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Facile and predictable means of separating the enantiomers of 5-arylhydantoins

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Abstract

The enantiomers of each member of a series of fifty-four 5-arylhydantoins of systematically varied structure are readily separated by high-performance liquid chromatography (HPLC) on CSP 1 (commercially available as the Whelk-O 1) and elute in a consistent order. The separation factors for these enantiomers of the hydantoins typically exceed two, thus rendering preparative scale separations facile. When used with subcritical carbon dioxide containing 10% methanol, enantioselectivity is reduced but resolution, R_s, increases. A chiral recognition mechanism accounting for these separations is presented. © 1997 Elsevier Science B.V.

Keywords: Enantiomer separation; Arylhydantoins; Hydantoins

1. Introduction

A number of hydantoins are pharmacologically active, several (e.g., Dilantin, Phenatoin) having been used as pharmaceuticals for some years. Since pharmacological activity is generally influenced by stereochemistry, a perceived need for enantiopure hydantoins has caused hydantoins to be used frequently as analytes in papers dealing with chromatographic enantioseparations. Indeed, several chiral stationary phases (CSPs) have been shown to be capable of separating the enantiomers of selected hydantoins. These CSPs include amino acid-derived synthetic CSPs [1,2], β- and γ-cyclodextrin phases [3,4], phases prepared by immobilizing Cinchona alkaloids [5] or macrocyclic antibiotics [6] and a synthetic CSP which takes advantage of solute–stationary phase base-pair interaction [7]. CSPs prepared from human plasma protein, α_1-acid glycoprotein [8], or polymers of (N^5-benzyl-L-glutamine) [9] also enable one to separate the enantiomers of some hydantoins. Additionally, two hydantoin-derived CSPs have been reported [10]. Typically, just the fact that separations of hydantoin enantiomers have been achieved is reported and little mention is made as to why or how the separations occur.

In general, chromatographic separation of enantiomers is regarded as a ''hit or miss'' proposition, something to be found by trial and error experiment. Although this is still often necessary, it is a regrettable situation which, hopefully, will someday change. Toward that end, we are involved in studies intended to put the chromatographic separation of enantiomers on a firmer mechanistic basis. We herein describe the chromatographic separation of the enantiomers of a series of hydantoins of systematically varied structure using the commercially available

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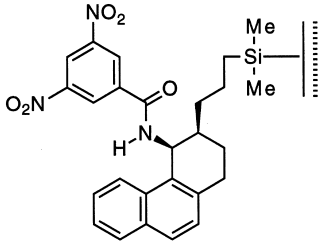
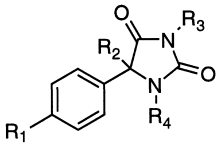
version of chiral stationary phase, CSP 1. The mechanistic explanation provided for the observed separations can be used to anticipate whether or not the enantiomers of a given hydantoin will be chromatographically separable on CSP 1 and to relate elution order to absolute configuration.



CSP 1



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2. Experimental

2.1. Apparatus

HPLC separations were performed using an Alcott Model 760 pump, a Rheodyne Model 7125 injector with a 20 μl sample loop, a Milton-Roy UV MonitorD (LDC Analytical, Riviera Beach, FL, USA) fixed-wavelength detector (254 nm) and a Hewlett-Packard HP 3394A integrating recorder. The brush-type HPLC column used in the study, the (3*R*,4*S*)-Whelk-O-1 (25×4.6 mm I.D., 5 μm spherical silica particles with 100 Å pore size), was obtained from Regis Technologies (Morton Grove, IL, USA). All HPLC experiments were carried out at a nominal flow-rate of 2.0 ml/min at ambient temperature. The void volume was determined by injection of 1,3,5-tri-*tert*.-butyl benzene. All chromatographic solvents were HPLC grade from EM Science. Subcritical fluid chromatography (SubFC) separations were carried out on a Hewlett-Packard G1205A SFC ChemStation (Avondale, PA, USA). The outlet pressure was maintained at 200 bar. The sign of optical rotation was measured by using a Autopol IV polarimeter (Rudolph Research, NJ, USA).

2.2. Materials

Substituted acetophenones and other alkylphenyl ketones were all obtained from Aldrich and were used without further purification as were the alkyl iodides. HPLC-grade solvents were graciously provided by EM Science. All the hydantoins were prepared as described [11]. Methylations and alkylations of the imide nitrogens also were carried out as described [12]. Methylations and alkylations of the amide nitrogens were accomplished by treating the 3-methylated (or alkylated) compound with potassium *tert*.-butoxide and then with methyl iodide or the appropriate alkyl halide.

3. Results and discussion

Prior papers have described the mechanistic rationale used to design CSP 1 and have, for several classes of compounds, demonstrated that this CSP functions as intended [13–15]. On mechanistic grounds, it was expected that the enantiomers of hydantoins having a π-basic substituent on (or near) the stereogenic center would be separable on CSP 1. For the preferentially retained enantiomer, this substituent, typically an aromatic group, is expected to fit into the cleft-like ''active site'' of the chiral selector owing to simultaneous face-to-face and face-to-edge π–π interactions. The adjacent carbonyl oxygen is expected to simultaneously hydrogen bond to the selector's amide hydrogen. The dihedral angle between the aryl substituent and the hydantoin ring will influence the ability of these interactions to occur simultaneously. Assuming typical bond angles at the sp^3 hybridized stereogenic center and that, for the sake of discussion, the planes of the two rings are roughly orthogonal, one expects the (*S*)-enantiomer of a 5-arylhydantoin to be preferentially retained on (3*R*,4*S*) CSP 1 (Fig. 1). As mentioned before, π–π face-to-face interaction is one of the key attractive interactions between the analyte and the selector. It was expected that different substituents on the aryl rings of these hydantoins would influence the

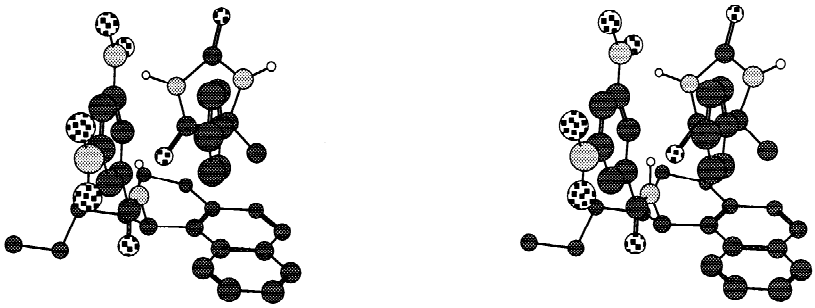


Fig. 1. Stereo view of the bimolecular complex of the *S* enantiomer of 5-methyl-5-phenylhydantoin and the chiral selector of CSP 1. Hydrogen atoms are omitted for clarity.

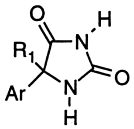
strengths of these aromatic–aromatic interactions and, consequently, there would be some correlation between the strengths of these π–π interactions and the degree of enantiodifferentiation. Since the mechanistic hypothesis does not require the hydantoin to bear hydrogen on either nitrogen, such hydrogens were regarded, a priori, as likely to contribute to hydrogen bonding interactions with the CSP which would tend to increase retention but decrease enantioselectivity [16].

An extensive series of hydantoins, 2, was prepared and chromatographed on a (3*R*,4*S*)-Whelk-O-1, the commercial version of CSP 1, using 2-propanol–hexane (20:80) as a mobile phase. This is not necessarily the best mobile phase to use in all cases, but was used to enable direct comparison of the effect of structural variation on the chromatographic properties of these hydantoins. An in-line polarimetric detector was used to relate the signs of the optical rotation at 365 nm to the elution order of the enantiomers. Tables 1–4 present the chromatographic data obtained from these HPLC studies. For each compound in these Tables, the (+)-enantiomer is preferentially retained on (3*R*,4*S*)-CSP 1.

Table 1 reports data obtained from a series of 5-arylhydantoins having hydrogen on the stereogenic center. The separation factors are modest, ranging between 1.16 and 1.54, but can be improved somewhat by reducing the amount of 2-propanol in the mobile phase relative to that shown in Table 1.

When the hydrogen on the stereogenic center is replaced by a methyl group (see Table 2), the retention factors of the (−) enantiomers are reduced and those of the preferentially retained (+) enantiomers are typically increased. Consequently, the separation factors for the enantiomers increase. The presumption is that the methyl group alters the rotational preference of the aryl substituent, more heavily populating the conformations better suited for enantiodiscrimination by CSP 1. Replacing the hydrogen by an ethyl group affords a further improvement in the separation factor. This compound, known as ethantoin, and its N-3-methyl derivative, methoin, have previously been assigned the (+)-(*S*) absolute configuration [17–19]. The sign of optical rotation of the (*S*)-enantiomer of its 1,3-N,N′-dimethylated derivative is also (+). This assignment follows from the observation that the enantiomers of an enantiomerically enriched sample of dimethylated compound prepared by the methylation of a sample

Table 1
HPLC enantioseparations of 5-arylhydantoins on CSP 1

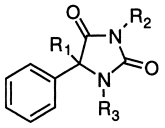


Ar	R_1	k_1'	α	R_s	Rot.
1-Naphthyl	H	1.80	1.54	1.46	+
Phenyl	H	1.15	1.20	0.61	+
4-Me-Phenyl	H	1.30	1.16	0.49	+
4-MeO-Phenyl	H	1.38	1.35	1.47	+
4-Cl-Phenyl	H	1.89	1.40	1.39	+
4-OH-Phenyl[a]	Et	0.54	3.63	8.67	+ (*S*)

Mobile phase: 2-propanol–hexane (20:80); k_1': retention factor of the less retained enantiomer; α: separation factor; R_s: resolution; Rot.: the sign of optical rotation at 365 nm for the more retained enantiomer.

[a] This compound was generously provided by Dr. Adrian Kuepfer.

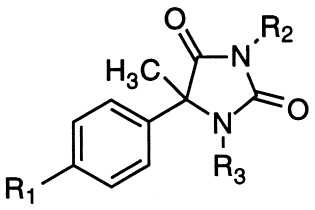
Table 2
HPLC enantioseparations of 5-alkyl-5-phenylhydantoins on CSP 1



R_1	R_2	R_3	k_1'	α	R_s	Rot.
Me	H	H	0.72	1.99	2.47	+
Me	Me	H	1.39	2.45	7.09	+
Me	Me	Me	3.83	3.41	9.54	+
Et	H	H	0.51	2.41	3.24	+ (*S*)
Et	Me	H	1.07	2.94	7.66	+
Et	Me	Me	3.08	4.83	19.9	+
iPr	H	H	0.45	3.02	5.18	+
iPr	Me	H	0.84	3.83	8.81	+
iPr	Me	Me	2.39	8.96	15.0	+
iBu	H	H	0.44	1.75	1.55	+
iBu	Me	H	0.79	1.99	4.02	+
iBu	Me	Me	1.98	2.56	6.19	+

Mobile phase: 2-propanol–hexane (20:80); k_1': retention factor of the less retained enantiomer; α: separation factor; R_s: resolution; Rot.: the sign of optical rotation at 365 nm for the more retained enantiomer.

Table 3
HPLC enantioseparations of 5-methyl-5-phenylhydantoins on CSP 1



R_1	R_2	R_3	k_1'	α	R_s	Rot.
H	H	H	0.72	1.99	2.47	+
H	Me	H	1.39	2.45	7.09	+
H	Me	Me	3.83	3.41	9.54	+
Me	H	H	0.73	2.34	3.57	+
Me	Me	H	1.45	2.99	8.89	+
Me	Me	Me	3.84	4.41	9.63	+
F	H	H	0.62	2.06	2.52	+
F	Me	H	1.17	2.52	4.90	+
F	Me	Me	3.59	3.40	8.72	+
Cl	H	H	0.62	2.61	4.45	+
Cl	Me	H	1.22	3.31	9.49	+
Cl	Me	Me	3.81	4.96	17.5	+
Br	H	H	0.66	2.82	4.35	+
Br	Me	H	1.31	3.58	9.43	+
Br	Me	Me	3.97	5.20	11.2	+
I	H	H	0.69	2.97	5.53	+
I	Me	H	1.41	3.90	10.3	+
I	Me	Me	4.29	5.80	13.1	+
NO_2	H	H	1.39	1.61	2.82	+
NO_2	Me	H	2.59	1.82	4.93	+
NO_2	Me	Me	8.60	2.27	6.51	+

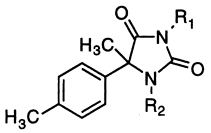
Mobile phase: 2-propanol–hexane (20:80); k_1': retention factor of the less retained enantiomer; α: separation factor; R_s: resolution; Rot.: the sign of optical rotation at 365 nm for the more retained enantiomer.

of methoin enriched in the (*S*)-enantiomer elute in the same order as those of the (*S*)-enriched methoin. These three 5-ethyl-5-phenylhydantoins serve to anchor the configurational assignments made in this paper. Additionally, the (*S*)-enantiomers of 5-ethyl-5-(4-hydroxyphenyl)hydantoin (See Table 1, the last entry) and 5-ethyl-3-methyl-5-(4-hydroxyphenyl)-hydantoin have also been found to be dextrorotatory [3]. Preferential retention of the (*S*)-enantiomer is expected from the aforementioned chiral recognition model and, with a single possible exception, discussed later, all of the hydantoins studied appear to conform to this model.

Table 2 shows the chromatographic consequences of changing the structure of the 5-alkyl group on 5-phenylhydantoin and its two N-methylated derivatives. Initially, larger 5-alkyl substituents decrease the retention of the (*R*)-enantiomers and increase the retention of the (*S*)-enantiomers, a separation factor of almost nine being observed for the 5-isopropyl N,N′-dimethyl analog. However, the 5-isobutyl substituent breaks the trend although the separation of these enantiomers is still quite easy. Presently, one can but speculate on the adverse effect on selectivity caused by the isobutyl group. Most likely, the greater size of this group either changes the conformational preference of the adjacent phenyl group or sterically alters the orientation of the (*S*)-enantiomer in the cleft of the selector.

To test the hypothesis that the two N–Hs detract from the enantiodifferentiation processes by participating in unwanted ‘‘achiral’’ retention processes, these hydrogens were replaced sequentially with methyl groups for a series of 5-aryl-5-methylhydantoins. The imide nitrogens are readily methylated while subsequent methylation of the amide nitrogens

Table 4
HPLC enantioseparations of 5-methyl-5-(4′-methylphenyl)hydantoins on CSP 1



R_1	R_2	k_1'	α	R_s
Me	H	1.45	2.99	8.89
Et	H	0.97	2.64	7.33
nPr	H	0.88	2.74	7.21
nBu	H	0.84	2.73	6.56
nPent	H	0.80	2.56	6.07
nHex	H	0.76	2.50	5.87
nHep	H	0.75	2.39	5.55
nOct	H	0.78	2.28	4.32
Me	Me	3.84	4.41	9.63
Me	Et	2.85	4.92	16.5
Me	nPr	2.25	6.31	10.8
Me	nBu	2.09	7.16	9.61
Me	nPent	2.17	7.37	15.6
Me	nHex	2.10	7.45	11.5
Me	nHep	2.00	7.71	25.3
Me	nOct	1.91	8.03	37.7

Mobile phase: 2-propanol–hexane (20:80); k_1': retention factor of the less retained enantiomer; α: separation factor; R_s: resolution.

requires more severe conditions (see Section 2). These data are also presented in Tables 2 and 3 in a format which makes it easy to see the chromatographic consequences of each methylation. Enantioselectivity is increased by these methylations as is retention. The former was expected on the grounds given before and because methylation of the imide nitrogen presumably makes the 4-carbonyl oxygen a better hydrogen bond donor, thus strengthening one of the interactions essential to chiral recognition. Methylation of the imide and amide nitrogens may have some beneficial conformational impact on the 5-aryl substituent, owing to a buttressing effect. As a matter of fact, crystal structures indicate that the dihedral angle between the phenyl ring and the heterocycle for methoin (77°) is increased by methylation at the imide nitrogen of ethantoin (60°) [18].

The increase in retention which accompanies N-methylation can be attributed, in part, to reduced solvation by the 2-propanol in the mobile phase. The two N–Hs are capable of hydrogen bonding to the 2-propanol and to the stationary phase as well. These hydrogen bonds are not possible once the N–Hs are replaced by methyl groups. N-Methylation also improves the resolution, R_s, partly through the increase in selectivity but mainly because of improved band shapes, also attributable to the loss of the aforementioned hydrogen bonds.

Note that contrary to ones intuition, the electronegative halogen substituents increase enantioselectivity, the effects being greater for the more polarizable halogens (see Table 3). Similar effects are noted for other classes of enantiomers in which the hydrogen bond donor is sufficiently far from the halogen-substituted aryl group to be insulated from the inductive effect of the halogen [20]. If not so insulated, enantioselectivity suffers. Although one may not often wish to resolve halogenated hydantoins, an understanding of the principles by which halogen substituents give rise to enhanced levels of enantioselectivity can profitably be used in the design of chiral selectors and chiral catalysts.

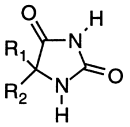
Table 4 shows the chromatographic consequences of systematically varying the length of each of the N-alkyl groups on 5-methyl-5-(4-methylphenyl)-hydantoin. This was done so as to ascertain whether intercalation effects [21] would be observed for this series of analytes. Such effects are mechanistically informative and can be used to good effect in the design of reciprocal CSPs [22]. Increasing the length of the N-alkyl substituent on the imide nitrogen reduces the retention of both enantiomers of each analyte in the series and progressively reduces separation factors as well. However, increasing the length of the N-alkyl substituent on the amide nitrogen of 1-N-methyl-5-methyl-5-(4-methylphenyl)-hydantoin leads to reduction of the retention of the (*R*)-enantiomer of each member of the series but increases the separation factors of the enantiomers. These two trends are typical of analyte–CSP combinations in which the necessarily different orientations of the two analyte enantiomers during interaction with the CSP causes different portions of each enantiomer to interact sterically with either the underlying silica support or one or more of the neighboring strands of bonded phase [21].

One might suppose, were it deemed desirable to design a hydantoin which would show a even higher level of enantiodifferentiation on CSP 1, that 1-N-octyl-3-N-methyl-5-isopropyl-5-(4-iodophenyl)hydantoin would achieve this goal. This assumes that

the various structural subunits contribute more or less independently to the overall chiral recognition processes. Rigorously, this need not be the case, for the size of the 1-N-alkyl substituent might influence the conformation of the adjacent isopropyl group which might, in turn, influence the conformation of the 5-(4-iodophenyl) substituent. This hydantoin, not yet prepared, would be expected to be a close analog of a likely candidate for incorporation into a reciprocal CSP capable of resolving the selector used in CSP 1. However, 1, 3-N,N′-dimethyl-5-isopropyl-5-(4-iodophenyl)hydantoin has been prepared and its enantiomers show an α of 18.2 on CSP 1 at 25°C [$k_1' = 2.14$, 2-propanol–hexane (20:80), 2.0 ml/min]. This separation factor is increased to 28.9 by reducing the temperature of the column to 0°C ($k_1' = 3.42$). Such large separation factors are not needed for analytical separations but would make feasible the preparative resolution of a racemate by batch adsorption techniques or by hollow-fiber membrane methods [23].

Table 5 illustrates the chromatographic behavior of four hydantoins which deviate somewhat from the general structure of the hydantoins in Tables 1–4. Two of these have two aromatic groups on the stereogenic center. This would be expected to reduce the ability of CSP-1 to differentiate between the enantiomers. Indeed, it does. In the case of 5-(4-methylphenyl)-5-phenylhydantoin, the preferentially retained enantiomer is levorotatory. However, the relationship between absolute configuration and sign of rotation has not been established and the (*S*)-enantiomer may be retained preferentially on the column. That is, the change of the sign of optical rotation in this case does not necessarily indicate an inversion of the usual elution order [17]. One expects the 5-(4-methylphenyl) group to be a better π-base [20] than the 5-phenyl and consequently to associate with the DNB group of the chiral selector more strongly than the phenyl group. If so, the (*S*)-enantiomer would be expected to be preferentially retained. The remaining two entries show the consequences of increased distance between the aryl substituent and

Table 5
HPLC enantioseparations of 5-arylhydantoins on CSP 1

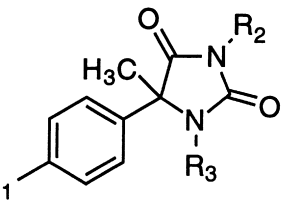


R_1	R_2	k_1'	α	R_s	Rot.
4-OH-Phenyl	Phenyl	8.81	1.00	0.00	−
4-Me-Phenyl	Phenyl	2.28	1.04	0.45	−
Styrenyl	Me	1.76	1.43	2.28	+
Benzyl	Me	1.92	1.16	1.56	+

Mobile phase: 2-propanol–hexane (5:95); k_1': retention factor of the less retained enantiomer; α: separation factor; R_s: resolution; Rot.: the sign of optical rotation at 365 nm for the more retained enantiomer.

These compounds were generously provided by Dr. Adrian Kuepfer.

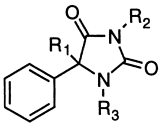
Table 6
SubFC enantioseparations of 5-methyl-5-phenylhydantoins on CSP 1



R_1	R_2	R_3	k_1'	α	R_s
H	H	H	1.75	1.45	6.09
H	Me	H	1.24	1.62	7.18
H	Me	Me	0.98	2.19	11.5
Me	H	H	1.36	1.47	3.95
Me	Me	H	1.34	1.85	9.82
Me	Me	Me	1.06	2.55	13.2
F	H	H	1.36	1.47	6.19
F	Me	H	0.89	1.67	6.41
F	Me	Me	0.76	2.21	10.0
Cl	H	H	1.90	1.69	9.15
Cl	Me	H	1.33	1.98	10.3
Cl	Me	Me	1.09	2.85	16.8
Br	H	H	2.26	1.76	10.7
Br	Me	H	1.63	2.06	12.8
Br	Me	Me	1.28	2.98	17.8
I	H	H	2.93	1.81	11.9
I	Me	H	2.09	2.14	14.6
I	Me	Me	1.75	3.13	21.4
NO_2	H	H	2.67	1.27	4.80
NO_2	Me	H	1.71	1.37	5.00
NO_2	Me	Me	1.52	1.65	8.48

Mobile phase: methanol–carbon dioxide (10:90); k_1': retention factor of the less retained enantiomer; α: separation factor; R_s: resolution.

Table 7
SubFC enantioseparations of 5-alkyl-5-phenylhydantoins on CSP 1



R_1	R_2	R_3	k_1'	α	R_s
Me	H	H	1.75	1.45	6.09
Me	Me	H	1.24	1.62	7.18
Me	Me	Me	0.98	2.19	11.5
Et	H	H	1.66	1.65	8.26
Et	Me	H	1.19	1.84	8.90
Et	Me	Me	0.91	2.97	16.2
iPr	H	H	1.41	2.07	11.5
iPr	Me	H	1.00	2.38	12.5
iPr	Me	Me	0.91	4.76	23.8
iBu	H	H	1.45	1.39	5.59
iBu	Me	H	1.01	1.46	4.76
iBu	Me	Me	0.81	1.70	6.00

Mobile phase: methanol–carbon dioxide (10:90); k_1': retention factor of the less retained enantiomer; α: separation factor; R_s: resolution.

the stereogenic center. Typically, one expects this to reduce enantioselectivity and this is what is observed.

CSP 1 is now routinely being used with sub/supercritical CO_2 mobile phases [24,25]. Tables 6 and 7 show data obtained by chromatographing the various hydantoins at 29°C using 10% methanol in CO_2 on CSP 1. The separation factors are somewhat reduced but the resolution values, R_s, are typically larger than those reported in the other Tables. This is partly attributed to the ability of methanol to increase both the extent of solvation of the analytes and stationary phase and to increase the rates of analyte desorption from the stationary phase. The former reduces selectivity by increasing enantioselective desolvation (of the preferentially retained enantiomer) on analyte adsorption and the latter improves band shapes.

4. Conclusions

CSP-1 shows broad applicability in the separation of the enantiomers of hydantoins bearing π-basic substituents on the stereogenic center. A wide variety of other substituents can be present without causing loss of the resolution capability. A mechanistic explanation has been advanced to account for the origin and stereochemical sense of the observed enantiodifferentiation.

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