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# Chiral Separations of Ibuprofen and Propranolol by TLC. A Study of the Mechanism and Thermodynamics of Retention

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**Abstract:** In contrast with gas and column liquid chromatography, both of which enable very efficient separation of enantiomers, thin-layer chromatography (TLC) has never proved particularly successful in the same field. This can be regarded as puzzling because although the performance of TLC is substantially lower than that of the instrumental modes of chromatography, it still seems efficient enough to ensure even difficult separations of pairs of analytes. There is a steady demand for simple, inexpensive, and successful chiral separations, preferably executed with the aid of TLC. The best proof of this is a few documented and promising attempts reported by reliable laboratories in developing countries. Some of these reports, however, describe experiments performed with glass plates coated in the laboratory, which gives rise to questions regarding the accuracy and repeatability of the results obtained. Similar concerns are evoked by traditional visualization of the outcome of a separation by use of dyeing agents, rather than by densitometry (which furnishes concentration profiles of the bands and the possibility of in-situ identification also). In this study, we have repeated chiral separations of two widely used drugs, ibuprofen and propranolol, adapting working conditions reported elsewhere to a system based on standardized and commercially available chromatographic plates. We also performed detection and identification on the developed chromatograms by means of densitometry. In our experiments with the modified chromatographic procedures, the results obtained proved at least as good as those reported in the original papers and occasionally somewhat better. For both ibuprofen and propranolol, preliminary thermodynamic evaluation of the standard chemical potentials of adsorption ($\Delta\mu_a$) for each of the two enantiomers considered was also performed. The results obtained look promising and

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realistic; it seems that adsorption TLC can be used in the future for thermodynamic assessment of the racemization process.

**Keywords:** TLC, Silica gel sorbent, L-Arginine impregnation, Enantiomer separations, *S*-(+)- and *R*-(−)-ibuprofen, *S*-(−)- and *R*-(+)-propranolol

## INTRODUCTION

Chiral separations are among the most demanding and challenging experimental tasks in the separation sciences, and for this particular purpose gas chromatography (GC) and column liquid chromatography (LC) are both employed. Planar chromatography, however, is used much less frequently than its column liquid counterpart because of its relatively poorer separation performance compared to the column mode. Thin layer chromatography (TLC) is, on the other hand, an invaluable tool in multiple pharmaceutical analyses and in pharmaceutical quality control, and chirality is commonplace among drugs. Even these superficial considerations readily lead to the simple yet sound conclusion that more effort—both theoretical and practical—ought to be invested in adapting planar chromatography for successful handling of enantiomer separations.

The objective of the work described in this paper was to modify procedures described elsewhere,[1,2] that enabled the chiral separation of the enantiomers of ibuprofen and propranolol on laboratory-prepared TLC plates to contemporary practice of using commercial precoated glass plates and densitometric detection. The mechanisms of retention and energetics of the two separations are discussed.

## EXPERIMENTAL

### Chiral Separation of Ibuprofen

#### Test Analytes

Our experiment was performed with two different test analytes: *R, S*-(±)-ibuprofen and *S*-(+)-ibuprofen (Sigma–Aldrich, St Louis, MO, USA; cat. #I-4883 and #I-106, respectively). Solutions of *R, S*-(±)-ibuprofen and of the *S*-(+) enantiomer were prepared at a concentration of $1\,\mu g\,\mu L^{-1}$ (ca. $5.8 \times 10^{-3}\,mol\,L^{-1}$) in 70% ethanol, and 10-μL volumes were applied to the plates, side-by-side. The *R, S*-(±)-ibuprofen sample contained two antipodes, which we intended to separate effectively. The sample of *S*-(+)-ibuprofen was meant as an external standard, marking the position of one antipode. Because *R*-(−)-ibuprofen is no longer commercially available there was virtually no chance of using a second external standard. The

chemical structures of the two ibuprofen enantiomers separated in this experiment are presented in Figure 1.

## Commercial TLC Silica Gel Layers and Their Pretreatment

We used commercial glass TLC plates precoated with 0.25 mm layers of silica gel 60 $F_{254}$ (Merck, Darmstadt, Germany; cat. #1.05715). Before use, the plates were washed by predevelopment with methanol–water, 9 : 1 (v/v) and then dried at ambient temperature for 3 h. Washing of the plates before initiating more sensitive separations is often recommended by the manufacturer.

The washed and dried plates were then impregnated with a $3 \times 10^{-2}$ mol $L^{-1}$ solution of L-arginine in methanol by conventional dipping. This procedure was different from that used in the original paper,[1] which consisted of direct addition of L-arginine to the silica gel slurry before coating of the glass plates. The concentration of the impregnating solution was calculated to deposit on the adsorbent layer the same amount of amino acid as previously reported.[1]

## One-Dimensional Development

The impregnated chromatographic plates with adjacent spots from 10 μL volumes of the solutions of *R, S*-(±)-ibuprofen and the *S*-(+) enantiomer were developed to a distance of 15 cm using the ternary mobile phase recommended in the original paper [1], i.e., acetonitrile (ACN)–methanol

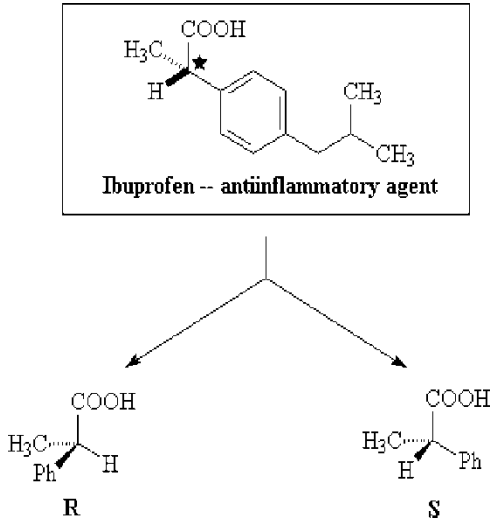


***Figure 1.*** General structure of ibuprofen and demonstration of its chirality.

(MeOH)–$H_2O$ (5 : 1 : 1) plus several drops of acetic acid to adjust the pH to 4.8. After development, the plates were dried in an ambient atmosphere for 3 h and the two lanes—one for *R, S*-(±)-ibuprofen and the other for the *S*-(+) counterpart—were scanned densitometrically. The results obtained (as $R_F$ values) are given in Table 1. This experiment was repeated at least five times.

### Two-Dimensional Development

Plates with a single 10 μL spot of the *R, S*-(±)-ibuprofen solution at the corner were developed to a distance of 15 cm in the first direction with ACN–MeOH–$H_2O$ (5 : 1 : 1) plus several drops of acetic acid as the mobile phase. The plates were then dried in an ambient atmosphere for 3 h, and 10 μL of the solution of the *S*-(+) enantiomer was applied to the origin of the second direction of development, adjacent to the first, already developed, sample. The chromatograms were developed to a distance of 15 cm in the second direction (perpendicular to the first) with the same mobile phase. After development, the plates were again dried in an ambient atmosphere, and the developed lanes were scanned densitometrically. This experiment was repeated at least five times.

### Densitometric Assessment of Separation Performance for S-(+)- and R-(−)-Ibuprofen

The separation of the two ibuprofen enantiomers (as measured by the numerical values of the retardation factor, $R_F$) was evaluated by densitometry. Densitograms were acquired with a Desaga (Heidelberg, Germany) model CD 60 densitometer equipped with Windows-compatible ProQuant software. Concentration profiles of the developed lanes were recorded in ultraviolet (UV) light from the deuterium lamp (in the reflectance mode) at 210 nm. This wavelength corresponded fairly well with the more pronounced maximum of the two in the UV spectrum of ibuprofen. The dimensions of the rectangular light beam were 0.02 mm × 0.4 mm. The maxima of the

***Table 1.*** Numerical values of $\Delta\mu_a$ estimated for *S*-(+)- and *R*-(−)-ibuprofen chromatographed on silica gel with ACN–MeOH–$H_2O$ (5 : 1 : 1) adjusted to pH 4.8 by addition of a trace amount of acetic acid as the mobile phase

| Development direction | Enantiomer | $R_F$ | $\Delta\mu_a$ (kJ mol$^{-1}$) | $\Delta\Delta\mu_a$ (kJ mol$^{-1}$) |
|---|---|---|---|---|
| First | *S*-(+) | 0.82 | −1.9 | 0.4 |
| | *R*-(−) | 0.79 | −2.3 | |
| Second | *S*-(+) | 0.83 | −1.7 | 1.1 |
| | *R*-(−) | 0.76 | −2.8 | |

separated concentration profiles of the two species were used for calculation of $R_F$ values.

As well as recording the densitograms and calculating $R_F$ and $\Delta R_F$ values to produce evidence of improved enantioseparation, the densitometer was also used to record UV absorption spectra of the separated chromatographic bands directly from the plates (i.e., in situ). It was intended to use these spectra as direct proof of satisfactory separation, because one expects identical UV absorption spectra from any two enantiomers making a pair of antipodes.

## Chiral Separation of Propranolol

### Test Analyte

This part of our experiment was performed with *R, S*-(±)-propranolol (Astra Hässle, Molndal, Sweden; cat. #1393) as the test analyte. A solution of *R, S*-(±)-propranolol was prepared at a concentration of $1\,\mu g\,\mu L^{-1}$ (ca. $3.3 \times 10^{-3}\,mol\,L^{-1}$) in 70% ethanol, and 10 μL volumes were applied to the plates (this was our normal solution). Because the amount of the *S*-(−) enantiomer in this mixture was very low (ca 5%), we also prepared a three times more concentrated (i.e., fortified) solution of the same sample ($1 \times 10^{-2}\,mol\,L^{-1}$; applied to the plate as 10 μL volumes). The fortified solution contained a substantial concentration overload of *R*-(+)-propranolol (resulting in a characteristic triangular peak shape), but the larger amount of the *S*-(−) antipode facilitated monitoring of the separation process. The chemical structures of the two propranolol enantiomers separated in this experiment are presented in Figure 2.

### Commercial TLC Silica Gel Layers and Their Pretreatment

For separation of the two enantiomers of propranolol, the same commercially available TLC silica gel layers as described above for ibuprofen were used. Their further modification (i.e., predevelopment with the methanol–water mixture and then impregnation with a solution of $3 \times 10^{-2}\,mol\,L^{-1}$ L-arginine in methanol) was also different from that described in the original paper,[2] although the same as described above for ibuprofen.

### One-Dimensional Development

Chromatographic plates with spots from 1 μL volumes of the normal and fortified solutions of *R, S*-(±)-propranolol were developed to a distance of 15 cm with the binary mobile phase recommended in the original paper,[2] i.e., ACN-MeOH (15 : 4) containing strictly controlled and relatively small amounts of aqueous ammonia ($NH_3 \cdot H_2O$), namely 0, 50, 100, 300, 400, 500, and 1000 μL. Apart from investigating the chiral separation itself, the impact of the amount of an added ammonia on the overall enantiomer separ-

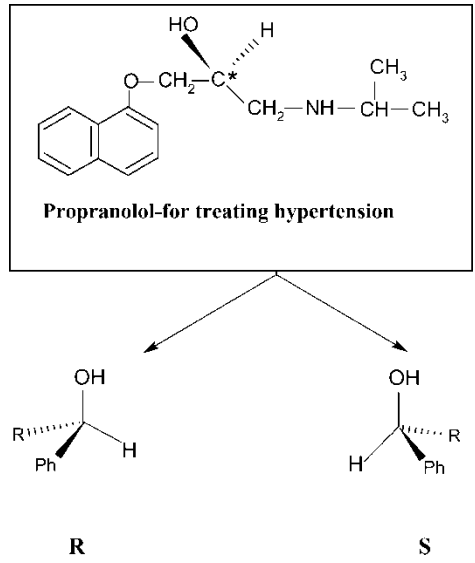


***Figure 2.*** General structure of propranolol and demonstration of its chirality.

ation procedure was also investigated. The results obtained (as $R_F$ values) and their dependence on the amount of ammonia added and on mobile phase pH are given in Table 2. This experiment was repeated at least five times.

Two-Dimensional Development

Plates with a single 10 μL spot of *R, S*-(±)-propranolol solution at the corner were developed to a distance of 15 cm in the first direction, with ACN–MeOH

***Table 2.*** Numerical values of $\Delta\mu_a$ estimated for *S*-(−)- and *R*-(+)-propranolol chromatographed in the first direction on silica gel with ACN–MeOH (15 : 4) containing trace amounts of aqueous ammonia as the mobile phase

| Mobile phase | | $R_F$ (±0.02) | | $\Delta\mu_a$ (kJ mol$^{-1}$) | | |
|---|---|---|---|---|---|---|
| Volume of $NH_3 \cdot H_2O$ (μL) | pH | *S*-(−) | *R*-(+) | *S*-(−) | *R*-(+) | $\Delta\Delta\mu_a$ (kJ mol$^{-1}$) |
| 0 | 7.75 | 0.01 | 0.11 | −16.9 | −10.8 | 6.1 |
| 50 | 10.2 | 0.02 | 0.12 | −15.2 | −10.5 | 4.7 |
| 100 | 10.7 | 0.02 | 0.12 | −15.2 | −10.5 | 4.7 |
| 300 | 10.8 | 0.03 | 0.14 | −14.2 | −10.1 | 4.1 |
| 400 | 10.9 | 0.04 | 0.16 | −13.4 | −9.7 | 3.7 |
| 500 | 10.9 | 0.03 | 0.16 | −14.2 | −9.7 | 4.5 |
| 1000 | 11.0 | 0.02 | 0.18 | −15.2 | −9.4 | 5.8 |

(15 : 4) plus 400 μL aqueous ammonia as the mobile phase. The plates were dried in an ambient atmosphere for 3 h and the chromatograms were again developed to a distance of 15 cm in the second direction (perpendicular to the first) with the same mobile phase. After development, the plates were dried for the second time in an ambient atmosphere, and the developed lanes were scanned densitometrically. This experiment was repeated at least five times.

Densitometric Assessment of Separation Performance for S-(−)- and R-(+)-Propranolol

The procedure was analogous to that described above for ibuprofen. Concentration profiles of the developed chromatograms were recorded at 210 nm, which corresponded fairly well with the wavelength of the more pronounced maximum in the UV spectrum of propranolol.

## RESULTS AND DISCUSSION

### Chiral Separation of Ibuprofen

Densitometric Profiles of the Developed Lanes

A typical densitogram obtained from one-dimensional development is given in Figure 3. On this densitogram, the positions of *S*-(+)-ibuprofen and its *R*-(−) antipode are clearly marked.

After numerous replicate one-dimensional developments, we evaluated the mean retardation factors ($R_F$) of the two enantiomers and, from the areas under the respective concentration profiles, the relative proportions of the enantiomers. The mean $R_F$ values were 0.82 (±0.02) for *S*-(+)-ibuprofen and 0.79 (± 0.02) for its *R*-(−) counterpart. This result is in agreement with data reported elsewhere[1] (the $R_F$ values for twice-developed *S*-(+)- and *R*-(−)-ibuprofen were reported to be 0.80 and 0.77, respectively). Quantitative analysis (i.e., estimation from relative areas) showed our (±) mixture to contain approximately 10% *R*-(−)-ibuprofen, in agreement with literature reports of the enantiomeric composition of the commercial form of this drug (i.e. of *R, S*-(±)-ibuprofen).

Densitometry, after development in the second direction, enabled further assessment of the resolution of the two ibuprofen antipodes. The respective mean $R_F$ values were 0.83 (±0.02) for *S*-(+)-ibuprofen and 0.76 (±0.02) for its *R*-(−) counterpart. After the two-dimensional development, resolution of the two antipodes was enhanced to $\Delta R_F = 0.07$.

To obtain better insight into the substantially enhanced chiral separation of *S*-(+)-ibuprofen from its *R*-(−) counterpart (compared with that obtained by Bhushan and Parshad[1]) and into the "skewed" arrangement of the two

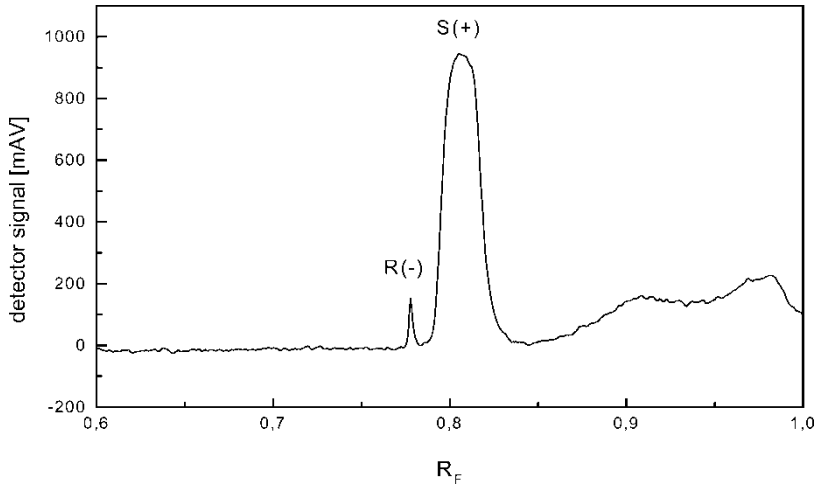


***Figure 3.*** Typical densitogram obtained from one-dimensional development, with the positions of the *S*-(+) and *R*-(−) antipodes of ibuprofen marked.

species on the chromatographic plate, the three-dimensional (3D) presentation of part of the TLC plate with the two development directions indicated (as 1 and 2) is given in Figure 4. This illustration was obtained by densitometric scanning (in parallel 1-mm intervals) of the 15-mm wide track in the second direction of development of the chromatogram.

## Densitometric UV In Situ Identification of Separated S-(+)- and R-(−)-Ibuprofen

The most persuasive proof of successful separation of the two enantiomers is in situ identification of the resolved chromatographic bands, e.g., by acquiring their UV absorption spectra. In such circumstances, one can justifiably expect two identical spectra. The identical UV absorption spectra of the two chromatographic bands marked in Figure 3 as *S*-(+)- and *R*-(−)-ibuprofen are illustrated in Figure 5 by the single spectrum of *R*-(−)-ibuprofen (i.e., the antipode with the lower abundance in the racemic mixture investigated and, hence, considerably more challenging to record).

The UV spectrum shown in Figure 5 is identical with that of *S*-(+)-ibuprofen (the only difference between the two is the different intensity of the absorption bands, because of the different amounts of the two separated species on the adsorbent layer). It was, thus, clearly proven that the two resolved chromatographic bands are of two enantiomers present in different quantitative proportions and yet with identical chemical structure (except for the spatial arrangement of the substituents around the asymmetric carbon atom). This result provides up-to-date instrumental confirmation of successful complete TLC separation of the two ibuprofen antipodes.

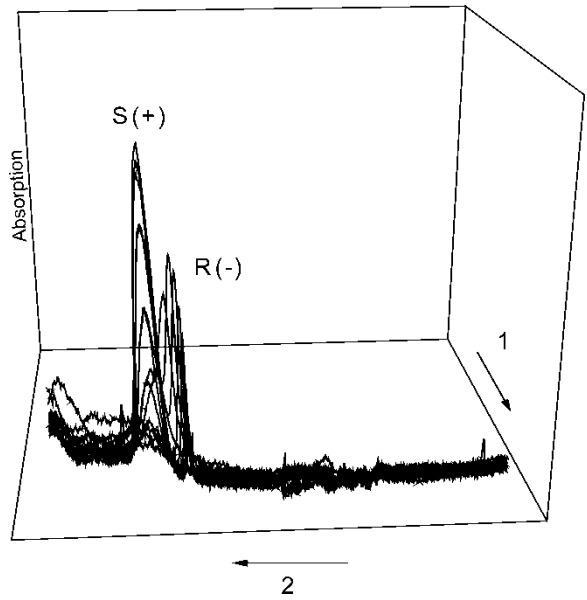


***Figure 4.*** 3D representation of part of the TLC plate with the two directions of development, 1 and 2, indicated. Densitometric scanning as described in the text was performed to illustrate better the separation performance and the "skewed" arrangement of *S*-(+)-ibuprofen relative to its *R*-(−) counterpart.

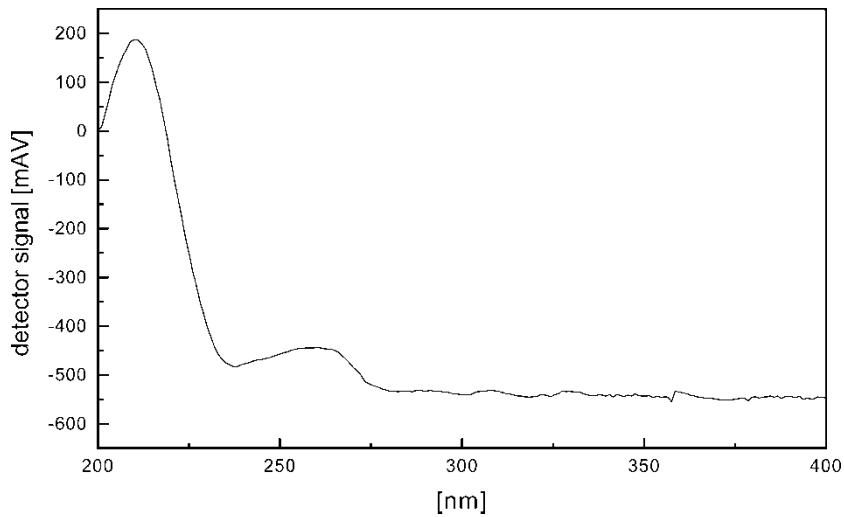


***Figure 5.*** The in situ UV spectrum of the chromatographic band of *R*-(−)-ibuprofen measured from the chromatogram densitometrically recorded and shown in Figure 3.

On the Mechanism and Thermodynamics of the Chiral Separation of Ibuprofen

Trace amounts of acetic acid were added to the ternary mobile phase to maintain its pH at the solid-liquid interface at 4.8, i.e., well below the p*I* (isoelectric) point of L-arginine (10.8), thereby maintaining the impregnating amino acid in the cationic form. Because ibuprofen is a carboxylic acid (Figure 1) and, therefore, apt to dissociate (and form an organic anion), the mechanism of chiral discrimination in the system discussed can generally be viewed in terms of the energy difference for ion-pair formation (i.e., in the formation of the two diastereomeric salts) according to the scheme:

$$\text{L-arginine}^{(\text{cation})} + \text{S-(+)-ibuprofen}^{(\text{anion})} \leftrightarrow \text{ion pair (thermodynamically characterized by } K_1) \quad (1)$$

$$\text{L-arginine}^{(\text{cation})} + \text{R-(−)-ibuprofen}^{(\text{anion})} \leftrightarrow \text{ion pair (thermodynamically characterized by } K_2) \quad (2)$$

Separation of the two enantiomers of ibuprofen can be achieved only because the thermodynamic equilibrium constants ($K$) for the ion-pair-formation process for the two enantiomers ($K_1$ and $K_2$, respectively) have different numerical values ($K_1 \neq K_2$).

From the theory of adsorption liquid chromatography it is well known[3] that the thermodynamic equilibrium constant of adsorption, $K$, can be defined as:

$$\log K = -\Delta\mu_a/(2.303RT) \quad (1)$$

where $\Delta\mu_a$ is the standard chemical potential for adsorption of the analyte on the adsorbent surface, $R$ is the universal gas constant, and $T$ is the temperature of the experiment. From the chromatographic results (i.e., $R_F$ values) obtained for the two ibuprofen enantiomers and keeping in mind another fundamental relationship of adsorption liquid chromatography,[3] namely:

$$R_F = 1/(1 + K\phi) \quad (2)$$

where $\phi$ is the so-called phase ratio (i.e., the ratio of the volume of the adsorbed mobile phase to the volume of the flowing mobile phase), we estimated the thermodynamic magnitudes of $\Delta\mu_a$ for *S*-(+)- and *R*-(−)-ibuprofen; these are given in Table 1. In our calculation, we assumed $\phi$ is approximately equal to 0.1; $T$ was measured as 295°K.

From the numerical values of $\Delta\mu_a$ given in Table 1 it is clearly evident that the affinity of *R*-(−)-ibuprofen for the adsorbent layer is considerably greater than that of its enantiomeric antipode. This readily apparent difference between the standard chemical potentials of adsorption of the two antipodes is evidently because of their different ability to form ion pairs, although the energetics of ion-pair formation and the energetics of adsorption of ibuprofen's

phenyl ring on active sites of silica both contribute to the numerical value of $\Delta\mu_a$. The next step ought to be measurement of the enthalpy and entropy of partitioning of the two ibuprofen antipodes in the chromatographic system applied and drawing of the relevant conclusions from the results obtained.

## Chiral Separation of Propranolol

### Densitometric Profiles of the Developed Lanes

A typical densitogram obtained from one-dimensional development of the normal solution of the enantiomers mixture is given in Figure 6. On this densitogram the positions of *S*-(−)-propranolol and its *R*-(+)-antipode are clearly marked.

To obtain a better densitometric picture of the less abundant enantiomer, we chromatographed a fortified sample of the enantiomer mixture. This resulted in evident overload of the *R*-(+) enantiomer (confirmed by the triangular shape of the overloaded chromatographic band) and a nicely formed concentration profile of *S*-(−)-propranolol. This chromatogram was also evaluated densitometrically; the densitogram is shown in Figure 7.

To gain better insight into the enhanced chiral separation of *S*-(−)-propranolol from its *R*-(+) counterpart and into the "skewed" arrangement of

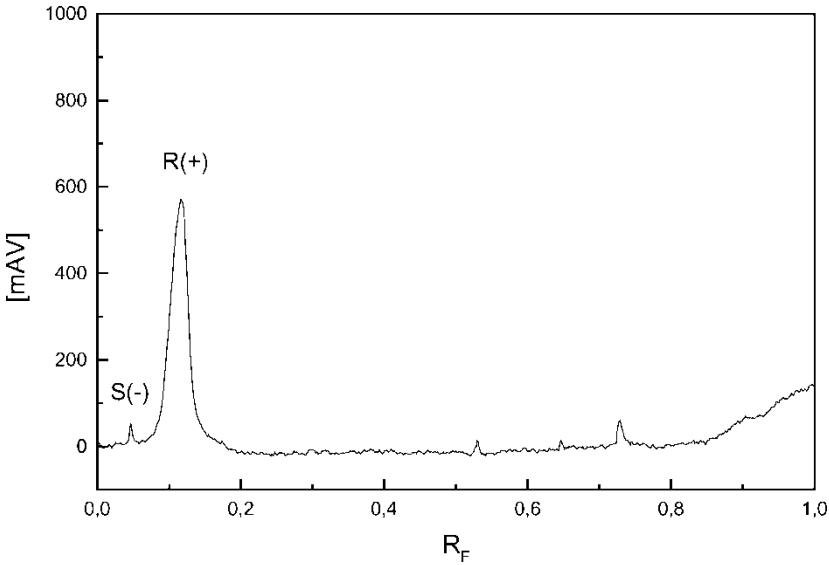


***Figure 6.*** Typical densitogram obtained from one-dimensional development with the positions of the *S*-(−) and *R*-(+) antipodes of propranolol marked. The normal solution of the enantiomer mixture was used as the test solution and ACN–MeOH (15 : 4) plus 400 μL of aqueous ammonia was used as the mobile phase.

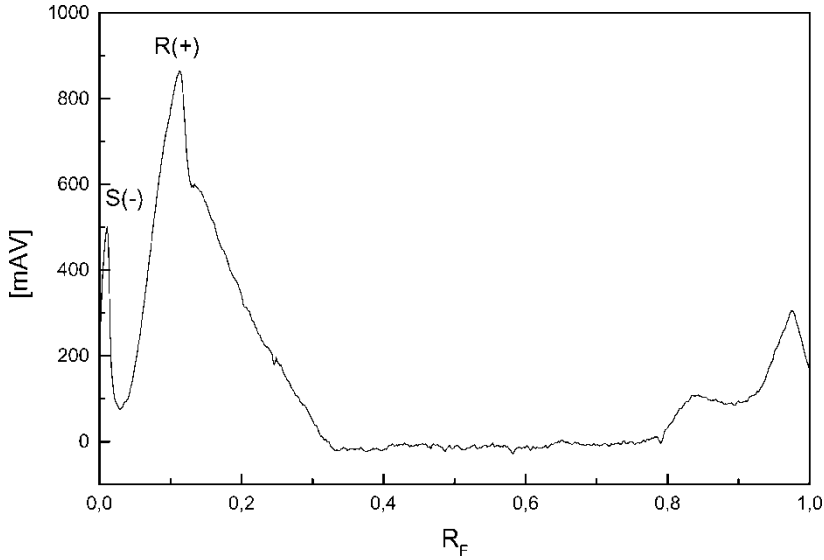


***Figure 7.*** Typical densitogram obtained from one-dimensional development of the fortified solution of the enantiomer mixture; the positions of the *S*-(−) and *R*-(+) antipodes of propranolol are marked. ACN–MeOH (15 : 4) plus 400 μL of aqueous ammonia was used as mobile phase.

the two species on the plate, the 3D representation of part of the TLC plate with the two development directions (1 and 2) indicated is also given (see Figure 8). This illustration was obtained by densitometric scanning (in parallel 4-mm intervals) of the 65-mm-wide track in the second direction of development of the chromatogram.

## Densitometric UV In-Situ Identification of Separated S-(−)- and R-(+)-Propranolol

Instrumental proof of successful separation of the two enantiomers is demonstrated by the almost identical UV spectra of the two chromatographic bands marked in Figures 6–8 as *S*-(−)- and *R*-(+)-propranolol, respectively, and illustrated in Figure 9. As in Figure 5 for ibuprofen, the only difference between the two is the different intensity of the absorption bands, because of the different amounts of the two separated species on the adsorbent layer.

## On the Mechanism and Thermodynamics of the Chiral Separation of Propranolol

Trace amounts of aqueous ammonia were added to the binary mobile phase to maintain its pH at the solid-liquid interface above the p*I* (isoelectric) point

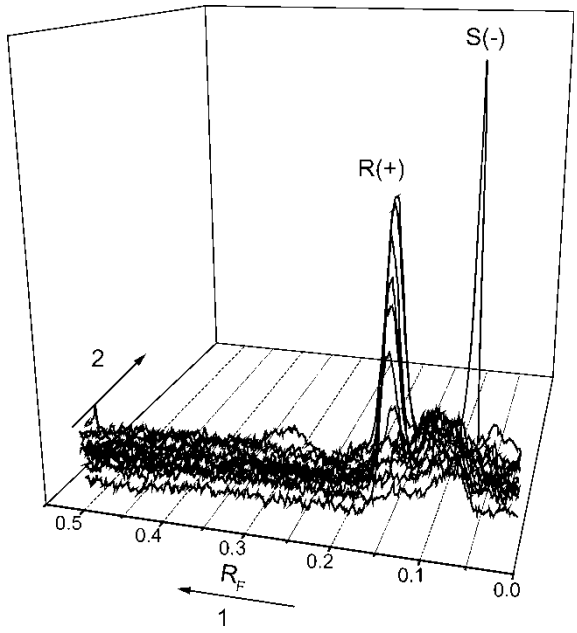


***Figure 8.*** 3D representation of part of the TLC plate with the two development directions, 1 and 2, indicated. Densitometric scanning as described in the text was performed to illustrate better the separation performance and the "skewed" arrangement of *S*-(−)-propranolol relative to its *R*-(+) counterpart.

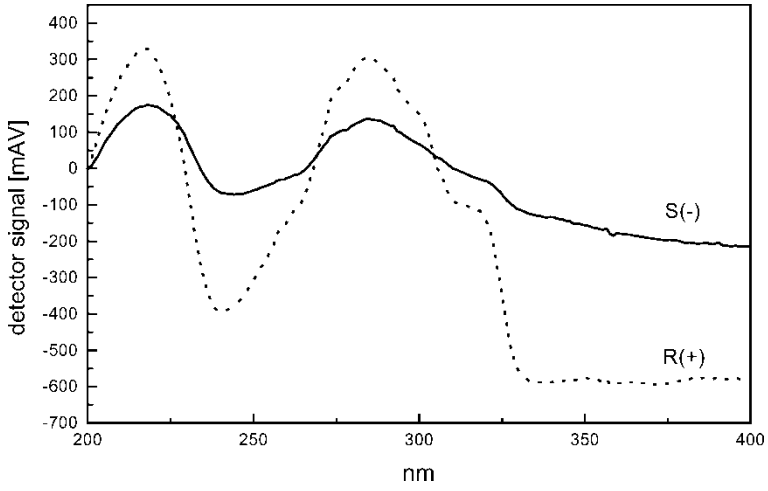


***Figure 9.*** In situ UV spectra of the chromatographic bands of *S*-(−)- and *R*-(+)-propranolol recorded densitometrically from the chromatogram shown in Figure 7.

(10.8) of L-arginine and keep the impregnating amino acid in the anionic form. Because propranolol cannot dissociate, however (see the chemical structure given in Figure 2), the mechanism of its retention seems substantially different from that described above for ibuprofen; for that compound the mechanism involved ion-pair formation or, in other words, formation of diastereomeric salts. In the enantioseparation of the antipodes of propranolol it seems more probable that the anion derived from L-arginine interacts by hydrogen bonding with either of the two propranolol antipodes to form the two *pseudo*-diastereomers, as shown below:

$$\text{L-arginine}^{(\text{anion})} + \text{S-(}-\text{)-propranolol} \leftrightarrows \text{H-bonded } \textit{pseudo}\text{-diastereomer (thermodynamically characterized by } K_3) \quad (3)$$

$$\text{L-arginine}^{(\text{anion})} + \text{R-(}+\text{)-propranolol} \leftrightarrows \text{H-bonded } \textit{pseudo}\text{-diastereomer (thermodynamically characterized by } K_4) \quad (4)$$

Separation of the two enantiomers of propranolol can be achieved only because the thermodynamic equilibrium constants ($K$) for the process of *pseudo*-diastereomer formation for the two enantiomers ($K_3$ and $K_4$, respectively) have different numerical values ($K_3 \neq K_4$).

We used Eqs (3) and (4) to estimate the effect of the amount of ammonia added on the magnitudes of $\Delta\mu_a$ for *S*-(−)- and *R*-(+)-propranolol; the results are given in Table 2. In the calculation, we assumed $\phi$ was approximately equal to 0.1; $T$ was measured as 295°K.

From the numerical values of $\Delta\mu_a$ given in Table 2, it is evident that the affinity of *S*-(−)-propranolol for the adsorbent layer is substantially greater than that of its enantiomeric antipode. It can also be stated that the numerical $R_F$ values for the enantiomers of propranolol are considerably smaller than the analogous values for the enantiomers of ibuprofen. From these two observations, the following conclusions can be drawn. First, adsorption of propranolol and ibuprofen on this stationary phase is governed not only by the moieties containing the asymmetric carbon atom but, in the first instance, by the aromatic moieties contained in their structures (propranolol with its naphthalene moiety is retained much more strongly than ibuprofen with its benzene moiety). Moreover, structural moieties of propranolol and ibuprofen play a secondary, yet a decisive discriminating (i.e., a fine-tuning) role in separating the respective pairs of enantiomers. This role is played either by ion-pair-type interactions (ibuprofen) or by hydrogen-bond interactions of the anion-dipole type (propranolol). For this separation, the next step should consist in measurement of the enthalpy and entropy of partitioning of the two propranolol antipodes in the chromatographic systems, and using the results obtained to draw relevant conclusions.

## ACKNOWLEDGMENT

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