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The Enhancement of Enantioselectivity by Halogen Substituents

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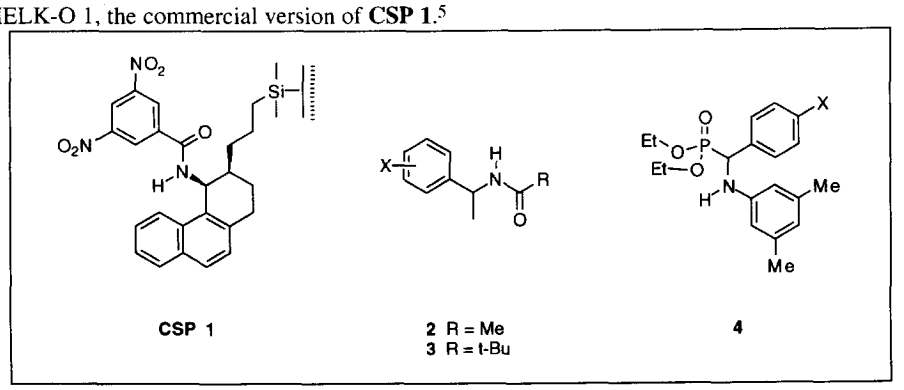
Abstract: For amide derivatives of 1-phenyl-1-ethylamines and for diethyl 1-(N-3,5-dimethylphenyl)amino-1-phenylmethanephosphonates with halogen substituents in the meta or para position of the benzenoid ring, increased retention and enantioselectivity are noted relative to their nonhalogenated counterparts. This is unexpected on the basis of prior observations that halogen substituents on benzenoid rings presumably undergoing face to face π–π interactions show reduced retention and enantioselectivity. These observations raise questions concerning the effect of polarizable electron-withdrawing substituents on the π–basicity of benzenoid systems. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Halogen substituents on benzenoid rings presumably being used as π-basic sites by π-acidic chiral stationary phases have been reported to reduce the retention and separation factors of the enantiomers studied.[1,2] Although we had not systematically studied the effects of halogen substituents heretofore, it seemed plausible that an electron withdrawing substituent might reduce the π-basicity of an aromatic ring and reduce retention and enantioselectivity when that ring is involved in a π–π interaction essential to the chiral recognition process. This is not always the case!

RESULTS AND DISCUSSION

As part of a study intended to afford a better understanding of the mode of action of chiral stationary phase **1** (**CSP 1**),[3] we prepared and chromatographed racemic samples of various amide derivatives of 1-phenylethylamine and several of its ring-halogenated counterparts. Unexpectedly, *para* and *meta* halogen substituents **increase** both retention and enantioselectivity when nonaqueous organic mobile phases are used.[4] The more polarizable the halogen, the greater the effect. Similar results are afforded by the enantiomers of diethyl 1-(*N*-3,5-dimethylphenyl) amino-1-(aryl)methanephosphonates in which the 1-aryl substituent is phenyl or halogenated phenyl. The structure of **CSP 1** and generalized structures of the amide derivatives, shown as **2** and **3**, and the phosphonates, shown as **4**, are provided. Table 1 reports the relevent chromatographic data obtained at ambient temperature using 20% 2-propanol in hexane as a mobile phase in conjunction with an (*3R, 4S*)- WHELK-O 1, the commercial version of **CSP 1**.[5]



Interestingly, the pivalamides show greater enantioselectivities than the corresponding acetamides and rather large separation factors were observed for the *p*-iodo and *p*-bromo analogs. In other CSP-analyte systems, "intercalation effects" have been found to increase enantioselectivity.[6] Initially, this was considered as a possible explanation of the unexpected increase in enantioselectivity. However, in hexane / 2-propanol mixtures, the "intercalation effect" increases enantioselectivity by diminishing the retention of the less retained enantiomer, not by increasing the retention of the more retained enantiomer. In the present

Table 1. Effects of halogen substituents on enantioselectivity on **CSP 1**

Analyte	X	k_1'	α
2	H	3.72	3.17
2	*p*-I	4.10	5.12
3	H	1.39	6.74
3	*p*-F	1.17	7.29
3	*p*-Cl	1.48	11.6
3	*p*-Br	1.61	12.8
3	*p*-I	1.75	13.7
3	*m*-Br	1.61	13.1
4	H	0.87	1.29
4	*p*-F	0.83	1.39
4	*p*-Cl	0.84	1.55
4	*p*-Br	0.86	1.66

α: separation factor of the enantiomers; k_1': retention factor for the first eluted enantiomer.

instance, the halogens clearly enhance retention, presumably by enhancing an attractive interaction. In the case of the phosphonates, halogen substituents tend to slightly reduce the retention of the less retained enantiomer but do increase both the retention of the more retained enantiomer and the enantioselectivity. Judging from the signs of optical rotation at 365 nm,[7] the enantiomers of each member in these series elute in a uniform order. In the case of the amides, the (*S*)-(-)-enantiomers are more strongly retained. This is in accord with the results of a recent NMR study of the solution structure of the more stable diastereomeric complexes of a closely related pivalamide and an analog of the selector used in **CSP 1**.[8]

All indications are that the aromatic portion of the more retained enantiomer of these pivalamides fits into a cleft-like active site, undergoing face to face and face to edge π–π interactions with the chiral selector. Substituents in the *ortho-* positions interfere with correct entry into the cleft, presumably for steric and conformational reasons. Although the data in Table 1 suggest that bonding interactions are being strengthened as one proceeds through the halogen series, reduced solvation by the mobile phase might also explain the increased retention. However, since enantiomers are solvated identically by an achiral mobile phase, the substantially increased enantioselectivity argues against reduced solvation as being solely responsible for the large increases in retention of the more retained enantiomers. Because both enthalpy and entropy influence retention and enantioselectivity, it was desirable to determine these thermodynamic parameters for the pivalamides. This was accomplished by chromatographing each of them at several different temperatures.[9] These thermodynamic values (listed in Table 2 and given in Kcal or eu) are obtained from the slopes and intercepts of plots of the

natural logarithms of the retention factors against the reciprocal of the absolute temperatures at which these values were determined. The values for ΔH_1 and ΔS_1 are for the least retained enantiomer, ΔH_2 and ΔS_2, are for the most retained enantiomer, while $\Delta\Delta H$ or $\Delta\Delta S$ values are the enthalpy or entropy differences in the adsorption of the enantiomers by the CSP. One can see that ΔH_2 and $\Delta\Delta H$ become progressively more exothermic as the halogen substituents become more polarizable and that the values of ΔS_2 and $\Delta\Delta S$ become increasingly negative as the bonding forces become stronger.

Table 2. Thermodynamic parameters for the adsorption of the type **3** pivalamides on CSP **1**

X	ΔH_1	ΔH_2	$\Delta\Delta H$	ΔS_1	ΔS_2	$\Delta\Delta S$
H	-3.59	-6.00	-2.40	-11.3	-15.8	-4.5
p-F	-3.36	-6.27	-2.91	-10.7	-16.6	-5.9
p-Cl	-3.61	-6.86	-3.25	-11.3	-17.5	-6.2
p-Br	-3.45	-6.86	-3.41	-10.6	-17.1	-6.6
p-I	-3.76	-7.28	-3.52	-11.4	-18.2	-6.8

If halogen substituents enhance π–π interactions, why do these substituents often diminish retention and enantioselectivity? The most plausible rationalization is that the inductive effect of the halogen sometimes reduces electron density at a site which is being used by the chiral selector as a hydrogen bond acceptor. Consequently, the reduced strength of the hydrogen bond overrides any beneficial effect of the substituents polarizability. In the case of the type **2-4** analytes, the hydrogen bonding sites are somewhat insulated from the inductive effects of the halogens and the beneficial effects of substituent polarizability become evident.

The preceeding observations may have practical utility. Owing to the reciprocal nature of chiral recognition,[10] one expects that introduction of halogen substituents onto the aromatic ring of an appropriate chiral selector will increase the enantioselectivity shown by that selector. The aromatic ring to be substituted must be utilized as a π-base and the inductive effect of the substituent must not diminish the strength of a hydrogen bond which is essential to the chiral recognition process. Clearly, chiral selectors similar to the type **2-4** analytes are candidates for this type of modification. The concept is not restricted to selectors used for chromatographic purposes but should extend to chiral reagents and chiral catalysts as well.

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REFERENCES AND NOTES

1. Tambute, A.; Siret, L.; Caude, M.; Rosset, R. *J. Chromatogr.* **1991**, *541*, 349.
2. Siret, L.; Tambuté, A.; Caude, M.; Rosset, R. *J. Chromatogr.* **1990**, *498*, 67.
3. Pirkle, W. H.; Welch, C. J. *Tetrahedron Asymm.*, **1994**, *5*, (5) 777.
4. Pirkle, W. H. presented at the EUCHEM-Conference on Mechanism of Chiral Recognition in Chromatography and the Design of Chiral Phase Systems, Aug. 14-18, 1995, Göteborg, Sweden.

5. Regis Technologies Inc. Morton Grove, IL 60053. The (*S*, *S*) label on this column should in fact read (3*R*, 4*S*).
6. Pirkle, W. H.; Murray, P. G.; *J. Chromatogr*. **1993**, *641*, 11 and references therein.
7. The signs of optical rotation at 365 nm were related to elution order using an Autopol IV as an online chromatographic detector.
8. Pirkle, W. H.; Selness, S. *J. Org. Chem.*, **1995**, *60*, 3252.
9. The retention of each of the pivalamides was determined at 20, 40, 50, 60, and 66°C. Linear vant' Hoff plots (R > 0.995) were obtained.
10. Pirkle, W. H.; Pochapsky, T. *J. Am. Chem. Soc.*, **1986**, *108*, 352.

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