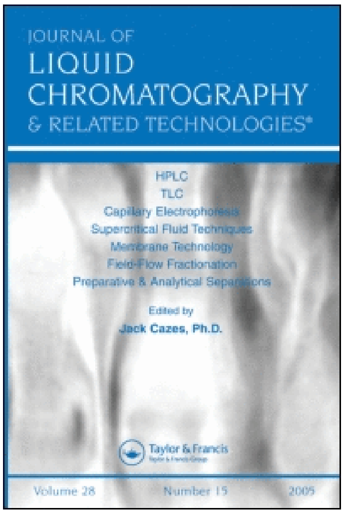

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Substituent Effects in High-Performance Liquid Chromatography of Diarylacrylonitriles

S. Caccamese[a]; V. Iacona[a]; G. Scarlata[a]; R. M. Toscano[a]
[a] Dipartimento di Scienze Chimiche, Universitá di Catania viale Doria 6, Catania, Italy

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SUBSTITUENT EFFECTS IN HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY OF DIARYLACRYLONITRILES

S. Caccamese, V. Iacona, G. Scarlata and R.M. Toscano
Dipartimento di Scienze Chimiche
Università di Catania
viale Doria 6, Catania, Italy

ABSTRACT

Thirty diarylacrylonitriles, carrying various para substituents in the phenyl ring attached to the position 1 of the ethylenic bridge and various heterorings (thienyl, furyl, pyrryl, N-methylpyrryl) attached to the position 2, have been investigated on silica gel. An additional substituent is present in the thienyl derivatives. The capacity factors of all the compounds can be grouped in only five or six families, according to the variation in the para-phenyl substitution or in the heteroring moiety, respectively. The strongest effect in the enhancement of the capacity factors is given by a methoxy or nitro group in the para-phenyl position.

Other minor effects as well as the relationship between capacity factors and solvent mixtures polarity are discussed.

INTRODUCTION

Recently it has been observed that the substitution of a hydrogen atom in the ethylenic bridge by a cyano group in stilbenes modifies the behaviour to the photoisomerization and dimerization(1). In this respect,we

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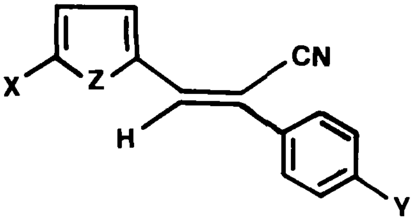
are concerned with heteroaryl analogs of general formula



X=H	Z=O,NH,NCH$_3$	Y=H,CH$_3$,Cl,OCH$_3$,NO$_2$
X=H,CH$_3$,Br	Z=S	Y=H,CH$_3$,Cl,OCH$_3$,NO$_2$

Thirty compounds of this class were available from previous studies of one of us on their infrared and ultraviolet (2), ^{1}H (3) and C 13 NMR (4) spectroscopies.

During a work on the solid-state irradiation of such compounds it was clear that photoisomerization rate was greatly effected by the X, Y and Z substituents pattern and, since the reaction was monitored by HPLC, a relationship between these substituents and the chromatographic behaviour on straight silica gel became apparent.

In this report, a rationalization for this correlation is given. Furthermore, the interaction of these compounds with solvent mixtures of different polarity is illustrated.

EXPERIMENTAL

Apparatus

The liquid chromatography used was a Varian Model 5060 equipped with a JASCO Model Uvidec-100 III UV spectrophotometer at 240 nm, cell volume 8 µl. The detector was connected to a Varian CDS 401 Data System with data collection. The sample was introduced with a Valco air-actuated valve equipped with a 10 µl external loop.

Chromatographic conditions

Each compound was examined at least in duplicate in order to determine elution time and capacity factor. Separations were carried out on a LiChrosorb Si 100 column (25 cm. x 4 mm. I.D.) packed with 10 µm silica particles (Merck, Darmstadt, G.F.R.). The solvent flow-rate was 1.0 ml/min. Temperature was 18°C for the analyses done in methylene chloride-hexane mixtures and 26°C for the analyses done in tert-butylmethylether-hexane mixtures. Reproducibility of elution time was better than 0.4% at constant temperature. A temperature increase from 18° to 26°C, using the same solvent mixture, resulted in a decrease of about 5% in the elution times.

Chemicals and solvents

Compounds 1-30 were previously prepared by condensation of 2-heteroaromatic aldehyde with the appropriate acrylonitrile in the presence of bases and their physical characterization is reported elsewhere (3-5).

All compounds were of the Z configuration as previously shown (3), for many of them, by a ^{1}H NMR stereochemical study. They demonstrated a high purity and so were used without further purification. The methylene chloride and n-hexane were HPLC grade from J.T.Baker (Phillipsburgh, N.J., U.S.A.). The tert-butylmethylether was HPLC grade from Fluka (Buchs, Switzerland).

RESULTS AND DISCUSSION

The capacity factors *k'* were calculated by the usual equation $k'=t_R - t_0/t_0$ where t_R= elution time of compound, t_0= the time of zero retention measured as the time of the non-retained solvent peak. They are listed in Table 1 for the solvent system methylene cloride-n-hexane (80:20). An example of the achievable resolution in the separation of an *ad hoc* prepared mixture of thienyl derivatives is illustrated in Figure 1.

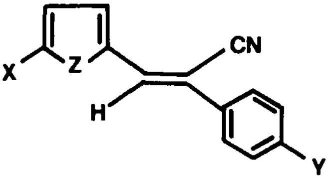
The substituents in the molecules induce extensive conjugation between X and cyano group as well as between an Y electron-releasing group and the cyano group. However, polar effects play a major role in the interaction of the functional groups with the silica adsorption sites competitively with the solvent molecules. Figures 2 and 3 illustrate, in fact, the correlation between the capacity factor and the substitution pattern in the acrylonitrile skeleton. These plots use log *k'* versus log $k'_\varkappa$

In fact, being the logarithm of a capacity factor proportional to the free energy change (ΔG) associated with the chromatographic distribution process (6), this type of plot relates the $\Delta(\Delta G)$ obtained when an additional substituent is introduced (ordinate) in a sequence of $\varkappa$ compounds having a particular substitution pattern (abscissa).

A similar plot has already been used in HPLC (7).In Figura 2, $\varkappa$ refers to compounds 2,3,1,4,5 carrying as Y substituent Cl,CH_3,H,OCH_3 and NO_2 respectively. All thirty compounds reported in Table 1 are on six lines (A to F)

TABLE 1

Capacity Factors of
Z -[1-(Phenyl)-2-(Heteroaryl)] Acrylonitriles [a]



Compound	X	Z	Y	K'
1	H	S	H	0.26
2	H	S	Cl	0.21
3	H	S	CH$_3$	0.24
4	H	S	OCH$_3$	0.48
5	H	S	NO$_2$	0.56
6	Br	S	H	0.15
7	Br	S	Cl	0.12
8	Br	S	CH$_3$	0.13
9	Br	S	OCH$_3$	0.31
10	Br	S	NO$_2$	0.43
11	CH$_3$	S	H	0.22
12	CH$_3$	S	Cl	0.17
13	CH$_3$	S	CH$_3$	0.20
14	CH$_3$	S	OCH$_3$	0.45
15	CH$_3$	S	NO$_2$	0.53
16	H	O	H	0.32
17	H	O	Cl	0.27
18	H	O	CH$_3$	0.31
19	H	O	OCH$_3$	0.59
20	H	O	NO$_2$	0.72
21	H	NH	H	0.41
22	H	NH	Cl	0.36
23	H	NH	CH$_3$	0.39
24	H	NH	OCH$_3$	0.78
25	H	NH	NO$_2$	0.98
26	H	N-CH$_3$	H	0.48
27	H	N-CH$_3$	Cl	0.39
28	H	N-CH$_3$	CH$_3$	0.46
29	H	N-CH$_3$	OCH$_3$	0.94
30	H	N-CH$_3$	NO$_2$	0.99

[a] Solvent system n-hexane-methylene chloride (20:80) on LiChrosorb 100.

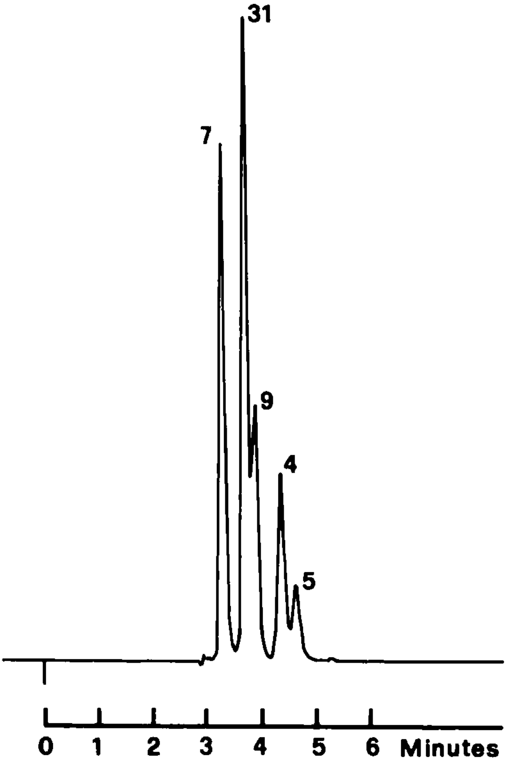


FIGURE 1. Separation of diarylacrylonitriles (for peaks 4, 5, 7 and 9 see Table 1) and E-[α -phenyl,β-2-thienyl)] ethylene (for peak 31 see text). For conditions see Table 1.

defining six acrylonitriles series each of them having the same heteroaryl moiety (X,Z = H,NCH_3; H,NH; H,O; H,S; CH_3,S; Br,S respectively). It can clearly seen that introduction of a methoxy or nitro group in para-phenyl position increases drastically the capacity factor, whereas introduction of a methyl or chloro group reduces slightly the capacity factor. This fact can be rationalized on the basis only of the local dipole moments induced either by a strong electron-demanding group (nitro) or by a strong

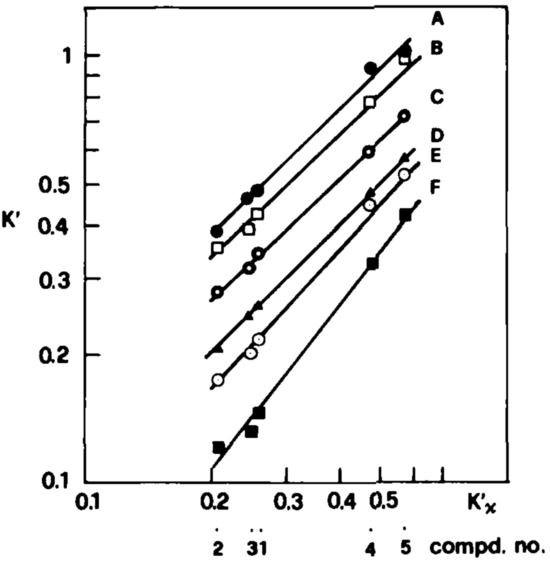


FIGURE 2. Effect of the heteroaryl moiety on the elution of diarylacrylonitriles. Logarithmic plot of *k*' *vs*. k'_x with x= compounds 2, 3, 1, 4 and 5 for the solvent mixture hexane-methylene chloride (20:80). A, series with X=H and Z=NCH_3 (compounds 27, 28, 26, 29, 30); B, series with X=H and Z=NH (compounds 22, 23, 21, 24, 25); C, series with X=H and Z=O (compounds 17, 18, 16, 19, 20); D, series with X=H and Z=S (compounds 2, 3, 1, 4, 5); E, series with X=CH_3 and Z=S (compounds 12, 13, 11, 14, 15); F, series with X=Br and Z=S (compounds 7, 8, 6, 9, 10). Compounds in each series are listed according to increasing k' values.

electron-releasing group (methoxy). Conjugative effects cannot account for the "same-sense" strong *k*' increase given by these two groups. Particularly, if we plot the capacity factors *k*' for each X, Z series *versus* the σ^+ Hammett substituent constants of the Y groups we obtain a typical U-shaped curve in which methoxy and nitro groups are located at the upper opposite bounds.

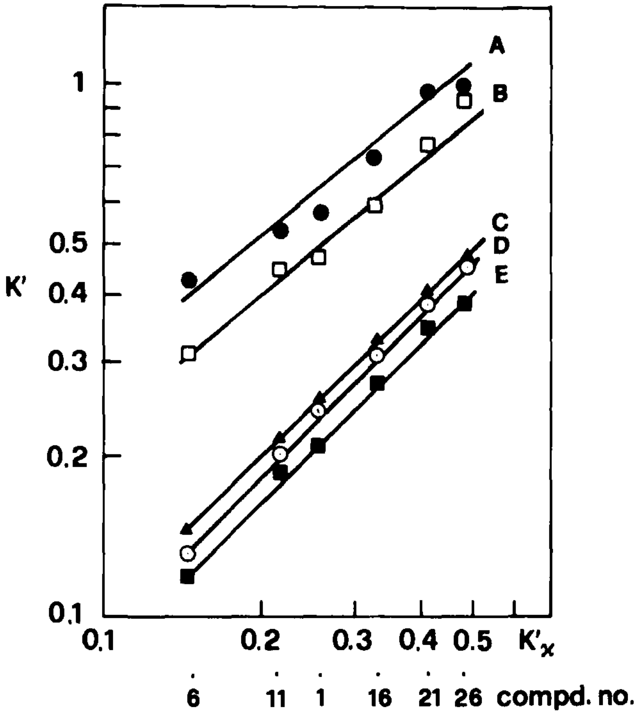


FIGURE 3. Effect of the para-phenyl substitution on the elution of diarylacrylonitriles. Logarithmic plot of *k*' *vs*. k'_χ with χ= compounds 6, 11, 1, 16, 21 and 26 for the solvent mixture hexane-methylene chloride (20:80). A, series with Y=NO_2 (compounds 10, 15, 5, 20, 25, 30); B, series with Y=OCH_3 (compounds 9, 14, 4, 19, 24, 29); C, series with Y=H (compounds 6, 11, 1, 16, 21, 26); D, series with Y=CH_3 (compounds 8, 13, 3, 18, 23, 28); E, series with Y=Cl (compounds 7, 12, 2, 17, 22, 27). Compounds in each series are listed according to increasing k' values.

Selectivity between compounds with different X and/or Z substituents but with the same Y substituent remains constant,as it can be seen from the nearly parallel lines A,B,C,D and E. Only bromine substitution in the thiophene ring (line F) affects more markedly the increase in the elution time.

Furthermore, from Figure 2 it can be observed the sequence in the capacity factors 2-thienyl<2-furyl<2-pyrryl<2-N-methylpyrryl acrylonitriles. This fact cannot be rationalized on the basis of hydrogen-bonding interaction between the lone pair electrons of the heteroatom and the silica active hydroxy sites; probably the actual availability of these electrons, involved in conjugation, and the conformational preferences of the heteroring have to be taken into account.

In Figure 3, x refers to compounds 6,11,1,16,21 and 26. In this way, the abscissa is sensitive to the X substituent as well as to the Z substituent. Since compounds on each line (A to E) belong either to 5-substituted thienyl- or to heteroaryl-substituted acrylonitriles, it can be implied that both substitution patterns (X and Z) affect in an equal amount the capacity factor.Moreover, it can be again observed the marked effect on the increase in the capacity factor induced by the nitro (line A) and methoxy (line B) para-substituents in the phenyl ring.

The nearly parallel lines indicate that selectivity factor between compounds having different para-phenyl substituents but the same heteroaryl moiety remains constant.

Thus, these data support the hypothesis that the "pivoting" groups in the competition with the solvent for the adsorption silica sites are the strong polar para-phenyl substituents regardless of the direction of their dipole moments. A less marked influence on the adsorption equilibrium is due to the heteroaryl moiety.

In order to evaluate the influence of the cyano group, we have measured the capacity factor of the

E-[α-phenyl,β-2-thienyl]ethylene, compound 31, $\underline{k}$'= 0.25, in the same solvent system, column ad temperature. If we compare this value with that of compound 1 ($\underline{k}$'= 0.26), we observe that -at least in this case- the introduction of the cyano substituent in the ethylenic bridge has not practical effect on the adsorption equilibrium on the silica.

Coming now to the effect of the solvent strength on the retention, Figure 4 shows, as expected (8), a logarithmic decrease in $\underline{k}$' with increasing concentrations of methylene chloride in n-hexane. All the compounds, except 1, reported in Figure 4, carry a methoxy group in the para-phenyl-position and differ only in the heteroaryl moiety.

The nearly parallel lines among pyrryl 24, furyl 19 and thienyl 4 derivatives indicate that the separation factor between these classes is independent of the methylene chloride content in the solvent, at least for the concentration studies. Slope of the line referring to compound 1, which lacks the polar methoxy substituent in the para-phenyl position, is instead less pronounced indicating a milder interaction of the solute with the methylene chloride.

Figure 5 shows the dramatic effect on the capacity factors of compounds 1, 4 and 31 of small concentration of tert-butylmethylether in n-hexane. This ether has been recently introduced in HPLC because of clear advantages over other aliphatic ethers (9). Although its solvent strength parameter ($\varepsilon^\circ_{Al_2O_3}$ = 0.2) is low, we believe that its interaction with compounds shown in Figure 5 should be due to polar effects between the cyano group and the

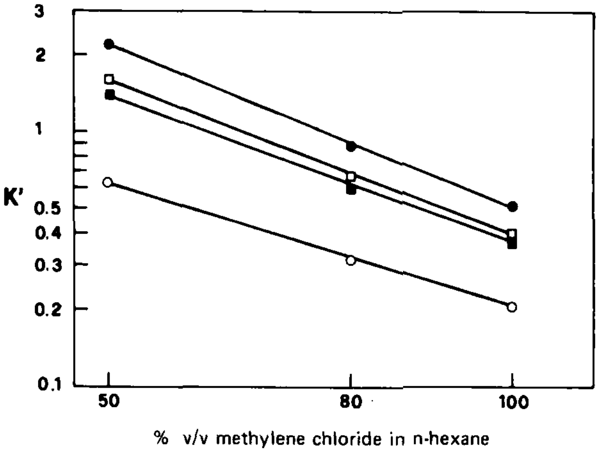


FIGURE 4. Effect of the methylene chloride concentration in hexane on the capacity factor of: ● compound 24; □ compound 19; ■ compound 4; ○ compound 1 (for numbers see Table 1).

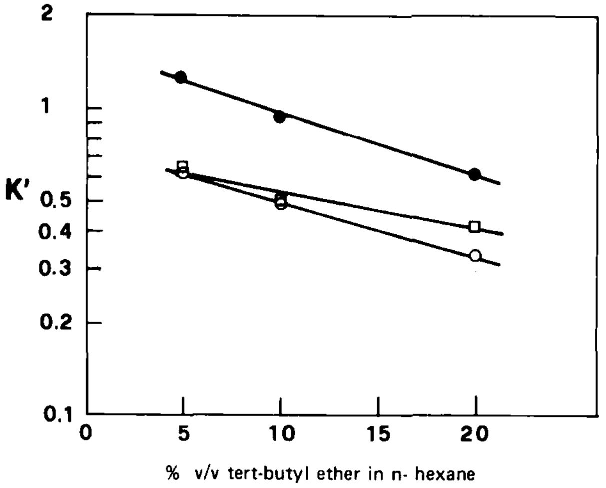


FIGURE 5. Effect of ter-butylmethylether concentration in hexane on the capacity factor of: ● compound 4; ○ compound 1; □ compound 31 (for numbers see Table 1 and text).

solvent. Compounds 31, lacking the cyano group, is in fact much less affected by the increasing concentration of tert-butylmethylether in n-hexane with respect to the other two.

Hence, it clearly appears that the order of elution of Z-[1-(p-substituted phenyl)2-(5-substituted-2-heteroaryl)acrylonitriles] is well related to their substitution pattern on the acrylonitrile skeleton.

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