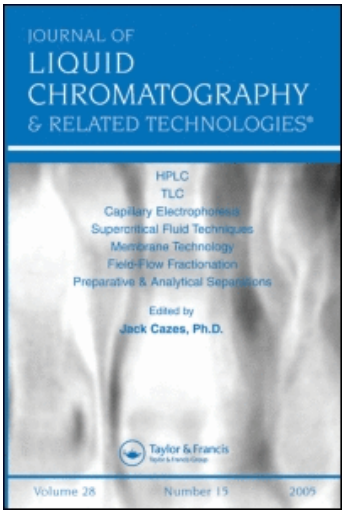

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ENANTIOSEPARATIONS BY CAPILLARY ELECTROPHORESIS USING CHIRAL GLYCOSIDIC SURFACTANTS. II. COMPARISON OF CHIRAL CYCLOHEXYL-ALKYL-β-D-MALTOSIDE SURFACTANTS

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ABSTRACT

Three different glycosidic surfactants, namely cyclohexyl-butyl-β-D-maltoside (CYMAL-4), cyclohexyl-pentyl-β-D-maltoside (CYMAL-5), and cyclohexyl-hexyl-β-D-maltoside (CYMAL-6), were compared in the enantioseparation of some dansyl amino acids and methylated tryptophans. The three CYMAL surfactants have the same chiral maltoside head group but differ in the length of the hydrophobic tail. Increasing the length of the hydrophobic tail seems to shift the optimum surfactant concentration for maximum enantioresolution towards lower concentration values. In order to extend the range of optimum surfactant concentration over which maximum enantioresolution can be achieved, mixed CYMAL surfactant systems were introduced and evaluated. They consisted of mixing CYMAL-6 with either cyclohexyl-methyl-β-D-maltoside (CYMAL-1) or cyclohexyl-ethyl-β-D-maltoside (CYMAL-2).

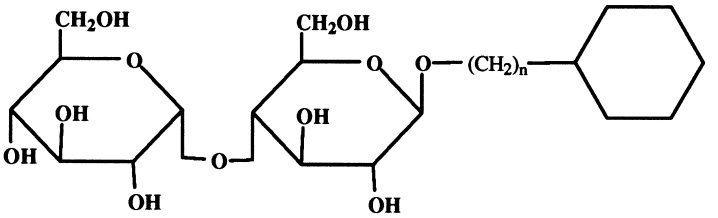

Figure 1. Structures of the CYMAL surfactants used in this study.

INTRODUCTION

In a recent article from our laboratory,[1] CYMAL-5 surfactant was demonstrated as a useful chiral selector to perform enantiomeric separations by CE. This present report is concerned with (i) the comparison of the enantioselectivity of three different CYMAL surfactants, namely, CYMAL-4, CYMAL-5, and CYMAL-6, and (ii) the evaluation of mixed micelle systems of CYMAL-6 / CYMAL-1 and CYMAL-6 / CYMAL-2. CYMAL surfactants have in common the same chiral head group but differ in the hydrophobic tail (for structures, see Figure 1), thus allowing the assessment of the effect of the hydrophobic tail on selectivity.

It is possible to employ combinations of different chiral selectors to alter separation selectivity. Recently, our laboratory has reported the enantiomeric separation of phenoxy acid herbicides using electrolyte systems based on mixed cyclodextrins (CDs).[2] Since the various CDs exhibited different chiral selectivity toward the phenoxy acid herbicides derivatized with 7-aminonaphthalene-1,3-disulfonic acid, electrolyte systems composed of mixed CDs yielded a unique chiral selectivity that could not be achieved by either of the CDs alone.

Thus far, enantiomeric separations by CE using chiral micelles have involved mixed chiral/achiral system, or CD-modified micellar system. In the first approach, Otsuka and Tarabe[3] used a nonionic chiral surfactant, digitonin, with anionic sodium dodecyl sulfate (SDS) to form mixed micelles. Under acidic conditions (pH 3.0), phenylthiohydantoin-derivatized amino acids were optically resolved with a 25 mM digitonin-50 mM SDS solution, although a long separation time was required (90 minutes). A mixed micelle consisting of glycyrrhizic acid, octyl-β-D-glucoside, and SDS has been used to separate the enantiomers of several Dns-AA's.[4] In the second approach, a CD-modified SDS micellar phase was introduced for the separation of chiral drugs thiopental and pentobarbital in their enantiomers at pH 9 in the presence of SDS and γ-CD.[5]

As shown in this report, the CYMAL surfactants do not need to be mixed with SDS or other charged achiral surfactants for the separation of charged enantiomers. This fact is one of the various advantages of CYMAL, which include, among other things, high solubility in aqueous solution, transparency in the UV, ability of complexing with borate thus leading to the formation of in situ charged micelles.[6-8]

EXPERIMENTAL

Reagents

Cyclohexyl-alkyl-β-D-maltoside surfactants, namely CYMAL-1, 2, 4, 5, and 6 were purchased from Anatrace (Mumee, OH, USA). For structures, see Figure 1. All dansyl amino acids (Dns-AA's), including Dns-phenylalanine (Dns-Phe), Dns-leucine (Dns-Leu), Dns-methionine (Dns-Met), and Dns-valine (Dns-Val), were purchased from Sigma (St. Louis, MO, USA). All methyl substituted tryptophans (Met-Trp's), namely, 5-methyl-tryptophan (5-Met-Trp), 6-methyl-tryptophan (6-Met-Trp), and 7-methyl-tryptophan (7-Met-Trp) were also purchased from Sigma. Sodium phosphate monobasic was obtained from Mallinckrodt Specialty Chemical Co. (Paris, KY, USA). Phosphoric acid was purchased from EM Science (Cherry Hill, NJ, USA). Sodium phosphate dibasic was from Fisher Scientific (Pittsburgh, PA, USA).

Capillary Electrophoresis Instrument

The capillary electrophoresis instrument was assembled in-house from commercially available components. It consisted of two 30-kV d.c. power supplies of positive and negative polarity, Models MJ30P400 and MJ 0N400, respectively, from Glassman High Voltage (Whitehouse Station, NJ, USA) and a UV-Vis variable wavelength detector, Model 200, from Linear Instrument (Reno, NV, USA) equipped with a cell for on-column detection. Detection was performed at 254 nm for all solutes. The electropherograms were recorded with a Shimadzu data processor Model CR601 (Kyoto, Japan). Fused-silica capillaries were obtained from Polymicro Technology (Phoenix, AZ, USA) with 50 μm I.D. and 360 μm O.D. The total length of the capillary was 80 cm, the distance from injection end to the detection point was 50 cm.

RESULTS AND DISCUSSION

To assess the effect of the hydrophobic tail of CYMAL surfactants on enantiomeric resolution, three different CYMAL possessing hydrophobic tails of

Table 1

Effect of Surfactant Concentration on Enantioresolution*

	CYMAL-4					CYMAL-5					CYMAL-6					
	8	**10**	**12**	**18**	**30**	**6**	**8**	**10**	**12**	**18**	**2**	**6**	**8**	**10**	**12**	**18**
Dns-Phe	0	0.41	0.30	0.27	0	0.18	0.25	0.41	0.42	0.10	0	0.14	0.10	0.07	0	0
Dns-Val	0	0	0.50	0.70	0.90	0.41	0.50	0.65	1.05	1.11	0	0.90	1.05	1.12	1.08	1.00
Dns-Met	0	0	0.75	1.25	1.18	0.70	1.00	1.26	1.44	1.57	0	1.26	1.26	1.27	1.27	1.35
Dns-Leu	0.28	0.71	0.92	1.50	1.50	1.00	1.57	1.87	1.86	1.30	0.57	1.85	1.70	1.56	1.39	1.04

* Running electrolyte 75 mM sodium phosphate, pH 6.5, containing various concentrations of CYMAL-4, 5, or 6; voltage, 20 kV; capillary, bare fused-silica, 80 cm (total length) x 50 μm I.D. with detection window at 50 cm.

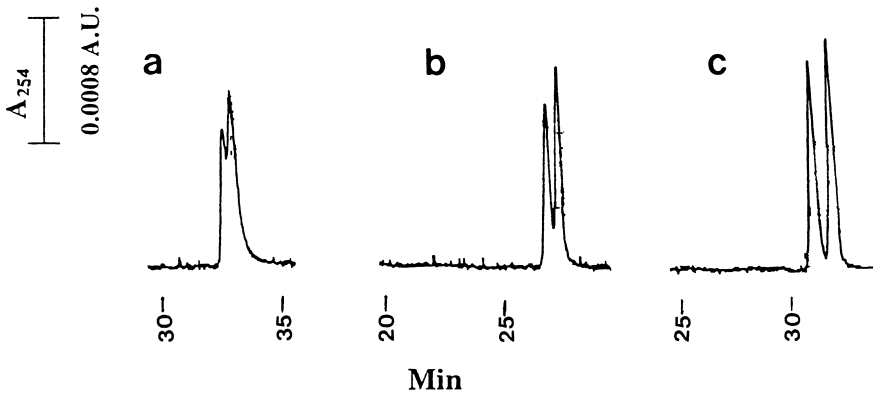

Figure 2. Electropherograms of Dns-Leu obtained with CYMAL-4, 5, and 6. Conditions: running electrolyte, 75 mM sodium phosphate, pH 6.5, containing (a) 10 mM CYMAL-4 (b) 6 mM CYMAL-5 (c) 6 mM CYMAL-6; voltage, 20 kV; capillary, bare fused-silica, 80 cm (total length) x 50 µm I.D. with detection window at 50 cm.

different size were compared over a wide range of surfactant concentration. Furthermore, to alter the enantioselectivity of the CYMAL surfactants, mixed micelles were studied. Dns-AA's and methylated tryptophans were used as the model chiral solutes.

Comparison of CYMAL-4, 5, and 6

Table 1 shows the dependence of the enantiomeric resolution on the concentration of CYMAL-4, CYMAL-5, and CYMAL-6. The enantiomeric resolution of Dns-Leu was best achieved at 6 mM CYMAL-6, while the maximum resolution of the same chiral compound was only attained at 10–12 mM CYMAL-5 and 18–30 mM CYMAL-4. Figure 2 shows the electropherograms of Dns-Leu in the presence of the different CYMAL surfactants. As can be seen in Figure 2, Dns-Leu was baseline separated at 6 mM CYMAL-6, and only slightly separated at 10 mM CYMAL-4. No enantioresolution was observed at 8 or 10 mM CYMAL-4 for Dns-Val and Dns-Met. Conversely, these two chiral compounds were well separated into their corresponding enantiomers at as low as 6 mM CYMAL-6. Since the size of the nonpolar tail of the surfactants increases in the order: CYMAL-4 < CYMAL-5 < CYMAL-6, it is obvious that the CMC decreases in the order: CYMAL-4 > CYMAL-5 > CYMAL-6. CYMAL-6 has a CMC value of 0.56 mM while the CMC values of CYMAL-5 and CYMAL-4 are relatively high reaching 2.4 and 7.6 mM, respectively. The smaller the CMC value of a given surfactant the bigger the size of its micelle, and consequently the greater the solubilization of a given solute into that micelle.

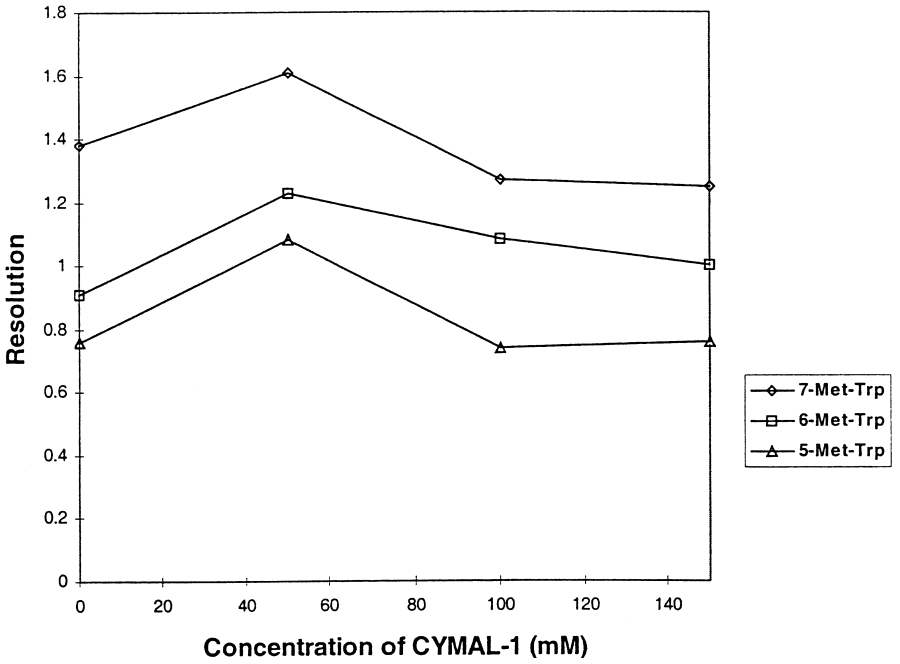

Figure 3. Effect of CYMAL-1 concentration on the enantiomeric resolution of Met-Trp's in the mixed CYMAL-6 / CYMAL-1 system. Conditions: running electrolyte, 75 mM sodium phosphate, pH 2.5, containing 50 mM CYMAL-6 and various concentration of CYMAL-1; voltage, 20 kV; capillary, bare fused-silica, 80 cm (total length) x 50 μm I.D. with detection window at 50 cm.

This may explain the fact that CYMAL-6 is more effective in enantioseparation than CYMAL-4 and CYMAL-5. The enantiomeric resolution is achieved when the two enantiomers exhibit different association constants with the chiral micelles.

Mixed Chiral Micelles

Since the various CYMAL surfactants (e.g., CYMAL-4, 5, and 6) exhibited different dependence between resolution and surfactant concentration (e.g., the concentration range for maximum resolution), it was interesting to evaluate the effect of mixing CYMAL surfactants of shorter hydrophobic tail (e.g., CYMAL-1 and 2) with CYMAL-6 in order to extend the concentration range over which the maximum enantioresolution can be achieved. It is well established that the addition of a co-surfactant changes the physical properties of

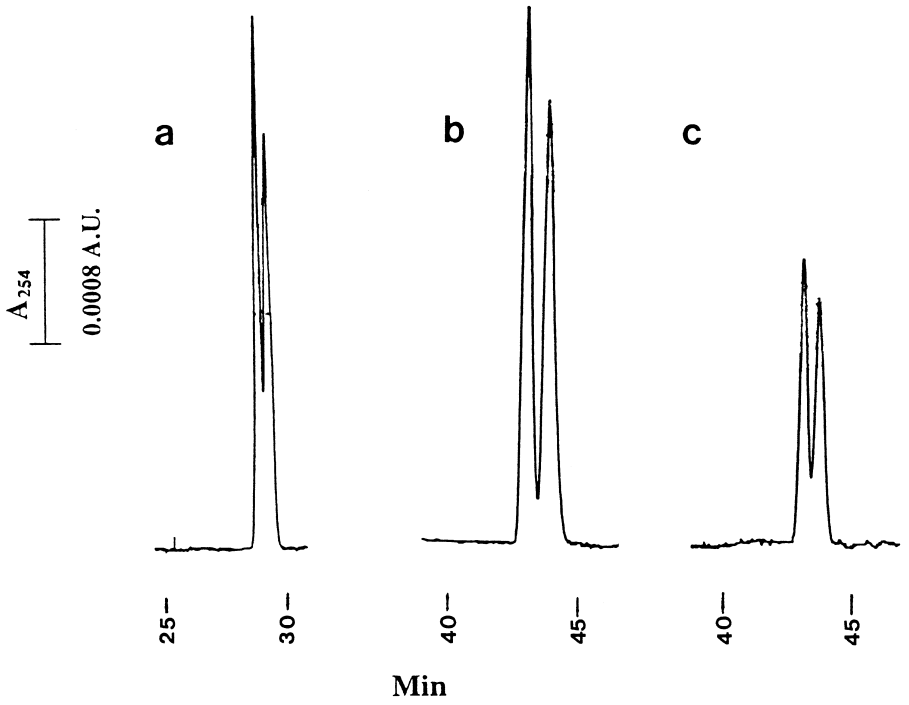

Figure 4. Electropherograms of 6-Met-Trp obtained with the mixed CYMAL-6 / CYMAL-1 system. Conditions: running electrolyte, 75 mM sodium phosphate, pH 2.5, containing 50 mM CYMAL-6 and (a) 0 mM (b) 50 mM and (c) 150 mM CYMAL-1; voltage, 20 kV; capillary, bare fused-silica, 80 cm (total length) x 50 μm I.D. with detection window at 50 cm.

the micelle, e.g., CMC and aggregation number. The CMC of binary surfactant mixtures (CMC_{mix}) may be less than (synergism), an intermediate of, or greater than (negative synergism) the CMC of the two components.[9,10] For neutral micelles (e.g., CYMAL), the CMC_{mix} is usually an intermediate value between the two individual surfactants, but it is disproportionally influenced by the lower CMC component, i.e., by the longer hydrophobic tail surfactant (e.g. CYMAL-6). Mixed micelle formation in aqueous solutions arises from hydrophobic and electrostatic interactions.

While mixed cationic-anionic micelles are termed nonideal because of electrostatic attraction between dissimilar charges, micelles formed from surfactants of like charges behave ideally.[11] Thus, mixed micellar systems composed of neutral surfactants (e.g., CYMAL-6 / CYMAL-1 or CYMAL-2) will obey ideal mixing behavior.[11]

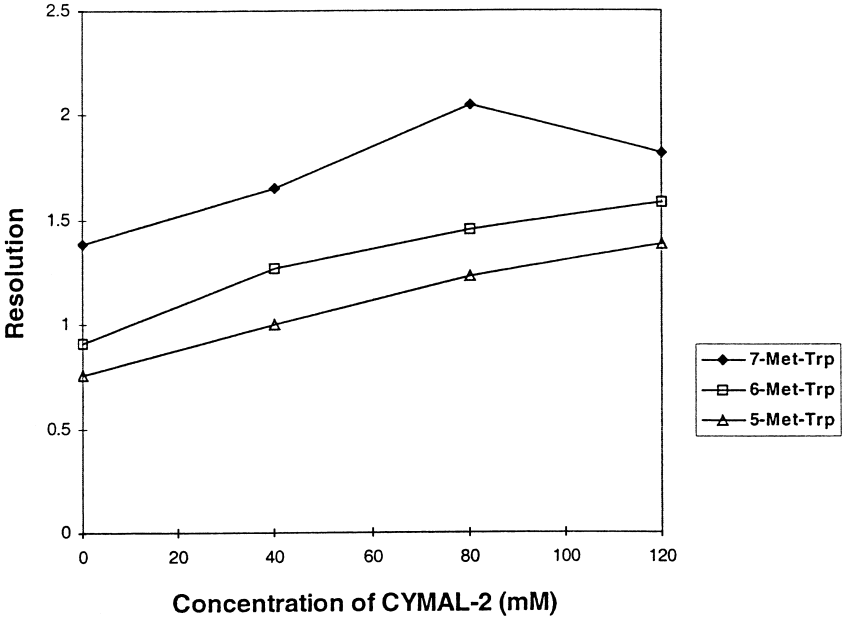

Figure 5. Effect of CYMAL-2 concentration on the enantiomeric resolution of Met-Trp's obtained with the mixed CYMAL-6 / CYMAL-2 system. Conditions: running electrolyte, 75 mM sodium phosphate, pH 2.5, containing 50 mM CYMAL-6 and various concentration of CYMAL-2; voltage, 20 kV; capillary, bare fused-silica, 80 cm (total length) x 50 μm I.D. with detection window at 50 cm.

Mixed CYMAL-6 / CYMAL-1

Improvement in the selectivity of an enantiomeric separation can be achieved by employing mixed chiral micellar systems. CYMAL-1 has a CMC of 340 mM. When CYMAL-1 monomers are mixed with CYMAL-6 micelles, they can associate in between the surfactant molecules of the CYMAL-6 micelle, thus modifying the micelles and providing different selectivity.

With the addition of CYMAL-1 to CYMAL-6, resolution increased first, reached a maximum, and then decreased.

As shown in Figure 3, it seems that too much CYMAL-1 (> 50 mM) monomer leads to decreasing the aggregation of CYMAL-6 micelle and consequently resolution. Figure 4 illustrates electropherograms of 6-Met-Trp in mixed micelles of CYMAL-6 / CYMAL-1.

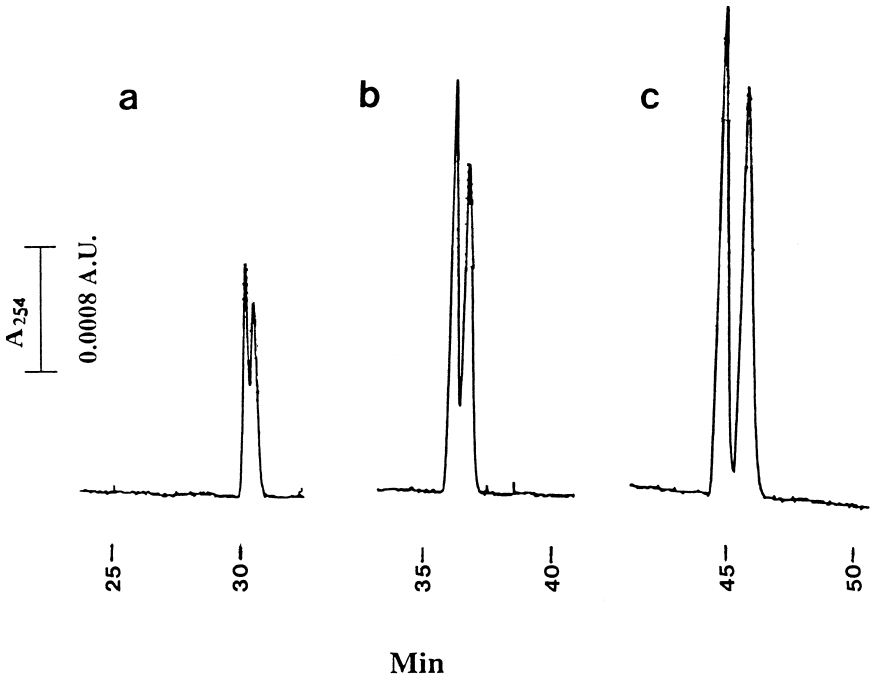

Figure 6. Electropherograms of 5-Met-Trp obtained with the mixed CYMAL-6 / CYMAL-2 system. Conditions: running electrolyte, 75 mM sodium phosphate, pH 2.5, containing 50 mM CYMAL-6 and (a) 0 mM (b) 40 mM (c) 120 mM CYMAL-2; voltage, 20 kV; capillary, bare fused-silica, 80 cm (total length) x 50 μm I.D. with detection window at 50 cm.

Mixed CYMAL-6 / CYMAL-2

The CMC of CYMAL-2 is 120 mM. CYMAL-2 has one additional carbon atom in its hydrophobic tail than in the hydrophobic tail of CYMAL-1. This leads to 3 times decrease in CMC value when going from CYMAL-1 to CYMAL-2. Figure 5 shows that the enantiomeric resolution of the three model solutes is very much improved even at higher concentration of CYMAL-2.

This is contrary to the obtained behavior with CYMAL-1 / CYMAL-6 system. CYMAL-1 or 2 can be regarded as suitable additives for manipulating the resolution of chiral system. Figures 6 and 7 show the electropherograms of 5-Met-Trp and 6-Met-Trp in CYMAL-6 / CYMAL-2 system, respectively.

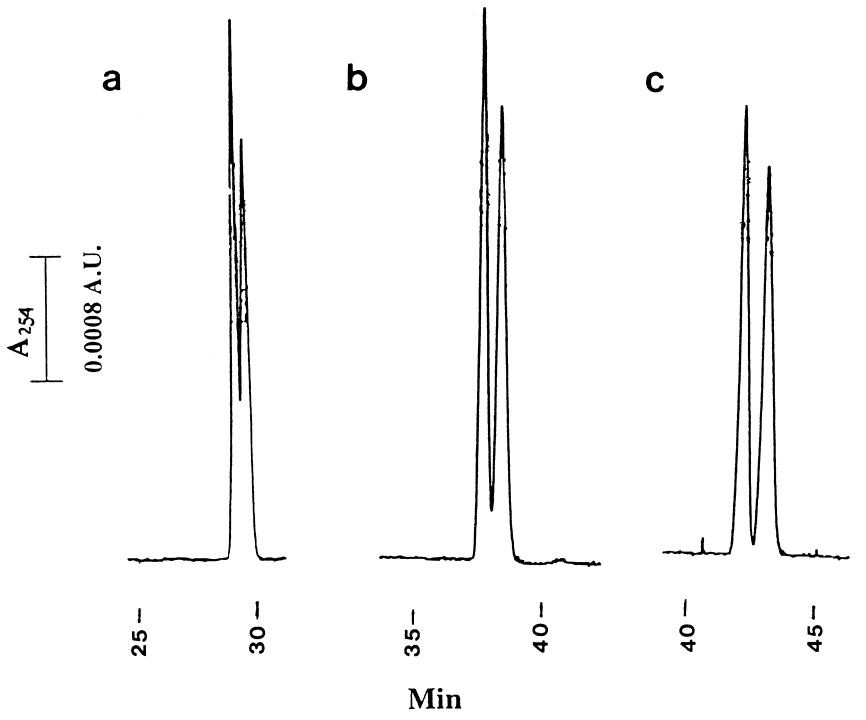

Figure 7. Electropherograms of 6-Met-Trp obtained with the mixed CYMAL-6 / CYMAL-2 system. Conditions: running electrolyte, 75 mM sodium phosphate, pH 2.5, containing 50 mM CYMAL-6 and (a) 0 mM (b) 40 mM and (c) 120 mM CYMAL-2; voltage, 20 kV; capillary, bare fused-silica, 80 cm (total length) x 50 μm I.D. with detection window at 50 cm.

maximum enantioresolution is obtained at lower surfactant concentration with the CYMAL of larger hydrophobic tail (e.g., CYMAL-6) than with the CYMAL of smaller hydrophobic tail (e.g., CYMAL-4). However, maximum resolution is located over a narrow range of surfactant concentration in the case of CYMAL-6, which makes the optimization of separation rather tedious because a narrow concentration range leads to either hit or miss the optimal concentration.

This limitation observed with the CYMAL of a larger size hydrophobic tail, e.g., CYMAL-6, was alleviated by mixing CYMAL-6 with CYMAL of small hydrophobic tails, e.g., CYMAL-1 and CYMAL-2, of relatively large CMC values.

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