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Combination of capillary electrophoresis, molecular modelling and nuclear magnetic resonance to study the interaction mechanisms between single-isomer anionic cyclodextrin derivatives and basic drug enantiomers in a methanolic background electrolyte

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ABSTRACT

In order to improve our knowledge of the mechanisms of enantiomer recognition pattern in non-aqueous systems, an approach combining nonaqueous CE (NACE), molecular modelling and NMR was undertaken. Bupivacaine and propranolol were selected as model compounds and their interactions with two single-isomer highly charged β-CD derivatives, namely heptakis(2,3-di-*O*-methyl-6-*O*-sulfo)-β-CD (HDMS-β-CD) and heptakis(2,3-di-*O*-acetyl-6-*O*-sulfo)-β-CD (HDAS-β-CD), were studied. The CD-bupivacaine complexes were evaluated by 2-D Rotating-frame Overhauser Effect SpectroscopY (ROESY) experiments. From these experiments, it can be assumed that inclusion complexes are not formed, whatever the CD derivative used. Molecular modelling was performed at the RHF/MINI-1 or B3LYP/6-31G(d) level. External as well as inclusion type complexes with the alkyl chain of propranolol into both CD cavities were located. Interaction energies calculated for bupivacaine and propranolol correlated with the enantiomer migration order observed in the NACE experiments using both anionic CD derivatives. The interaction of propranolol with HDMS-β-CD or HDAS-β-CD gives rise to a family of external and inclusion complexes in which some are more probably obtained.

1. Introduction

It is now well-established that nonaqueous CE (NACE) is a very powerful tool for enantioseparations [1]. Nonaqueous electrolytes enable to use chiral selectors and analytes with a low solubility in water, to reduce adsorption onto the capillary wall and to generate reduced electric current. Moreover, organic solvents with lower dielectric constants than water constitute, in principle, a more favourable environment for chiral discrimination due to their ability to promote intermolecular interactions [2]. Although the set of chiral selectors is rather large, cyclodextrins (CDs) and their derivatives have been extensively used in chiral NACE [1,3,4]. The interest of using single-isomer highly charged β-CD derivatives such as heptakis(2,3-di-*O*-methyl-6-*O*-sulfo)-β-CD (HDMS-β-CD) or heptakis(2,3-di-*O*-acetyl-6-*O*-sulfo)-β-CD (HDAS-β-CD) for the enantioseparation of basic drugs in NACE is now well established [5–9]. If the analytical interest of CDs is obvious, their enantiomer recognition pattern in nonaqueous systems is still not fully understood.

In a previous paper, a reversal of the enantiomer migration order (EMO) of propranolol was observed when HDMS-β-CD was replaced by HDAS-β-CD using a methanolic BGE in NACE [10]. The enantioselective intermolecular mechanisms were studied by using nuclear Overhauser effect spectroscopy and it was found that the enantiomers of propranolol form inclusion complexes with HDAS-β-CD while external complexes are observed in the presence of HDMS-β-CD. Very recently, bupivacaine enantiomers were also completely resolved in a methanolic BGE containing HDMS-β-CD or HDAS-β-CD in NACE but the EMO as well as the geometry of the complexes were not investigated [9].

Molecular modelling constitutes an essential tool for exploring mechanisms of molecular chiral recognition. In the present study, different complexes between two model compounds (bupivacaine and propranolol) and two single-isomer highly sulfated CD derivatives (HDMS-β-CD and HDAS-β-CD) were studied by

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quantum chemistry calculations. With respect to theoretical chemistry, two approaches can be considered, i.e. molecular mechanics and quantum chemistry. A crucial problem encountered in molecular mechanics is their limitation to classical molecules such as native CDs. This empirical approach cannot be applied to single-isomer charged CD derivatives as no complete set of parameters is available. The Hartree–Fock *ab initio* level solves the Roothaan equation using a basis set which can be minimal (MINI-1 [11,12]) or extended (double, triple. . .ζ) without approximation in the calculation of the bielectronic integrals. The most interesting feature of the *ab initio* level is the quality of the calculated geometry very often in good agreement with experimental data and also the estimation of reliable interaction energies [13]. A more accurate approach computes the energy function derived from the Density Functional Theory (DFT) as B3LYP [14] using the double ζ basis set 6-31G(d) with additional polarization functions basis set [15]. In this study, anionic CD derivatives are used to separate protonated basic drugs in nonaqueous systems with low dielectric constant. These NACE systems provide a particularly favourable environment for ion-pair formation, probably due to their ability to promote hydrogen-bonding interactions [16]. Quantum chemistry methods are well suited to describe multiple molecular interactions [17,18]. As an example, Barillaro et al. studied the incidence of organic acids in cyclodextrin complexes at several calculation levels [19]. In the past, many calculations have been performed at a semi-empirical level as AM1 [20] or PM3 [21]. In many cases, the AM1//AM1 energies are reliable when compared with *ab initio* values. Nevertheless, it has been recently demonstrated that high level energy calculations at a AM1 or PM3 geometry can significantly modify the interaction and complexation energies [22]. In this study, the results obtained by quantum chemistry were compared to the EMO observed in NACE as well as to the structures of complexes provided by NMR experiments.

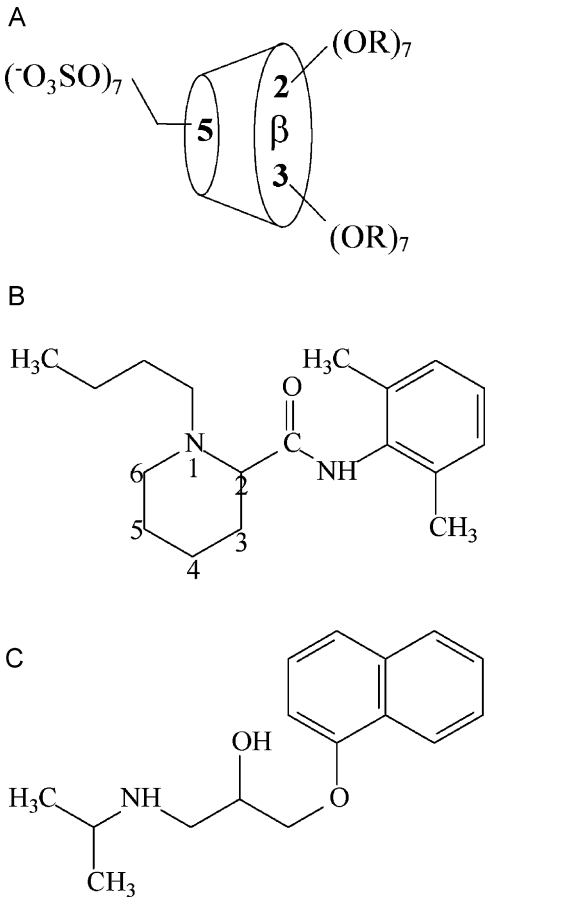

Fig. 1. Schematic plots of HDMS-β-CD (R: CH_3) and HDAS-β-CD (R: $COCH_3$) (A) as well as structures of bupivacaine (B) and propranolol (C).

2. Materials and methods

2.1. CE instrumentation

CE experiments were carried out on a HP^{3D}CE system (Agilent Technologies, Waldbronn, Germany) equipped with a DAD detector and a temperature control system (15–60 °C ± 0.1 °C). A CE Chemstation (Hewlett-Packard, Palo Alto, CA, USA) was used for instrument control, data acquisition and data handling. Fused-silica capillaries were provided by ThermoSeparation Products (San Jose, CA, USA).

2.2. Chemicals and reagents

Bupivacaine was kindly supplied by a pharmaceutical company and propranolol hydrochloride by Sigma–Aldrich (Saint-Louis, MO, USA). HDMS-β-CD and HDAS-β-CD were obtained from Analytical Controls (Rotterdam, the Netherlands). The structures of HDMS-β-CD, HDAS-β-CD, bupivacaine and propranolol are shown in Fig. 1.

Nitromethane was obtained from Sigma–Aldrich and ammonium acetate from Acros-Organics (Geel, Belgium). Methanolic background electrolytes (BGEs) were prepared with 98–100% formic acid (Merck, Darmstadt, Germany) at 0.75 M concentration and with 10 mM ammonium acetate. Each BGE-CD solution was prepared by adding HDMS- or HDAS-β-CD to the BGE. All reagents were of analytical grade. Methanol (Merck) was of HPLC grade. The BGE and samples solutions were filtered through a Polypure polypropylene membrane filter (0.2 μm) from Alltech (Laarne, Belgium) before use.

2.3. Electrophoretic technique

Electrophoretic separations were carried out with uncoated fused-silica capillaries having 50 μm internal diameter and 48.5 cm length (40 cm to the detector). At the beginning of each working day, the capillary was washed with methanol and the BGE for 15 min. Before each injection, the capillary was washed successively with methanol for 2 min and then equilibrated with the BGE-CD for 2 min. At the end of each working day, the capillary was rinsed for 30 min with 1 M formic acid in methanol, 30 min with the BGE without CD and 15 min with methanol. Capillary wash cycles were performed at a pressure of approximately 1 bar. The voltage was 25 kV and UV detection was set at 230 nm. Injections were made by applying a pressure of 50 mbar for a period of 3 s (corresponding to 8.8 nL, i.e. 0.9% of the total volume of the capillary) and the capillary was thermostated at 15 °C. Two sample solutions were prepared, one containing 50 μg/mL of racemic bupivacaine and 25 μg/mL of S-bupivacaine in methanol and the other one containing 50 μg/mL of racemic propranolol and 25 μg/mL of S-propranolol in methanol. Resolution (R_s) was calculated according to the standard expression based on peak width at half height [23].

2.4. Molecular modelling

The geometries of the complexes were fully optimized without any constraint by minimisation of the energy analytical gradient using redundant internal coordinates in order to ensure an efficient convergence of each component of the gradient lower than 2×10^{-6} hartree. In the present study, different starting geometries

have been chosen depending on the arrangement of the ligand on the narrow opening (NO) or wider opening (WO) of cyclodextrin. All the minima are local ones. The goal is to determine if significant interaction energy differences between the complexes formed by R or S enantiomers can be found. The nature of the located critical points is determined by vibrational frequency calculation derived from the second derivative matrix. When all the eigenvalues of this Hessian matrix are positive, the energy is minimum in each direction associated to the geometry variables.

All the calculations have been performed using the Gaussian 03 suite of programs [24]. The calculation procedure is the following: starting from the optimized geometry of each complex, their components – analyte and CD – were reoptimized separately. This procedure allows the determination of consistent energetic data, as each relative energy is calculated by reference to the geometry of the complex.

2.5. NMR measurements

2.5.1. Sample preparation

The concentration of bupivacaine in the NMR sample was 60-fold higher than in NACE experiments to obtain reproducible NMR spectra. NMR samples were prepared in methanol-d_4 (Sigma–Aldrich) acidified with 0.75 M formic acid-d_2 (Acros-Organics).

2.5.2. NMR spectra

All spectra (^{1}H NMR and Rotating-frame Overhauser Effect SpectroscopY (ROESY)) were recorded at 300 K on a Bruker Avance 500 MHz NMR spectrometer (Bruker BioSpin, Rheinstetten, Germany) operating at a proton NMR frequency of 500.13 MHz for 1H and equipped with a 5 mm cryoprobe. Deuterated methanol was used as the internal lock. For ^{1}H NMR, 128 scans of 32 K data points with a spectral width of 10,330 Hz were recorded with the following parameters: pulse width (PW) = 30° (length of 90° pulse: 7.80 μs) and relaxation delay (RD) = 1.0 s. The acquisition time was 3.17 s. FIDs were Fourier transformed with LB = 0.3 Hz. The resulting spectra were manually phased and calibrated to the internal standard TMSP at δ 0.00, using topspin (version 2.1; Bruker). ROESY spectra were recorded using a mixing time of 400 ms, 16 scans and the Bruker standard parameters for roesyph experiment.

3. Results and discussion

3.1. Bupivacaine interactions with HDMS-β-CD and HDAS-β-CD

In a previous paper dealing with the enantioseparation of basic drugs in NACE using single-isomer anionic CDs, the NACE system leading to the highest R_s value (i.e. 16.9) for bupivacaine enantiomers was made up of 20 mM heptakis(2-*O*-methyl-3-*O*-acetyl-6-*O*-sulfo)-β-CD and 10 mM ammonium camphorsulfonate in MeOH acidified with 0.75 M formic acid [9]. Nevertheless, this CD derivative was no longer commercially available at that time. Two other NACE systems were also tested, containing either 40 mM HDMS-β-CD or 40 mM HDAS-β-CD in a methanolic solution of 10 mM ammonium acetate acidified with 0.75 M formic acid. It was found that bupivacaine enantiomers could still be completely resolved using both NACE systems (R_s values: 10.0 using HDMS-β-CD and 5.8 using HDAS-β-CD) [9].

In the present study, the EMO of bupivacaine was investigated in these conditions. As shown in Fig. 2, the EMO was the same using both anionic CD derivatives, the R-enantiomer being the first migrating compound.

The CD bupivacaine complexes were evaluated by 2-D ROESY experiments. No correlation spot could be detected, whatever the CD derivative used. Therefore, it can be assumed that inclusion complexes are not formed. Similar observations were previously made for enantioseparation of propranolol with HDMS-β-CD (cf. Section 3.2 and ref. [10]), aminoglutethimide with heptakis(2-methyl-3,6-disulfo)-β-CD [25] and femcamfamine with various CD derivatives [26]. On the other hand, shifts from 0.11 to 0.13 ppm of CH-2 of bupivacaine were observed in the presence of HDMS-β-CD and HDAS-β-CD (Supplementary data 1A and B). According to the CE experiments, it can be deduced that bupivacaine interacts with external parts of HDMS-β-CD and HDAS-β-CD (otherwise no enantioseparation could be observed). As ^{1}H NMR spectra of HDMS-β-CD and HDAS-β-CD were not modified in the presence of bupivacaine, it can be assumed that these interactions should involve the sulfate groups of the CD derivatives.

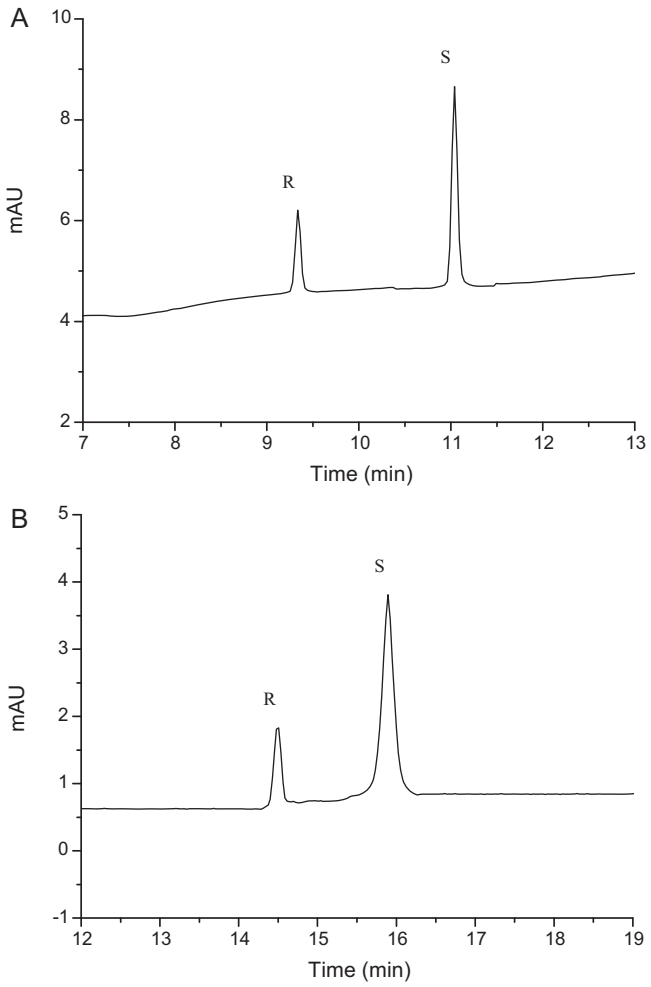

Fig. 2. Separation of bupivacaine enantiomers in a methanolic BGE made up of 40 mM HDMS-β-CD (A) or 40 mM HDAS-β-CD (B) and 10 mM ammonium acetate acidified with 0.75 M formic acid. Other conditions as described in Section 2.

Molecular modelling was then applied to study the possible structures of the complexes between bupivacaine enantiomers and both anionic CD derivatives as well as to determine the most energetically favourable geometries. It is worth noting that, even if HDMS-β-CD and HDAS-β-CD are available as sodium salts, the latter ones were replaced by protons for calculation simplification reasons and basis set choice. Moreover, in order to reflect the influence of the nonaqueous medium on the molecules, analyte/CD complexes were considered as globally neutral complexes. As the basic analyte is positively charged under the NACE conditions, one proton was added on its amino group while one proton of the sulfate of the CD derivative was removed. Indeed, it was previously demonstrated that the global dissociation of the sodium salt of the studied

Table 1
Interaction, deformation and complexation energies in kcal/mol for 1:1 complexes (bupivacaine/CD) at the RHF/MINI-1′ level.

		HDMS-β-CD		HDAS-β-CD	
		NO	WO	NO	WO
R-bupivacaine	E_{int}	−75.340	−64.248	−73.700	−67.743
	$\|E_{def(bup)}\|$	3.790	5.434	3.464	2.033
	$\|E_{def(CD)}\|$	6.892	4.951	6.789	7.319
	E_{cplx}	−64.658	−53.863	−63.447	−58.391
S-bupivacaine	E_{int}	−85.176	−83.362	−75.005	−71.000
	$\|E_{def(bup)}\|$	3.177	4.810	2.692	2.004
	$\|E_{def(CD)}\|$	10.000	15.581	7.635	7.778
	E_{cplx}	−72.000	−62.970	−64.678	−61.217

E_{int}: energy of the complex – sum of the energies of both partners at their complex geometry. E_{def}: energy of the partner – energy of the partner at the complex geometry. E_{cplx}: energy of the complex – sum of the energies of both partners at their respective equilibrium geometry.

anionic CDs is very low, the concentration of free sodium ions being nearly the same compared to sodium formate [27]. Results for bupivacaine are presented in Table 1 as energetic outcomes expressed as complexation, deformation and interaction energies. The interaction energy (E_{int}) is determined as the difference between the energy of the complex and the sum of the energies of both entities at their complex geometry. The deformation energy (E_{def}) is defined as the difference between the energy of one of the entities of the complex at its equilibrium geometry (which is obtained by reoptimization of the one found in the complex) and its energy at the complex geometry. The complexation energy (E_{cplx}) is the difference between the energy of the complex and the sum of the energy of each entity at their respective equilibrium geometry.

Two types of 1:1 external complexes were studied: a first one where the analyte is located towards the sulfate groups of the CD at the narrower opening (NO notation) and a second one where the interaction takes place around the wider opening (WO notation).

3.1.1. Bupivacaine/HDMS-β-CD interactions

The calculations obtained with a minimal basis set (MINI-1) were performed. As can be seen in Table 1, higher values were obtained when the guest-molecule is oriented towards the sulfate groups of HDMS-β-CD (NO), suggesting higher probability for this geometry. This is not surprising since electrostatic interactions play a crucial role in an electrolyte having a low dielectric constant such as methanol [2]. It is worth noting that even though the electrostatic interaction between the anionic HDMS-β-CD and the cationic analyte is not stereoselective, it can contribute to the chiral recognition [28]. When both enantiomers are compared, the highest E_{int} and E_{cplx} values are obtained for S-enantiomer, indicating that this complex is the most energetically favourable. For this complex, there are more possibilities of interactions between the protonated amine and the sulfate groups than for the complex with the R-enantiomer. This result is in complete accordance with the CE experiments. Indeed, S-bupivacaine is the second-migrating enantiomer, which means that this enantiomer has the highest affinity for HDMS-β-CD. The structure of S-bupivacaine/HDMS-β-CD complex in which the interaction takes place around the sulfate groups is presented in Fig. 3.

3.1.2. Bupivacaine/HDAS-β-CD interactions

Bupivacaine/HDAS-β-CD complex was also studied and, as can be seen from Table 1, difference of E_{int} values between both enantiomers was found to be not significant for both given conformations. Since bupivacaine enantiomers were clearly separated in NACE using this CD derivative (cf. Fig. 2B), it can be concluded that these conformations are not representative of the complexes experimentally observed in NACE experiments.

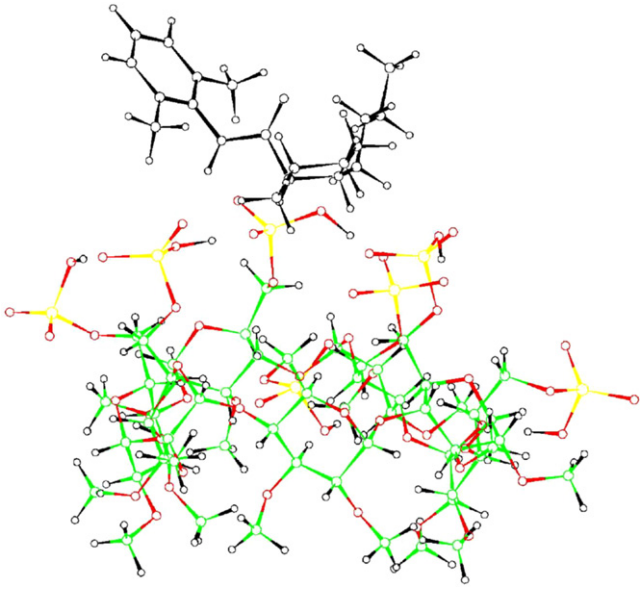

Fig. 3. Structure of S-bupivacaine/HDMS-β-CD complex. The interaction takes place around the sulfate groups (NO) at the MINI-1 geometry. The atoms of S-bupivacaine are all in black. For HDMS-β-CD, the atoms of carbon, hydrogen, oxygen and sulfur are coloured in green, black, red and yellow, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

3.2. Propranolol interactions with HDMS-β-CD and HDAS-β-CD

The enantioseparation of propranolol was also evaluated using 40 mM HDMS-β-CD or 40 mM HDAS-β-CD in a methanolic solution made up of 10 mM ammonium acetate acidified with 0.75 M formic acid. As can be seen in Fig. 4, in the presence of HDMS-β-CD, the first migrating enantiomer was found to be the S-enantiomer. When HDMS-β-CD was replaced by HDAS-β-CD, a reversal of the EMO was observed. NMR experiments suggested that external complexes were formed in the methanolic BGE containing HDMS-β-CD while in the presence of HDAS-β-CD, the alkyl chain of R-propranolol was assumed to enter into the CD macrocycle through the wider opening [10]. Moreover, recent 1-D ROESY studies revealed that S-propranolol forms a tighter complex with HDAS-β-CD than R-propranolol [29].

3.2.1. External interaction studies

In this study, external complexes between propranolol enantiomers and both anionic CD derivatives were studied at the RHF/MINI-1 level (Table 2). It is worth noting that the calculations for external complexation have only been performed with the conformation where the analyte is located towards the sulfate groups (NO). In the presence of HDMS-β-CD, the highest E_{int} value is obtained for R-enantiomer, which is confirmed by the EMO in the

Table 2
Interaction, deformation and complexation energies in kcal/mol for 1:1 external complexes (propranolol/CD) at the RHF/MINI-1′ level.

		HDMS-β-CD (NO)	HDAS-β-CD (NO)
R-propranolol	E_{int}	−85.339	−86.256
	$\|E_{def(prop)}\|$	9.073	10.796
	$\|E_{def(CD)}\|$	6.700	8.346
	E_{cplx}	−69.565	−67.114
S-propranolol	E_{int}	−79.669	−86.451
	$\|E_{def(prop)}\|$	2.805	16.176
	$\|E_{def(CD)}\|$	7.860	8.154
	E_{cplx}	−69.000	−62.121

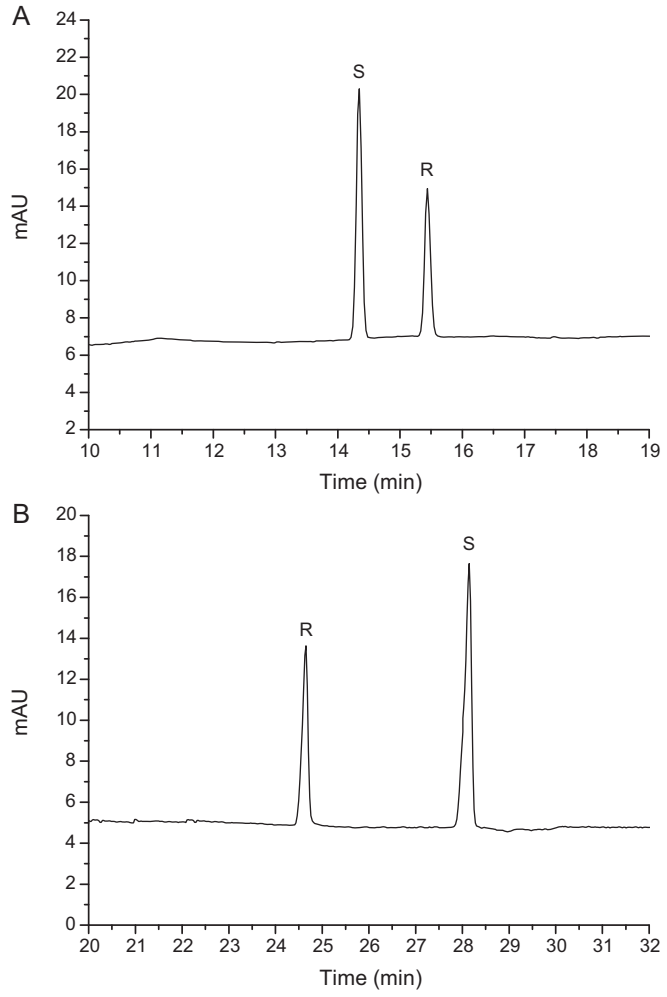

Fig. 4. Separation of propranolol enantiomers in a methanolic BGE made up of 40 mM HDMS-β-CD (A) or 40 mM HDAS-β-CD (B) and 10 mM ammonium acetate acidified with 0.75 M formic acid. Other conditions as described in Section 2.

NACE experiments (cf. Fig. 4A). In the presence of HDAS-β-CD, as it was observed for bupivacaine, no significant difference in the E_{int} values of both enantiomers was found. Therefore, this conformation is not representative of the complex experimentally observed in NACE since HDAS-β-CD can resolve propranolol enantiomers.

3.2.2. Inclusion complex studies

As the previous study revealed that intermolecular nuclear Overhauser effects with two protons located inside the cavity of HDAS-β-CD were observed upon irradiation of the methyl groups of R-propranolol [10], attempts to locate inclusion complexes with both anionic CD derivatives were also considered. In this case, calculations were performed at the B3LYP/6-31G(d) level (cf. Table 3). Indeed, in the MINI-1 basis set, the overestimation of the interatomic distances may influence the interactions in a so closed environment [22]. As can be seen in Table 3, S-propranolol/HDMS-β-CD inclusion complex presents the lowest E_{int} value, which is in complete accordance with the CE experiments (cf. Fig. 4A).

S-propranolol/HDAS-β-CD complex shown in Fig. 5A refers to a geometry where the alkyl chain of propranolol deeply enters into the CD cavity through the wider opening. Interestingly, in this inclusion complex, the extended alkyl side chain attempts to perform such electrostatic interactions with the sulfate that one hydrogen has migrated from the ammonium head to the sulfate (distance between nitrogen and hydrogen atoms: 2.48 Å). This

Table 3
Interaction, deformation and complexation energies in kcal/mol for 1:1 complexes between propranolol and HDMS-β-CD or HDAS-β-CD at the B3LYP/6-31G(d) level.

		HDMS-β-CD (WO)	HDAS-β-CD (WO)
R-propranolol	E_{int}	−102.716	−101.427
	$\|E_{def(prop)}\|$	6.338	17.170
	$\|E_{def(CD)}\|$	6.261	11.310
	E_{cplx}	−90.116	−72.947
S-propranolol	E_{int}	−86.239	−165.485
	$\|E_{def(prop)}\|$	8.060	94.352
	$\|E_{def(CD)}\|$	6.336	34.280
	E_{cplx}	−71.843	−36.854

feature significantly increases the interaction energy and thus the deformation energies of both partners (cf. Table 3). A structure for R-propranolol/HDAS-β-CD complex was also optimized using S-propranolol/HDAS-β-CD complex as geometry guess (starting geometry) (Fig. 5B). As shown in this figure, the alkyl chain of

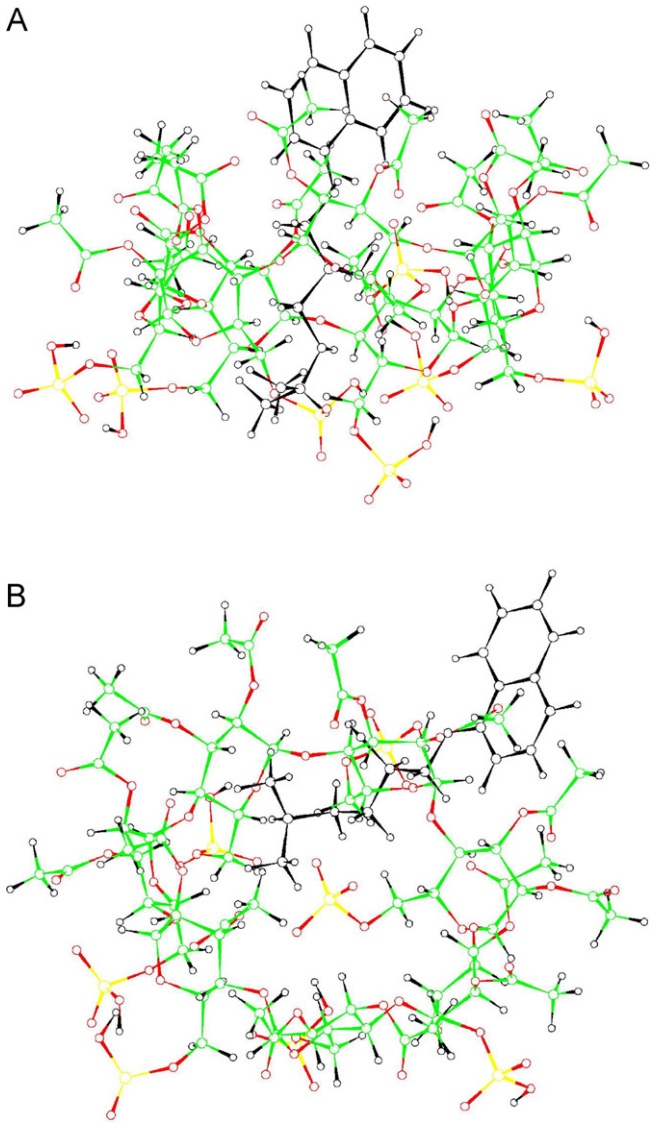

Fig. 5. (A) Structure of an inclusion complex between S-propranolol and HDAS-β-CD at the B3LYP/6-31G(d) level. The atoms of S-propranolol are all in black. For HDAS-β-CD, the atoms of carbon, hydrogen, oxygen and sulfur are coloured in green, black, red and yellow, respectively. (B) Structure of an inclusion complex between R-propranolol and HDAS-β-CD using S-enantiomer/HDAS-β-CD complex at the B3LYP/6-31G(d) level as geometry guess (starting geometry). Colour codes are the same as in A.

R-propranolol enters less deeply into the CD cavity. Moreover, there is no migration of the hydrogen atom which remains on the amino group. In this conformation, it is very interesting to point out that the ammonium group tries to interact not only with the oxygen atom of one sulfate group (distance between hydrogen atom of the ammonium group and oxygen atom of the sulfate group: 1.78 Å) but also with the oxygen atom of the carbonyl function present in the acetyl moiety (distance between hydrogen atom of the ammonium group and oxygen atom of the carbonyl function: 1.94 Å). Therefore, this conformation is also energetically favourable, as assessed by the E_{int} and E_{cplx} values. When both enantiomers are compared in this conformation, the most energetically favourable complex is observed for S-enantiomer (E_{int}: −165.485 kcal/mol). This result is in complete accordance with the EMO observed in the NACE experiments as S-propranolol is the second-migrating enantiomer (cf. Fig. 4B).

4. Concluding remarks

Calculations were first performed at the RHF/MINI-1 level for external complexes for both model compounds. As expected, the conformation with bupivacaine located towards the sulfate groups of HDMS-β-CD was found to be the most energetically favourable. Moreover, EMO observed in the NACE experiments using this CD derivative confirmed interaction energies calculated for both enantiomers of bupivacaine and propranolol at the MINI-1 geometry. For bupivacaine/HDAS-β-CD complexes, the located conformations were not representative of the separation obtained in NACE and other types of complexes have to be investigated.

Inclusion complexes for which the alkyl chain of propranolol enters into the cavity of HDMS-β-CD or HDAS-β-CD were located at the B3LYP/6-31G(d) level. Interaction between propranolol and both anionic CD derivatives should be considered as a dynamic process giving rise to a set of external and inclusion complexes with different statistical population.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2011.10.010.

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