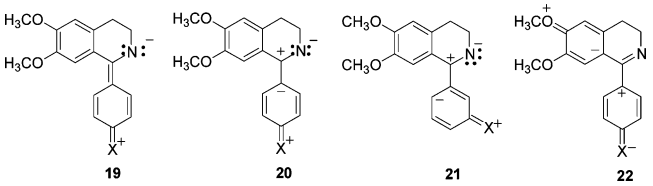
parameters (σ_F, σ_R) is used for eq 2 in our case as was used by Szatmári et al., our ρ values at C-1 ($\rho_R = -1.22$ and $\rho_R = 0.73$; Table S6) are in the limits of error quite the same as those obtained for the *trans* isomer of the naphthoxazine derivatives.[16] Another analogous case of an RSE of a saturated ring carbon has been observed.[4c] We conclude that part of the substituent dependence of the chemical shift of the C-1 carbon and N-2 nitrogen can be attributed to the polar character of the CH−NH bond (**15**) and part to the stereoelectronic effects (**16**, Scheme 6).[16] Resonance structures **16a** and **16b** are stabilized by the ED substituents. As compared with the structure **15** hybridization of both C-1 and that of N-2 are changed from sp^3 to sp^2, resulting in more high-frequency (low-field) $^{13}C/^{15}N$ NMR chemical shifts. Consequently, an RSE is observed at C-1 and N-2 when the contribution of the structures **16** is increased. The effects of the two concurrent interaction mechanisms on the chemical shift, the polarization of the CH−NH bond and the stereoelectronic effect, are parallel at C-1 whereas they are opposite at N-2. The reverse effect at C-1 of the THIQ sets is about half of that observed at C-1 of the DHIQ sets, while the extent of the reverse effect at N-2 of the THIQ series is only ca. 20% of the normal effect observed at N-2 of the DHIQ series. The reverse effect at N-2 suggests that the stereoelectronic effect predominates.

C-8a exhibits the largest reverse inductive effect [$\rho_F = -2.12$ (*para*), -2.37 (*meta*)] observed for the THIQ sets. The effects are markedly larger than those observed at C-8a for the DHIQ sets [$\rho_F = -1.22$ (*para*), -1.41 (*meta*)] and their numerical values are 3−4 times as large as the ρ_F values at C-6 of the DHIQ or THIQ sets (from 0.56 to 0.72; Tables 1 and 2). This fact can be explained by contribution of resonance structure **17** (Scheme 6; the analogous structure can be drawn for the *meta* series). ED substituents inductively destabilize it, with a decrease of the electron density at C-8a and low-field chemical shifts as a consequence. The shorter distance between the substituent and the probe site again explains the higher effect at the *meta* series. With the DHIQ sets the contribution of the analogous resonance structures (cf. **13**, Scheme 5) is contradicted by the appearance of the resonance structure **14** possessing an elongated conjugative system. In other words, in the DHIQ derivatives the negative charge is more delocalized than in the THIQ compounds, and this explains the smaller effects at C-8a. Interestingly, at C-8 the DHIQ set exhibits stronger inductive effects [-1.16 (*para*), -1.21 (*meta*)] than the THIQ set [-0.53 (*para*), -0.47 (*meta*)]. Obviously the localization of significant partial negative charge at C-8a for THIQ diminishes the probability of the negative charge at C-8. In other words, the relative contribution of resonance structure **18** is smaller than that of **12** (Scheme 5).

Resonance Effects. The positive ρ_R values are observed for the *para* DHIQ and THIQ sets (0.14, 0.31, respectively), but the negative ones are seen for the corresponding *meta* sets (-0.47, -0.20, respectively) at C-1. As compared with the inductive effects prevailing at the same sites the ρ_R values are clearly smaller. The interpretation of the resonance effect is more complicated than that of the inductive effect.[4a−d,12] Generally, two different transmission mechanisms have been considered: the (direct) resonance **9** ↔ **19** and the resonance

SCHEME 7



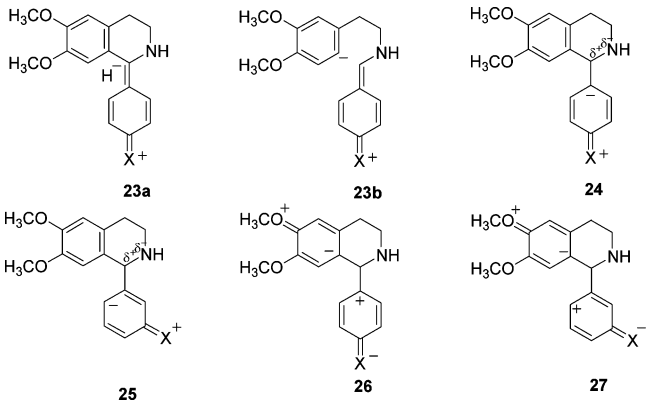
19 **20** **21** **22**

induced polar effect (**9** ↔ **20**) resulting in positive and negative ρ_R values, respectively (Scheme 7).[4,12] The former interaction where electron donation by conjugation increases electron density at the imine carbon is possible only for the *para*-substituted derivatives. When the resonance induced polar effect is effective, contribution of resonance structure **20** is significant (for ED substituents) and electron density at the probe carbon is decreased, resulting in low-field ^{13}C NMR chemical shifts at C-1 ($\rho_R < 0$). With EW substituents the situation is opposite. With the *para* series both the direct resonance mechanism ($\rho_R > 0$) (**19**) and the resonance induced polar effect ($\rho_R < 0$) (**20**) can occur concurrently. In the present case the former one dominates resulting in $\rho_R > 0$ at C-1. For the *meta* derivatives of the DHIQ set the direct resonance effect is excluded and the reverse effect ($\rho_R < 0$) observed at C-1 can nicely be explained by the resonance induced polar effect (**21**) alone. For the *para* derivatives the influence of the resonance induced polar mechanism can be more prominent than for the *meta* derivatives because the negative charge induced by ED substituents is situated at the *ipso* carbon adjacent to the C=N bond. At N-2 a positive ρ_R value is observed for both the *para* and *meta* DHIQ series, the effect being for the *para* series four times as large as that for the *meta* series, indicating the appearance of the direct conjugation (**19,** Scheme 7) for the *para* series.

For C-8 and C-8a a reverse resonance effect ($\rho_R < 0$) is observed for both DHIQ sets, and their values are close to each others [at C-8 -0.53 (*para*), -0.33 (*meta*) and at C-8a -0.81 (*para*), -0.64 (*meta*)]. These observations can be rationalized by inspecting the contribution of resonance structures such as **22** [shown for C-8a (*para*), Scheme 7]. By this resonance induced polar mechanism the EW substituents stabilize the induced negative charge at C-8 and C-8a (cf. **12** and **13** in Scheme 5) resulting in the upfield (low-frequency) shift values and a reverse substituent effect ($\rho_R < 0$).

The normal resonance effect at C-1 ($\rho_R = 0.31$) observed for the *para* THIQ set suggests that conjugation between polarized CH−NH bond and the substituted phenyl ring is possible as a result of the stereoelectronic effects, **23** (Scheme 8). As compared to structure **15**, in structures **23** electron density is transferred from the phenyl substitutent to C-1, resulting in a normal substituent effect. Competition of the normal (**23**) and reverse (**24**) resonance effects occurs as with the *para* DHIQ set, but the transmission mechanism of the direct resonance is different. Increased contribution of resonance structures **23** (by ED substituents) decreases the partial negative charge at N-2 (**15**). The small ρ_R (<0) at N-2 possibly reflects that character. A small reverse resonance effect for C-1, analogously with *meta*-substituted dihydroisoquinolines, is observed with the *meta* derivatives due to the resonance induced polar effect (**25**).

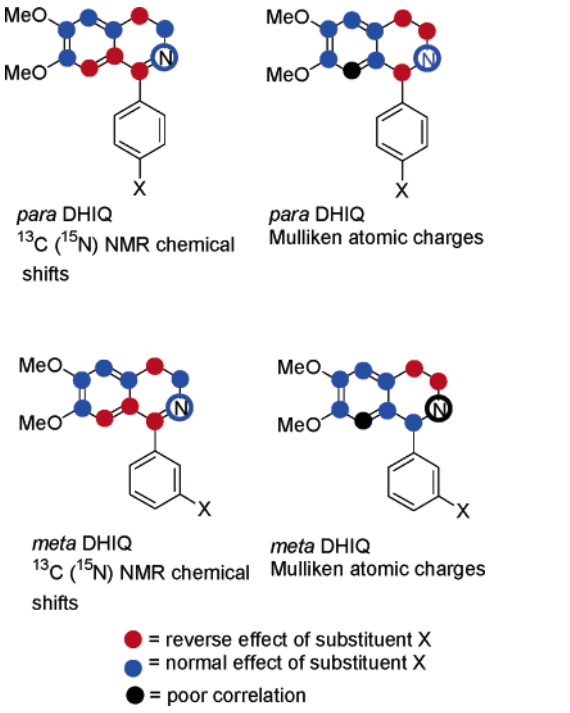
SCHEME 8



For the THIQ sets negative ρ_R values observed at both C-8a and C-8 suggest contribution of resonance structures such as **26** and **27** (Scheme 8; shown for C-8a, *para* and *meta*) analogously with the DHIQ sets. There is, however, an interesting difference. With the DHIQ sets the observed resonance ρ values at C-8 are close to those at C-8a, but with the THIQ sets the behavior of C-8 and C-8a differ considerably from each other. The resonance effect at C-8a is markedly higher for the *para* THIQ ($\rho_R = -2.03$) than for the *meta* ($\rho_R = -0.88$). In addition, the resonance effects at C-8 are small [$\rho_R = -0.18$ (*para*), -0.10 (*meta*)]. So, the resonance effects verify the conclusion drawn on the basis of the inductive effects: with the THIQ sets the partial negative charge seems to be localized into C-8a because of the absence of the conjugative effects with the C=N unit, which are possible for the DHIQ set (cf. **14**). The higher negative charge development at C-8a for THIQ as compared with DHIQ is a clear difference between these two sets. The observed reverse resonance effects with THIQ reflect the contribution of the resonance induced polar effect only. These ρ_R values [*meta* (-0.88) and *para* (-2.03)] allow the evaluation of their relative strengths, giving the value of 2.3 for the *para*/*meta* effect, which reflects the shorter distance between the probe site and X with the *para* series.

Atomic Charges. In many cases good correlations between the NMR chemical shifts and the computational atomic charges have been observed.[4c,d,5b,6−10] Therefore we also probed the ability of the Mulliken atomic charges to predict the observed effects of substituents at the isoquinoline moiety by calculating on the ab initio level the atomic charges for the DHIQ sets (Tables S11 and S12). A good correlation with a slope of -1 for q_N(N-2) vs q_C(C-1) of the *para* DHIQ set (slope $= -1.06 \pm 0.10$, $r = 0.9670$) is in accordance with the substituent-sensitive polarization of the C=N bond. The atomic charges of the DHIQ sets were correlated with Hammett substituent constants σ (Table S1; cf. entries 4−6). Satisfactory correlations were observed in most cases for the *para* series, and the trends (normal/reverse) of the substituent effects are similar with those observed with the NMR chemical shifts (Scheme 9) with exception of C-3, C-8, and C-8a. This similarity supports the idea that the substituent effects both on the atomic charges and on the chemical shifts reflect electronic substituent effects. Satisfactory correlations in accordance with the chemical shift behavior (Scheme 9) were observed also for the *meta* series for q vs σ correlations, with exception of C-1, C-3,

SCHEME 9



C-8, and C-8a. For the *meta* DHIQ set the situation is more complicated. According to the calculations the *meta*-DHIQ derivatives can exhibit two conformations due to the orientation of the 1-phenyl group [*syn* (specified by us as 1 or *in*-conformation) or *anti* (specified by us as 2 or *out*-conformation) in respect to the benzo moiety; see Pictures S1 and S2], the energies of which are relatively close to each other. Because the results obtained with the minimum energy structures were in some cases unsatisfactory, calculations were extended also to the sets where the orientation is not varied with C-1, N-2, and C-8. It was interesting to see that improvement was observed. With both N-2 and C-8 the charge correlations gave satisfactory results in the case of orientation 2 (*out*). This fact shows that at least partly the unsatisfactory results observed (δ vs q) are connected to appearance in solution of a different conformational equilibrium as compared with the gas phase. The fact that the slopes for the q vs σ correlations (Table S1; entries 4−6) in most case are higher for the *meta* series than for the *para* series is in accordance with the fact that substituent effects on the NMR chemical shift are stronger in the *meta* series than in the *para* series (cf. Table 1; especially ρ_F values). Correlations between the NMR chemical shifts and the Mulliken atomic charges (Table S1; entries 2 and 3) are in most cases satisfactory, although in some cases they fail. The poor correlation for C-1 and the negative sign for the correlation of C-8a are intriguing. To investigate in more detail the origin of this fact, we performed a dual substituent parameter (DSP) analysis (with σ_F and σ_R^+, σ_R^0, σ_R^{BA}, or σ_R^-) also for the atomic charge data. The results are interesting. In most cases from excellent to satisfactory correlations are observed, especially for the *para* series (Tables S1, entries 7−10). This verifies the electronic substituent effects on the atomic charges. The varying signs of the ρ values support the idea of the substituent-sensitive polarization of the molecule. The discussion is given in Supporting Information.

Conclusions

The effect of the phenyl substituent X extends all over the isoquinoline moiety. The negative charge develops at C-8 and C-8a as a result of electron-donating resonance of the methoxy substituents, and a positive one develops at C-1 as a result of contribution of resonance structures **9** (Scheme 5) and **15** (Scheme 6), resulting to a strongly substituent-sensitive polarization. Negative charge delocalization via conjugation for dihydro but not for tetrahydro derivatives causes a characteristic difference in behavior of the dipolar character at C-8/C-8a. For DHIQs the negative charge is situated evenly at C-8 and C-8a, whereas for THIQs it is concentrated at C-8a. With the THIQ set, delocalization of the nitrogen lone pair (stereoelectronic effect) contributes to the observed substituent effects at C-1. The appearance of the reverse/normal substituent effects at different π-units can be explained by either the π-polarization mechanism or by the resonance polarization model. Even if the π-polarization theory predicts the trends of the ^{13}C NMR chemical shift behavior, it explains neither the appearance of the unbalanced ρ_F values observed at C-6 and C-8a nor the characteristic differences observed between the DHIQ and THIQ sets. Polarization induced by a substituted phenyl group is until now discussed as a combination of two different substituent-sensitive effects: the localized π-polarization and the extended π-polarization. We suggest the resonance polarization concept for dealing with this phenomenon. This approach is convenient in prediction of the enhanced sensitivity of measurable properties, such as ^{13}C NMR shifts, to substitution. The resonance polarization concept can successfully be used to explain the localized π-polarization of the C=N and C=O units. As a summary, instead of two overlapping and sometimes tedious concepts, in many cases a single procedure can be used to explain propagation of polar substituent effects. Illustrative examples of the availability of the resonance polarization concept are given in Supporting Information.[1,2,4d,17]

The Mulliken atomic charges estimate the substituent-sensitive polarization of the dihydroisoquinoline moiety. Linear correlations between the NMR chemical shifts and the atomic charges are, however, not obtained for all atoms. The substituent sensitivities of the atomic charges (gas phase) show different blends of the inductive and resonance effects than the substituent sensitivities of the NMR chemical shifts (in solvent).

Experimental Section

NMR Measurements. NMR spectra were recorded at 25 °C on an NMR spectrometer operating at 125.78 MHz for ^{13}C and 50.69 MHz for ^{15}N on 0.1 M solutions in $CDCl_3$. ^{13}C spectra were referenced internally to tetramethylsilane (0.00 ppm), and ^{15}N spectra were referenced externally to CH_3NO_2 (0.00 ppm) containing 10% w/w CD_3NO_2 for locking purposes. The signal of the deuterium of the solvent was used as a lock signal for ^{13}C spectra. ^{13}C NMR spectra were acquired with ^1H broadband decoupling and NOE ^1H nondecoupling techniques. ^{13}C Spectra were acquired with the following conditions: spectral width of 30 kHz, 32 K data points (^1H decoupled)/64 K data points (^1H coupled), digital resolution 0.92 Hz/point (^1H decoupled)/0.46 Hz/point (^1H coupled), pulse width 4.35 μs (45°), acquisition time 1.09 s (^1H decoupled)/2.18 s (^1H coupled), number of transients 1000−12000, pulse delay 3 s (^1H decoupled)/5 s (^1H coupled), pulse sequence (JEOL) SGBCM (^1H decoupled)/SGNOE (^1H coupled). Exponential windowing with a line-broadening term of 2 Hz (^1H decoupled)/1 Hz (^1H coupled) was applied prior to Fourier transformation. ^{15}N NMR spectra were acquired with 2D ^1H−^{15}N heteronuclear FG HMBC correlation experiments. ^{15}N NMR spectra utilized a $^1J_{NH}$ coupling of 95 Hz and were optimized for a long-range $^nJ_{NH}$ coupling (n = 2 or 3) of 8 Hz. FG HMBC experiments were acquired in magnitude mode with spectral widths appropriately optimized from the 1D spectra and processed with zero-filling (×2, ×4), a 2Π/3-shifted sinebell function, and exponential weighting applied in both dimensions prior to Fourier transformation.

Theoretical Calculations. The ab initio program package Gaussian 03[18] was used for all calculations. The calculations were carried out at the Hartree−Fock level by means of 6-31G* split-valence basis set.[19] The geometry optimizations were performed without restrictions.

The Mulliken atomic charges were calculated. The Tripos modeling software SYBYL 7.0[20] was used for preparation of input data and visualization of results. All quantum-chemical calculations were processed on SGI Octane and a Linux cluster at Potsdam University.

Statistical Calculations. The sources of the substituent constants used are as follows: σ, σ^+, ref 21; σ_F, σ_R, ref 22a, except σ_F and σ_R for Br, ref 21; σ_R^+, σ_R^0, σ_R^{BA}, and σ_R^- are from ref 22b. Also the suitability of an alternative set of σ_F and σ_R^0 (from ref 23) was tested. The statistical correlations were calculated with Fig.P Version 2.98 or FigSys Version 2.4.3 (BIOSOFT, Cambridge).

General Method for the Synthesis. The synthesis of 1-aryl-6,7-dimethoxy-3,4-dihydro- and 1,2,3,4-tetrahydroisoquinolines were performed by standard procedures previously reported.[24] First homoveratrylamine was reacted with substituted benzoyl chlorides by the Schotten−Baumann procedure, followed by Bischler−Napieralski cyclization by $POCl_3$ result-

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ing in the 3,4-dihydroisoquinolines, which were later reduced to 1,2,3,4-tetrahydroisoquinolines. Melting points are uncorrected. All new compounds (see Tables S9 and S10) gave satisfactory microanalyses (C, H, N).[25,26]

Supporting Information Available: Statistical data for the correlations of the atomic charges of the DHIQ sets. ^{13}C and ^{15}N NMR chemical shifts for the DHIQ and THIQ sets. Correlation parameters obtained from eq 2 using alternative sets of substituent parameters (σ_F and σ_R or σ_F and σ_R^0). Discussion concerning the DSP analysis of atomic charges. Examples of the usefulness of the resonance polarization concept. Energies, atomic charges, and Cartesian coordinates for the optimized structures of the DHIQ sets. Pictures S1 and S2 describing the X-*in* and X-*out* conformations for the *meta* DHIQ sets, respectively. Analytical data for the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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