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ORIGINAL ARTICLE

Theoretical study of β and γ-cyclodextrins inclusion complexes with nineteen atropisomeric polychlorobiphenyls

Georgiana Mindrila · Cristina Mandravel · Iuliana Dobrica · Paula Bugheanu · Ioana R. Stanculescu

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Abstract Inclusion complexes of β and γ-cyclodextrins (CDs), chirally selective macrocycles, with 19 atropisomeric polychlorinated biphenyls (PCBs), stable at physiological temperatures, were studied by molecular mechanics optimized potential for liquid simulations and semi-empirical quantum AM1 methods. Bimodal manual docking, geometry optimization and single point calculations were done. PCB:CD complex formation was studied considering two ways of entry in the large base of CD cavity: with biphenyl C1–C1′ bond axis of PCBs oriented parallel and anti-parallel with the CD trunk height axis. A distance dependent dielectric constant was used to account for the solvent effect. The values of complexation and binding energies were calculated, confirming the existence of a specific van der Waals (vdW) type interaction. β and/or γ-CD chiral recognition of the 19 atropisomeric PCBs, is described by means of the complexation and binding energy values. The binding energy is a better discriminator of PCBs enantiomers than complexation energy considering the average energy differences between (+) and (−) PCB: β/γ-CD complexes. The chromatographic elution order of several PCB enantiomers from literature was correlated with the complexation and binding energies. The molecular modeling of inclusion complexes is recommended to be used as enantiomer identification tool in correlation with chromatographic data.

Keywords Chiral PCBs · Cyclodextrins · Molecular modeling · Inclusion complexes · Atropisomerism · Binding energy

G. Mindrila · C. Mandravel · I. Dobrica · P. Bugheanu · I. R. Stanculescu
Department of Physical Chemistry, Faculty of Chemistry, University of Bucharest, 4-12 Regina Elisabeta Bd., District 3, 030018 Bucharest, Romania

I. R. Stanculescu (✉)
IRASM Irradiation Technology Center, Horia Hulubei National Institute for Physics and Nuclear Engineering, 407 Atomistilor str., 077125 Magurele, Ilfov, Romania
e-mail: istanculescu@nipne.ro

Introduction

The production of the polychlorinated biphenyls (PCBs) is forbidden, but the problems related with their persistence in the environment remains of actuality, due to partitioning, biotransformation and bioaccumulation of these hazardous chemicals [1]. Seventy-eight of the 209 PCBs congeners which have chlorine substituents in the *ortho* positions (see Fig. 1) display axial chirality, due to a limited rotation of the phenyl group around the C1–C1′ bond, and are considered atropisomers. Racemization or inter-conversion of enantiomers depends of energy barrier which limits the free rotation around that axis or bond.

Krupcik et al. [2] correlated the values of the inter-conversion energy barrier, calculated by the AM1 semi-empirical quantum chemical method with those determined by gas-chromatography on a chirally selective modified cyclodextrin (CD) phase. Oki [3] predicted that only enantiomers that have a racemization half life greater than 1,000 s and a conversion energy barrier larger than 22.3 kcal/mol at 300 K can be isolated. Consequently, only 19 atropisomeric PCBs are stable at physiological temperatures have an influential role in partitioning, bioaccumulation and toxicological activity (see Table 1) [1, 3].

We selected from the enormous number of existent references to all PCBs only those related with the 19 atropisomeric PCBs stable at physiological temperatures.

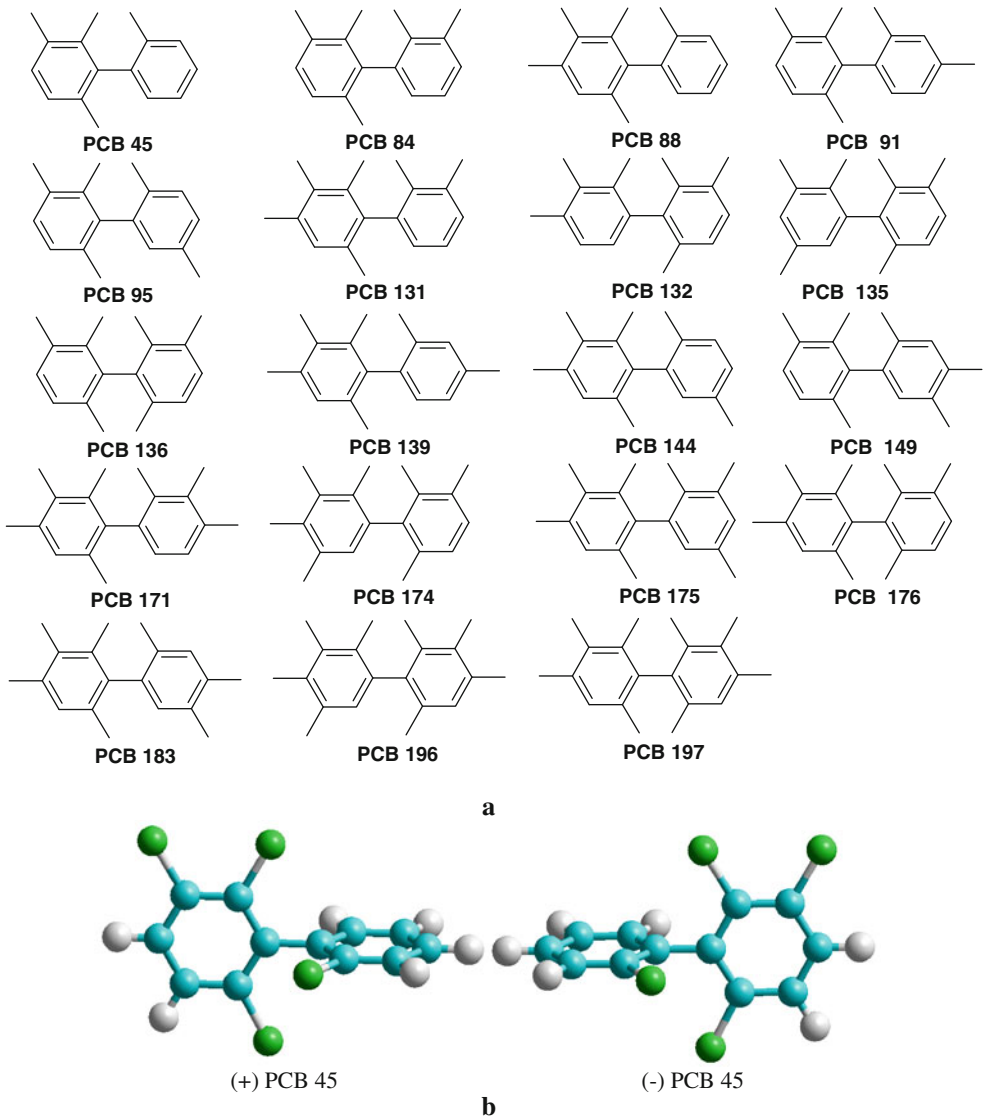


Fig. 1 The structural formula of **a** nineteen atropisomeric PCBs stable at room temperature **b** 2,3,6,2′-tetrachlorobiphenyl (PCB 45) (+) and (−) enantiomers

Swedish authors [4] effected chiral separation and isolation by reversed phase high performance liquid chromatography (RP-HPLC) for PCBs: 84, 131, 132, 135, 136, 144, 149, 174, 175, 176, 183 and 196 (e.g., 12 atropisomeric PCBs). Thermal racemization and thermal degradation was studied in [4] for PCB 136 and PCB 176 by GC–MS hyphenated method. Nine of the conformational stable atropisomeric PCBs are present in commercial mixtures (the so called Arochlors) above 1% concentration and are, therefore, expected to be released in the environment. Finally, these authors made a comparison of the calculated by different quasi-empirical quantum methods and experimentally determined rotational energy barriers for all 19 atropisomeric PCBs. More recent studies [5–10] demonstrate the utility of using chiral analysis of PCBs to investigate biotransformation within biota of Arctic food webs. Modeling and prediction of some physical properties: the vapor pressure, the water solubility, the octanol–water partitioning coefficient and the Henry's laws coefficients for all PCB congeners from molecular descriptors was developed in 2001 by Oberg [11]. This approach encouraged us to pursuit the correlation of chromatographic elution order with the PCB-stationary phase covalently bonded molecules interaction energy calculated by molecular modeling.

CDs, cyclic oligosaccharides produced from starch by enzymatic conversion, are composed of 5 or more α-D-glucopyranoside units linked 1 → 4. The 5, 6 and 7-membered macrocycles are called α, β and γ-CDs. Structure and host properties of CDs, for various organic compounds are studied in many works with experimental

Table 1 Chlorine substitution and dipole moment of 19 atropisomeric PCBs

Crt. no.	PCB	Number of chlorine atoms	First ring substitution	Second ring substitution	μ (D)
1	45	4	2,3,6	2′	1.392
2	84	5	2,3,6	2′,3′	2.082
3	88	5	2,3,4,6	2′	1.908
4	91	5	2,3,6	2′,4′	1.867
5	95	5	2,3,6	2′,5′	0.933
6	131	6	2,3,4,6	2′,3′	2.077
7	132	6	2,3,4	2′,3′,6′	2.409
8	135	6	2,3,5	2′,3′,6′	1.585
9	136	6	2, 3, 6	2′,3′,6′	1.187
10	139	6	2,3,4,6	2′,4′	1.19
11	144	6	2,3,4,6	2′,5′	1.239
12	149	6	2,3,6	2′,4′,5′	1.717
13	171	7	2,3,4,6	2′,3′,4′	1.846
14	174	7	2,3,4,5	2′,3′,6′	2.259
15	175	7	2,3,4,6	2′,3′,5′	1.024
16	176	7	2,3,4,6	2′,3′,6′	1.523
17	183	7	2,3,4,6	2′,4′,5′	0.823
18	196	8	2,3,4,5	2′,3′,4′,6′	1.343
19	197	8	2,3,4,6	2′,3′,4′,6′	0.989

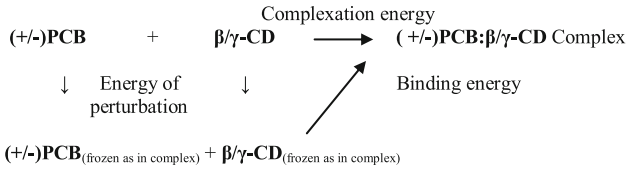
and computational methods [12–16]. Investigation on the inclusion of achiral PCB 1, PCB 4, PCB 16 and PCB 52 with CDs by molecular modeling methods has been performed in [17, 18].

Aim of the present study was to emphasize the PCB chiral recognition with CDs by molecular modeling. The energetics of the interactions between the 38 (±) PCB enantiomers with chirally selective *β*/*γ*-CDs was correlated with the chromatographic elution order, when known [2, 4, 6].

Calculation details

Modeling of the interaction between thirty-eight (+) and (−) enantiomers of chiral PCBs, stable at environmental and physiological temperature, and CDs (*β* and *γ*, *β*-CD and *γ*-CD) was done with molecular mechanics Optimized potential for liquid simulations (OPLS) force field and quantum semi-empirical (AM1) methods, included in Hyperchem program [19]. Starting geometry of CD's was obtained from the Protein Data Bank using the X-ray structures 1VFO for *β* and 1D3C for *γ*-CD [20]. To construct an accurate model, a single point AM1 calculation in restricted Hartree–Fock approximation was done to obtain charges on the atoms and then molecular mechanics optimization with Polack–Ribiere algorithm and gradient of 0.01 kcal/mol Å followed. A constant dielectric constant, scale factor 10, was used to account for the solvent effect. Geometry minimization was done for the interaction partners 38 enantiomers, 2 CDs and 152 inclusion complexes. To see the influence of the chlorine substitution on the interaction, starting structures of complexes with biphenyl C1–C1′ bond axis of PCBs oriented parallel and anti-parallel with the CDs trunk height axis were considered for each enantiomer. In all cases the starting PCB docking position was near the CD larger aperture, at about 0.5 Å.

For modeling the host–guest interaction, a typical schema [21–24] was used:



starting from general consequences of thermodynamics and using this schema one can obtain the relations for calculation of complexation and binding energy:

$$\Delta E_{\text{complexation}} = E_{\text{PCB:CD}} - (E_{\text{PCB}} + E_{\text{CD}}) \quad (1)$$

$$\Delta E_{\text{binding}} = E_{\text{PCB:CD}} - (E_{\text{PCBfrozen}} + E_{\text{CDfrozen}}) \quad (2)$$

From these relations results that for complexation or binding energy calculation one needs the values of the total energy for correspondent species. In the frame of molecular mechanics OPLS force field [10, 20–24] the total energy is described by the following relation:

$$E_{\text{total}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{dihedral}} + E_{\text{vdW}} + E_{\text{H bond}} + E_{\text{electrostatic}} \quad (3)$$

Results and discussion

Table 1 gives the chlorine substitution pattern and the dipole moment values of the 19 atropisomeric PCBs, calculated with the AM1 method. Chlorine substitution of the entering phenyl ring is very important for the host–guest interaction because of differences in Keesom and London, indirect electrostatic forces [22].

Figure 2 presents the structure of two inclusion complexes of PCB 131 and 176, the phenyl ring near the CDs cavity at the beginning of the geometry optimization being indicated.

Generally, one may observe that the PCBs are placed near the center of the CD cavity but not fully included, lying at about 45° of the CDs trunk height axis. The partial included ring of PCB forms non classical H-bonds of the Cl–H–O type (see Fig. 2, dotted lines). *γ*-CD cycle is larger and the structure of the corresponding complexes vary more.

The total energy, the complexation energy, the binding energy and vdW components were calculated for 152 complexes. Tables 2 and 3 give the values of the most stable 76 complexes, only one docking mode being selected, the one providing the most stable complex. Small differences in binding energy of the two complexes orientations considered are observed when the PCB dipole moment is small; larger differences are observed when the PCB dipole moment is high.

From examination of the data in Tables 2 and 3, all the values of complexation and binding energy are comparable with literature data [13, 25, 26], showing the stability of the inclusion complexes. The E_{vdW} component is the largest component of the complexation and binding energy showing the non-covalent nature of the interaction [24]. The rest of the energy terms in Eq. 3 are negligible and for this reason they are not given.

The influence of the entering phenyl ring substitution pattern on the interaction and of the chlorine atoms number is difficult to evaluate because of the special structural requirements (2, 3, 6 substitution) for axial chirality of all nineteen PCBs.

It is significant that the value of binding energies is higher than that of complexation energy for the same complex.

Selected examples from Tables 2 and 3 are illustrated in Fig. 3 to aid the interpretation of the results.

Analyzing values of complexation and binding energy one may predict the separation of chiral PCBs based on the differences between (+) and (−)-PCB complexes with β and γ-CD. Surely, the possibility of separation increases with these differences. From Fig. 3; Table 4 results, all enantiomers are theoretically separable but the possibility of discrimination is reduced for PCB 135 considering the values of complexation energy with β-CD, for PCB 135 and PCB 175 considering the binding energy with β and **γ**-CD, respectively.

The average of these energy differences shows that γ-CD is a better separator than β-CD. This may be explained by the greater flexibility of the **γ**-CD that allows greater variation among the complexes structures [25]. This is in accord with the statements from [25] concerning the structure of β and γ-CD, which shows that γ-CD posses a bigger cavity than the β-CD.

Generally, binding energy differences between (+) and (−) enantiomers are higher than complexation energies differences. Indeed, some energy differences are smaller than kT at room temperature.

The binding energy can be related with chromatographic retention indices [7, 27]. We aimed to correlate the known elution order [1] of several PCB enantiomers with binding/complexation energy. The value of binding energies were higher for complexes of (+)-PCB 84, 132, 136 and 176 with β and/or γ-CD which is consistent with the (−), (+)

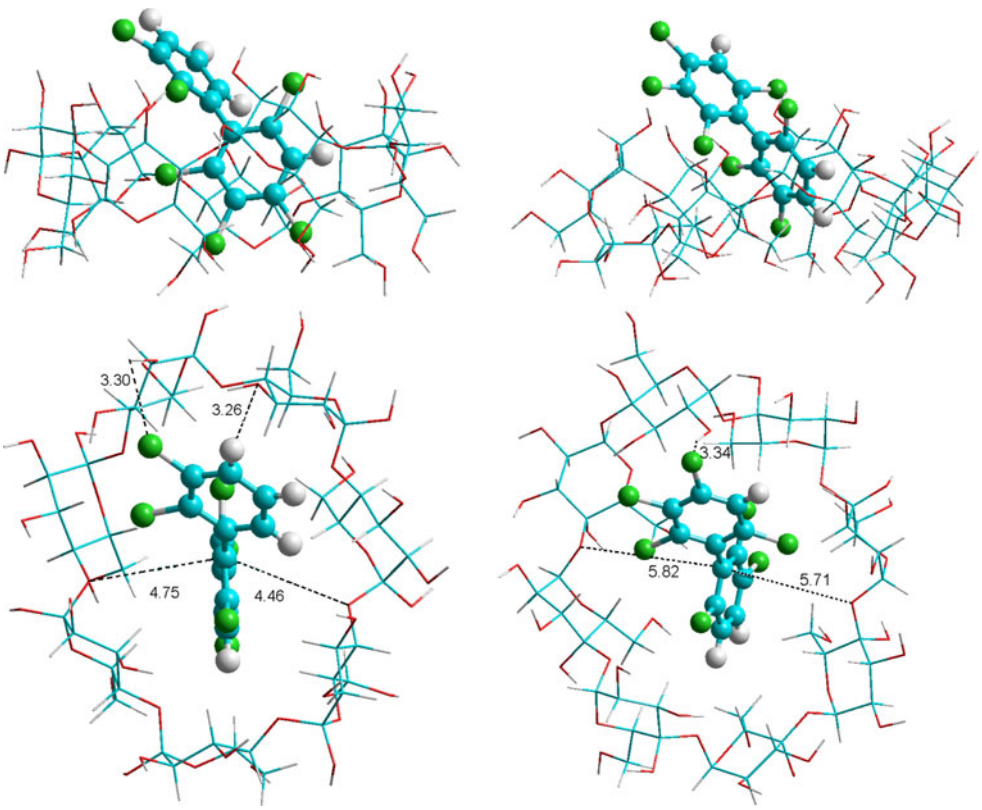


Fig. 2 The structure of complexes, *side view*: (+)-PCB 131; 2,3,4,6 entering phenyl ring:β-CD (*top left*) (+)-PCB 176; 2,3,6 entering phenyl ring:γ-CD (*top right*); *aerial view* (+)-PCB 131; 2,3,4,6 entering phenyl ring:β-CD (*bottom left*) (+)-PCB 176; 2,3,6 entering phenyl ring: γ-CD (*bottom right*); *dotted lines* two types of intermolecular distances indicated in Å: non classical H-bonds of about 3.3 Å and C1(PCB)–O(CD glycosidic linkage) distance)

Table 2 Complexation energy and van der Waals term for the **c**omplexes (±) PCB:β-CD and (±) PCB:γ-CD (kcal/mol)

Crt. no.	PCB	β-CD				γ-CD			
		(+)PCB		(−)PCB		(+)PCB		(−)PCB	
		$E_{complexation}$	E_{vdW}	$E_{complexation}$	E_{vdW}	$E_{complexation}$	E_{vdW}	$E_{complexation}$	E_{vdW}
1	45	−27.81	−28.81	−26.23	−25.64	−26.43	−27.39	−24.4	−25.34
2	84	−27.12	−30.49	−25.39	−25.67	−25.64	−27.92	−25.34	−27.74
3	88	−24.21	−24.2	−27.6	−30.28	−27.93	−30.66	−31.69	−32.84
4	91	−25.27	−24.78	−27.58	−30.54	−27.21	−28.06	−24.85	−26.85
5	95	−26.59	−29.55	−22.93	−23.28	−25.61	−27.74	−32.84	−33.39
6	131	−32.4	−34.67	−28.75	−33.12	−23.97	−25.28	−27.1	−28.48
7	132	−27.06	−30	−26.59	−29.38	−25.27	−25.3	−25.64	−26.57
8	135	−26.41	−26.2	−26.28	−26.71	−25.51	−27.79	−23.7	−25.06
9	136	−23.66	−23.42	−27.95	−31.12	−21.93	−30.87	−23.44	−23.74
10	139	−28.95	−32.44	−31.04	−28.14	−28.4	−29.26	−25.72	−27.58
11	144	−28.26	−27.89	−29.48	−28.61	−24.49	−26.12	−27.91	−28.42
12	149	−31.13	−30.95	−30.58	−33.27	−24.47	−33.28	−34.03	−34.16
13	171	−28.9	−26.46	−28.16	−29.35	−28.38	−28.14	−27.59	−27.38
14	174	−30.55	−33.03	−26.99	−28.56	−22.96	−24.23	−33.01	−30.24
15	175	−28.87	−28.42	−26.42	−27.61	−25.26	−26.45	−26.86	−30.49
16	176	−30.25	−32.27	−24.83	−27.02	−30.29	−37.36	−33.43	−35.78
17	183	−30.91	−31.42	−31.52	−32.17	−24.93	−26.24	−28.95	−30.77
18	196	−28.85	−30.89	−29.99	−33.97	−23.2	−29.93	−29.33	−32.69
19	197	−23.32	−24.76	−24.45	−27.36	−29.04	−34.99	−26.28	−31.52

Table 3 Binding energy and van der Waals term for the **c**omplexes (±) PCB:β-CD and (±) PCB:γ-CD (kcal/mol)

Crt. no.	PCB	β-CD				γ-CD			
		(+)PCB		(−)PCB		(+)PCB		(−)PCB	
		$E_{binding}$	E_{vdW}	$E_{binding}$	E_{vdW}	$E_{binding}$	E_{vdW}	$E_{binding}$	E_{vdW}
1	45	−28.31	−28.34	−27.84	−25.7	−26.48	−26.4	−27.92	−28.06
2	84	−33.85	−33.74	−26.83	−26.79	−34.04	−34.09	−28.88	−29.07
3	88	−30.35	−30.29	−30.38	−30.39	−33.78	−33.76	−30.63	−30.68
4	91	−26.02	−25.95	−30.23	−30.19	−29.82	−29.77	−26.01	−25.86
5	95	−29.5	−29.53	−24.28	−24.39	−35	−35.01	−31.75	−31.74
6	131	−34.65	−34.58	−32.28	−32.31	−32.14	−31.97	−29.55	−29.66
7	132	−30.39	−30.24	−29.29	−29.16	−32.97	−34.69	−27.58	−27.73
8	135	−27.27	−27.18	−27.74	−27.64	−32.42	−32.49	−26.08	−26.09
9	136	−24.51	−24.49	−28.39	−31.83	−27.87	−30.5	−26.02	−26.03
10	139	−31.17	−31.17	−30.04	−29.85	−36.53	−36.44	−29.02	−28.99
11	144	−29.08	−29.01	−30.42	−30.28	−33.63	−33.62	−30.18	−30.29
12	149	−31.77	−31.69	−33.03	−32.94	28.36	−32.76	−33.05	−32.98
13	171	−29.53	−29.44	−30.8	−30.82	−31.86	−31.74	−30.12	−30.25
14	174	−33.28	−33.31	−28.67	−28.77	−27.43	−27.45	−26.06	−26.08
15	175	−29.47	−29.35	−28.91	−28.9	−27.36	−27.51	−27.53	−27.48
16	176	−31.32	−31.43	−26.22	−26.25	−26.92	−37.36	−33.83	−31.76
17	183	−33.22	−33.25	−32.71	−32.62	−27.27	−27.35	−31.78	−31.8
18	196	−31.18	−31.15	−33.86	−33.84	−27.74	−24.02	−32.75	−32.83
19	197	−24.09	−24.09	−26.92	−26.9	−29.57	−29.59	−26.94	−27.08

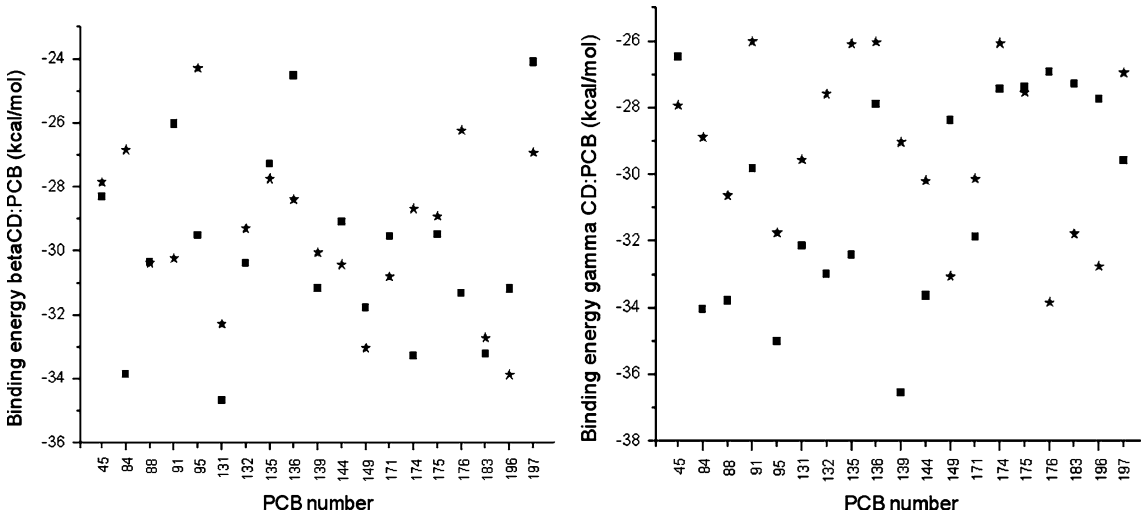


Fig. 3 Variation of binding energies for different PCBs complexes formed with the two host CDs: (+)PCB (*filled square*), (−)PCB (*asterisks*) complexes; *left* (β-CD) *right* (γ-CD)

Table 4 Elution order and absolute values of energy differences (ΔE) between (+) and (−) PCBs complexes with β and γ-CDs

Crt. no.	PCB	Elution order [1]	ΔE (kcal/mol)			
			Complexation energy		Binding energy	
			PCB:β-CD	PCB:γ-CD	PCB:β-CD	PCB:γ-CD
1	45	na	1.58	2.03	0.47	1.44
2	84	−, +	1.73	0.3	7.02	5.16
3	88	na	3.39	3.76	0.03	3.15
4	91	na	2.31	2.36	4.21	3.81
5	95	na	3.66	7.23	5.22	3.25
6	131	na	3.65	3.13	2.37	2.59
7	132	−, +	0.47	0.37	1.1	5.39
8	135	+, −	0.13	1.81	0.47	6.34
9	136	−, +	4.29	1.51	3.88	1.85
10	139	na	2.09	2.68	1.13	7.51
11	144	na	1.22	3.42	1.34	3.45
12	149	na	0.55	9.56	1.26	4.69
13	171	na	0.74	0.79	1.27	1.74
14	174	+, −	3.56	10.05	4.61	1.37
15	175	na	2.45	1.6	0.56	0.17
16	176	−, +	5.42	3.14	5.1	6.91
17	183	na	0.61	4.02	0.51	4.51
18	196	na	1.14	6.13	2.68	5.01
19	197	na	1.13	2.76	2.83	2.63
average ΔE (kcal/mol)			2.11	3.51	2.42	3.74

na not available

elution order and of (−)-PCB 135 with β-CD which is consistent with the (+), (−) elution order [1]. In enantiomeric chromatographic separations of PCBs modified β-CDs are employed such as tert-butyldimethylsilylated) β-CD, heptakis (2,3,6-tri-*O*-methyl)β-CD and permethylated β-CD [4]. Nevertheless the use of the unmodified β and γ-CDs, the simplest host model combined with the manual docking procedure offered information on the PCB chiral separation possibilities. Using accurate methods DFT/ab initio, extensive docking procedures or molecular dynamics one may obtain a better picture of the binding selectivity.

Conclusions

The present molecular modeling study showed that chiral recognition of the 19 atropisomeric PCBs stable at physiological temperature is possible through the PCB:β/γ-CD inclusion complexes by means of complexation and binding energy. The binding energy is a better discriminator of PCBs enantiomers than complexation energy considering the average energy differences between (+) and (−) PCB:β/γ-CD complexes. The value of binding energies of inclusion complexes were correlated with the (+), (−) chromatographic elution order, experimentally determined. For these reasons the molecular modeling of inclusion complexes is recommended to be used as enantiomer identification tool in correlation with chromatographic data.

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