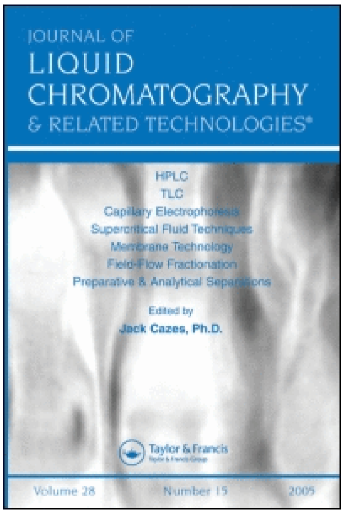

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QUANTITATIVE STRUCTURE RETENTION RELATIONSHIPS OF CHLORO-N-BENZYLIDENEANILINES IN NORMAL PHASE LIQUID CHROMATOGRAPHY

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ABSTRACT

Quantitative Structure Retention Relationships (QSRRs) of disubstituted N-benzylideneanilines are studied in normal phase liquid chromatography. Structural descriptors for each solute are calculated. Among the descriptors, four are retained to establish the QSRRs. The first descriptor, the dipolar moment is the most important parameter governing the retention, as it represents more than 90% of the log(k') variation. The influence of three electronic descriptors, ionization potential and Hammett's constants σ_X and σ_Y, is emphasized by the comparison of the QSRRs obtained.

Considering the solvatochromic parameters of the solvants, it appears that hydrogen bond acidic and basic interactions constitute a secondary effect governing the behavior of the solutes. These specific interactions are explained with molecular conformation and charge transfer.

INTRODUCTION

The N-benzylideneanilines (NBA) are easily accessible by the classical synthesis of Schiff bases.[1] NBA structure is a basic constituent of many compounds which have liquid-Crystal properties.[2] Over the past two decades, NBA structure has been studied with various semi-empirical methods[3-6] and molecular spectroscopy such as UV absorption,[7-12] NMR,[13-16] and IR.[17-22] X ray cristallography[23-25] studies of NBA have found that the aniline ring is twisted out of the C-C=N-C plane with an angle in the range 41° to 55° and the benzylidene ring also lies out of the previous plane with a smaller and opposite angle 8°-14°. The transmission of the electronic effects of the substituent on the benzyliden group X and/or on the aniline group Y substituents through the conjugated double bonds has been intensively studied.[14,20]

Due to the non planarity of the two rings, the transmission of the electronic effect of the X and Y substituents through the conjugated double bond C=N is very low. Spectroscopic studies (NMR, IR)[14,20] of the physico-chemical properties of the NBA have found that the same substituent has a stronger contribution to the electronic effects on the benzyliden group (X position) than on the aniline group (Y position).

NBA has been studied by various chromatography techniques such as gas chromatography,[26-30] thin-layer chromatography,[31-33] and supercritical fluid chromatography.[34] The mechanism of NBA retention partly reflects the molecular structure and the electronic distribution in the molecule. The interest of systematic chromatographic studies is to correlate molecular descriptors and experimental measurements quantitatively.

Over the last twenty years, several methods have emerged for the evaluation and prediction of the chromatographic behavior of compounds. In liquid chromatography, QSRRs[35-41] have shown the greatest promise. QSRRs established between retention measurements (such as log k') and physico-chemical descriptors of solute give a good understanding of the retention mechanism. These descriptors represent the complexity of the molecular structure and the diversity of the chromatographic interactions involved.

In normal and reversed phase liquid chromatography, the relevant molecular descriptors must represent steric, electronic, and hydrophobic effects on the retention. The choice of the relevant descriptors is strongly related to the molecular structure and the chromatographic mode (normal or reversed phase). From the literature, the most relevant descriptors can be classified in three groups: steric or geometric descriptors, electronic descriptors, and physico-chemical descriptors. The steric or geometric descriptors often used are molecular shape,[42,43] molecular cavity, or surface area.[44] Dipolar moment,[45-47] submolecular polarity parameter,[46] and charge-transfer energy[47] are the most representative electronic descriptors. In the group of physico-chemical descriptors, hydrophobicity parameter (log P),[44,48] solvatochromic parameters,[45] and Hammett's constants[49,50] are commonly chosen.

The aim of the present work is the study of chloro NBA to investigate the relationships existing between molecular structure and chromatographic behavior. The chromatographic study is carried out using amino bonded silica as stationary phase and heptan plus one modifier, tetrahydrofuran, ethyl acetate, or octanol 1, as eluent.

QSRRs are studied with the following descriptors: dipolar moment (μ), submolecular polarity parameter (Δ), ionization potential (PI), energy of the lowest unoccupied molecular orbital (E_{lumo}) and Hammett's substituent constants (σ_x, σ_y).

EXPERIMENTAL

Compounds

The compounds included in the present investigation are disubstituted N-benzylideneanilines (NBA) which have been obtained by the classical reaction of an aromatic amine with an aromatic aldehyde. The general formula of the NBA is: $X\text{-}C_6H_4\text{-}CH{=}N\text{-}C_6H_4\text{-}Y$, where X is the substituent in position 4 or 3 and Y substituent in position 4' or 3' (Figure 1). These disubstituted NBA will be denoted as X-Y. Twenty-seven NBA have been studied:

14 compounds have the benzylidene moiety substituted with chlorine (Cl) in position para or meta.

13 compounds have the aniline moiety substituted with chlorine in position para or meta.

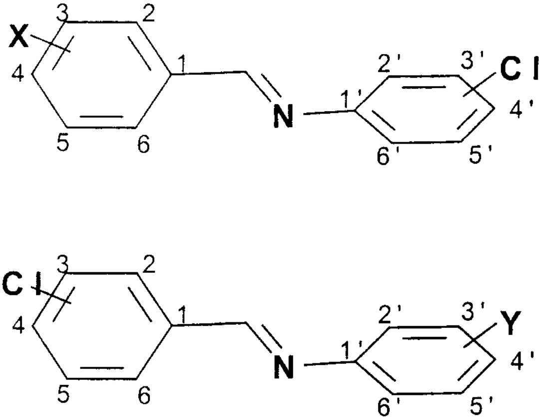

Figure 1. Disubstituted N-benzylideneanilines (ChloroSchiff bases).

Equipment

The HPLC equipment includes an L6200 Intelligent Pump, an autosampler model 655A-40, a L3000 Multi channel photo Detector and the corresponding D-6000 software for detection and acquisition (Merck-Hitachi, Darmstadt, Germany).

The compounds are studied in NP-LC with an amino bonded stationary phase, 7-µm Lichrospher 100 NH_2 (125*4 mm ID) column used with an oven model 655A-52 (Merck-Hitachi, Darmstadt, Germany) thermostated at 60°. The flow rate was 1mL/min and the volume of injection was 10µL.

Structural analysis was carried out with Sybyl 6.0 (Tripos associate, St Louis, MO) on VAX station 3100. Molecular geometry was optimized and the distribution of electronic charges within the molecule was calculated by appropriate molecular orbital package procedures (MOPAC) using semi-empirical method (AM1).

Chromatographic Eluents

The mobile phases consist of mixtures of solvents based on heptan and one modifier. The solvents used include heptan for HPLC (Fisons, Loughborough, Great Britain), tetrahydrofuran (Merck, Darmstadt, Germany),

Table 1

Composition of the Eluents for the Three Chosen Chromatographic Systems

Label	**Eluent**	
THF	tetrahydrofuran/heptan	5/95 (v/v)
AC	ethyl acetate/heptan	6/94 (v/v)
OC	octanol-1/heptan	2/98 (v/)

octanol-1 (Merck, Darmstadt, Germany) and ethyl acetate (Prolabo, Paris, France). The three modifiers have been selected with the Snyder triangle[51,52] in order to obtain three different selectivities. The exact eluent composition of the three chosen chromatographic systems are given in Table 1. The eluent composed with tetrahydrofuran is labeled THF, that with octanol 1 OC and that with ethyl acetate AC.

RESULTS AND DISCUSSION

The molecular descriptors calculated for each solute (Table 2) are:

-Dipolar moment (μ) which characterizes the polarity of the compound.

-Ionization potential (PI) which represents the ability of the solute to donate electrons.

-Energy of the lowest unoccupied molecular orbital E_{lumo}. This parameter is related to the ability of the solute to form charge transfer complexes.

-Submolecular polarity parameter Δ which measures the possibility of the solute to develop polar solute-stationary phase interactions. Parameter Δ represents the largest difference in atomic charges, reflecting the largest molecular local dipole. To determine $\mathit{\Delta}$, the electron charge on each atom in the molecule is calculated first and then, the atoms with the highest and the lowest electron charge are localized. The difference between the two atomic charges is calculated as $\mathit{\Delta}$. An example is given in Figure 2.

-Hammett's constants of substituents X and Y (σ_X, σ_y) in position meta or para reflect the electron density. The values were obtained from the literature.

Table 2

Logarithm of Capacity Factors Measured With the Three Eluents THF, AC, OC, and Structural Descriptors of the Twenty-seven Chloro-N-Benzylidenalines

Compounds	**Log k′**			**Descriptors**					
X - Y	**THF**	**AC**	**OC**	μ	**PI**	E_{lumo}	Δ	σ_x	σ_y
4Cl-4Me	-0.29	-0.30	-0.57	2.04	8.81	-00.70	0.34	0.227	-0.170
4Cl-H	-0.25	-0.25	-0.49	1.80	8.97	-0.71	0.31	0.227	0.000
4Cl-4F	-0.21	-0.25	-0.54	1.44	8.98	-0.88	0.32	0.227	0.062
4Cl-4Cl	-0.24	-0.26	-0.58	1.41	9.01	-0.88	0.31	0.227	0.227
4Cl-3Cl	-0.21	-0.26	-0.58	2.36	9.14	-0.85	0.32	0.227	0.373
4Cl-3NO$_2$	0.35	0.31	0.03	4.06	9.47	-1.26	0.93	0.227	0.710
4Cl-4NO$_2$	0.33	0.30	0.01	5.41	9.58	-1.49	0.93	0.227	0.778
3Cl-4OMe	0.14	0.12	-0.12	1.84	8.64	-0.64	0.38	0.373	-0.268
3Cl-4Me	-0.24	-0.24	-0.52	2.59	8.850	-0.65	0.35	0.373	-0.170
3Cl-H	-0.20	-0.21	-0.46	2.47	9.02	-0.67	0.32	0.373	0.000
3Cl-4F	-0.14	-0.17	-0.50	2.63	9.02	-0.84	0.33	0.373	0.062
3Cl-3Cl	-0.16	-0.18	-0.53	1.82	9.17	-0.81	0.32	0.373	0.373
3Cl-4CN	0.57	0.50	0.29	4.13	9.34	-1.08	0.33	0.373	0.660
H-4Cl	-0.23	-0.21	-0.44	2.25	8.94	-0.69	0.31	0.000	0.227
4NO$_2$-4Cl	0.34	0.30	0.00	4.61	9.38	-1.58	0.92	0.778	-0.227
4OMe-4Cl	0.15	0.17	-0.06	2.23	8.75	-0.63	0.37	-0.268	0.227
4Me-4Cl	-0.26	-0.25	-0.53	2.59	8.85	-0.68	0.34	-0.170	0.227
4F-4Cl	-0.21	-0.23	-0.54	1.40	9.00	-0.86	0.34	0.062	0.227
4CF$_3$-4Cl	-0.24	-0.29	-0.64	2.53	9.24	-1.15	0.63	0.540	0.227
3NO2-4Cl	0.47	0.42	0.15	5.90	9.29	-1.33	0.93	0.710	0.227
H-3Cl	-0.23	-0.23	-0.45	1.48	9.06	-0.64	0.31	0.000	0.373
4NO$_2$-3Cl	0.34	0.30	0.01	5.04	9.52	-1.58	0.92	0.778	0.373
4OMe-3Cl	0.14	0.15	-0.10	1.83	8.81	-0.60	0.37	-0.268	0.373
4Me-3Cl	-0.25	-0.25	-0.49	1.82	8.96	-0.63	0.34	-0.170	0.373
4F-3Cl	-0.20	-0.22	-0.49	2.41	9.12	-0.84	0.34	0.062	0.373
3NO$_2$-3Cl	0.44	0.39	0.14	5.42	9.43	-1.32	0.93	0.710	0.373

In the first step of the study, Principal Component Analysis (PCA)[53-56] is applied to determine the independent descriptors. In the second step, multiple linear regression (MLR) is used to establish the quantitative relationship between the chromatographic retention and the set of independent descriptors.

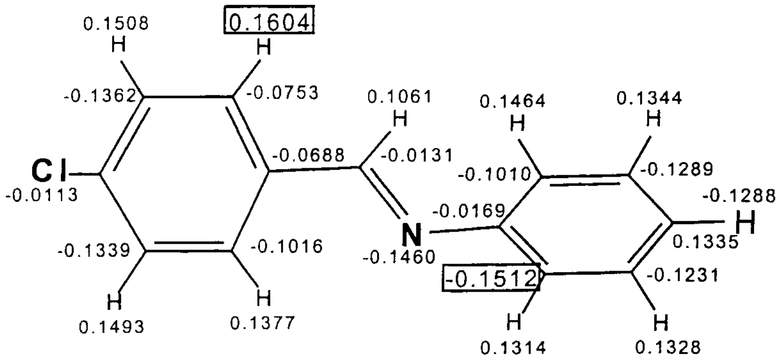

Figure 2. Example of the Determination of the Submolecular Polarity Parameter Δ. The Electronic Charges are indicated for each Atom. Δ is calculated with the Highest and the Lowest Electronic Charges. $\Delta = 0.1604 - [-0.1512] = 0.3116$

The first data matrix studied is composed of the logarithm of the capacity factors (k') measured with the three eluents (THF, AC, OC) and the six descriptors (μ, PI, E_{lumo}, σ_X, σ_Y and Δ). This first matrix is studied by PCA. The plot of the first and second components of k' and descriptors (Figure 3) shows that dipolar moment μ and submolar polarity parameter Δ are correlated. These two descriptors measure the same molecular property related to the polarity of solute. The dipolar moment μ is a global dipolar moment calculated for the entire molecule. The submolar polarity parameter Δ can be defined as a local dipolar moment. From the correlation matrix (Table 3), it appears that μ is more correlated to the chromatographic retention than Δ. The submolar polarity parameter will not be considered for the determination of the QSRRs.

The electronic parameters are now examined. Descriptors E_{lumo} and PI which both represent the electronic interactions, are highly correlated. From the correlation matrix (Table 3), descriptor PI has a lower correlation to dipolar moment than descriptor E_{lumo}. Descriptors μ and PI are more independent than descriptors μ and E_{lumo}. Descriptor PI is retained for multilinear analysis of the chromatographic retention. Hammett's constants σ_X and σ_Y define the second factorial component. They are not correlated to the other descriptors selected, μ and PI, and they must be retained to describe the chromatographic behavior of solutes. It must be emphasized that PI and Hammett's constants are related to electronic interactions. Parameter PI is a global electronic effect whereas σ_X and σ_y account for local electronic effects.

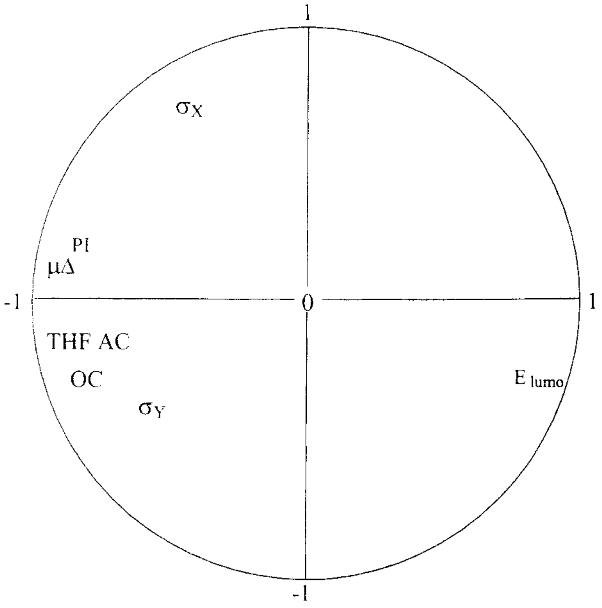

Figure 3. Principal Component Analysis (PCA). Circle of Correlation.

Table 3

Correlation Matrix

	THF	**AC**	**OC**	**μ**	**Δ**	**E_{lumo}**	**PI**	**σ_x**	**σ_y**
THF	1.000								
AC	0.997	1.000							
OC	0.983	0.991	1.000						
μ	0.827	0.811	0.776	1.000					
Δ	0.741	0.728	0.676	0.882	1.000				
E_{lumo}	-0.705	-0.672	-0.602	-0.857	-0.905	1.000			
PI	0.605	0.569	0.507	0.787	0.782	-0.901	1.000		
σ_x	0.440	0.394	0.327	0.629	0.603	-0.714	0.598	1.000	
σ_y	0.487	0.479	0.454	0.451	0.422	-0.493	0.713	-0.083	1.000

In the second part of the study, the logarithm of capacity factors and the relevant structural descriptors are mutually related by multiparameter regression analysis. Two models are calculated, both more or less related to the dipolar moment μ and one electronic descriptor. For the first model the electronic effects are taken into account by the ionization potential PI and for the second model by Hammett's constants (σ_X, σ_Y).

The parameters of the regression between the logarithm of k' for the twenty-seven solutes studied with the three eluents THF, AC, OC and the selected descriptors are given in Table 4. For the solutes studied, the results confirm the important part played in the retention mechanism by the dipolar interactions. The electronic effects, represented by descriptors ionisation potential or by Hammett's constants, have the lowest influence on the retention mechanism but they cannot be considered as negligible specially on the selectivity involved by the three solvents.

The models for the three eluents THF, AC, OC show that the μ coefficients increase respectively from THF to OC, while the coefficients for AC have medium values. This seems to indicate that the modifiers tetrahydrofuran and octanol-1 induce specific effects on the retention mechanism.

To analyze the relative importance of each descriptor and modifier on chromatographic retention, descriptors are transformed. For each descriptor μ, PI, σ_X and σ_Y, the center (c) and the range of variation (r_v) were calculated with the highest and the lowest values of each descriptor.

$$c = \frac{\text{Highest value} + \text{Lowest value}}{2} \quad \text{and}$$

$$r_v = \frac{\text{Highest value} - \text{Lowest value}}{2}$$

Then, each descriptor is transformed into coded descriptor (X) by the relation:

$$X = \frac{\text{Value of descriptor } - c}{r_v}$$

Table 4

Quantitative Structure-Retention Relationships (QSRR) for the Three Eluents (THF, AC, OC) and theTwo Models (μ, PI) and μ, σ_x, σ_y)

QSRR of the Model (μ, PI)

	Model	**Coefficients of the Model**		
	μ, PI	**μ**	**PI**	**Constant**
THF	R=0.830	0.191	-0.138	0.701
Log(k′)	F(2,24)=26.566			
AC	R=0.819	0.190	-0.201	1.256
Log (k′)	F(2,24)=24.469			
OC	R=0.794	0.206	-0.315	1.963
Log (k′)	F(2,24)=20.417			

QSRR of the Model (μ, σ_x, σ_y)

	Model		**Coefficients of the Model**		
	μ, σ_x, σ_y	**μ**	**σ_x**	**σ_y**	**Constant**
THF	R=0.838	0.169	-0.062	0.131	-0.509
Log (k′)	F(3,23)=18.031				
AC	R=0.827	0.173	-0.138	0.082	-0.511
Log (k′)	F(3,23)=16.605				
OC	R=0.827	0.195	-0.254	0.012	-0.803
Log (k′)	F(3,23)=16.605				

The new models are written as follows:

$$\log(k') = b_0 + b_\mu X_\mu + b_{IP} X_{\mathrm{IP}}$$

or

$$\log(k') = b_0 + b_\mu X_\mu + b_{\sigma x} X_{\sigma x} + b_{\sigma y} X_{\sigma y}$$

Table 5

Pareto Analysis. Weight of Coefficient (P_i) of each Descriptor i for the Three Eluents THF, AC, and OC

	Weight of Effect (P_i) %		
	Eluent		
Model (μ, PI)	**THF**	**AC**	**OC**
Dipolar moment (μ)	97.77	05.31	90.77
Ionization potential (PI)	2.23	4.69	9.23
Model (μ, σ_x, σ_y)			
Dipolar moment (μ)	96.18	95.60	91.60
Hammet's constant (σ_x)	0.70	3.36	8.39
Hammet's constant (σ_y)	3.11	1.15	0.02

To check the weight of the different coefficients of the new model, a Pareto analysis is performed. The weight of coefficient (P_i) of each descriptor i is calculated as follows:

$$P_i = 100\left(\frac{b_i^2}{\sum_{j=1}^{4} b_j^2}\right)$$

The determination of P_i for each descriptor i and the three eluents (Table 5 and Figure 4) confirms that the most important descriptor is the dipolar moment; $X\mu$ explains between 90 and 98% of the log(k') variation. The $X\mu$ contribution decreases from THF to OC eluent.

The electronic contribution X_{PI} or $X_{\sigma x}$ and $X_{\sigma y}$, becomes significant with octanol 1 as modifier. When the solvatochromic parameters of solvents (Table 6) are considered, the two solvents tetrahydrofuran and ethyl acetate have significant terms for dipolarity/dipolarisability $(\bar{\pi}*)$ and hydrogen bond basicity $(\bar{\beta})$ while their hydrogen bond acidity $(\bar{\alpha})$ term is null. The solvent octanol 1 has a significant hydrogen bond acidity $(\bar{\alpha})$ term.

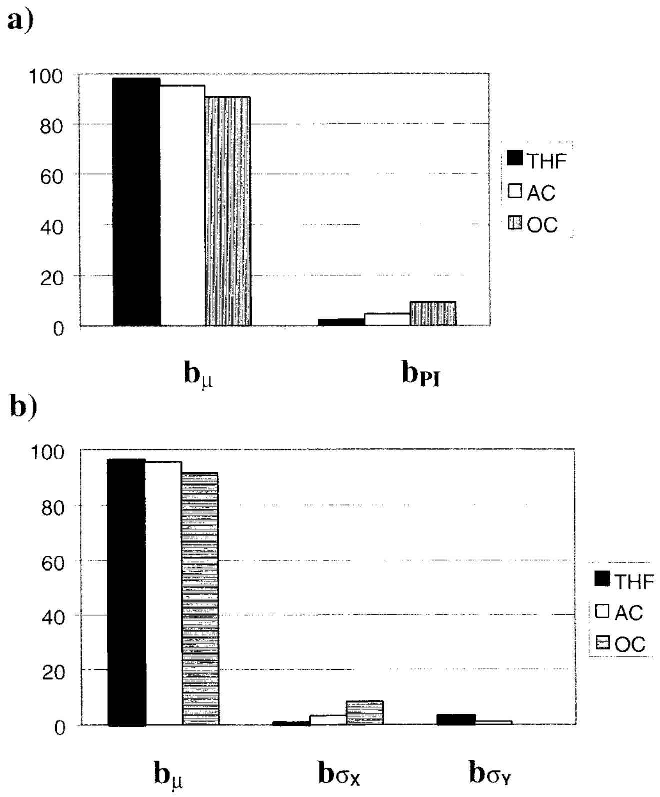

Figure 4. Pareto Analysis. Weight of Coefficient (P_i) of each Descriptor i for the Three Eluents THF, AC and OC with the Two Models: Model (μ,PI). b) Model (μ, σ_X, σ_Y).

Table 6

Values of Solvatochromic Parameters

Solvent	$\overline{\alpha}$	$\overline{\pi}$ *	$\overline{\beta}$
tetrahydrofuran	0.00	0.51	0.49
ethyl acetate	0.00	0.55	0.45
octanol 1**	0.37	0.33	0.41

** approximated values from those of butanol

The variation of the weight of the electronic descriptor coefficient, b_{PI} or $b\sigma_X$ and $b\sigma_Y$, from THF or AC to OC eluent, reflects the variation of the hydrogen-bond acidity interactions. This variation is extremely weak since the electronic descriptors PI, σ_X and σ_Y, explain only 9% of the log(k') variation with OC eluent.

With octanol 1 as modifier, the contribution of the electronic effect σ_Y on the retention is negligible ($P\sigma_Y$ =0.02%). The electronic effect of substituent Y on the retention is weak. Substituent X has a higher electronic contribution to retention. It can be supposed that substituent X has a higher electronic influence on the nitrogen basicity than substituent Y. This is probably due to the non planarity of the two rings since the aniline ring (substituent Y) is twisted out of the C-C=N-C plane by around 50° and the benzilydene ring (substituent X) lies outside with a smaller angle around 10°.

In conclusion, the dipolarity/dipolarisability interaction principally governs the retention of the chloro N-benzylideneanilines in normal phase liquid chromatograhy. The study of the retention with the three modifiers indicates that the electronic effects have very low influence on the retention mechanism. These experimental results confirm the importance of the molecular conformation on the charge transfer and certainly, the very weak conjugation between the two aromatic rings.

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