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Halogenation effects of pheniramines on the complexation with β-cyclodextrin

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ABSTRACT

This study investigated the inclusion complexes of β-cyclodextrin with pheniramine and its halogenated derivatives chlorpheniramine and brompheniramine both experimentally and theoretically to characterize the effects of a halogenated phenyl ring on the intermolecular interactions. Fourier transform infrared and nuclear magnetic resonance (NMR) experiments provided evidence of the formation of inclusion complexes and NMR were conducted to evaluate the apparent binding constants. The two-layered hybrid ONIOM method, ONIOM(B3LYP/6-31G(d):PM3), was adopted to optimize the geometry. The linear relationships between the calculated and experimental values for frequencies (with a scaling factor of 0.96) and for magnetic properties (with a scaling factor of 1.05) demonstrate that the quantum chemical calculations were consistent with the experimental spectra. Additionally, the calculated binding energies were consistent with the experimental results: the stability order of the complexes and the trend of the binding energy is: brompheniramine > chlorpheniramine > pheniramine; *S*-enantiomer > *R*-enantiomer. Natural Bond Orbital analysis further demonstrated three major electronic delocalizations—from the substituent on the phenyl moiety of pheniramine to β-CD and from β-CD to the phenyl and amine moieties in pheniramine—which were the dominant intermolecular forces that were responsible for the substantially different binding strengths. Geometrical data and the partial charge distribution obtained by NBO analysis are provided as supplementary data.

1. Introduction

Pheniramine (N,N-dimethyl-3-phenyl-3-pyridin-2-ylpropan-1-amine, $C_{16}H_{20}N_2$, Pha) has a chiral carbon atom with a hydrogen atom, a pyridyl group, a alkyl amine group, and a phenyl group as the four substituents (Fig. 1(a)). Native pheniramine and the halogenated derivatives, chlorpheniramine (ClPha) and brompheniramine (BrPha), are highly potent and applied extensively as antihistaminic drugs that are given orally to relieve hypersensitive symptoms, such as urticaria, rhinitis, and pruritic skin disorders [1–3]. However, pharmacological activity of such compounds is attributed primarily to their *S*-enantiomers, which have been reported to exhibit higher plasma concentrations and a longer half-life than the *R*-enantiomers. *S*-enantiomers are approximately 100 times more potent than the *R*-enantiomers, while *R*-enantiomers are largely responsible for the sedative side effects of these drugs [4–6]. Thus, methods of separation to obtain single-enantiomer forms to improve the efficacy of the drug or suppress the side effects associated with the other enantiomer must be developed [1,7].

β-Cyclodextrin (β-CD) possessing chiral centers and having a cone-like structure with an appropriate width of the cavity (Fig. 1(b)) remains the most extensively used selector for discriminating between pheniramine enantiomers and for different halogenated derivatives [8–11]. The interior of the cavity is hydrophobic, so providing a favorable environment for the inclusion of hydrophobic moiety of the analytes in aqueous solution and the exterior of the cavity, laced with hydroxyl groups, is hydrophilic, typically inducing selector-analyte interactions, stabilizing the inclusion complex [12,13]. Both the internal motion and the overall tumbling of β-CD complexes have been studied using NMR relaxation methods [14].

To elucidate the interactions that are involved in the discrimination of analytes, and to exploit them effectively in separation strategies, the driving forces, such as van der Waals' forces, hydrophobic interactions, electronic effects and steric factors associated with the inclusion complexation of β-CD with analytes have been extensively studied [15,16]. X-ray diffraction [17], fluorescence [18,19], infrared (IR) [20,21], ultraviolet (UV) [22,23] and nuclear magnetic resonance (^{1}H, ^{13}C-NMR) [24–26] spectroscopy have enabled the structure, stoichiometry and binding constant of the supramolecular system to be investigated. Wenzel et al. [13] adopted ^{1}H-NMR to gain information on the geometry of association between pheniramines and β-CD. They suggested that the less polar phenyl ring of pheniramine inserts into the β-CD cavity,

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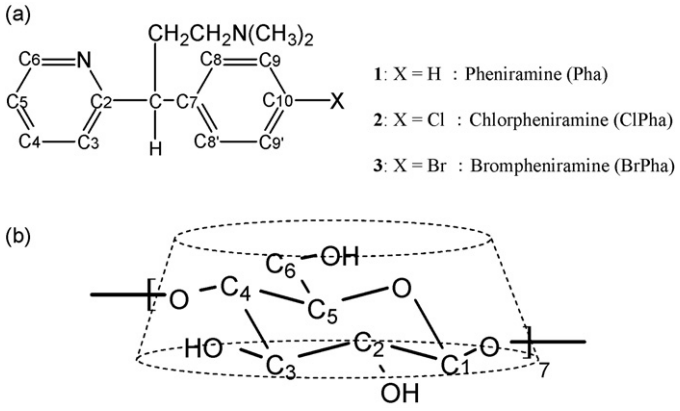

Fig. 1. Schematic structures and numbering of atoms for the isolated compounds: (a) pheniramines and (b) β-cyclodextrin.

while the more polar groups, pyridyl and amine moieties, are outside the opening of the cavity. Chankvetadze et al. [17,24,27] applied UV, NMR, electrospray ionization mass and X-ray diffraction to investigate the binding constants of β-CD with chlorpheniramine and brompheniramine. The results demonstrate the reason for the migration order of the pheniramine enantiomers towards β-CD and methylated β-CD in capillary electrophoresis.

Quantum chemical calculations provide quantitative insight into possible inclusion geometries and thereby the relative stabilities of complexes [20,28,29]. Lima et al. [30] investigated the interaction between organometallic complexes and β-CD using a two-layered hybrid ONIOM (our Own N-layer Integrated Orbital molecular Mechanics) method. The organometallics were treated as the high layer, using Hartree–Fock (HF)/LanL2DZ while the β-CD was set as the low layer in the semiempirical Austin Model 1 (AM1) [31]. The calculations reveal a stable 2:1 channel-type inclusion complex, which correlates with experimental X-ray. Ziémons et al. [22] utilized AM1 and Fourmentin et al. [32] employed a Monte Carlo procedure to calculate the binding energy of cyclodextrin with tagitinin C and chlorinated compounds, respectively. The calculated binding energies are consistent with the experimental obtained binding constants. Vrielynck et al. [33] obtained the experimental and theoretical vibrational frequencies of phenylurea/β-CD complexes using the three-parameter hybrid function of Becke with the correlation functional of Lee et al. (B3LYP) [34–36]. Consistent results were obtained with a scaling factor of 0.981. Salvatierra et al. [37] studied the enantiodifferentiation of a series of racemic mixtures by complexation with β-CD. Free energy perturbation calculations correctly predict the most stable diastereomer when enantiomers are individually complexed with β-CD.

However, the molecular modeling of the intermolecular interaction between pheniramines and β-CD has seldom been investigated. This study describes a combined experimental and theoretical study of the interactions of β-CD with pheniramine, chlorpheniramine and brompheniramine. Fourier transform infrared (FTIR) analysis and NMR spectroscopy were adopted, and complementary quantum chemical calculations made, to characterize the various affinities for pheniramine enantiomers and the halogenation effects of the phenyl ring on the intermolecular interactions with β-CD.

2. Experimental section

2.1. Complexes preparation

β-Cyclodextrin (β-CD, $C_{42}H_{70}O_{35}$, ≥98% purity), racemic compounds, *RS*-pheniramine maleate (Pha, $C_{20}H_{24}N_2O_4$, ≥99% purity), *RS*-chlorpheniramine maleate (ClPha, $C_{20}H_{23}N_2O_4Cl$, ≥99% purity), *RS*-brompheniramine maleate (BrPha, $C_{20}H_{23}N_2O_4Br$), and the *S*-enantiomers, *S*-chlorpheniramine maleate (*S*-ClPha, ≥98% purity) and *S*-brompheniramine maleate (*S*-BrPha) were all purchased from Sigma–Aldrich. Complexes of β-CD with all studied pheniramines were obtained by preparing equimolar aqueous solutions at room temperature. After 24 h of stirring, a solid complex was obtained by slow evaporation to remove most of the solvent, before it was dried in a vacuum oven at 50 °C for 24 h. To calculate the binding constants, complexes with pheniramine:β-CD molar ratios of 8:2, 7:3, 5:5, 3:7, 2:8 were prepared by shaking suitable amounts of pheniramine with β-CD, such as 14 mM pheniramine with 3.5–56 mM β-CD.

FTIR experiments were conducted for β-CD, all studied pheniramines, and their equimolar complexes. The spectra were obtained using the Bio-Rad FTS-40A Fourier transform infrared spectrophotometer purged with dry air. Sixty-four scans at 2 cm^{-1} resolution were signal-averaged. ^1H- and ^{13}C-NMR spectral analyses were performed using a Bruker NMR-spectrometer at 500 MHz. D_2O was used as a solvent, and a solution of tetramethylsilane (TMS) in tetrachloromethane was the external standard. The diastereotopic signals of the studied pheniramines in the isolated and complexed form are well resolved from each other at 132 ppm in ^{13}C-NMR spectra, apparent binding constants (K_a) of the studied pheniramines and β-CD pairs were calculated using Scott's method based on ^{13}C-NMR chemical shifts [38,39]:

$$\frac{[\beta\text{-CD}]}{\Delta\delta_{obs}} = \frac{[\beta\text{-CD}]}{\Delta\delta_s} + \frac{1}{(K_a\Delta\delta_s)}$$

where [β-CD] is the total molar concentration of β-CD; $\Delta\delta_{obs}$ is the observed chemical shift for a given β-CD concentration, and $\Delta\delta_S$ is the difference between the chemical shift of a pure sample of the complex and that of the isolated component at saturation. If the resulting plot of $[\beta\text{-CD}]/\Delta\delta_{obs}$ against [β-CD] yields a straight line, then a 1:1 complexing system is expected and the apparent binding constants are given as K_a = slope/intercept.

2.2. Quantum chemical calculations

All calculations were made using the Gaussian03 program package [40]. Starting from the Parameterized Model number 3 (PM3) [41] optimized geometries of isolated and complexed compounds, the two-layered hybrid ONIOM method [28], ONIOM(B3LYP/6-31G(d):PM3) was adopted to optimize the geometry further and to calculate the IR vibrational frequencies of these compounds. The high-level layer, pheniramine, and low-level layer, β-CD, are treated by B3LYP/6-31G(d) level of theory and PM3 method, respectively. For comparison, the B3LYP/6-31G(d) level of theory and PM3 method were used to calculate the optimized geometrical structures for isolated pheniramine and β-CD, respectively. Theoretical magnetic properties (GIAO method) of NMR were determined at B3LYP/6-31+G(d,p) level of theory to include the effect of diffuse basis set. Single point calculations and Natural Bond Orbital (NBO) analysis [42–45] were conducted at ONIOM(MP2/6-31+G(d,p):B3LYP/6-31G(d,p)) and B3LYP/6-31+G(d,p) level, respectively. To understand and to compare the stabilities of the studied supramolecular structures, the binding energies (ΔE_{bind}) were calculated by energetic difference between complexed form and isolated species.

3. Results and discussion

3.1. Experimental

Fig. 2 presents the infrared spectra of β-CD, *S*-BrPha, and the complex *S*-BrPha/CD. Characteristic bands that correspond to C=N

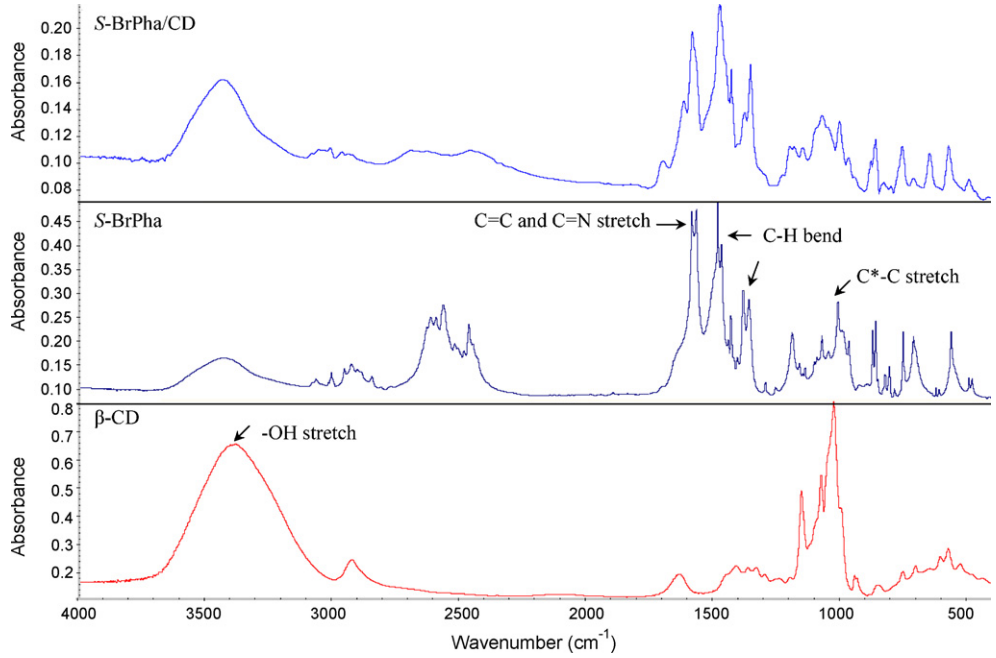

Fig. 2. Experimental FTIR spectra of β-CD, *S*-BrPha, and the complex *S*-BrPha/CD.

and C=C stretching of the pyridyl and phenyl ring (1589 and 1571 cm^{-1}), and the C–H bending of the phenyl ring (1487 cm^{-1}) from *S*-BrPha were observed to have shifted to 1587 cm^{-1} in the spectrum of *S*-BrPha/CD. Also, the C–H bending of amine (1472 and 1364 cm^{-1}) and C*–C stretching (1013 cm^{-1}) were shifted to 1479, 1357 and 1006 cm^{-1}, respectively. The change in the intensity and shape of the bands for the complex revealed that the formation of a complex restricts the vibration and bending of the pheniramine molecule [21,46]. A similar feature was observed for the *S*-ClPha complexes.

NMR spectral analyses of all studied racemic and *S*-enantiomer samples were conducted. Table 1 presents the ^{1}H-chemical shift values of only the β-CD and *S*-BrPha in the isolated and complexed form since *S*-BrPha and *S*-BrPha/CD are representative examples of the behavior of all the explored guest compounds and complexes respectively. The chemical shifts of β-CD protons notably demonstrated up-field changes in the protons H_3 (0.150 ppm) and H_5 (0.207 ppm), which are located on the inner surface of the β-CD cavity. The values H-6 and H-4 of *S*-BrPha shifted to a low field by changing 0.102 and 0.072 ppm. These two shifts indicated the formation of the inclusion complex [25,37]. The clear splitting of ^{13}C-NMR resonance signals at C-9/9′ in pheniramines because of complexation-induced chemical shift nonequivalence of the enantiomers was observed in the presence of β-CD [24,27]. Accordingly, the resonance signals at 132 ppm (C-9/9′) were used to obtain Scott's plots to determine the binding constants of the studied complexes (Fig. 3). Table 2 summarizes the complexation-induced chemical shifts at saturation ($\Delta\delta_S$) and the apparent binding constants (K_a). β-CD exhibited a markedly different binding ability toward the enantiomers Pha, ClPha and BrPha. The stability followed the order BrPha > ClPha > Pha, and *S*-enantiomers bound more strongly than *R*-enantiomers.

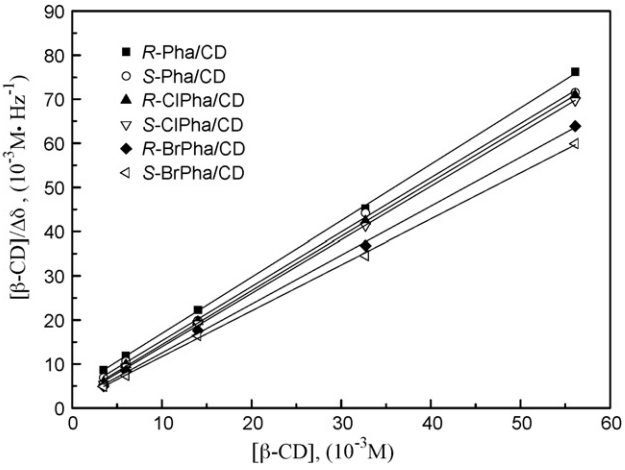

Fig. 3. Scott's plots for complexes Pha/CD, ClPha/CD, and BrPha/CD.

Table 1
^{1}H-NMR chemical shifts (ppm) of β-CD and *S*-BrPha before and after complexation.

Assignments[a]	β-CD	*S*-BrPha	*S*-BrPha/CD	$\Delta\delta$
H_1	5.093	–	5.058	−0.035
H_3	3.978	–	3.828	−0.150
H_6	3.904	–	3.681	−0.223
H_5	3.882	–	3.675	−0.207
H_4	3.610	–	3.592	−0.018
H-6	–	8.451	8.553	+0.102
H-4	–	7.852	7.924	+0.072

[a] H_n and H-*n* denote the hydrogen at carbon n of β-CD and *S*-BrPha, respectively. The atomic numbering scheme for carbon atom was depicted in Fig. 1.

Table 2
Complexation-induced chemical shifts[a] at saturation ($\Delta\delta_S$) and apparent binding constants (K_a) for studied complexes.

Complex	$\Delta\delta_S$, ppm	K_a, M^{-1}	ΔE_{bind}[b], kJ mol^{-1}
R-BrPha/CD	0.92	787	124.8
R-ClPha/CD	0.85	485	104.5
R-Pha/CD	0.79	261	73.2
S-BrPha/CD	0.97	819	132.2
S-ClPha/CD	0.89	632	107.8
S-Pha/CD	0.81	394	86.0

[a] ^{13}C-NMR resonance signal at 132 ppm (C-9/9′ of pheniramine).
[b] ΔE_{bind} is the calculated binding energies.

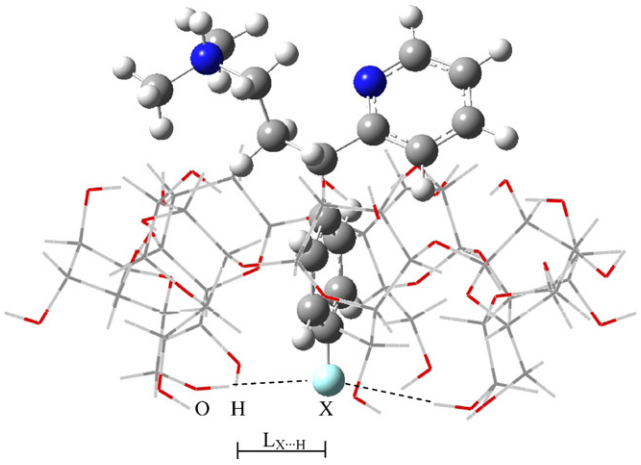

Fig. 4. Optimal geometry of pheniramines/β-CD complex.

3.2. Quantum chemical calculations

Quantum chemical calculations were performed for each of the studied complexes to yield the geometries and energies that were derived exclusively from inclusion processes. For comparison, calculations were also made for the pheniramine with fluorine substituents, *S*- and *R*-fluorpheniramine (*S*-FPha and *R*-FPha). Fig. 4 depicts the optimized structure of complex, which agrees with the X-ray and NMR data in the literature [13,27]: the phenyl ring of pheniramine inserts into the β-CD cavity from the wider opening (secondary mouth), while the pyridyl and amine moieties are outside the opening of the cavity. The theoretical frequencies and magnetic properties for *S*-ClPha and *S*-BrPha were compared with the results of experimental FTIR and NMR, Fig. 5. A linear relationship obtained (with a scaling factor of 0.96 for frequencies and 1.05 for magnetic properties) reveals that the quantum chemical calculations were consistent with the experimental spectra. Also, the binding energies between β-CD and pheniramine were calculated and shown in Table 2. The calculations were consistent with the order of the binding constants given by ^{13}C-NMR. The strength of interaction followed the order (*S*)-brompheniramine > (*R*)-brompheniramine > (*S*)-chlorpheniramine > (*R*)-chlorpheniramine > (*S*)-pheniramine > (*R*)-pheniramine.

The intermolecular interaction is considered based on NBO analysis as presented in Table 3. Nitro (NO_2), hydroxy (OH), amino (NH_2) and methyl (CH_3)-substituted pheniramines were included to understand further the effect of the substituent on the interaction. According to the NBO analysis, the substituent binds with the primary hydroxyl groups of β-CD, mainly through its lone pairs. Thus, the delocalization energy $E_{X\rightarrow CD}$ from the substituent of pheniramine to β-CD depended strongly on the lone pair of the substituent and its ability to donate. Nitro (NO_2)-substituted pheniramines (NO_2Pha) with two strong electronic donors, the oxygen lone pair, yielded the greatest $E_{X\rightarrow CD}$. With respect to the halogen substituent, the heavier (softer) bromo halogen provided electrons to O–H more effectively than the other halogen, thereby increasing the delocalization and strengthening the interaction of pheniramine with the β-CD.

Calculations further demonstrate that the delocalizations from β-CD to pheniramine phenyl ($E_{CD\rightarrow pha,ph}$) and amine ($E_{CD\rightarrow pha,am}$) moieties are also important to the interaction between pheniramine and β-CD (Table 3). $E_{CD\rightarrow pha,ph}$ and $E_{CD\rightarrow pha,am}$ depended strongly on the electro-withdrawing ability of substituent. An electron-withdrawing group (such as nitro or fluoro) reduces the electron density of phenyl and consequently increases the delocalizations from β-CD to pheniramine.

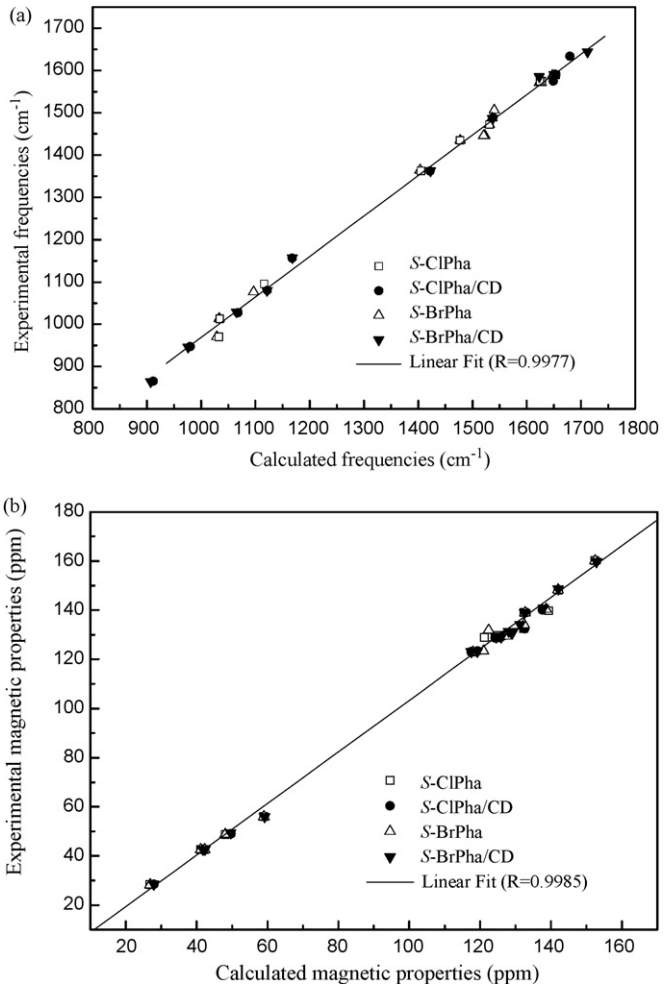

Fig. 5. Relationships between calculated and experimental (a) frequencies (in cm^{-1}); (b) magnetic properties (in ppm) of the *S*-ClPha and *S*-BrPha in the isolated and complexed form.

Table 3
Calculated binding energies (ΔE_{bind}, kJ mol^{-1}) and delocalization energy[a] of studied complexes.

Compound	ΔE_{bind}	Pheniramine as donor	Cyclodextrin as donor	
		$E_{X\rightarrow CD}$	$E_{CD\rightarrow Pha,ph}$	$E_{CD\rightarrow pha,am}$
R-NO_2Pha/CD	138.3	13.16	4.72	4.70
R-BrPha/CD	124.8	6.57	4.48	4.49
R-ClPha/CD	104.5	5.51	4.65	4.52
R-FPha/CD	90.3	0.08	4.69	4.63
R-OHPha/CD	88.6	1.66	4.39	3.31
R-NH_2Pha/CD	87.1	0.95	4.33	3.56
R-Pha/CD	73.2	–	3.96	3.24
R-CH_3Pha/CD	66.9	–	3.31	3.15
S-NO_2Pha/CD	146.2	14.69	5.34	5.49
S-BrPha/CD	132.2	6.64	4.75	4.38
S-ClPha/CD	107.8	6.37	4.75	4.41
S-FPha/CD	103.4	0.47	5.15	5.39
S-OHPha/CD	101.8	1.90	4.66	3.88
S-NH_2Pha/CD	100.4	0.99	4.55	3.75
S-Pha/CD	86.0	–	4.32	3.27
S-CH_3Pha/CD	71.6	–	3.87	2.72

[a] $E_{X\rightarrow CD}$ is the delocalization energy (kJ mol^{-1}) from substituent X of pheniramine to β-CD. $E_{CD\rightarrow Pha,ph}$, and $E_{CD\rightarrow pha,am}$ are from β-CD to the phenyl and amine moieties in pheniramine, respectively.

The different spatial arrangement of the functional groups of *R* and *S*-pheniramine is responsible for the different strengths of interaction between enantiomers and β-CD. Upon complexation, *S*-pheniramine showed a greater electronic delocalization associated with $E_{X\rightarrow CD}$ than did *R*-pheniramine (Table 3). Additionally, *S*-pheniramine with a lower electron density on N_{py}, N_{am} and Ph was associated with greater delocalization $E_{CD\rightarrow pha,ph}$ and $E_{CD\rightarrow pha,am}$, and therefore a stronger interaction with β-CD.

4. Conclusions

β-Cyclodextrin formed inclusion complexes with pheniramine (Pha) and its halogenated derivatives chlorpheniramine and brompheniramine. Consistent with the experimental FTIR and NMR measurements, quantum chemical calculations provided valuable insight into the possible inclusion geometries and, hence the relative stabilities of the complexes. The calculated binding energies supported the experimental results, revealing that they followed the order BrPha > ClPha > Pha, and *S*-enantiomer > *R*-enantiomer. The delocalization energy $E_{X\rightarrow CD}$ from the halogen of pheniramine to β-CD, along with $E_{CD\rightarrow Pha,ph}$ and $E_{CD\rightarrow pha,am}$ from β-CD to the phenyl and the amine moieties in pheniramine, respectively, are the dominant intermolecular forces that are responsible for host–guest coordination, stabilizing the complex. The form of enantiomer (*S*- or *R*-form) and the substituent on the phenyl moiety of pheniramine markedly affected the intermolecular forces. The existence of lone pairs on the substituent facilitates the interaction. The electro-withdrawing substiutent reduces the charge density of the benzene ring, further strengthening the inclusion of pheniramine in the cavity of β-CD.

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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.jpba.2009.05.027.

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