Received: 6 January 2019 | Revised: 1 March 2019 | Accepted: 5 March 2019

DOI: 10.1002/chir.23067

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Method for determination of optical purity of 2-arylpropanoic acids using urea derivatives based on a 1,1′-binaphthalene skeleton as chiral NMR solvating agents: Advantages and limitations thereof

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Funding information
Czech Science Foundation, Grant/Award Number: 17-00089S

Abstract

Five optically active urea derivatives (**1**-**5**) were used as NMR solvating agents for analysis of the optical purity of different 2-arylpropanoic acids commonly used as nonsteroidal anti-inflammatory drugs. These novel chiral solvating agents were more efficient at discriminating the respective enantiomers of targets than the chiral solvating agents known so far, without the need to add a base for achieving the signal splitting. The advantages and limits of the use of these novel chiral solvating agents were studied.

KEYWORDS

arylpropanoic acids, binaphthalene, chiral solvating agent, nonsteroidal anti-inflammatory drugs, urea

1 | INTRODUCTION

Nonsteroidal anti-inflammatory drugs are widely used drugs among which 2-arylpropanoic acids (profens) are probably the most common. Profens are used for the treatment of inflammatory diseases, as both analgesics and antipyretics. Despite the fact that the anti-inflammatory effect of profens resides exclusively in (*S*)-enantiomers,[1,2] they are usually administered in racemic forms, except naproxen where only the (*S*)-enantiomer is registered as API. The distomeric (*R*)-enantiomer undergoes unidirectional metabolic conversion to the (*S*)-enantiomer in some cases, but the extent of this inversion can differ due to variation in metabolism and pharmacological effects.[3] Administration of the (*S*)-enantiomers of these drugs in therapy can reduce the total required dose and thus toxicity. Also, toxicity associated with the (*R*)-enantiomer or because nonstereospecific mechanisms is reduced.[4-9]

Therefore, controlling the enantiomeric purity of profens is potentially important in the synthesis of optically pure profens.

Studying the metabolism of profens is another field where the accurate determination of both enantiomers plays a significant role. Many studies concerning the metabolism of profens in various animals have been accomplished.[10-14]

Therefore, a simple and reliable method for assessing the enantiomeric ratio in samples of profens is very important.

At present, a variety of methods is available for determination of the enantiomeric purity of chiral compounds. For example, high-performance liquid chromatography (HPLC),[15-21] gas chromatography (GC),[22] capillary electrophoresis (CE),[23] or nuclear magnetic resonance (NMR)[24] can be employed. Among these methods, NMR methods are advantageous, provide fast results, and at the same time, direct structural information.

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To the best of our knowledge, there have been only a few studies performed concerning chiral solvating agents (CSAs) for profens.

More specifically, four different substances were tested with naproxen. Three of them gained a difference between the signals of both enantiomers of 0.014 ppm,[25] 0.045 ppm,[26] and 0.09 ppm[27], respectively. The best result was achieved with a thiourea derivative (0.137 ppm), but the addition of DMAP into the sample was necessary.[28]

Ibuprofen was also tested with four potential CSAs. Differences of 0.006 ppm,[25] 0.018 ppm,[29] and 0.039 ppm[26] were reported. Macrocyclic compounds containing pyridine rings have also been described, where the best result obtained was a nonequivalence of 0.01 ppm, but the use of 4 equivalents of a CSA was necessary.[30]

Macrocyclic amines interacted with flurbiprofen causing a difference between signals of 0.011 ppm.[25] The abovementioned macrocycles containing pyridine rings led to a nonequivalence of 0.014 ppm in the spectrum of flurbiprofen, but the use of 2 equivalents of CSA was necessary, and the measurement was performed in deuterated benzene.[30] Benzene is not the solvent of choice in NMR measurements due to its cost and toxicity, and in most cases, deuterated chloroform is preferable.

Similarly, in the case of ketoprofen, a 0.03-ppm ineqivalence was observed using 2 equivalents of CSA in deuterated benzene.[30] A CSA based on (1*R*,2*R*)-diaminocyclohexane lead to signal splitting in the ketoprofen NMR spectrum of 0.084 ppm.[26]

In summary, we feel that the addition of simple CSAs, which provide good resolution in spectra without the necessity of adding another compound (base), in standard NMR solvent (deuterated chloroform), in less than equimolar amounts, would be valuable.

2 | MATERIALS AND METHODS

2.1 | Instruments

The ^{1}H (400.1 MHz) and ^{13}C (100.6 MHz) NMR spectra were measured on a Bruker Avance 400 spectrometer at 25°C. The ^{1}H and ^{13}C NMR spectra were referenced to the line of the solvent (δ/ppm; δ_H/δ_C: $CDCl_3$, 7.26/77.16).

2.2 | Materials

All purchased chemicals were used without further purification. The solvents were dried and distilled using conventional methods.

Compounds **1** to **5** were synthesized in our laboratory previously.[31] Racemic ibuprofen **6**, naproxen **7**, etodolac **12**, loxoprofen **13**, and zaltoprofen **14** were purchased from Fluorochem, Hadfield, United Kingdom. Ketoprofen **9** was purchased from Sigma-Aldrich. Suprofen **10**, tiaprofenic acid **11**, and (*S*)-flurbiprofen were a generous gift from Prof Svoboda (Department of Organic Chemistry, UCTP Prague). *rac*-Flurbiprofen **8** was prepared by racemization from (*S*)-flurbiprofen via the following method described in literature.[32]

rac-Flurbiprofen (**8**) (*S*)-Flurbiprofen (10 g, 40.93 mmol) was dissolved in isopropyl acetate (100 mL). Acetic anhydride (0.42 g, 0.39 mL, 4.09 mmol) and sodium acetate (0.34 g, 4.09 mmol) were added. The resulting mixture was heated to reflux for 24 hours. Water (20 mL) was added to the warm reaction mixture, and after cooling of the solution, hydrochloric acid (conc., 2 mL) was added. The layers were separated, and the organic layer was washed with water (20 mL) and dried by anhydrous sodium sulfate. The filtrate was evaporated to dryness under vacuum. The target product was obtained as a white powder in 78% yield (7.79 g). Measurement of optical rotation revealed complete racemization.

2.3 | sNMR shift experiments

The chiral shift experiments were performed on a NMR spectrometer at 25°C. Samples for analysis were prepared by combining appropriate amounts of urea (**1**-**5**) (see Figure 1) and profen (**6**-**14**) (see Figures 2 and 4) in $CDCl_3$ (0.5 mL).

3 | RESULTS AND DISCUSSION

Herein, we examine the suitability of five chiral ureas (**1**-**5**)—based on the binaphthalene skeleton—as CSAs for

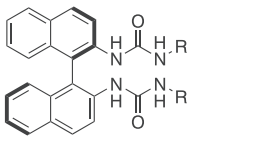


FIGURE 1 Structure of compounds **1** to **5**

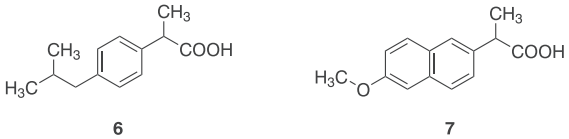


FIGURE 2 Structure of ibuprofen **6** and naproxen **7**

the determination of enantiomeric excesses of different arylpropanoic acids used as nonsteroidal anti-inflammatory drugs. All the ureas can be easily prepared from the commercially available starting materials in a one-step synthesis.[31] In addition, compound **1** is often used by chemists as an enantioselective catalyst[33-36] in various reactions. As in catalysis, these molecules can form stable diastereomeric complexes with compounds containing carbonyl, carboxylic acid, sulfoxide, and hydroxy groups and to some extent even with those containing an amino group. These complexes, possessing two sets of signals in NMR spectra, enable the assessment of the enantiomeric ratio of the substrate by a simple one-step measurement.

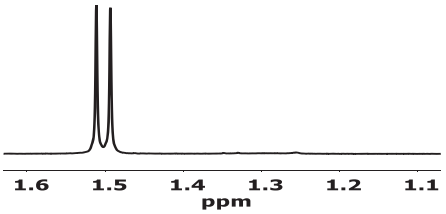
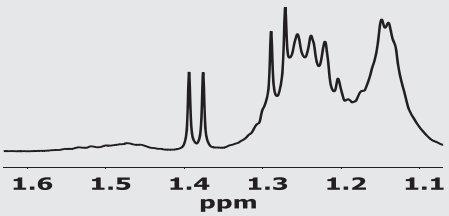
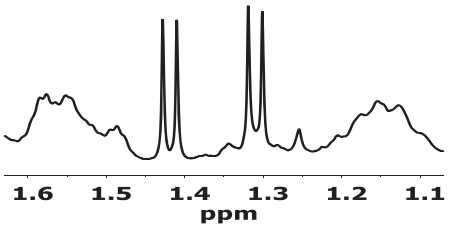
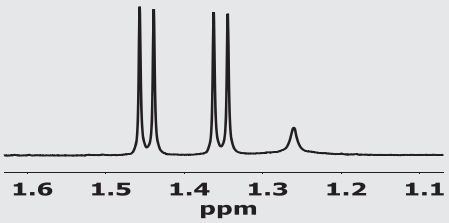
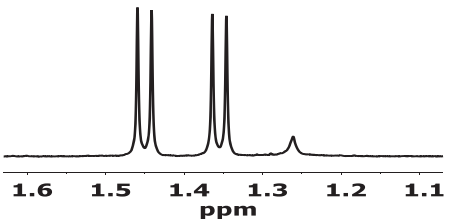
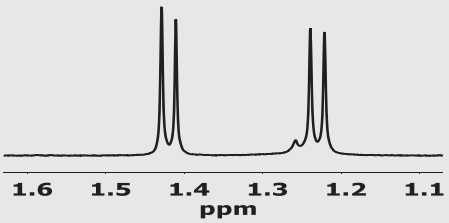
As we described earlier, urea derivatives **1** to **5** can be used as CSAs for chiral sulfoxides.[31] The resulting diastereomeric complexes are based on hydrogen bonding, which, in principle, also makes these compounds suitable candidates for complexation of profens. Deuterated chloroform was used as a solvent for the complexation studies for two reasons; first, $CDCl_3$ is the most common, low-cost solvent for NMR; second, it does not compete with the target molecule for hydrogen bonding toward the urea derivative, which makes the resulting complexes more stable.

Initially, we performed ^{1}H-NMR studies with compounds **1** to **5** to determine their abilities to split the signals of acid enantiomers using two profens: ibuprofen, as a leading member of this group, and naproxen, as a substance commonly used in therapy in an enantiomerically pure form.

Equimolar amounts of all prepared ureas **1** to **5**, relative to the amount of acid (21.7 mM), were added, and their ability to discriminate among the corresponding enantiomers (Tables 1 and 2) was studied. In all the cases, (*R*)-enantiomers of compound **1** to **5** used for experiments induced higher shift of signals of (*R*)-enantiomers of studied profens. The signal splitting was particularly significant with urea **1,** achieving values of 75.85 and 61.53 Hz (at 400 MHz) for the α-methyl groups in acids **6** and **7**, respectively. Interestingly, the interaction is so strong that even the signals of the *iso*-butyl group in ibuprofen and of the methoxy group in naproxen were split, although to a lesser extent. The splitting of the signal belonging to the OCH_3 group in naproxen can be useful because of easier and more precise integration of the singlet signal in comparison with the *J*-coupled doublet of α-CH_3.

Decreasing the overall concentration reduces the amount of complex; therefore, we repeated the above studies at a higher dilution, ie, with a lower amount of acids in 1-mL $CDCl_3$, to determine whether splitting of the NMR signals could be retained. The results are summarized in Table 3.

TABLE 1 ^{1}H chemical shift nonequivalencies (ΔΔδ and Hz, 400 MHz) of ibuprofen **6** in the presence of equimolar amounts of compounds **1** to **5** at 25°C in $CDCl_3$[a]

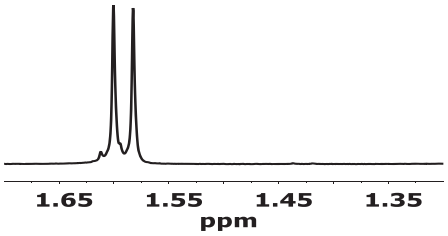
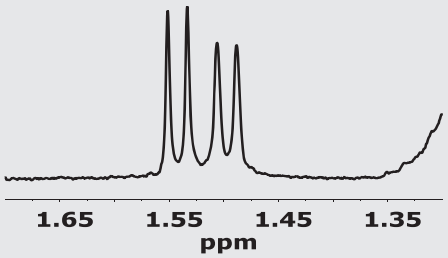
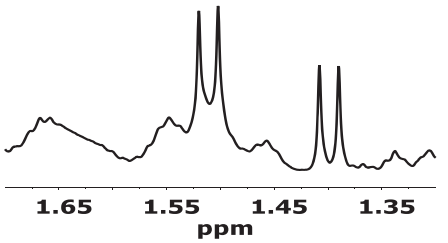
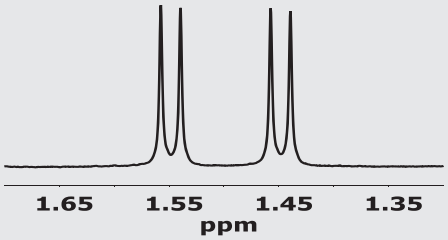
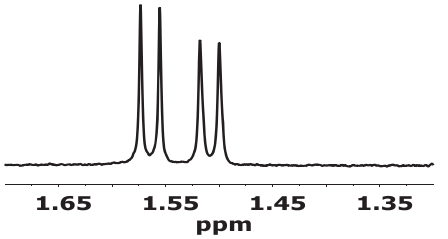
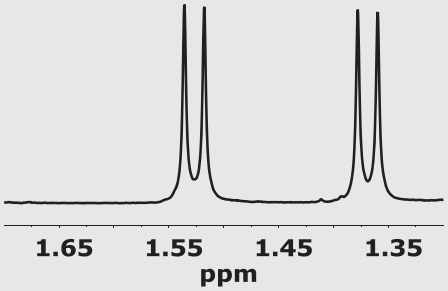
Urea	ΔΔδ (Hz) α-CH_3	A part of ^{1}H NMR spectra with signal of α-CH_3
None	0	
5	41.87	
4	43.65	
3	37.75	
2	38.16	
1	75.85	

Abbreviation: NMR, nuclear magnetic resonance.

[a]5 mg of ibuprofen in 1 mL of $CDCl_3$ was used; ie, molar concentrations of compounds **1** to **5** were 24.2 mM in each case.

In order to check how many equivalents of respective urea derivative is necessary to cause splitting of the

TABLE 2 ^{1}H chemical shift nonequivalencies (ΔΔδ in ppm and Hz, 400 MHz) of naproxen **7** in the presence of equimolar amounts of compounds **1** to **5** at 25°C in $CDCl_3$[a]

Urea	ΔΔδ (Hz) α-CH_3	A Part of ^{1}H NMR Spectra with Signal of α-CH_3
None	0	
5	18.07	
4	44.83	
3	40.05	
2	22.21	
1	61.53	

Abbreviation: NMR, nuclear magnetic resonance.

[a]5 mg of naproxen in 1 mL of $CDCl_3$ was used; ie, molar concentrations of compounds **1** to **5** were 21.7 mM in each case.

TABLE 3 ^{1}H chemical shift non-equivalencies (ΔΔδ and Hz, 400 MHz) of ibuprofen **6** and naproxen **7** in the presence of equimolar amounts of compounds **1** to **5** at 25°C in $CDCl_3$[a] at a higher dilution

Urea	Ibuprofen 6 ΔΔδ (Hz) α-CH_3	Naproxen 7 ΔΔδ (Hz) α-CH_3
5	20.83	17.45
4	23.7	28.12
3	24.64	29.02
2	21.49	21.34
1	51.01	44.34

[a]0.625 mg of ibuprofen and 0.5 mg of naproxen in 0.5-mL $CDCl_3$ was used, which corresponds to concentrations of 3.03 and 2.17 mM, respectively.

ibuprofen signals and how many equivalents of it cause the best possible splitting of the target signals, we performed the stepwise addition of compounds **1** to **5** to a 24-mM solution of ibuprofen in $CDCl_3$. The results are interpreted in the following graphs, showing the dependency of chemical shifts belonging to the signal of the alpha-methyl groups of both ibuprofen enantiomers after addition of respective CSAs. The different chemical shifts of the signals appear immediately after addition of 0.1 equivalent of urea derivatives, but taking into account the *J* coupling of the observed doublet (about 7 Hz), in all the cases tested except for urea **1**, more than 0.2 equivalents of urea are necessary to achieve splitting, which allows for accurate integration. For urea **1**, bearing electron-accepting CF_3 groups, splitting sufficient for integration can be achieved by adding only 0.15 equivalents of this compound to ibuprofen at this concentration. The electron accepting groups of this derivative cause increased acidity of the protons of the urea group, which leads to the formation of stronger complexes with ibuprofen and therefore in more profound signal splitting.

As shown in the graphs (Figure 3), the maximal splitting at this concentration of ibuprofen is achieved after addition of approximately 2 (for urea **1**) to 3 equivalents of the respective urea. Addition of a higher amount of CSA will not bring any other benefits. In the case of *n*-hexyl substituted urea **5**, after addition of more than two equivalents of CSA the signal of (S)-ibuprofen becomes covered by the signals of the *n*-hexyl group of the CSA. In the other cases, because of very good solubility of all the compounds **1** to **5** in chloroform, the use of higher amounts of CSAs is possible. This makes the method of determination of the enantiomeric ratio in ibuprofen solutions, using compounds **1** to **4**, very robust; good results can be obtained even without accurate weighting and also without knowing the exact concentration of the ibuprofen samples.

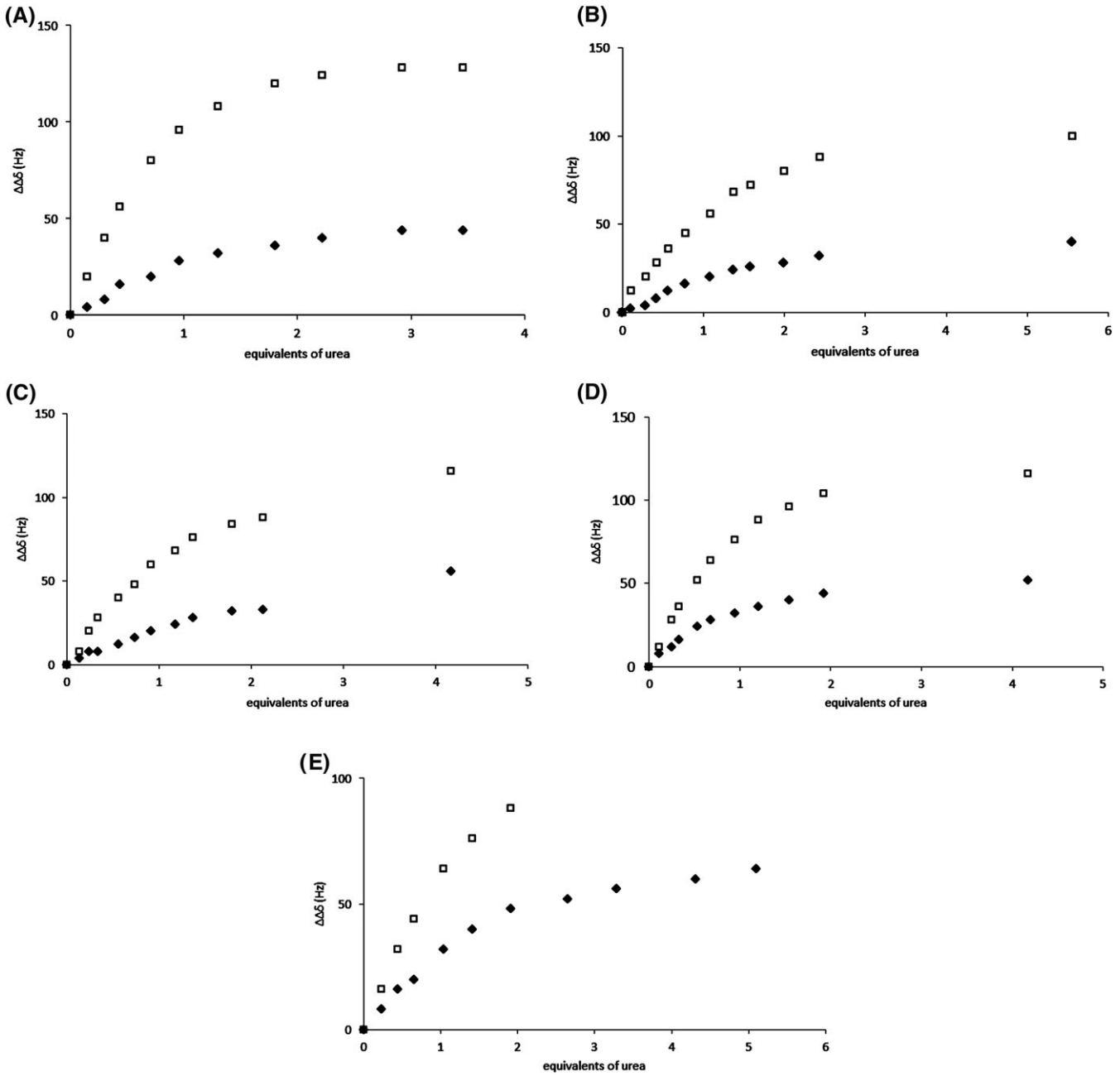


FIGURE 3 Dependency of chemical shift of ibuprofen enantiomers after stepwise addition of ureas. □ (*S*)-ibuprofen, ♦ (*R*)-ibuprofen, (A) compound **1**, (B) compound **2**, (C) compound **3**, (D) compound **4**, (E) compound **5**; $CDCl_3$, signal of α-CH_3 group

As compound **1** revealed the best results in all the experiments we performed, seven additional compounds were used as guests to screen the versatility of this compound as a CSA: flurbiprofen **8**, ketoprofen **9**, suprofen **10**, tiaprofenic acid **11**, etodolac **12**, loxoprofen **13**, and zaltoprofen **14** (Figure 4).

The results are summarized in Table 4 (higher dilution) and Table 5 (lower molar amount of urea **1**).

In the cases where the lowest possible amounts of CSA were to be used, we performed titration studies to find the smallest amount of compound **1** causing useful splitting of the signals of the above mentioned profens. For samples of 5 mg of a profen in 1 mL of CDCl3, addition of 0.1 to 0.2 molar equivalents of compound **1** in most cases results in well separated signals of the respective enantiomers.

According to these results, compound **1** was found to be a very versatile CSA for common profens. For all the tested compounds, after addition of compound **1**, well-separated signals of both enantiomers were observed,

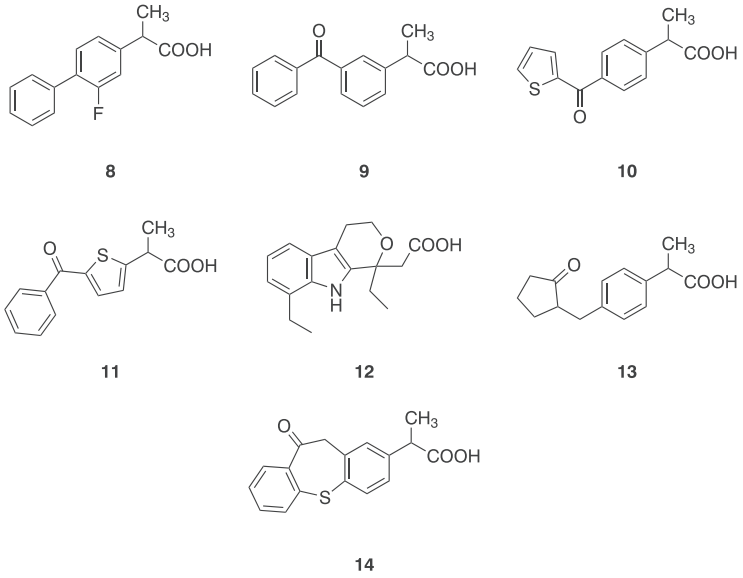


FIGURE 4 Structures of compounds **8** to **14**

TABLE 4 ^{1}H chemical shift non-equivalencies (ΔΔδ in Hz, 400 MHz) of different profens in the presence of equimolar amounts of compound **1** at 25°C in $CDCl_3$

Compound (concentrated; 5 mg of profen/ 1 mL of $CDCl_3$ + equimolar amount of respective urea)	ΔΔδ (Hz) α-CH_3	Compound (higher dilution; 0 .5mg of profen/ 1 mL of $CDCl_3$+ equimolar amount of respective urea)	ΔΔδ (Hz) α-CH_3
6 (c = 24.24 mM)	75.85	**6** (c = 2.424 mM)	51.01
7 (c = 21.71 mM)	61.53	**7** (c = 2.171 mM)	44.34
8 (c = 20.47 mM)	64.35	**8** (c = 2.047 mM)	35.37
9 (c = 19.66 mM)	56.45	**9** (c = 1.966 mM)	31.2
10 (c = 19.21 mM)	64.29	**10** (c = 1.921 mM)	36.02
11 (c = 19.21 mM)	67.34	**11** (c = 1.921 mM)	34.46
12 (c = 17.40 mM)	[a]22.236	**12** (c = 1.74 mM)	[a]12.437
13 (c = 20.30 mM)	84.84	**13** (c = 2.03 mM)	53.74
14 (c = 16.76 mM)	71.67	**14** (c = 1.676 mM)	37.64

[a]For etodolac, the signal of the CH_2 group in ethyl was used.

TABLE 5 ^{1}H chemical shift non-equivalencies (ΔΔδ in Hz, 400 MHz) of different profens in the presence of less than equimolar amounts of urea **1** at 25°C in $CDCl_3$[a]

Compound	Molar Equivalents of the Urea 1	ΔΔδ (Hz)
6 (c = 24.24 mM)	0.10	16.11
7 (c = 21.71 mM)	0.20	18
8 (c = 20.47 mM)	0.10	29.95
9 (c = 19.66 mM)	0.20	23.15
10 (c = 19.21 mM)	0.20	22.99
11 (c = 19.21 mM)	0.20	26.77
12 (c = 17.40 mM)	1.00	22.236
13 (c = 20.30 mM)	0.10	21.67
14 (c = 16.76 mM)	0.20	35.93

[a]5 mg of profen in 1 mL $CDCl_3$ was used. The values in the parentheses represent the corresponding molar concentrations. For etodolac **12**, the CH_2 of the ethyl group was employed.

with nonequivalencies of about 50 Hz in 24.2-mM solutions. For etodolac, the signal splitting was lower. The structure of etodolac possesses an "observable" ethyl group, which is, in contrast to the other profens studied, not in the α position to the carbonyl. As the hydrogens of the observed signal are not in close proximity to the complexation site, the changes in the chemical environment of the respective hydrogens are not so dramatic, unlike for the other profens, causing less profound separation of the signals. Nevertheless, the splitting observed under the stated conditions was still sufficient for the purpose of determining the enantiomeric excess in this compound.

4 | CONCLUSION

In conclusion, we found that urea derivatives **1** to **5** are useful as CSAs for various profens. The electron-withdrawing substituents attached to the urea derivative strongly enhance the binding ability of compound **1**, which results in better splitting of the NMR signals of the corresponding guests. Moreover, the method of measurement of enantiomeric ratio of profens by ^{1}H NMR using these CSAs is very versatile and robust. Compound

1 forms diastereomeric complexes with a variety of known and commonly used profens in a wide range of concentrations. These features make the urea derivatives **1** to **5**, especially compound **1**, very potent and useful tools for determining the enantiomeric ratio of profens, where previously such separation of the signals belonging to the α-methyl group of a profen were unobserved. The addition of other compounds, eg, a base, is not necessary for separation. The only limitation for the use of compounds **1** to **5** as CSAs is the use of a solvent, which does not compete with the profen for hydrogen bonding toward the CSA.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Czech Science Foundation grant no. 17-00089S for financial support.

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How to cite this article: Cuřínová P, Hájek P, Janků K, Holakovský R. Method for determination of optical purity of 2-arylpropanoic acids using urea derivatives based on a 1,1′-binaphthalene skeleton as chiral NMR solvating agents: Advantages and limitations thereof. *Chirality*. 2019;1–8. https://doi.org/10.1002/chir.23067