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Capillary electrophoresis and ^{1}H NMR studies on chiral recognition of atropisomeric binaphthyl derivatives by cyclodextrin hosts

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Abstract

The usefulness of ^{1}H NMR spectroscopy is illustrated for a detailed study of a selector–solute interactions which maintain enantioseparations in capillary electrophoresis. The apparent binding constants (K_a) of enantiomers and the chemical shift differences at saturation ($\Delta\delta_c$) were calculated using ^{1}H NMR spectroscopy. Some problematic aspects concerning the application of NMR spectroscopy for the explanation of the chiral recognition mechanisms in separation techniques are also shortly discussed. The enantioseparation of a cationic chiral analyte using a cationic cyclodextrin derivative is reported for the first time. This result supports the possibility of enantioseparations in a selector–solute pair carrying the same net charge as recently reported for a negatively charged selector–solute pair.

Keywords: Enantiomer separation; Derivatization, electrophoresis; Nuclear magnetic resonance spectrometry; Binaphthyl derivatives; Cyclodextrins

1. Introduction

Atropisomeric binaphthyl derivatives are extensively used as chiral resolving agents [1,2], chiral selectors in HPLC phases [3], ligands for dissymmetric catalysts [4,5] and as building blocks in the synthesis of chiral macrocycles [6].

Over the last few years several papers have been published on capillary electrophoretic (CE) enantioseparations of various chiral binaphthyl derivatives [7–14]. In some of these papers the stoichiometry and binding constants of the selector–solute complexes have been also determined [10,13] and some correlations have been observed between binding pattern and chiral recognition in CE [10].

The successful enantioseparation of (±)-1,1′-binaphthyl-2,2′-diyl-hydrogen phosphate [(±)-BDHP] in the anionic form at pH 6.0 with anionic cyclodextrin (CD) derivatives, such as carboxymethyl ether of β-CD (CM-β-CD), sulfoethyl ether of β-CD (SEE-β-CD) and sulfobutyl ether of β-CD (SBE-β-CD) has been reported [14]. This result disagrees with a supposed decisive role of electrostatic interactions and ion pairing for a complexation and chiral recognition using charged CDs [16–18]. Enantioseparation of other negatively-charged chiral pharmaceuticals were recently reported [19]. Additionally, enantioseparation of a selector–solute pair carrying the same net charge offers unique possi-

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bilities for the reversal of enantiomer elution order in CE [20].

Application of NMR spectroscopy is reported for studies on the chiral recognition mechanism in HPLC [21–27], GC [28,29] and CE [30–32]. Most reliable correlations should be expected between CE and NMR since the selector–solute interactions take place in a similar or even identical environment (free solution) in both techniques.

The aim of this study is to gain more insight into the interactions of neutral and anionic CDs with the negatively-charged chiral analyte (±)-BDHP using ^{1}H NMR spectroscopy and to check correlations between ^{1}H NMR and CE. Additionally, the enantioseparation of positively charged (±)-1,1′-binaphthyl-2,2′-diamine was studied using various neutral, negatively- and positively-charged CDs.

2. Experimental

2.1. Instrumentation

2.1.1. CE

A Grom capillary electrophoresis system 100 (Herrenberg, Germany), equipped with a Linear Instruments (Reno, NV, USA) UVIS 200 detector and a HP 3396 A integrator (Hewlett-Packard, Avondale, PA, USA) was used with an untreated fused-silica capillary (Grom) of 60 cm total length× 50 μm I.D. The samples were introduced hydrostatically (10 cm) during 5 s. Detection of the solutes was carried out at 210 nm. The electric field was 400 V/cm, the temperature was 21±1°C.

The selectivity of the enantioseparation was characterized with α_{rel} which is the ratio of the effective mobilities of the enantiomers and is an average value of two measurements. The resolution of enantiomers was calculated according to the following equation:

$$R_s = \frac{2(t_2 - t_1)}{(w_1 + w_2)} \quad (1)$$

where t_2 and t_1 are the migration times and w_1 and w_2 baseline peak width of the first and second eluted enantiomers, respectively.

2.1.2. NMR

^{1}H and ^{13}C NMR, homonuclear correlated spectroscopy (HOMCOR), heteronuclear chemical shift correlation (HETCOR), attached proton test (APT) and distortionless enhancement by polarization transfer (DEPT) spectral analysis were carried out with a Varian Gemini 200 NMR-spectrometer at 200 MHz (^{1}H) and 50 MHz (^{13}C). ^2H_2O+10% $C^2H_3O^2H$ was used as a solvent and a solution of tetramethylsilan (TMS) in tetrachloromethane served as external standard. The peak assignments of (±)-BDHP in ^{1}H and ^{13}C NMR spectra were performed using HOMCOR, HETCOR, APT and DEPT spectra. CD signals in ^{1}H NMR spectra were assigned using literature data [33] for β-CD. The stoichiometry of the selector–solute complexes was determined by the continuous variation method [34]. The total concentration of the interacting species was kept constant at 3 m*M* and the molar fraction of the guest was varied in the range 0.25–0.75. Binding constants of the enantiomers of (±)-BDHP with CD derivatives were calculated on the basis of Scott's modification [35] of the Benesi–Hildebrand equation as described in Ref. [32].

2.2. Chemicals and reagents

The racemic compounds (±)-BDHP [(±)-**1**] and (±)-1,1′-binaphthyl-2,2′-diamine [(±)-**2**] and optically pure enantiomers of them were all purchased from Aldrich (Steinheim, Germany). α-, β- and γ-CD, hydroxypropyl-β-CD (HP-β-CD) [average substitution degree (s.d.) ca. 4.2] and carboxymethyl-β-CD (CM-β-CD) (s.d. ca. 2.1) were donated by Wacker Chemie (Munich, Germany). Sulfobutyl ether of β-CD (SBE-β-CD) (s.d. ca. 4.0) was a gift from Prof. J.F. Stobaugh and Prof. V.J. Stella (Center for Drug Delivery Research, The University of Kansas, Lawrence, KA, USA). heptakis-2,3,6-Trimethyl-β-CD (TM-β-CD) was purchased from Sigma (Sigma–Aldrich Chemie, Deisenhofen, Germany). Trimethylammonium salt of β-CD, a positively-charged CD derivative prepared from the parent β-CD and a quaternary ammonium-substituted epoxide reagent to give a quaternary trimethylammonium ether of β-CD (TMA-β-CD) and mono-6-amino-6-deoxy-β-CD (6-Am-β-CD) (s.d. 1.0) both were prepared in our laboratory as described in Refs. [36] and [37], respectively. Analytical grade KH_2PO_4, H_3PO_4, NaOH, ^2H_2O and $C^2H_3O^2H$ were from Merck (Darmstadt, Germany).

2.3. Buffer and sample preparation

Stock solution of 50 m*M* KH_2PO_4 was prepared in double distilled, deionized water. The pH was adjusted with 0.5 *M* H_3PO_4 or 0.5 *M* NaOH to the desired value. The run buffers (90% phosphate buffer–10% methanol) were prepared accordingly after the addition of appropriate amounts of the chiral selectors. All solutions were filtered and degassed by sonication before use. Stock solutions of 1 mg/ml of the racemic solutes were prepared, stored at 4°C and diluted to 60 μg/ml before use.

3. Results and discussions

3.1. ^{1}H NMR study of chiral recognition of (±)-1,1′-binaphthyl-2,2′-diyl-hydrogen phosphate

The enantioseparation using CDs as chiral selectors in CE is basically maintained by stereoselective inclusion complex formation between the chiral solute and the CD host. Electrostatic (dipole–dipole) interactions are considered to play an important role in the inclusion complex formation by CD host. The best way to evaluate the role of this effect is by direct calculations of the stoichiometry, binding constants (K_a) and binding selectivity (α_{rel}) using spectroscopic techniques. ^{1}H NMR spectroscopy is potentially the most suitable technique for this purpose and allows the calculation of all above-mentioned parameters. Additionally, this technique provides direct confirmation of the inclusion complex formation and considerable information about the structure of these complexes. If diastereotopic signals are resolved from each other in a NMR spectrum, racemic samples can be used instead of enantiomerically pure ones and competitive complexation studies are also possible. This is a further important advantage over other spectroscopic techniques, which require the use of optically pure samples and are unsuitable for competitive complexation studies.

The ^{1}H NMR spectra of (±)-**1** (Fig. 1a) and of the equimolar solutions of (±)-**1** with β-CD (Fig. 1b), CM-β-CD (Fig. 1c) and SBE-β-CD (Fig. 1d) are given in Fig. 1. As this figure shows all signals in the ^{1}H NMR spectrum of (±)-**1** are substantially shifted due to the complexation with these CDs. Using

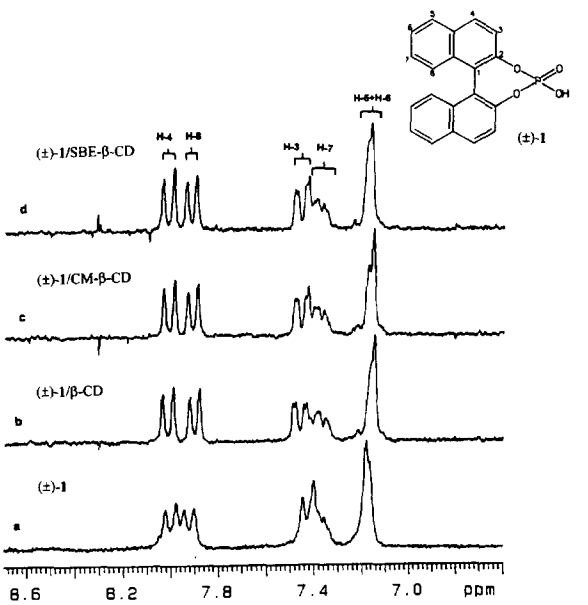

Fig. 1. ^{1}H NMR spectra of (±)-**1** (a), and of the equimolar solutions of (±)-**1** with β-CD (b), CM-β-CD (c) and SBE-β-CD (d).

200-MHz NMR equipment it was impossible to avoid substantial overlapping of signals of the protons H-5 and H-6 and partial overlapping of signals of the protons H-7 and H-3. Further discussion is based on the best resolved doublets centered at 7.44 ppm ($J_{3,4}$ = 9.40 Hz) (H-3) and at 7.92 ppm ($J_{7,8}$ = 7.96 Hz) (H-8). The doublet of H-3 is shifted downfield due to the complexation, whereas the doublet of H-8 is shifted upfield. The complexation-induced chemical shift nonequivalence between the enantiomers in equimolar solutions is most pronounced for the doublet of H-3 for all three CDs. An important conclusion is that the negatively charged CD derivatives are principally able to complex anionic chiral analytes via inclusion mechanism and to discriminate between enantiomers in confirmation of results observed in CE [14,20]. The complexation-induced chemical shift nonequivalence between enantiomers in these instances was not sufficiently high enough to use a racemic sample. Therefore, the pure *S*-(+)-**1** and *R*-(−)-**1** were used for determination of the stoichiometry of selector–solute complexes and for the calculation of the apparent binding constants (K_a). As Fig. 2 shows for *S*-(+)-**1**/β-CD and *R*-(−)-**1**/β-CD complexes the Job plots have a maximum at

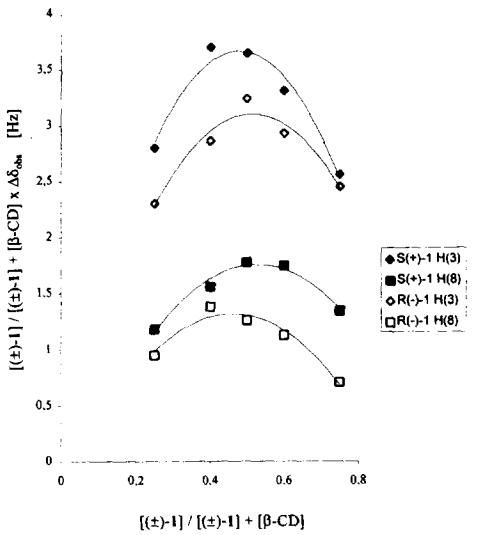

Fig. 2. Job plots of *S*-(+)-**1** and *R*-(−)-**1** in solutions with β-CD.

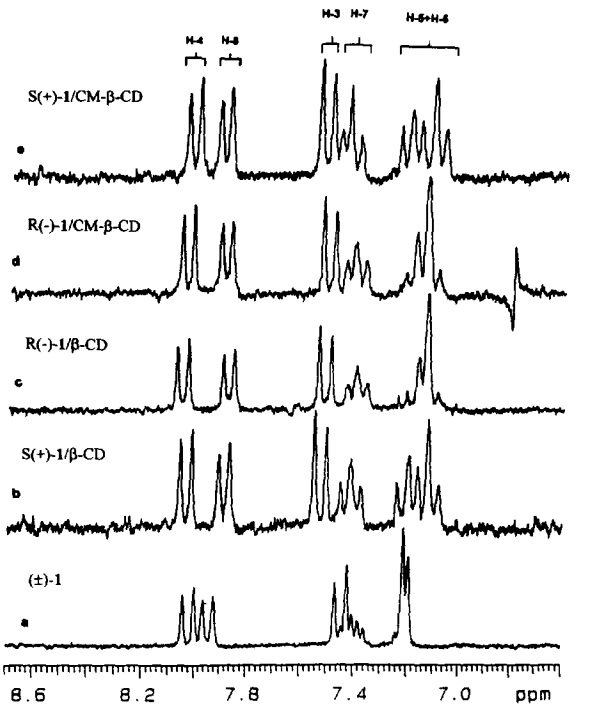

Fig. 3. ^{1}H NMR spectra of (±)-**1** (a), *S*-(+)-**1** (b,e) and *R*-(−)-**1** (c,d) in presence of 3:1 molar excess of β-CD (b,c) and CM-β-CD (d,e).

the selector–solute molar fraction in solution 0.5–0.5. This means that the complexes of 1:1 stoichiometry are predominant in solution. The 1:1 stoichiometry of complexes of *S*-(+)-**1** and *R*-(−)-**1** with CM-β-CD was confirmed in a similar way.

This 1:1 stoichiometry of the (±)-**1**/β-CD complex is in discrepancy with fluorescent spectroscopy measurements which showed that the 2:1 complexes of β-CD and *S*-(+)-**1** and *R*-(−)-**1** were predominant [15] but coincides well with the stoichiometry of the same complex determined by circular dichroism spectroscopy [10].

If one compares complexation-induced chemical shifts for *S*-(+)-**1** and *R*-(−)-**1** in solutions with β-CD (principally the same is true for CM-β-CD) it can established that for the doublet at 7.44 ppm (H-3) the complexation-induced chemical shift is higher for *S*-(+)-**1**, whereas for the doublet at 7.92 ppm (H-8) the complexation-induced chemical shift is higher for *R*-(−)-**1** (Fig. 3). If the existence of only one type of complex is assumed in this solution then it could be concluded that the use of the magnitude of the complexation-induced chemical shifts as a measure of the chiral recognition ability is not correct at any time. The complexation-induced chemical shift nonequivalence observed in the NMR spectra can principally be of two different origins: (a) two enantiomers may have the same apparent binding constants with the chiral selector, but the two diastereomeric complexes thus formed may have intrinsically different NMR spectra. In this case signals of the enantiomers will be resolved in the NMR spectrum, but no separation of the enantiomers will be observed in CE or in any other separation technique. No meaningful correlations between values of complexation-induced chemical shifts and enantioselectivities are expected in this case. (b) The two enantiomers may have different apparent binding constants with the chiral selector. In this case signal splitting can be observed in NMR as a result of the complexation-induced chemical shift nonequivalence and enantioseparation is principally possible in CE or other separation techniques. Combination of these two effects is most common.

The complexation-induced chemical shift at saturation ($\Delta\delta_c$) is one of the important parameters in the Scott's equation [35]:

$$\frac{[\text{selector}]_t}{\Delta\delta_{obs}} = \frac{[\text{selector}]_t}{\Delta\delta_c} + \frac{1}{K_a \Delta\delta_c} \quad (2)$$

$\Delta\delta_c$ gives information which enables the differentiation between the two above-mentioned cases.

Additionally, apparent binding constants (K_a) can be determined by solving the linear Eq. 2 in which $[\text{selector}]_t$ is the molar concentration of the chiral selector, $\Delta\delta_{obs}$ is the observed chemical shift difference for a given $[\text{selector}]_t$ concentration and $\Delta\delta_c$ is the chemical shift difference between a pure sample of complex and the free component at the saturation.

Scott plots of the complexes of *S*-(+)-**1** and *R*-(−)-**1** with β-CD and CM-β-CD are given in Fig. 4 and Fig. 5, respectively. The values of the complexation-induced chemicals shifts at saturation ($\Delta\delta_c$) and the apparent binding constants calculated for two different ^{1}H NMR signals are given in Table 1.

The data shown in Fig. 4 and Fig. 5 and summarized in Table 1 can be used more or less correctly only in the light of the discussion above. Particularly, although a higher complexation-induced chemical shift (upfield) can be observed for the doublet at 7.92 ppm (H-8) for *R*-(−)-**1** than for *S*-(+)-**1**, the apparent binding constant calculated on the basis of this signal for *S*-(+)-**1** is higher than that for *R*-(−)-**1** in case of β-CD (Table 1). The complexation-induced

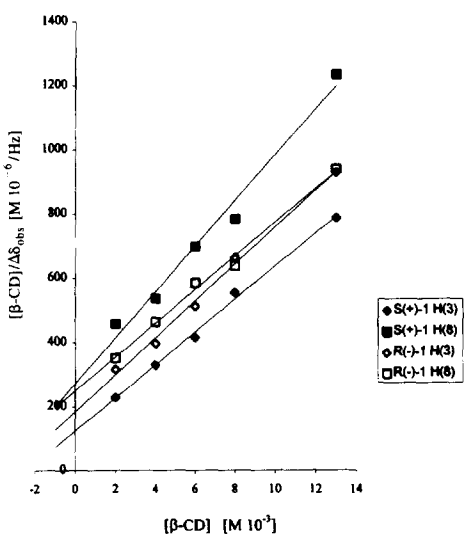

Fig. 4. Scott plots of *S*-(+)-**1** and *R*-(−)-**1** in solutions with β-CD.

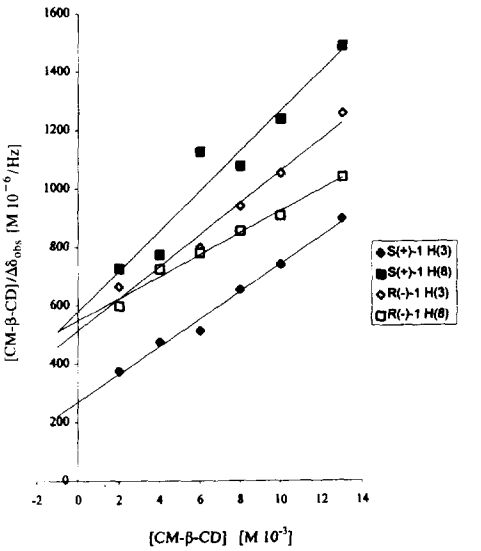

Fig. 5. Scott plots of *S*-(+)-**1** and *R*-(−)-**1** in solutions with CM-β-CD.

chemical shift for (H-3) protons (7.44 ppm) downfield is higher for *S*-(+)-**1** than for *R*-(−)-**1**. The apparent binding constants (K_a) calculated on the basis of this signal (Table 1) are 413 M^{-1} and 312 M^{-1}, respectively. Kano et al. also reported a higher apparent binding constant for *S*-(+)-**1** than for *R*-(−)-**1** with β-CD [10]. It seems worth mentioning that some quantitative differences exist between the magnitudes of the binding constants (K_a) calculated on the basis of different ^{1}H NMR signals (Table 1), as well as between data calculated using ^{1}H NMR and circular dichroism spectroscopy [10]. The stereoselectivity of binding determined using circular dichroism spectroscopy is markedly higher $\bar{K}_{aS}/\bar{K}_{aR} = 2.90$ [10] than the selectivity determined in this study using ^{1}H NMR spectroscopy $\bar{K}_{aS}/\bar{K}_{aR} = 1.30$. Previous binding studies [10,15] as well as ^{1}H NMR results presented in this paper show that *S*-(+)-**1** is stronger bound by β-CD than *R*-(−)-**1**. These results are in good agreement with the enantiomer elution order of (±)-**1** in CE (*R* before *S*) using β-CD as chiral selector [8,10].

Presently, the data are not sufficient to draw any conclusion concerning the mono- or multimodal complexation in pairs of (±)-**1** with β- and/or CM-β-CD.

Table 1
Complexation-induced chemical shifts at saturation ($\Delta\delta_c$) and average apparent binding constants (K_a) for the complexes of *S*-(+)-1,1′-binaphthyl-2,2′-diyl-hydrogen phosphate and *R*-(−)-1,1′-binaphthyl-2,2′-diyl-hydrogen phosphate with β-CD and CM-β-CD

CD	$\Delta\delta_c R(-)$ (Hz)		$\Delta\delta_c S(+)$ (Hz)		$K_{a[R-(-)]}$ (M^{-1})		$K_{a[S-(+)]}$ (M^{-1})		$\bar{K}_{a[R-(-)]}$ (M^{-1})	$\bar{K}_{a[S-(+)]}$ (M^{-1})	$\alpha_i = \frac{\bar{K}_{a[S-(+)]}}{\bar{K}_{a[R-(-)]}}$
	H-3	H-8	H-3	H-8	H-3	H-8	H-3	H-8			
β-CD	17.41	19.06	19.49	14.02	312	210	413	263	261	338	1.30
CM-β-CD	18.31	26.68	21.16	14.56	106	68	175	119	87	147	1.70

In complexes of CM-β-CD with *S*-(+)-**1** and *R*-(−)-**1** the complexation-induced chemical shifts of the (H-8) protons are not in direct proportional correlation with the calculated apparent binding constants as was found for the β-CD complexes (Table 1). It seems important to mention that the apparent binding constants are markedly lower in the case of CM-β-CD for both enantiomers compared to those found for β-CD. *S*-(+)-**1** is more strongly bonded than *R*-(−)-**1** ($\bar{K}_{aS}/\bar{K}_{aR} = 1.70$) with CM-β-CD. This result illustrates again that stronger binding to the chiral selector does not necessarily imply a higher binding selectivity. Dipole–dipole host–guest interactions apparently contribute in stronger binding but some specific weaker intermolecular interactions (such as hydrogen bonding) can contribute substantially in the stereoselectivity of binding. The stronger binding of *S*-(+)-**1** than of *R*-(−)-1 coincides well with the enantiomer elution order and selectivity of the enantioseparation observed in CE using CM-β-CD as chiral selector, if the pH of the separation medium is chosen properly. A recent more detailed discussion of the relation between binding patterns and enantiomer elution order in CE can be found in Ref. [20].

3.2. Enantioseparation of (±)-1,1′-binaphthyl-2,2′-diamine

The results of the enantioseparation of positively-charged (±)-**2** with various CDs in 50 m*M* phosphate buffer at pH 3.3 are summarized in Table 2. From this table one can see that native α-, β- and γ-CD as well as TM-β-CD do not exhibit sufficient chiral recognition abilities at a concentration of 1 mg/ml in the run buffer, since β-CD at a concentration of 2.5 mg/ml permits baseline enantioseparation of (±)-**2** under the same conditions. HP-β-CD, as well as anionic CM-β-CD and SBE-β-CD show a high chiral recognition to this analyte. The most interesting result in this table is the high chiral recognition ability of the positively-charged TMA-β-CD towards the also positively-charged chiral analyte (±)-**2** (Fig. 6). The enantioseparation of negatively-charged chiral solutes using anionic chiral selectors in CE was reported recently [14,20]. This seems to be the first example of the enantioseparation in a positively-charged chiral selector–solute pair in CE. This result confirms that, although electrostatic interactions can contribute in the binding of charged compounds with oppositely-charged CDs, these interactions do not always seem to be the major force. The inclusion of molecules carrying the same net charge as the CDs may be thermodynamically favoured in the CD cavity in aqueous solution. The highly hydrophobic naphthyl moiety in compound (±)-**2** seems to be the most likely reason for the complexation in this particular case, as well as for that mentioned in Ref. [14]. Unlike TMA-β-

Table 2
Enantioseparation of (±)-1,1′-binaphthyl-2,2′-diamine using various CDs

Selector	Concentration (mg/ml)	t_1 (min)	α_{rel}
None	–	16.75	–
α-CD	1.0	16.48	1.00
β-CD	1.0	17.25	1.00
β-CD	2.5	19.67	1.04
γ-CD	1.0	18.37	1.00
HP-β-CD	1.0	15.12	1.02
TM-β-CD	1.0	16.08	1.00
TMA-β-CD	1.0	17.95	1.03
CM-β-CD	1.0	19.41	1.06
SBE-β-CD	1.0	19.57	1.04
6-Am-β-CD	1.0	15.13	1.00
6-Am-β-CD	5.0	13.55	1.00

CE conditions: 50 m*M* KH_2PO_4 buffer pH 3.3, +400 V/cm.

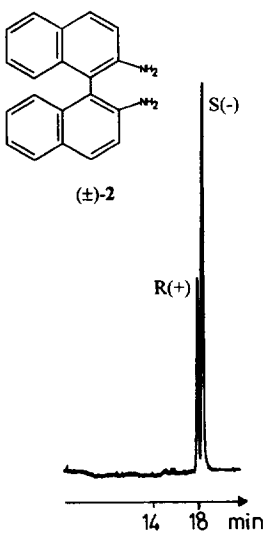

Fig. 6. Enantioseparation of (±)-1,1′-binaphthyl-2,2′-diamine [*S*-(−)-**2**/*R*-(+)-**2**=2:1] with 1.0 mg/ml TMA-β-CD at pH 3.3. The field strength was maintained at +400 V/cm.

CD, another positively-charged CD derivative – 6-Am-β-CD – does not show any measurable chiral recognition ability of compound (±)-**2** even at a concentration of 5 mg/ml in the run buffer.

It seems noteworthy that in the case of enantioseparation of (±)-**2** using CM-β-CD, the enantioselectivity decreases with increasing pH with a complete loss at pH 5.0 (for a given CM-β-CD concentration of 1 mg/ml). With a further increase of pH low, but measurable enantioselectivity appears again at pH 8.0. A more detailed study of this effect is a subject of our further research.

The very limited solubility of (±)-**2**, even in the salt form, in aqueous solutions did not allow us to perform more detailed ^{1}H NMR studies for this compound.

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