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High-performance liquid chromatographic separation of the enantiomers of N-aryloxazolinones, N-aryl thiazolinones and their sulfur derivatives on a synthetic chiral stationary phase

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Abstract

Forty atropisomers, generally described as N-aryloxazolinones, N-arylthiazolinones, and their thiono analogs, have been synthesized and the enantiomers of these compounds have been found to be easily separated on the synthetically derived chiral stationary phase now known as the WHELK-O 1. The observed retentions, elution orders (when known) and extents of enantioselectivity suggest that these enantiodifferentiations occur by a mechanism consistent with the chiral recognition rationale used to develop this chiral stationary phase.

Keywords: Enantiomer separation; Chiral stationary phases, LC; N-Aryloxazolinones; N-Arylthiazolinones

1. Introduction

Atropisomers are compounds which display stereoisomerism owing to restricted rotation about a single bond. N-Aryloxazolinones, **1**, and N-arylthiazolinones, **3**, and their thiono derivatives, **2**, and, **4**, display atropisomerism owing to restricted bond rotation about the N-aryl bond (Fig. 1). These compounds have long been of interest to Roussel and co-workers. When the aryl group bears an *ortho*-substituent, the barrier to rotation is often great enough to allow resolution of the enantiomers of these atropisomers, as demonstrated by liquid chromatography on acetylated cellulose stationary phases [1–6]. The chiroptic properties, racemization rates and absolute configuration of various compounds in these series have been studied by Roussel and co-workers who, several years ago, kindly provided several samples for chromatographic examination on our π-acidic chiral stationary phases (CSPs). Our attempts at resolution were largely successful but the work was not further pursued since our results at the time constituted no particular improvement on those reported by Roussel et al. Recently, our interest was rekindled as these compounds appeared to be well-suited for resolution on one of our recent CSPs, judging from the mechanistic hypothesis as to how this CSP differentiates between enantiomers. This CSP, the commercial version of which is now known as the WHELK-O 1 (Fig. 2), is widely applicable for the separation of enantiomers having both a π-basic site and a hydrogen bond acceptor site near a stereogenic center. Roussel's atropisomers fulfil these requirements. With the expectation that they

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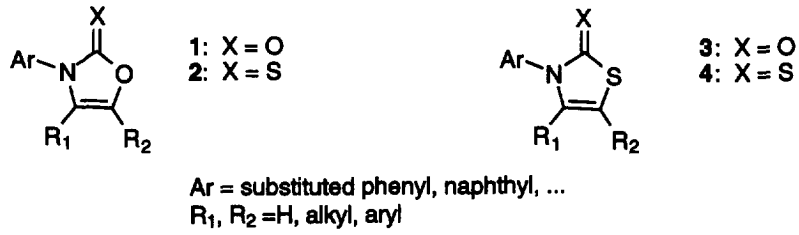


Fig. 1. General structure of the compounds used in this study.

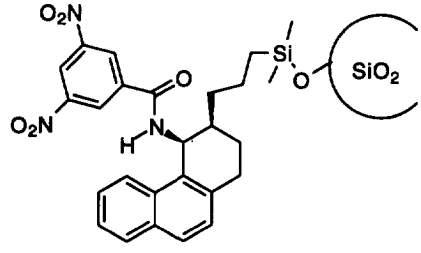
would be generally resolvable on WHELK-O 1, we prepared an extensive series of these compounds in order to conduct a study of the relationship between chromatographic behavior and analyte structure. This study was expected to confirm or deny the plausibility of the postulated chiral recognition processes employed by the WHELK-O 1 [7–9], and at the very least, would give an indication of the applicability of this CSP for the separation of the enantiomers of these atropisomers.

2. Experimental

The analytes used in this study were prepared using literature methods [1–6,10–12] outlined in Fig. 3, several of these analytes being previously described. All chromatographic solvents were HPLC grade from EM Science. Chromatography was carried out at ambient temperature using a commercial (*S,S*)-Whelk-O 1 brush-type HPLC column (250× 4.6 mm I.D., 5-μm spherical silica particles of 100-Å pore size) available from Regis Technologies (Morton Grove, IL, USA). To facilitate comparison of the data, all experiments were carried out at a flow-rate of 2.00 ml/min and a mobile-phase 2-propanol–hexane (20:80). Detection was by tandem ultraviolet and polarimetric detectors operating at 254 nm and 589 nm, respectively. Tri-*tert.*-butylbenzene was used as the void-volume marker.

3. Results and discussion

Chromatographic data are presented in Table 1, Table 2, Table 3, and Table 4. All analytes used in



(S,S) WHELK-O 1

Fig. 2. Synthetically derived chiral stationary phase used in this study.

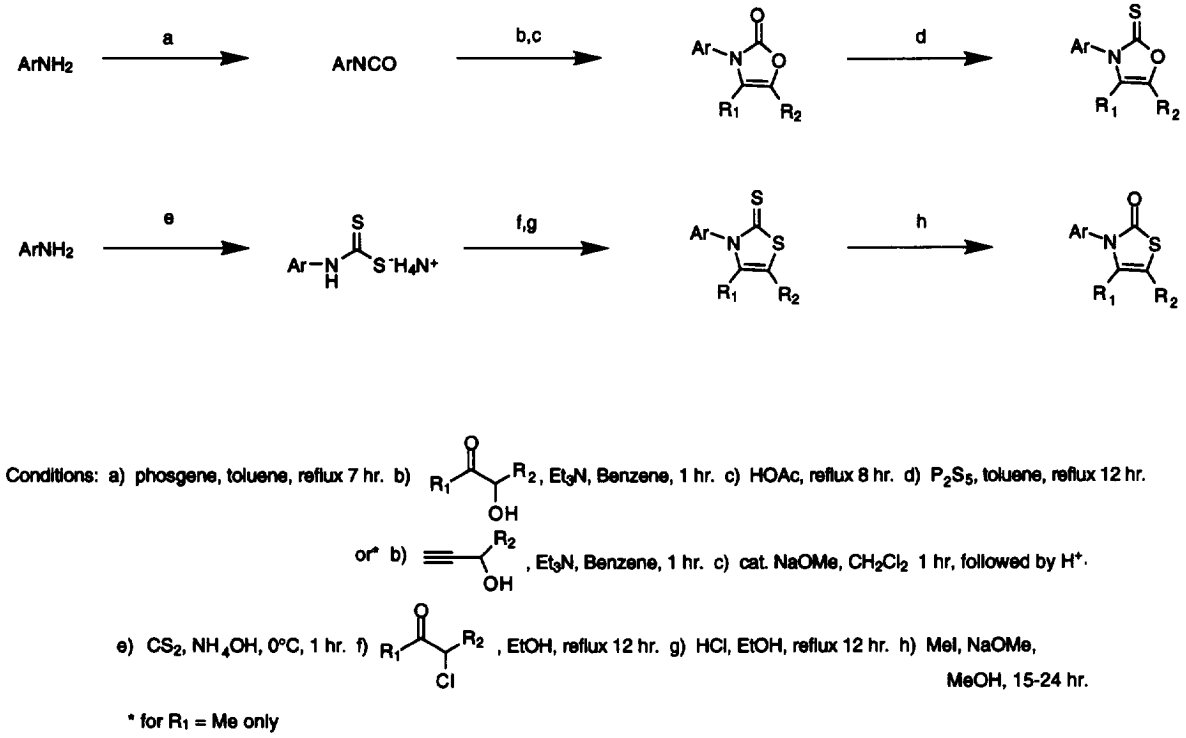
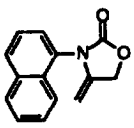


Fig. 3. Synthesis of N-aryloxazolinones, N-arylthiazolinones and their thiono analogs.

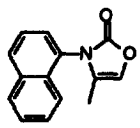
this study were stable to racemization on the chromatographic time-scale, with some of the compounds of type **1** showing a raised baseline (i.e., a plateau) between eluted enantiomers, indicative that a small fraction of the analyte enantiomers had changed absolute configuration sometime during the run. Studies of the effects of various substituents on the aromatic ring on the rates of racemization for compounds of this type will be reported elsewhere.

Our initial mechanistic hypothesis was that the aryl substituent of these analytes could be utilized as a site for face-to-face and face-to-edge π–π interactions by the π-acidic 3,5-dinitrobenzoyl and π-basic naphthyl portions of the CSP, respectively. The heterocyclic ring of these analytes, being roughly perpendicular to the aryl group, was expected to utilize the amide N–H bond of the CSP for hydrogen bonding to the exocyclic heteroatom of the analyte. Imagine that each enantiomer of one of these analytes was to undergo the three aforementioned simultaneous interactions. For one enantiomer, the less hindered edge of the unsymmetrical aryl group would be directed down toward the naphthyl portion of the CSP whereas for the other, the more hindered edge, the edge bearing the *ortho*-substituent, would be so directed. This would interfere with the face-to-edge π–π interaction, thus causing this enantiomer to be less retained. With but one special exception, baseline separation of the enantiomers is readily achieved. That exception is compound **4f**, where the aryl group has two *ortho*-substituents and the exocyclic heteroatom is sulfur. From the postulated mechanism, this is expected to be an unfavorable situation. Sulfur is a poor hydrogen bond acceptor and the two *ortho*-substituents, methyl and chlorine, are sterically similar. In effect, the CSP does not recognize them as being different and considers the analyte to be achiral. When a carbonyl oxygen is present, as in compound **3f**, a stronger hydrogen bond presumably causes closer association of the

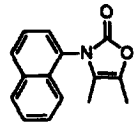
Table 1
Retention and separation factors for N-aryloxazolinones



1a
k_1'=10.06
k_2'=23.82
α=2.37



1b
k_1'=13.00
k_2'=33.47
α=2.57



1c
k_1'=14.18
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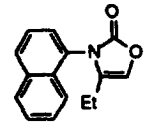
α=2.78



1d
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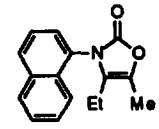
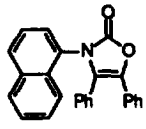
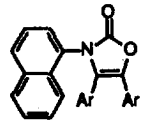
k_2'=34.06
α=2.74



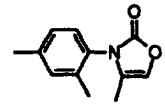
1e
k_1'=16.29
k_2'=51.35
α=3.15



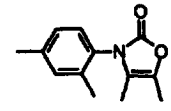
1f
k_1'=15.59
k_2'=58.29
α=3.74



1g
k_1'=4.06
k_2'=9.00
α=2.22



1h
k_1'=6.29
k_2'=14.18
α=2.25

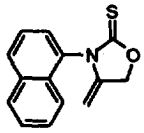


1i
k_1'=7.12
k_2'=17.12
α=2.40

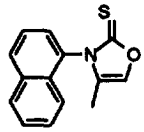
Ar = 

Mobile phase: 2-propanol–hexanes (20:80); flow-rate: 2 ml/min.

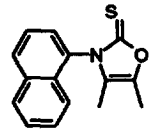
Table 2
Retention and separation factors for N-aryloxazolinethiones



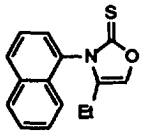
2a
k_1'=6.94
k_2'=9.41
α=1.36



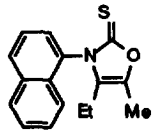
2b
k_1'=6.65
k_2'=9.00
α=1.35



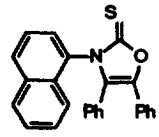
2c
k_1'=7.41
k_2'=10.94
α=1.48



2d
k_1'=7.12
k_2'=9.71
α=1.36



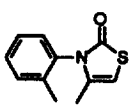
2e
k_1'=6.65
k_2'=10.00
α=1.50



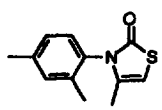
2f
k_1'=5.65
k_2'=9.24
α=1.64

Mobile phase: 2-propanol–hexanes (20:80); flow-rate: 2 ml/min.

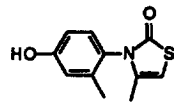
Table 3
Retention and separation factors for N-arylthiazolinones



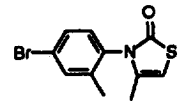
3a
k_1'=3.06
k_2'=6.76
α=2.21



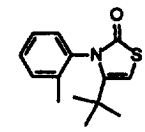
3b
k_1'=3.06
k_2'=7.59
α=2.48



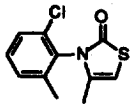
3c
k_1'=3.00
k_2'=10.29
α=3.43



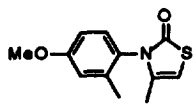
3d
k_1'=3.35
k_2'=10.71
α=3.20



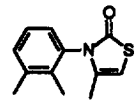
3e
k_1'=2.06
k_2'=8.94
α=4.34



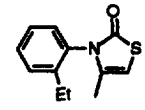
3f
k_1'=1.94
k_2'=2.18
α=1.12



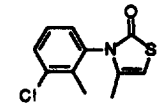
3g
k_1'=5.65
k_2'=20.53
α=3.63



3h
k_1'=2.41
k_2'=4.35
α=1.80



3i
k_1'=2.76
k_2'=5.24
α=1.90



3j
k_1'=3.12
k_2'=6.88
α=2.21

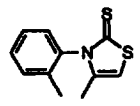
Mobile phase: 2-propanol–hexanes (20:80); flow-rate: 2 ml/min.

analyte with the CSP and a small amount of differentiation now occurs between the *o*-methyl of one enantiomer and the *o*-chlorine of the other.

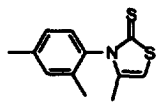
Note that this model relates the absolute configuration of the CSP and the elution order of the analytes. Specifically, the (*S,S*)-WHELK-O 1 is expected to preferentially retain the (*R*)-enantiomers of these analytes. When the vinyl substituent on the hetero ring is hydrogen or alkyl, the elution order is consistent as judged by the sign of the optical rotation at 589 nm. The dexrotatory enantiomers always elute first from the (*S,S*)-WHELK-O 1. Toward the conclusion of this study, a polarimeter capable of monitoring at six wavelengths (633, 589, 546, 435, 405 and 365 nm) became available and representative examples of these analytes were reexamined. As the enantiomers eluted, flow was stopped to hold the enantiomer in the flow cell for measurement of the relative magnitudes of rotation at the six wavelengths. These qualitative experiments afforded plain optical rotary dispersion (ORD) curves, the sign of rotation being the same at all six wavelengths, rotation increasing as the wavelength decreases. This same behavior was noted earlier by Roussel et al. for analytes of this type. By means of X-ray crystallography, the absolute configurations of compounds **3e** and **4e** have been assigned by Roussel and Chemlal as (+)-(*S*) [4]. Thus, a strong case can be made that all the analytes having hydrogen or alkyl vinyl substituents (except for possibly **3f** and **4f**) elute in the expected order, (*S*) before (*R*), from the (*S,S*)-WHELK-O 1. This behavior is to be contrasted to the varied elution orders noted for these compounds on triacetylcellulose columns. Indeed, elution order has been observed to be dependent on the size of the sample applied to a microcrystalline triacetylcellulose column [6], indicative of multiple types of binding sites.

When the vinyl substituents on the hetero ring are aromatic (**1f**, **1g** and **2f**), or when the hetero ring has a 4-methylene-substituent (**1a** and **2a**) the relationship between sign of rotation and elution order is altered. For such compounds in series **1**, the (−)-enantiomers elute first, while for such compounds in series **2**, the (+)-enantiomers elute first. We suspect that the chromatographic elution order of these compounds is unchanged and that the sign of rotation for the compounds in series **1** is sensitive to the substituents on the hetero ring. However, no proof of this can be offered since no rigorous configurational assignments are presently available for these atropisomers. In addition, no claim is made that the

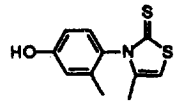
Table 4
Retention and separation factors for N-arylthiazolinethiones



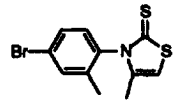
4a
k_1'=2.41
k_2'=4.00
α=1.66



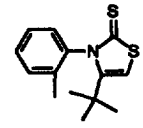
4b
k_1'=1.82
k_2'=3.18
α=1.75



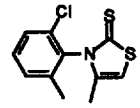
4c
k_1'=2.41
k_2'=6.29
α=2.61



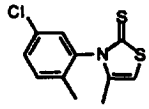
4d
k_1'=2.24
k_2'=4.53
α=2.02



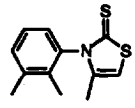
4e
k_1'=1.53
k_2'=2.82
α=1.84



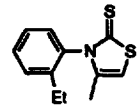
4f
k_1'=2.06
k_2'=2.06
α=1.00



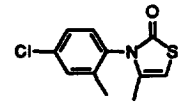
4g
k_1'=2.18
k_2'=3.18
α=1.46



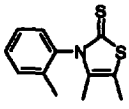
4h
k_1'=2.29
k_2'=4.12
α=1.80



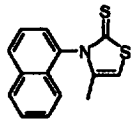
4i
k_1'=1.94
k_2'=3.59
α=1.85



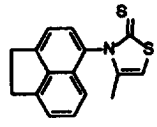
4j
k_1'=2.24
k_2'=3.24
α=1.45



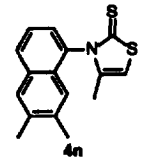
4k
k_1'=2.59
k_2'=4.41
α=1.70



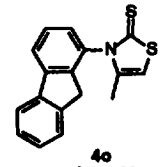
4l
k_1'=3.82
k_2'=6.18
α=1.62



4m
k_1'=4.12
k_2'=6.88
α=1.67



4n
k_1'=3.12
k_2'=7.47
α=2.39



4o
k_1'=4.00
k_2'=9.00
α=2.25

M

Mobile phase: 2-propanol–hexanes (20:80); flow-rate: 2 ml/min.

(*S*)-enantiomer of **3f** elutes first as this is presumably determined by how the selector differentiates between the methyl and chlorine substituents and this is not yet known [the (−)-enantiomer of **3f** elutes first].

Our chiral recognition model raises several other expectations. Because oxygen is a better hydrogen bond acceptor than sulfur, the compounds in series **2** and **4** would be expected to afford neither the retention nor the enantioselectivity of their counterparts in series **1** and **3**. Consistently, the thiono analogs afford less retention and smaller separation factors than the counterpart having a carbonyl oxygen. One also would expect that retention and enantioselectivity would increase as the π-basicity of the aryl substituent is increased, all other things being equal. Indeed, adding electron-donating groups to the aryl group does increase enantioselectivity.

The resolution factors (R_s) for these atropisomers on WHELK-O 1 are in the range of 1.14 for **3f** (not including **4f** which did not resolve) to 18.1 for **1e**. For the compounds in series **1**, the lowest R_s values are 10.5 and 10.6 for **1b** and **1h**, respectively, and the greatest R_s values are 14.5 and 18.1 for **1f** and **1e**, respectively. In series **2**, R_s values range from 2.92 and 3.36 for **2a** and **2b**, respectively, to 4.76 and 7.63 for **2c** and **2f**, respectively. In series **3**, R_s values range from 1.14 and 6.27 for **3f** and **3c**, respectively, to 14.6 and 16.3 for **3e** and **3g**, respec-

tively. In series **4**, R_s values range from 2.27 and 3.65 for **4j** and **4b**, respectively, to 10.0 and 14.0 for **4n** and **4o**, respectively.

4. Conclusion

The initially postulated chiral recognition mechanism is consistent with the experimental observations and may be of use in relating elution order to absolute configuration when analytes of these types are chromatographed on WHELK-O 1. The mechanistic model is but a first approximation and, while it indicates which sites in the CSP interact with which sites in the analytes, it does not give a detailed picture of their relative orientations. The model is being further tested and refined by NMR studies of analyte–selector mixtures.

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