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Enantioseparation of *erythro*-mefloquine and its analogues in capillary electrophoresis

Bezhan Chankvetadze [a,b,*], Naira Burjanadze [b], Gottfried Blaschke [b]

[a] *Molecular Recognition and Separation Science Laboratory, School of Chemistry, Tbilisi State University, Chavchavadze Avenue 1, 380028 Tbilisi, Georgia*

[b] *Institute of Pharmaceutical and Medicinal Chemistry, University of Münster, Hittorfstr. 58-62, 48149 Munster, Germany*

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Abstract

The enantioseparations of the chiral antimalaria drug (*R*,*S*)-*erythro*-α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (*erythro*-mefloquine, *erythro*-MQ) and its analogues were studied by capillary electrophoresis (CE) using cyclodextrins (CDs) as chiral selectors. The emphasis was put on the enantiomer affinity pattern of MQ towards different CDs as well as on simultaneous enantioseparations of *erythro*-MQ and its structural analogues. All three native CDs resolved the enantiomers of *erythro*-MQ and the enantiomer affinity pattern was the same, i.e. (+)-*erythro*-MQ was the more tightly bond enantiomer. However, the affinity pattern of *erythro*-MQ enantiomers was opposite in the case of heptakis-(2,3,6-tri-*O*-methyl)-β-CD (TM-β-CD), heptakis-(2,3-di-*O*-methyl-6-sulfo)-β-CD (HDMS-β-CD), heptakis-(3-*O*-methyl-2,6-di-*O*-sulfo)-β-CD (HMdiSu-β-CD) and randomly sulfated β-CD (SU-β-CD). Randomly hydroxyalkylated and acetylated derivatives of CDs appeared to be suitable chiral selectors for simultaneous enantioseparation of *erythro*-MQ and its analogues.

Keywords: Capillary electrophoresis; Cyclodextrins; Enantiomer migration order; Enantiomer separation; *erythro*-Mefloquine

1. Introduction

(*R*,*S*)-*erythro*-α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (*erythro*-mefloquine, *erythro*-MQ; Fig. 1) was synthesized in 1971 [1] and is in clinical use as an antimalaria agent since the late 1980s [2,3]. MQ contains two centers of chirality, and *R*,*S*-*erythro*-MQ is used in the clinical practice. The methods for the enantioseparation of MQ have been developed using high-performance liquid chromatography (HPLC) [2,4–8] and capillary electrophoresis (CE) [9–17]. The indirect HPLC enantioseparation method of *erythro*-MQ involves the derivatization with (+)- or (−)-naphthylisocyanate and separation of the diastereomeric derivatives on an achiral C-18 column [2]. A disadvantage of this method is a laborious derivatization step and involvement of harmful isocyanate-derivatising reagent. The first

* Corresponding author. Tel.: +49-251-8333342; fax: +49-251-8332144.
E-mail address: bchankvetadze@yahoo.com (B. Chankvetadze).

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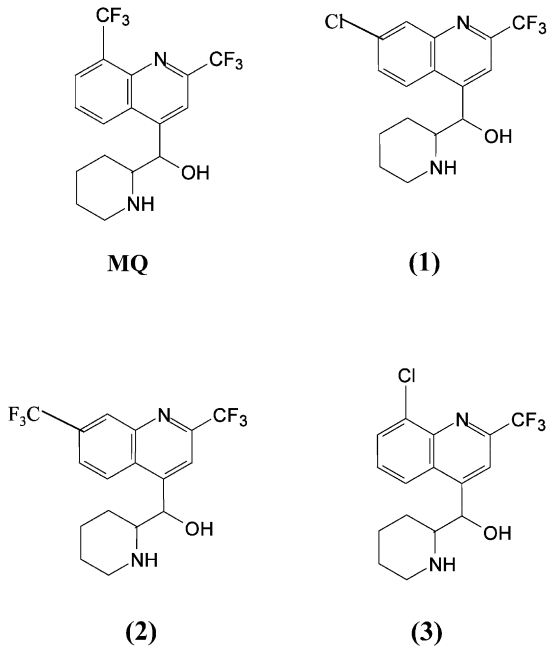

Fig. 1. Structure of MQ and its analogues, (*R*,*S*)-*erythro*-α-(2-piperidyl-)-2,7-bis(trifluoromethyl)-4-quinolinemethanol (**1**), (R,S)-*erythro*-α-(2-piperidyl-)-7-chloro-(2-trifluoromethyl)-4-quinolinemethanol (**2**) and (*R*,*S*)-*erythro*-α-(2-piperidyl-)-8-chloro-(2-trifluoromethyl)-4-quinolinemethanol (**3**).

direct enantioseparation method was developed using a cross-linked bovine serum albumin (BSA) column [2]. The peaks were very broad and the analysis time exceeded 1 h. Later, several direct HPLC methods were developed and used for the investigation of the enantioselective distribution and pharmacokinetics of *erythro*-MQ [4–8]. The main metabolites of *erythro*-MQ are achiral and no significant differences have been described between the antimalaria activity of the enantiomers. However, some unexplained neurotoxic effects have been observed during the treatment with this drug. For this reason, a stereoselective tissue distribution (especially in brain) study of *erythro*-MQ still remains actual [7,8] and micro-analytical methods are required for this purpose.

The enantiomers of *erythro*-MQ were previously resolved in CE using cyclodextrin (CD)-type chiral selectors [9–15], heparin [16] and cinchona alkaloids [17] as chiral selectors in aqueous [9–16] and nonaqueous buffers [17]. The aspects such as the enantiomer migration order, systematic screening of chiral selectors and simultaneous enantioseparation of *erythro*-MQ and structurally related compounds have not been addressed previously.

The goal of this work was to study the affinity pattern of *erythro*-MQ enantiomers towards native, randomly and selectively modified, uncharged and charged CDs as well as the simultaneous enantioseparation of *erythro*-MQ and its structural analogues.

2. Experimental

2.1. Chemicals and reagents

Racemic *erythro*-MQ and its analogues (Fig. 1) were provided by Novartis (Basel, Switzerland). The enantiomers of *erythro*-MQ were obtained in our laboratory via diastereomeric crystallization of (±)-MFQ with (+)- and (−)-ammonium-3-bromo-8-camphensulfonate as described previously [18]. Heptakis-(2,6-di-*O*-methyl)-β-CD (2,6-DM-β-CD) and heptakis-(2,3,6-tri-*O*-methyl)-β-CD (TM-β-CD) were obtained from Sigma (Deisenhofen, Germany). α-, β-, γ-CD and methyl-α-CD (Me-α-CD) with the degree of substitution (DS) 1.8, methyl-β-CD (Me-β-CD, DS = 1.8), hydroxypropyl-α-CD (HP-α-CD, DS = 1.8), hydroxypropyl-β-CD (HP-β-CD, DS = 1.8), hydroxypropyl-γ-CD (HP-γ-CD, DS = 2.1), carboxymethyl-β-CD (CM-β-CD, DS = 3.5), acetyl-β-CD (AC-β-CD, DS ≈ 1.0), hydroxyethyl-β-CD (HE-β-CD, DS = 4.2) and succinyl-β-CD (DS = 3.5) was a gift from Wacker Chemie (Munich, Germany). Sulfated β-CD (SU-β-CD, DS = 7–11) was from Aldrich (Steinheim, Germany). Single-component heptakis-(6-*O*-sulfo)-β-CD (HS-β-CD) [19], heptakis-(2,3-di-*O*-methyl-6-*O*-sulfo)-β-CD (HDMS-β-CD) [20], heptakis-(2,3-di-*O*-acetyl-6-sulfo)-β-CD (HDAS-β-CD) [21] and heptakis-(2-*O*-methyl-3,6-di-*O*-sulfo)-β-CD (HMdiSu-β-CD) [22] were kindly provided by Prof. G. Vigh from the Department of Chemistry, Texas A&M University, College Station, TX. Heptakis-(2,3-di-*O*-methyl)-β-CD (2,3-DM-β-CD) and heptakis-(2,3-di-*O*-acetyl)-β-CD (HDA-β-CD) were synthesized in our laboratory according to the methods

Table 1
Enantioseparation of *erythro*-MQ with various CDs

Chiral selector	Concentration of chiral selector (mg/ml)	t_1 (min)	t_2 (min)	t_2/t_1	Enantiomer migration order
Without chiral selector	–	10.84	10.84	1.00	–
α-CD	120	16.47	16.93	1.03	−/+
Me-α-CD	80	18.51	18.97	1.03	−/+
HP-α-CD	60	21.72	25.44	1.17	−/+
CM-α-CD	40	24.17	25.69	1.07	+/−
β-CD	18	13.73	13.95	1.02	−/+
Me-β-CD	80	24.19	25.14	1.04	−/+
2,6-DM-β-CD	40	24.34	26.22	1.08	−/+
2,3-DM-β-CD	40	15.93	16.08	1.01	−/+
TM-β-CD	70	19.55	19.55	1.00	–
	150	31.87	32.44	1.02	+/−
HP-β-CD	60	25.77	28.94	1.12	−/+
HE-β-CD	60	17.56	19.41	1.11	−/+
Acetyl-β-CD	60	31.52	32.35	1.03	−/+
Succinyl-β-CD	20	11.01	11.19	1.02	−/+
SBE-β-CD	0.2	12.84	15.33	1.19	−/+
HDAS-β-CD	5	17.98	22.04	1.23	−/+
HDMS-β-CD	40	42.09	43.67	1.04	+/−
HS-β-CD	2	12.39	12.70	1.03	−/+
	5	22.88	24.86	1.09	−/+
HMdiSu-β-CD	10	38.41	50.77	1.32	+/−
HDA-β-CD	20	11.97	12.35	1.03	+/−
CM-β-CD	10	28.69	54.72	1.91	−/+
SU-β-CD	5	36.80	42.40	1.15	+/−
γ-CD	100	22.63	22.94	1.01	−/+
HP-γ-CD	60	19.23	19.66	1.02	−/+

described in Ref. [23]. Carboxymethyl-α-CD (CM-α-CD, DS ca. 4.5) was synthesized in our laboratory according to the method described in Ref. [24]. Sulfobutyl-β-CD (SBE-β-CD, DS = 4.0) was obtained from Cydex (Overland Park, KS). Analytical grade triethanolamine and H_3PO_4 were purchased from Merck (Darmstadt, Germany).

2.2. Capillary electrophoresis

CE separations were performed using a Beckman P/ACE 5010 CE system (Beckman Coulter, Fullerton, CA) equipped with an UV detector. The samples were injected by pressure, 0.5 psi, for 3 s. A fused-silica capillary (Polymicro Technologies, Phoenix, AZ) of 37 cm (30 cm effective length) and 50 μm ID was used. The separations were performed in 100 mM triethanolamine phosphate buffer at pH 3.0 adjusted after the addition of a chiral selector. The separation temperature was 296 K. The applied voltage was 20 kV. The separation capillary was conditioned by flushing of 0.1 M sodium hydroxide for 3 min and the run buffer for 10 min. Other experimental conditions are given in the legends of the figures.

3. Results and discussion

3.1. Enantioseparation of erythro-MQ with various CDs

The results of the enantioseparation of *erythro*-MQ with various CDs as chiral selectors are summarized in Table 1. Chiral selectors have been used in different concentrations varying from 0.2 to 150 mg/ml. This was caused by different affinities and enantioselectivities of the binding of the *erythro*-MQ enantiomers to the chiral selectors. Enantioseparations were observed

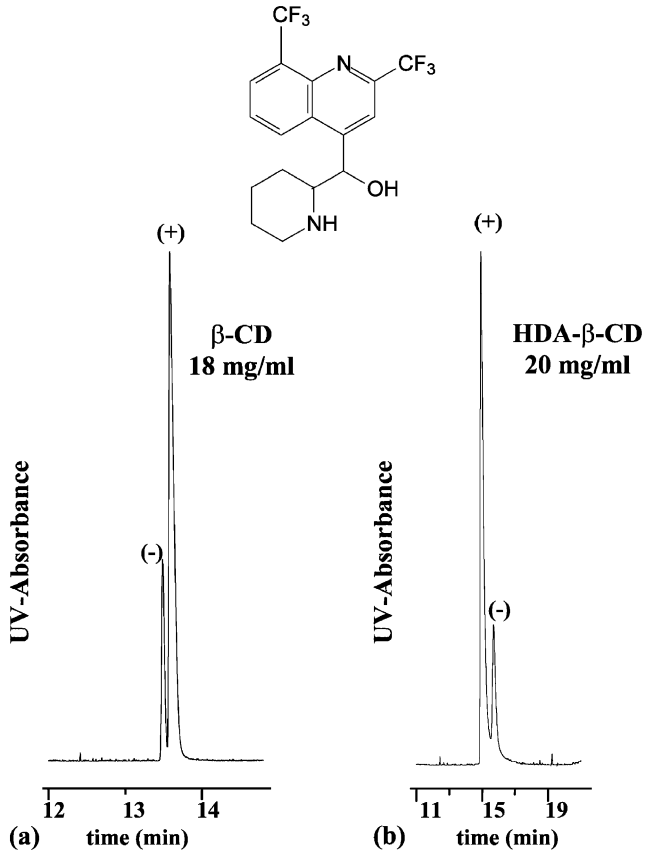

Fig. 2. Enantioseparation of a 3:1 mixture of (+)- and (−)-*erythro*-MQ in the presence of 18 mg/ml β-CD (a), and 20 mg/ml heptakis-(2,3-di-*O*-acetyl)-β-CD (b). Other conditions were as indicated in the experimental part.

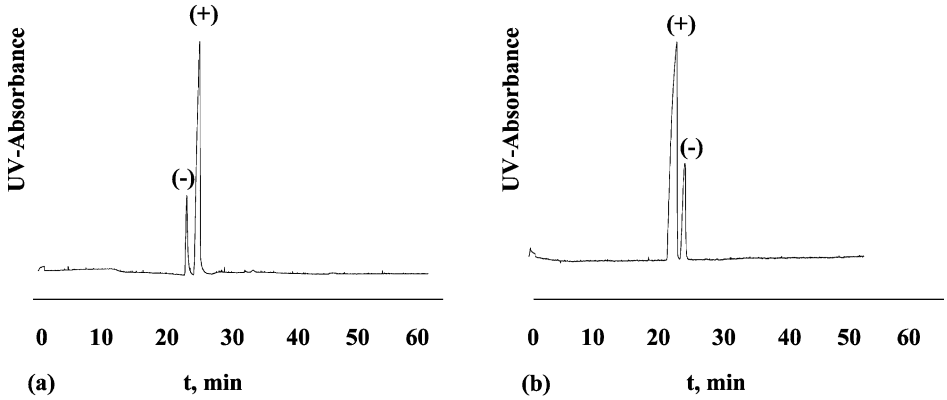

Fig. 3. Enantioseparation of a 3:1 mixture of (+)- and (−)-*erythro*-MQ in the presence of 5 mg/ml heptakis-(6-*O*-sulfo)-β-CD and 5 mg/ml randomly sulfated β-CD. Other conditions were as indicated in Section 2.

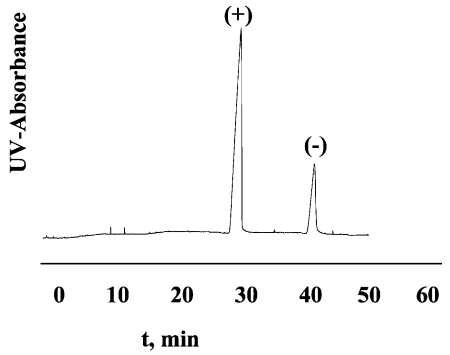

Fig. 4. Enantioseparation of a 3:1 mixture of (+)- and (−)-*erythro*-MQ in the presence of 10 mg/ml heptakis-(2-*O*-methyl-3,6-di-*O*-sulfo)-β-CD. Other conditions were as indicated in Section 2.

with all the three native CDs, α-, β-, and γ-CD, and the enantiomer migration order was the same in all cases. (+)-*erythro*-MQ was the more tightly bound enantiomer (Table 1). Among the native CDs, β-CD was the most efficient chiral selector and higher concentrations of α- and γ-CD were required for adequate enantioseparations. The hydroxyalkyl derivatives of α- and β-CDs appeared to be very efficient chiral selectors as well (Table 1).

From the viewpoint of the enantiomer migration order, it appears that a random acetylation of β-CD does not affect the enantiomer affinity pattern, whereas a selective acetylation in positions 2 and 3 of the glucose units reverts it (Fig. 2). The opposite was true in the case of sulfation. Thus,

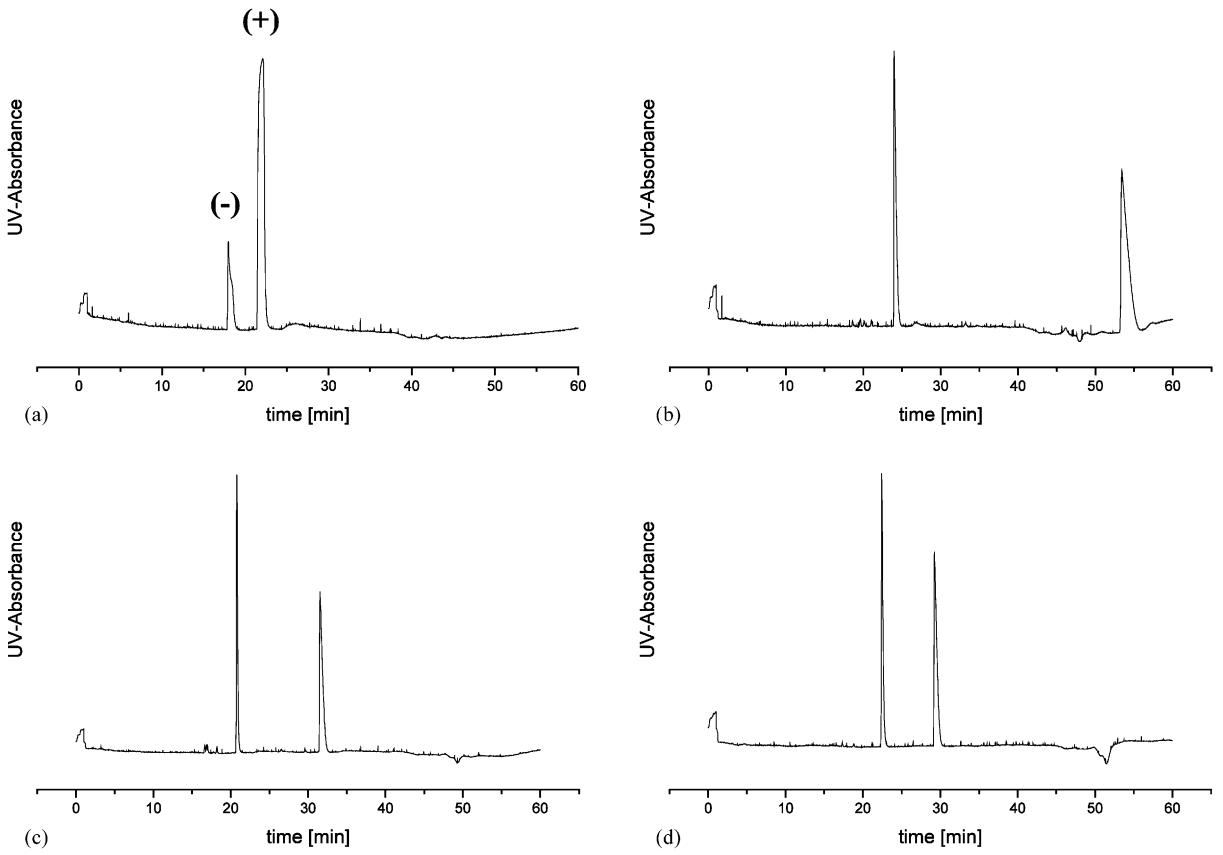

Fig. 5. Enantioseparation of (±)-*erythro*-MQ (a) and its analogues, (*R*,*S*)-*erythro*-α-(2-piperidyl-)-2,7-bis(trifluoromethyl)-4-chinolmethanol (b), (*R*,*S*)-*erythro*-α-(2-piperidyl-)-7-chloro-(2-trifluoromethyl)-4-chinolmethanol (c) and (*R*,*S*)-*erythro*-α-(2-piperidyl-)-8-chloro-(2-trifluoromethyl)-4-chinolmethanol (d) in the presence of 5 mg/ml heptakis-(2,3-di-*O*-acetyl-6-sulfo)-β-CD. Other conditions were as indicated in Section 2.

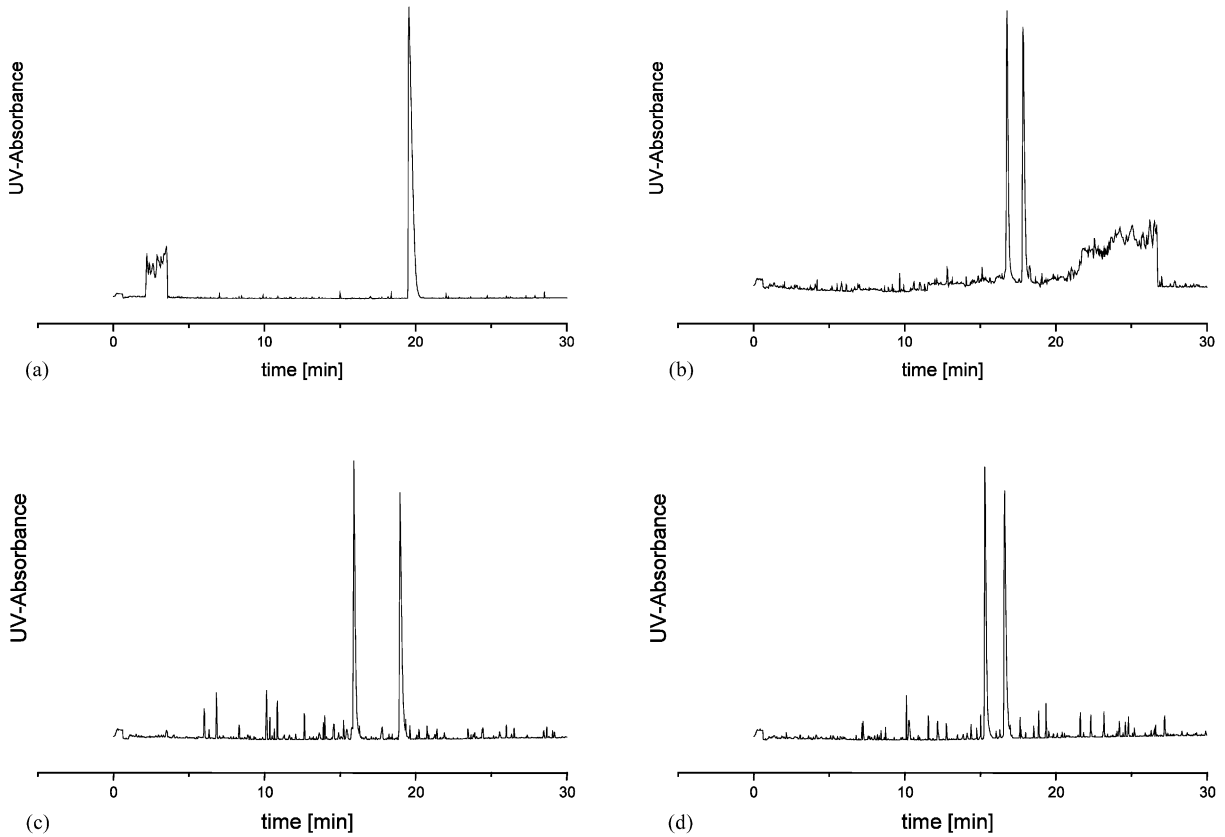

Fig. 6. Enantioseparation of (±)-*erythro*-MQ (a) and its analogues, (*R*,*S*)-*erythro*-α-(2-piperidyl-)-2,7-bis(trifluoromethyl)-4-quinolinemethanol (b), (*R*,*S*)-*erythro*-α-(2-piperidyl-)-7-chloro-(2-trifluoromethyl)-4-quinolinemethanol (c) and (*R*,*S*)-*erythro*-α-(2-piperidyl-)-8-chloro-(2-trifluoromethyl)-4-quinolinemethanol (d) in the presence of 70 mg/ml heptakis-(2,3,6-tri-*O*-methyl)-β-CD. Other conditions were as indicated in Section 2.

the enantiomer affinity pattern of *erythro*-MQ was identical towards native β-CD and β-CD derivative, which was selectively sulfated in position 6, but it was opposite in the case of randomly sulfated β-CD (Fig. 3). These results must be interpreted with certain care because not only the substituents but also the position of the substitution was different for selectively derivatized β-CD acetates and sulfates. The novel charged β-CD derivative, HMdiSu-β-CD, exhibited relatively high-enantiomer resolving ability of the enantiomers of *erythro*-MQ (Fig. 4). This result seems interesting because HMdiSu-β-CD is very crowded CD derivative [22] and not very suitable for inclusion-complex formation as shown in a recent study [25].

It seems interesting to examine which substituent dominates when different substituents are attached to the CD rims. Thus, for example, sulfation of primary hydroxyl groups in position 6 of β-CD does not revert the enantiomer migration order of (±)-*erythro*-MQ (Table 1) while acetylation in positions 2 and 3 of β-CD reverts it. Interestingly, a simultaneous 2,3-di-*O*-acetylation and 6-sulfation does not affect the enantiomer affinity pattern of *erythro*-MQ (Table 1).

3.2. The effect of structural modification of the analyte on the enantioseparation with CDs

The high separation efficiency of CE often allows the simultaneous separation and enantiose-

Table 2
Enantioseparation of the analogues of *erythro*-MQ, (*R*,*S*)-*erythro*-α-(2-piperidyl-)-7-chloro-(2-trifluoromethyl)-4-quinolinemethanol (**1**), (*R*,*S*)-*erythro*-α-(2-piperidyl-)-2,7-bis(trifluoromethyl)-4-quinolinemethanol (**2**) and (*R*,*S*)-*erythro*-α-(2-piperidyl-)-8-chloro-(2-trifluoromethyl)-4-quinolinemethanol (**3**) with various CDs

Chiral selector	Concentration of chiral selector	1			2			3		
		t_1	t_2	α	t_1	t_2	α	t_1	t_2	α
Without chiral selector	–	10.40	10.40	1.00	10.62	10.62	1.00	10.19	10.19	1.00
α-CD	120	24.83	24.83	1.00	25.54	26.23	1.03	16.86	17.52	1.04
Me-α-CD	80	25.18	25.18	1.00	25.78	25.78	1.00	21.45	23.15	1.08
HP-α-CD	60	29.65	30.15	1.02	27.48	28.64	1.04	20.11	23.71	1.18
CM-α-CD	2	14.72	15.59	1.06	20.89	26.26	1.25	13.15	13.53	1.03
β-CD	18	12.28	12.77	1.04	17.40	17.61	1.01	10.16	10.31	1.02
Me-β-CD	80	22.51	25.20	1.12	24.52	25.63	1.05	20.29	23.88	1.18
2,6-DM-β-CD	40	25.88	29.74	1.15	27.30	28.97	1.06	20.73	27.72	1.34
2,3-DM-β-CD	40	15.23	17.31	1.14	15.31	16.00	1.05	14.04	14.55	1.04
TM-β-CD	70	15.91	18.97	1.19	16.76	17.83	1.06	15.28	16.63	1.09
HP-β-CD	60	23.63	28.15	1.19	27.17	29.18	1.07	20.02	23.64	1.18
HE-β-CD	60	18.53	21.70	1.17	21.08	22.42	1.06	15.78	17.68	1.12
AC-β-CD	60	34.82	35.51	1.02	42.73	43.73	1.02	24.07	25.70	1.07
Succinyl-β-CD	20	11.58	12.06	1.04	13.44	13.70	1.02	10.00	10.17	1.02
SBE-β-CD	0.2	10.29	14.09	1.37	10.80	14.30	1.32	8.93	9.51	1.07
HDAS-β-CD	5	20.79	31.53	1.52	23.98	53.41	2.23	22.43	29.21	1.30
HDMS-β-CD	20	27.98	28.96	1.04	27.91	28.37	1.02	19.75	22.71	1.15
HS-β-CD	5	26.25	33.51	1.28	11.91	13.55	1.14	23.13	36.25	1.57
HMdiSu-β-CD	10	33.12	49.99	1.51	29.06	38.41	1.51	15.50	17.89	1.15
HDA-β-CD	20	12.40	12.63	1.02	12.74	12.99	1.02	12.18	12.40	1.02
CM-β-CD	5	15.79	23.90	1.54	17.67	23.60	1.34	9.94	11.03	1.11
SU-β-CD	3	22.75	23.49	1.03	27.89	30.62	1.10	21.70	23.28	1.07
	5	38.71	41.92	1.08	66.20	95.12	1.44	38.49	45.52	1.18
γ-CD	100	17.38	17.62	1.01	17.80	17.80	1.00	17.62	18.07	1.03
HP-γ-CD	60	13.94	14.29	1.03	14.47	14.69	1.02	15.15	15.70	1.04

paration of structurally closely related compounds [26,27]. This represents a certain interest for both, bioanalytical studies as well as for the understanding of the effect of fine structural modifications of the analytes on their interaction with chiral selectors. As shown above, the nature and position of substituents attached to the CD rim may affect the enantiomer affinity pattern of chiral analytes towards CDs. In this part, the effect of structural modification of analytes on their interactions with CDs is discussed. Even fine structural modification of the analyte may have a significant effect on its interaction with a chiral selector. Thus, for example, a shift of the trifluoromethyl group from position 8 (MQ) to position 7 drastically improved the enantioseparation in the case of most chiral selectors. The chlorine substituent was also preferable over the trifluoromethyl group in the same position 8. The examples shown in Fig. 5 were observed when using HDAS-β-CD as a chiral selector (Fig. 5).

Similar effects were also observed in the case of TM-β-CD as chiral selector. This CD does not resolve the enantiomers of *erythro*-MQ at a concentration of 70 mg/ml, but the enantiomers of all the three analogues of *erythro*-MQ were baseline resolved under the same experimental conditions (Fig. 6).

3.3. Simultaneous enantioseparation of erythro-MQ and its structural analogues

All CDs from Table 1 were screened for the enantioseparation of the analogues of *erythro*-MQ

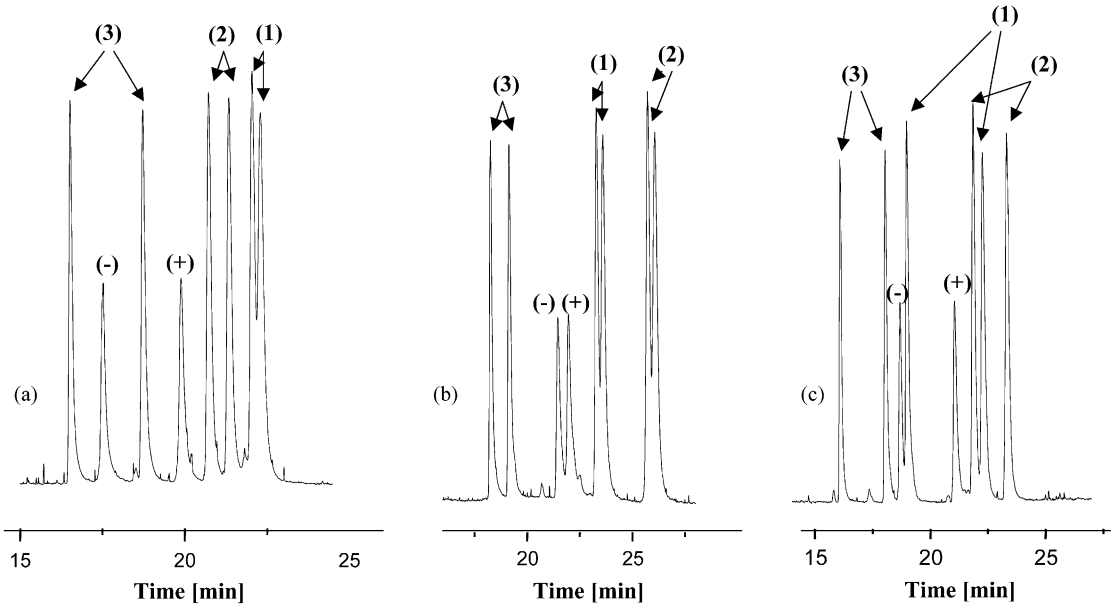

Fig. 7. Simultaneous enantioseparation of (±)-*erythro*-MQ and its analogues, (*R*,*S*)-*erythro*-α-(2-piperidyl-)-2,7-bis(trifluoromethyl)-4-quinolinemethanol (**1**), (*R*,*S*)-*erythro*-α-(2-piperidyl-)-7-chloro-(2-trifluoromethyl)-4-quinolinemethanol (**2**) and (*R*,*S*)-*erythro*-α-(2-piperidyl-)-8-chloro-(2-trifluoromethyl)-4-quinolinemethanol (**3**) in the presence of 60 mg/ml hydroxypropyl-α-CD (a), 60 mg/ml randomly acetylated β-CD (b) and 60 mg/ml hydroxyethyl-β-CD (c). Other conditions were as indicated in Section 2.

as well as for the simultaneous enantioseparation of *erythro*-MQ and analogues (Table 2). No optimization was performed, and all CDs were examined under similar conditions except for the concentration of the chiral selectors. Quite surprisingly, neither the native CDs nor the selectively substituted, single-component neutral or charged CDs but the randomly hydroxyalkylated CD and randomly acetylated CD derivatives appeared to be more suitable chiral selectors for the simultaneous enantioseparation of MQ and its structurally closely related analogues (Fig. 7). Similar results have been observed recently by Zhou et al. [28] for sulfated derivatives of β-CD. Different chemo- and enantioselectivity patterns were observed for HP-α-CD, acetyl-β-CD and HE-β-CD, the latter CD appearing to provide the best combination of chemo- and enantioselectivity. Apparently, a complex array of chiral selectors present in the randomly substituted CDs acts by chance in a co-operative way for the present set of compounds.

4. Conclusions

This study illustrates once again the need to carefully address the enantiomer affinity pattern of analytes towards CD-type chiral selectors in CE. A multivariate scenario may be observed depending on the nature of the substituents and the substitution pattern of the CDs. The functional groups and their position in the chiral analyte may also have significant effects on the analyte interaction with a chiral selector and the enantiorecognition. Even very fine changes in the structure of an analyte may drastically affect the binding and the enantiorecognition pattern. CE is a suitable technique for the separation of the enantiomers of

erythro-MQ as well as for the simultaneous enantioseparation of its structural analogues.

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