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SPECTROSCOPIC STUDIES ON THE INCLUSION COMPLEXATION OF VALINE ENANTIOMERS WITH β-CYCLODEXTRIN

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Abstract

Complexes of β-cyclodextrin (β-CD) with amino acid analytes such as valine are an ideal study of molecular recognition since L- and D-forms of valine are differently adsorbed on the chiral surface of the β-CD molecule in the aqueous phase. Therefore, the inclusion complex formation of valine enantiomers is extensively studied using spectroscopy methods to better understand the characteristics of the inclusion complexes. Hence, FTIR and UV spectroscopy were utilized to investigate the inclusion complexes formed by the enantiomers L-valine and D-valine in an aqueous solution with β-CD. According to the FTIR spectra, the differing relative intensities and characteristic band shifts of the two enantiomers show that they have different interactions when they are complexed with β-CD. Experiments with the FTIR spectrometer indicated a discernible decrease of the C-O stretching and ring deformation, both of which point to the embedding of valine into the β-CD cavity. In neutral pH, it seems that there is a significant difference in absorbance for the L- and D-valine complexes β-CD. The Benesi-Hildebrand plot was used to determine the stoichiometry ratio as well as the binding constant of the inclusion complexes. The inclusion complex involving β-CD and the enantiomer of valine had a stoichiometry ratio of 1:1. L-valine has a binding constant of 4922.47 M^{-1}, which is higher than that of D-valine, which is 1010.67 M^{-1}. Based on these findings, it appeared that L-valine had a strong interaction with the cavity of β-CD. According to the findings, the enantioselective reaction has been developed into an analytical method for determining enantiomeric excess via spectroscopic studies.

Keywords: β-CD, valine, inclusion complex, binding constant

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Introduction

The host-guest interaction plays a significant role in the formation of inclusion complexes between cyclodextrins (CDs) with a wide variety of molecules. CDs are cyclic oligosaccharides consisting of glucopyranose units connected by α -1, 4 bonds. CDs have a hydrophilic external surface but are slightly polar due to the presence of H atoms and OH bonds (Araújo et al., 2021). β-cyclodextrin (β-CD) is one of the three most significant cyclodextrins, which is the most interesting because its cavity size allows for the best match for numerous frequent guest moieties (Mohamadhoseini et al., 2021). In aqueous conditions, the hydrophobic cavity inside of β-CD enables guests to form inclusion complexes with hydrophobic substances, which impact the physical, chemical, and biological properties of the guest molecules (Sahu et al., 2023). Additionally, it enhances the guest molecule's application properties (Gao et al., 2020).

Molecules with diverse structural isomers and stereoisomers frequently have various physical, chemical, and biological characteristics (Xu et al., 2021). Two enantiomers only exhibit differing chemical properties in asymmetric settings, making one class of stereoisomers, the enantiomers, of relevance (Monika et al. 2019). Amino acids are biologically significant organic molecules whose physicochemical characteristics

have received a great deal of attention to better understand proteins (Zhang et al., 2022). Valine is an alpha acid that is involved in the production of proteins throughout the biosynthesis process (Zhang et al. 2019). It is categorized as a non-polar aliphatic amino acid since it has an alpha group, an alpha acid group, and an isopropyl group connected to its side chain. It is regarded as a necessary component because people are unable to create it on their own. D-valine is found in the cell walls of bacteria, whereas L-valine is used to generate proteins, making it very important to our healthy functioning (Sharma et al., 2023). As a result, there is a requirement for more efforts to be put into the manufacturing and commercialization of the enantiomer that is preferred the most by studying the chiral selector for these enantiomers. It is a challenge for analytical chemists to develop techniques that can either separate enantiomers or else reliably detect one such enantiomer in the presence of the other, even when there is a large concentration difference.

Different experimental approaches, including electrospray mass spectrometry, capillary electrophoresis, and gas chromatography, have been used to investigate the inclusion complex formation and chiral separation of amino acids and amino acid derivatives by CDs (Zhang et al., 2022). The impact of solvents and the pH of the media on the complex formation of β-CD has also been investigated for some amino acids (Alvira, 2020). To our knowledge, the chiral discrimination for both valine (Val) enantiomers by β-CD in the aqueous phase has not been examined, despite the fact that the influence of valine enantiomer configuration on the molecular dynamic simulation of their separation by β-CD has been investigated by Alvira in 2020.

This study was to investigate the characteristics of inclusion complexes L-valine and D-valine with β-CD using spectroscopy methods such as FTIR and UV-Vis. To the best of our knowledge, no study has ever been published on the comparison characteristics of β-CD complexes with L- or D-valine in an aqueous phase with different pHs and concentrations of β-CD. The binding constant and stoichiometry ratio of L- and D-valine inclusion complexes with β-CD were investigated. This straightforward and speedy procedure indicated that β-CD has the potential to be utilized as an effective chiral selector for valine enantiomers.

Methods

Materials

β-Cyclodextrin powder, $C_{42}H_{70}O_{35}$ with a purity of ≥97% was purchased from Sigma-Aldrich. L-valine and D-valine ($C_5H_{11}NO_2$) with purity ≥98% were purchased from Sigma-Aldrich. Buffer solutions for pH 2.00, 7.00, 10.00, and 12.00 (±0.01) were purchased from Thermo Fisher Scientific, Inc. All the experiments were carried out using deionized water.

Instruments

The FTIR spectra were recorded in the 500 – 4000 cm^{-1} range with 16 scans and a spectral resolution of 2 cm^{-1} using a Perkin-Elmer FT-IR Microscope Spotlight 200. The UV spectra were recorded by a UV-2600 spectrophotometer (Shimadzu, Japan) using standard quartz cells with a path length of 1 cm. Measurements were taken in the spectral range between 185 nm and 400 nm. The pH value was measured with a HANNA HI 5221-02 Laboratory Research Grade Benchtop pH/mV Meter with 0.001 pH resolution. All measurements were made against a blank solution of deionized water.

Sample Preparations

FTIR measurements

The mixture of a 10 mM stock solution of β-CD and individual L- and D-valine enantiomers was prepared with a 1:1 molar ratio to the final concentration of 6×10^{-4} M. In order to acquire FTIR spectra, 1-2 drops of the sample were deposited directly onto the ATR crystal.

Effect of different concentrations of β–CD using UV Spectrophotometer

Deionized water was used in the process of creating the stock solution of valine enantiomers with a concentration of 1 mM. Mixing valine with β-CD of different concentrations (0.30, 0.40, 0.50, 0.60, and 0.70 mM) allowed for the preparation of a mixture with varying concentration ratios. The total concentration of enantiomers of valine was found to be 0.02 mM. Before conducting the analysis, each solution was thoroughly mixed, sonicated for five minutes, and kept at 25°C for twenty-five minutes.

Effect of pH using UV Spectrophotometer

Using the appropriate quantity of buffer solution, a stock solution of β-CD with a concentration of 0.2 mM was made in volumetric flasks of 5 mL capacity and pH levels of 2, 7, 10, and 12, respectively. Both enantiomers of valine were tested at a concentration of 0.02 mM, while studies on the effect of pH were carried out.

Result and Discussion

Fourier-transform infrared (FTIR) spectroscopy analysis

FTIR spectroscopy provided evidence for the formation of an inclusion complex between β-CD and the L and D enantiomers of valine. As was to be anticipated, the mixture of β-CD and L- or D-valine appeared to contain peaks that correlated to both components. Figure 1 (a)–(d) shows that FTIR spectra of the β-CD, pure isomers, and inclusion complexes are all present in the 500–4000 cm^{-1} areas. The vibration peaks of these species are shown in Table 1.

In comparison with the spectra of β-CD (Figure 1 (a)) and valine enantiomers (Figure 1 (b) and (c)), the spectra of the complex of L- and D-valine-β-CD (Figure 1(d)) exhibited some distinct differences in their peak's appearance. The creation of a complex is indicated by changes in the band position and intensity. Also included are the primary peaks of these compounds. At 3294 cm^{-1}, 2920 cm^{-1}, and 1151 cm^{-1}, the peaks for β-CD were detected. These three wavenumbers matched the broad peaks of O-H, C-H, and C-C, respectively. The primary peaks that should be present as a result of the O-H and C-O stretching appear to be obscured by the β-CD hydroxyl peaks that are present in the same areas. The fact that the concentration of both components is 1:1 in terms of the molar ratio enables one to assume that the complex creation is responsible for the merging of these helpful vibration peaks. Absorption bands are seen in the spectra of L-valine and D-valine (Figure 1 (b) and (c)), and they are located at 2923 cm^{-1} (representing the C-H stretching vibration), 1573 cm^{-1} (representing the N-H bending vibration), and 1138 cm^{-1} (for the C-O stretching vibration). The pure valine enantiomer has a peak at 1323 cm^{-1} (C-N stretching) and a peak at 1138 cm^{-1} (C-O stretching) that are characteristic of L- and D-valine. Another prominent peak can be seen in the spectrum of the valine enantiomer at 878 cm^{-1} due to the C-H bond bending out of plane. Because of the formation of complexes, the intensity of these peaks is significantly diminished (Dehghani et al., 2020), as shown in Figure 1 (d). The following piece of evidence may be seen in the peak shift at 774cm^{-1}, where it is found to have decreased to 755cm^{-1} for the L-valine-β-CD complex, and none is observed for the D-valine-β-CD complex. The peak shift that occurs at 668cm^{-1} where it shifts to 657cm^{-1} for the L-valine-β-CD complex and to 655cm^{-1} for the D-valine-β-CD complex, is an additional indication that the complex has formed (Prabu et al., 2020). This peak, which corresponds to the in-plane ring and C-O-H bending in both β-CD and valine, goes through a significant shift to a lower wavenumber.

The frequencies of C-H, -C-N, and -C-O changed in the spectra of the L-valine-β-CD complex (Figure 1 (d)), shifting from 2923 cm^{-1} to 2958 cm^{-1}, 1324 cm^{-1} to 1381 cm^{-1}, and 1138 cm^{-1} to 1136 cm^{-1} correspondingly. The frequencies of C-H, -C-N, and -C-O moved in the spectra of the D-valine-β-CD complex (Figure 1 (d)), moving from 2923 -cm^{-1} to 2962 cm^{-1}, 1324 cm^{-1} to 1379 cm^{-1}, and 1138 cm^{-1} to 1114 cm^{-1} respectively. In addition, a broad hydroxyl band of pure β-CD that is located at 3294 cm^{-1} is

discovered to be narrowed in the spectra of the complex of L- and D-valine with β-CD (Figure 1 (d)), which is a good indication of the formation of the inclusion complex (Tanwar et al. 2019). When synthesizing the inclusion complex between β-CD as the host and guest molecules, this behavior can frequently be seen by most researchers (Tanwar et al. 2019). The formation of the inclusion complex is accountable for the alterations seen in the FT-IR spectra of the complex depicted in Figure 1(d). These changes are caused by a shift in the microenvironment. Therefore, the findings of the FT-IR spectroscopy led to the conclusion that an inclusion complex of L- or D-valine with β-CD had been formed. In addition, the L-valine complex behaves differently than the D-valine complex, which suggests that the two complexes engage in distinctively distinct molecular interactions. This finding shows that FTIR can be utilized as a method for performing chiral analysis of valine enantiomers when β-CD is used in the function of chiral selector.

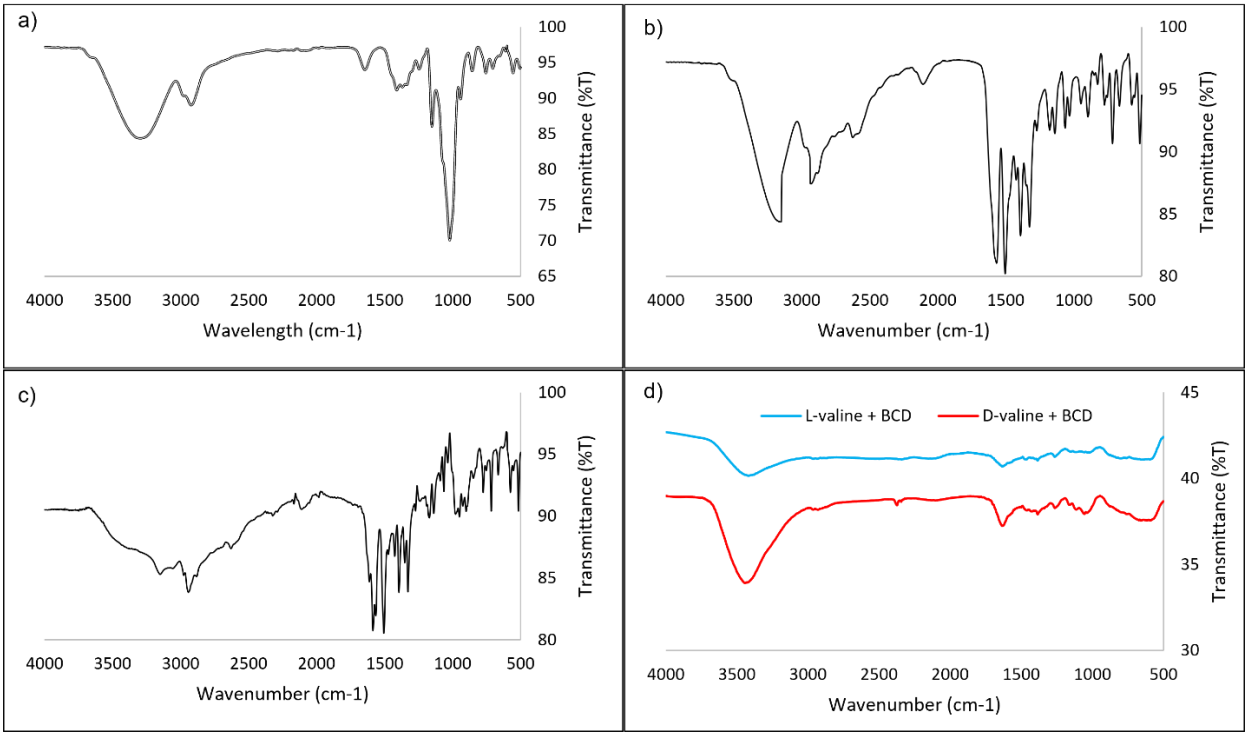

Figure 1. FTIR spectra of (a) β-CD, (b) L-valine, (c) D-valine and (d) L-valine-β-CD and D-valine-β-CD complexes.

Table 1. FTIR band assignments of β-CD, L-valine, D-valine, L-valine -β-CD complex and D-valine -β-CD complex

Band assignment	β-CD	L-valine	D-valine	L-valine- β-CD	D-valine- β-CD
	Wavenumbers (cm^{-1})				
O-H stretching	3294	3148	3149	3415	3432
C-H stretching	2920	2923	2923	2958	2962
N-H bending		1573	1573	2342	2342
C-H bending	755	744, 2107	744, 2105	755	
C=C stretching				1627	1633
O-H bending	1396			1467	
CH_3 antisymmetric deformation					
O-H bending		1423	1425		
C –C stretching; C - C - H deformation					
C-N stretching		1324	1324	1381	1379, 1053
C-O stretching				1261	1261
Ring deformation antisymmetric C-C-C					
C-O stretching	1029, 1245, 1151	1138	1138	1136	1114
C-CH_3 stretching		1080	1084		
C-O-H in plane bending, CH_3 rocking		878	878		
Breath of glucose ring	856				
Benzene derivative	704				
In plane ring bending; C-O-H bending		668	668	657	655

UV absorption spectra of inclusion complexes

When compared to the pure isomer, the interaction between L- and D-valine with the addition of β-CD did not result in any discernible change in the appearance of the solution. As a result, UV was utilized in order to gain further comprehension regarding the enantio-recognition relationship that β-CD has with both isomers (Vaid et al., 2022). To evaluate the effect of β-CD on the enantiomers of valine, the use of UV is a method that is both effective and straightforward. Figure 2 illustrates the differences in UV absorbance that exist between the two different enantiomer combinations.

Figure 2 shows the spectrum of β-CD, which exhibited the highest absorption at 201 nm. At a wavelength of 220 nm, the primary absorption peak of pure L- and D-valine enantiomers is observed. The increasing absorption band after the addition of β-CD to L- and D-valine separately is defined as the hyperchromic effect (Goh et al., 2022). This hyperchromic effect suggests there is a strong interaction between β-CD and L- and D-valine. In most cases, van der Waals and hydrophobic interactions are thought to be responsible for bonding. These interactions involve the rearrangement, addition, and removal of water molecules that surround the guest within the host cavity (Obaid et al. 2020). The obvious discrepancies between L- and D-valine absorbance when β-CD is added could have been produced by the noticeably different interactions

between the carboxyl group of L- and D-valine and the hydrophilic environment of β-CD (Hancu et al., 2022).

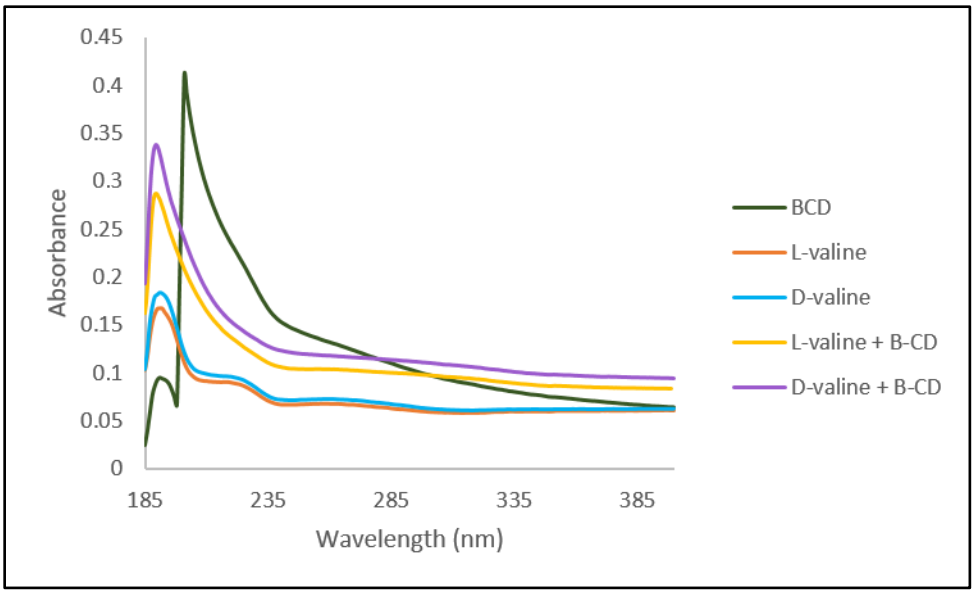

Figure 2. UV absorption spectra of β-CD, L-valine, D-valine, L-valine + β-CD complex and D-valine + β-CD complex.

Influence of concentration of β-CD

Figures 3 show the UV spectra of valine enantiomers mixed with β-CD at varying concentrations. It was discovered that the valine enantiomers' absorbance increased linearly when the concentration of CD rose due to the valine enantiomers' dissolution (Kapoor et al., 2022).

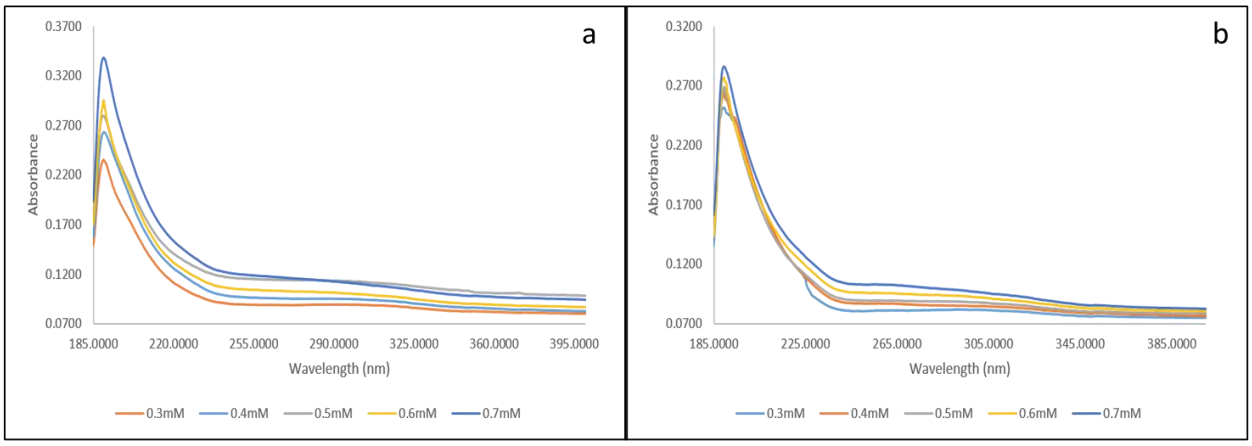

Figure 3. UV absorption spectra of L-valine (a) and D-valine (b) with different concentration of β-CD.

Using the Benesi-Hildebrand (BH) equation, the effect of raising the concentration of β-CD was studied for each unique isomer to determine the binding constant (K) and the stoichiometry ratio (n) (Dass et al., 2022).

$$\frac{1}{A - A_0} = \frac{1}{A' - A_0} + \frac{1}{K(A' - A_0)[\beta - \mathrm{CD}]}$$

Where, A = absorbance of β–CD at each concentration,
A_0 = absorbance of the analyte (either L-valine or D-valine) without β–CD,
A' = absorbance of the highest concentration of β–CD
K = binding constant.

As can be seen in Figures 4, good linear relationships of both enantiomers are obtained. The value of the correlation of determination for L-valine is found to be 0.9844, while the value for D-valine is found to be 0.9826. This demonstrated beyond a reasonable doubt that the stoichiometric ratio for both the L- and D-valine with β-CD inclusion complexes is 1:1.

The slope of the BH plot is used in conjunction with the following equation to derive the K value for both inclusion complexes:

$$K = \frac{1}{slope(A' - A_0)}$$

Both L-valine and D-valine are found to have a K of 4922.47M^{-1} and 1010.67M-1, respectively, at 303K, as shown in Table 2. These values indicated that β-CD formed inclusion complexes more preferentially with L-valine than D-valine, as proposed in the structure of the inclusion complex in Figure 5. The findings from the UV experiments provide compelling evidence supporting the FTIR findings that β-CD can act as a chiral selector for both L-valine and D-valine.

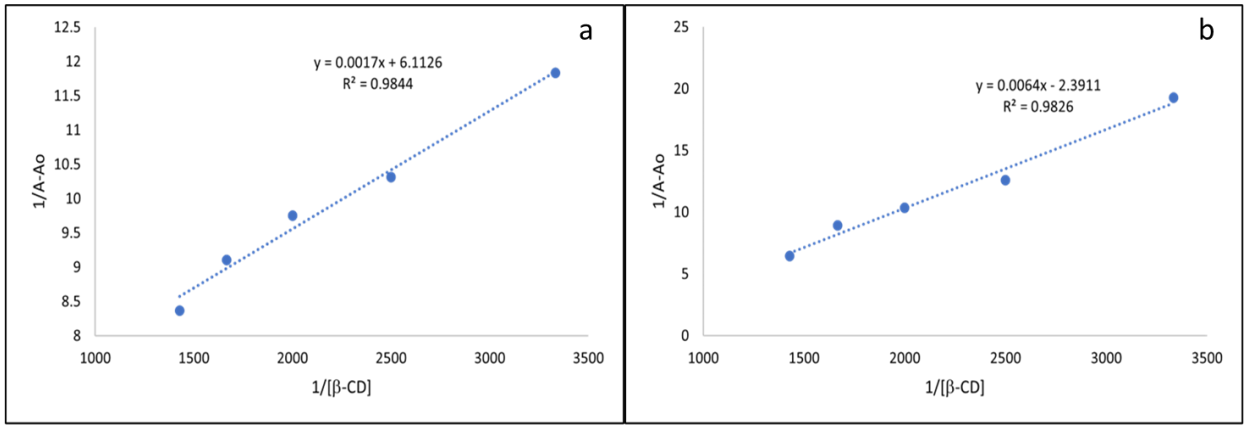

Figure 4. Benesi -Hildebrand absorption plot for the interaction of L-valine (a) and D-valine (b) with β-CD.

Table 2. Thermodynamic Parameter

Parameter	L-valine	D-valine
Stoichiometry	1:1	1:1
Slope	0.0017	0.0064
Correlation Coefficient (R^2)	0.9844	0.9826
Binding Constant (M^{-1})	4922.47	1010.67

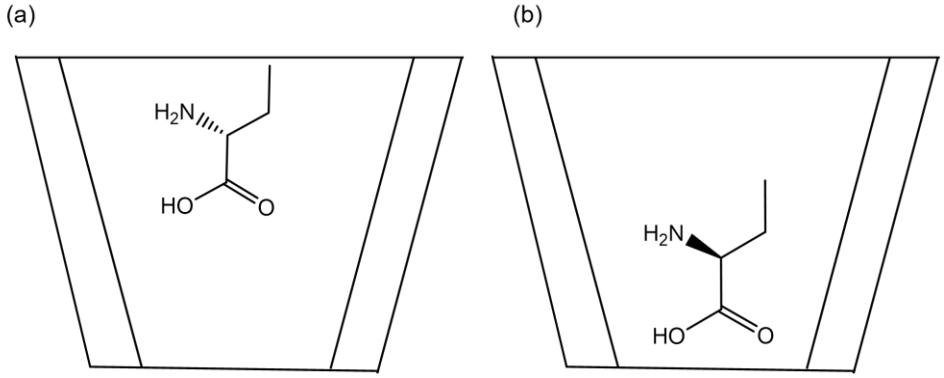

Figure 5. Proposed structure for inclusion complex (a) D-valine-β-CD and (b) L-valine-β-CD.

Effect of pH

The influence of pH on L-valine and D-valine as well as their inclusion complexes with β-CD can be seen in Figures 6 (a)–(d), and the relevant spectrum data can be found in Table 3. The maximum absorption of pure L-valine and D-valine at 220 nm corresponds directly to the protonation of the COOH group, which results in the unionized form of valine at an acidic pH (Borkowski et al., 2022). As the pH drops, the maximum absorption shifts toward longer wavelengths. Increases in both the intensity and the interaction of hydrogen bonding are generated by the addition of β-CD, and these changes correspond to a shift in the spectra of the inclusion complexes (Obaid et al., 2020). The powerful interaction between the unionized valine form and β-CD is responsible for the extremely high absorbance seen at a pH value of 2 (shown in Figure 6 (a)). The rise in pH causes the absorbance values of pure valine enantiomers and those containing β-CD to diverge significantly from one another. Without the presence of β-CD, the neutral (pH 7) and alkaline (pH 10 and pH 12) media exhibited very similar absorption maxima, which are measured to be approximately 192-220 nm. The shift in the spectrum of the pure analyte that occurred because of a change in the pH value can be attributed to either the protonation or deprotonation of COOH in valine. The shift in the spectra of pure L-valine and D-valine from 220 nm to 200 nm is due to the deprotonation of the COOH, forming ionized species. Due to the fact that the spectra of L-valine and D-valine with β-CD complexes at an acidic and alkaline pH are very similar to one another, the absorbance maximum for both L-valine and D-valine with β-CD complex is the same, which is at pH 2, the absorbance maxima is 217 nm, and for pH 10 and pH 12, it is 192 nm and 195 nm, respectively, as shown in Table 3. Thus, enantio-recognition of L-valine and D-valine is not possible. The findings that are obtained from UV experiments reveal that the interaction of both enantiomers with β-CD is not comparable, regardless of whether the pH is acidic or alkaline. The unionized form of valine enantiomers (in acidic pH) interacts with β-CD, forming an inclusion complex that is analogous to one another. Therefore, the recognition of valine enantiomers was only feasible at a pH of 7 and not at an acidic or alkaline value.

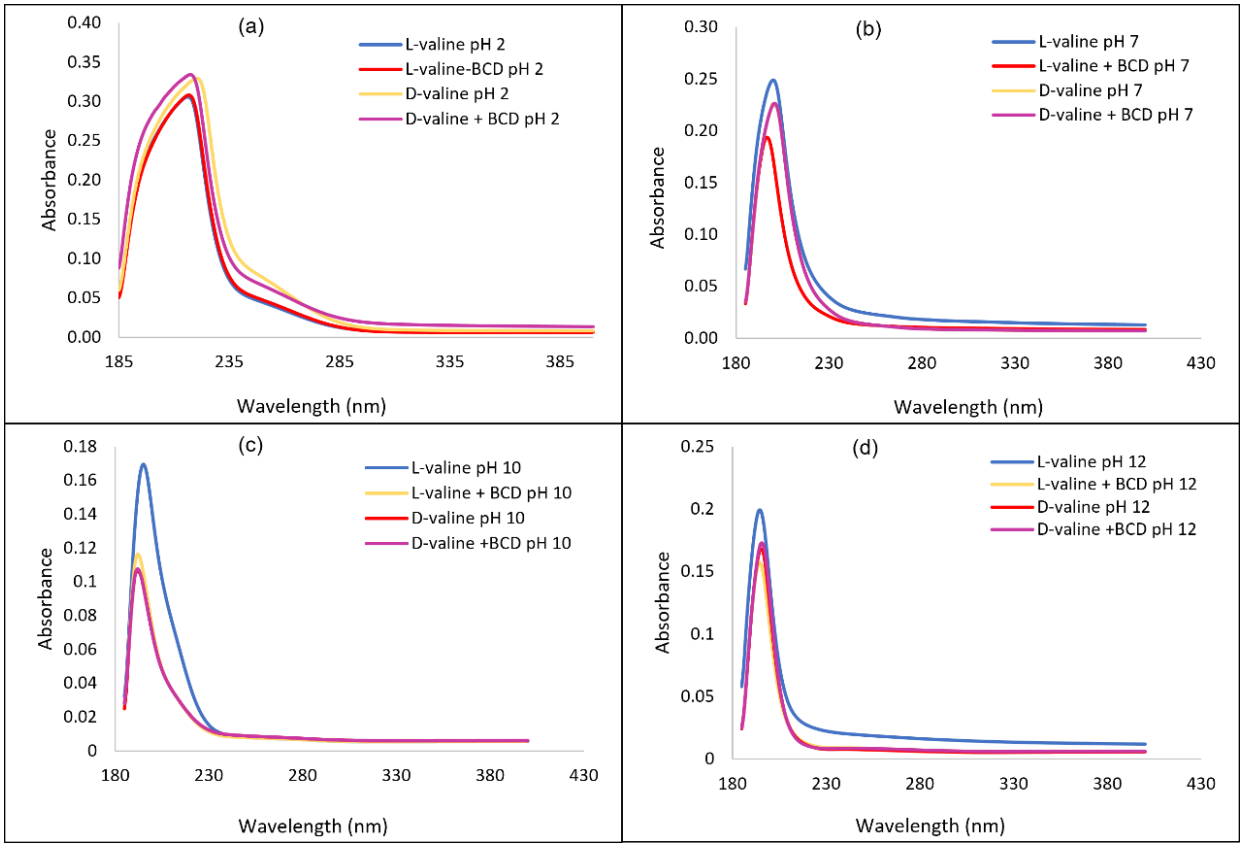

Figure 6. UV absorption spectra of pure valine enantiomers and their inclusion complexes at (a) pH 2, (b) pH 7, (c) pH 10 and (d) pH 12.

Table 3. Absorption spectral maxima of valine enantiomers in aqueous and β-CD media.

pH	Absorption maxima(nm)			
	L-Valine		D-Valine	
	Aqueous medium	β-CD medium	Aqueous medium	β-CD medium
2	216	217	220	217
7	200	197	199	200
10	195	192	192	192
12	195	195	195	195

Conclusion

The findings of this research made it abundantly clear that inclusion complexes can be formed between L-valine and D-valine enantiomers and β-CD. The proof that β-CD formed the inclusion complex with valine enantiomers was provided by the results that were acquired from FT-IR. Furthermore, it was shown that the L-valine and the D-valine behave differently when introduced to the β-CD complex. This suggests that the molecular interactions of the two complexes are distinct, demonstrating that β-CD can function as a chiral selector for valine in particular. The spectra that were obtained by using β-CD on the two chiral substances exhibit a discernible difference in neutral pH, which can serve as the basis for chiral analysis. The formation of a host-guest interaction ratio is 1:1, and the BH plot revealed outstanding steady binding constant values, specifically 4922.47 M^{-1} for the L-valine-β-CD complex and 1010.67 M^{-1} for the D-valine-

β-CD complex. Studying the guest and host molecule binding by spectroscopic techniques (FTIR and UV) has proven to be an easy, quick, and cost-effective way for enantio-recognition.

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Author Contribution

Nur Qausar Md Saad: Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. Goh Soen Qeng: Visualization, Writing – review & editing, Nurul Yani Rahim: Conceptualization, Methodology, Visualization, Resources, Writing – review & editing, Supervision, Project administration.

Conflict of Interest

No potential conflict of interest was reported by the author(s).

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