Bull. Chem. Soc. Ethiop. **2023**, 37(4), 973-982.
DOI: https://dx.doi.org/10.4314/bcse.v37i4.13
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ISSN 1011-3924
Printed in Ethiopia
Online ISSN 1726-801X

SYNTHESIS AND CHARACTERIZATION OF INCLUSION COMPLEX OF β-CYCLODEXTRIN AND TRIAZOLE PICRATE

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(Received March 14, 2022; Revised March 24, 2023; Accepted March 31, 2023)

ABSTRACT. Inclusion complex between 3-amino-1,2,4-triazole picrate and β-cyclodextrin was synthesized in order to increase the picrate solubility. The complex was obtained by co-precipitation method and its stoichiometry is 1:1 (guest–host). The structure of picrate and complex has been established by UV, X-ray diffractometry powder spectra, TGA, DSC, IR, ^{1}H NMR, and ^{13}C NMR. The influence of the effect of pH on the complexation has been discussed. The value of apparent formation constant is 1.2 x 10^{4}.

KEY WORDS: Amino triazole, Picrate, Inclusion complex, pH

INTRODUCTION

Cyclodextrins (CDs) are a class of cyclic oligosaccharides with six, seven, or eight-glucose units linked by α-1,4 glycosidic bond. These three types of CD are named α, β, and γ-CD, respectively [1]. These oligomers are capable of enclosing a large number of organic and inorganic species in their cavity. The neutral lipophilic cyclodextrins were recognized by three types of noncovalent interactions, conventional hydrophobic bonding, –N–H---N and N–C–H---N hydrogen bonding, and Van der Waals forces, cooperatively determine the inclusion complex behavior of the cyclodextrin host [2, 3]. Native water-soluble cyclodextrins have been rendered lipophilic and used for molecular and ionic recognitions [4]. This property has led to the wide application of cyclodextrins in various fields, such as analytical chemistry, enzymology [5], they have been widely used in pharmaceutical [6], in food industry [7]. They can be utilized in foods mainly as carriers for molecular encapsulation of flavours [8], in separate chromatography technique [9, 10], and in environmental protection [11, 12]. The CDs are well known to form inclusion complexes with a variety of organic compounds, among them, with drug substances [13-15].

3-Amino-1,2,4-triazole (AT), is known as an herbicide and it has fungicide activity [16, 17]. AT is absorbed on soil particles and organic matter by proton association. It was found to cause cancer of the thyroid in rats and mice. AT is also of interest as a ligand, which forms complexes both in aqueous solution and in the solid state. It has at least two donor centers available for coordination [18].

On account of all the previous reasons, we report here the synthesis and spectroscopic studies of 3-amino-1,2,4-triazole picrate and the synthesis of the new inclusion complex formed from picrate and β-cyclodextrin in order to increase the solubility of 3-amino-1,2,4-triazole in water.

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EXPERIMENTAL

Reagents

β-Cyclodextrin, picric acid, and 3-amino-1,2,4-triazole (AT) were obtained from across chemical Co. Other chemical reagents of analytical reagent grade were used as commercial.

Instruments

IR spectra were recorded on Perkin Elmer Paragon 1000 PC spectrometer using a sample dispersed in spectroscopically pure potassium bromide pellets. Spectra resolution was 4 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded with DMSO-d6 solvent containing TMS (tetramethylsilane) on a Bruker 300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75.47 MHz). The chemical shifts (δ) are reported in ppm relative to TMS (internal reference). For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet.

The powder X-ray diffraction patterns were obtained by PHILIPS PW1729 diffractometer. The UV–Visible spectrum was recorded in the range 200–400 nm with an UV JENWAY 6405 spectra photometer equipped with a stoppered quartz cell with 1.0 cm optical path length.

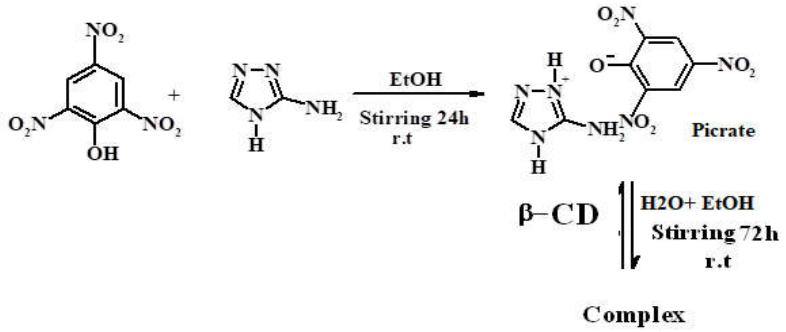
DSC–TGA analysis was performed using TA DSC-TGA SDT-2960 instrument in flowing N_2 with an average heating rate of 5 °C/min, between room temperature and 450 °C.

Synthesis of 3-amino-1,2,4-triazole picrate

To 5 mmol (1.14 g) of picric acid was dissolved in ethanol was added dropwise with stirring 5 mmol (0.42 g) of 3-amino-1,2,4-triazole dissolved in ethanol. The stirring operation was kept for at least 24 h at room temperature (Scheme 1). After evaporating the solvent in vacuo, the resulting solid product was recrystallized from acetone \ ethanol (20/80), a great deal of yellow powder (yield = 90%), the picrate was obtained by filtration. The product obtained was confirmed by powder X-ray diffractometry, ^{1}H NMR, ^{13}C NMR, IR and UV spectra, DTA-TGA and DSC.

Synthesis of inclusion complex

10^{-4} mol (1.13 g) of β-CD was dissolved in 20 mL distilled water. Then 10^{-4} mol (0.31 g) of 3-amino-1,2,4-triazole (AT) picrate in ethanol solution was dropped into β-CD aqueous solution with continuous stirring. The stirring operation was left for 72 h at room temperature (Scheme 1).



Scheme 1. Synthesis of picrate in first step and Synthesis of the inclusion complex of AT picrate with β-CD in second step.

The inclusion complex of AT picrate and β –CD was obtained by filtration, which yielded a yellow solid product. The product was washed with ether for three times in turn to clean the residual guest and host monomers. Then it was dried in a vacuum oven at 50 ºC for 48 h. (yield = 70%). The product was confirmed by powder X-ray diffractometry, ^{1}H NMR, ^{13}C NMR, IR and UV spectra, TDA-TGA, DSC.

RESULTS AND DISCUSSION

X-Ray powder diffraction

The formation of the inclusion complex was confirmed by X-ray diffractometry [19-20]. Figure 1 refers to the powder X-ray diffraction patterns of physical mixture; complex; picrate and β-CD. Difference was observed between the reflection intensities of these two patterns which may be attributed to the inclusion phenomena. In the other hand, we noticed, the appearance of new peaks related to the formation of the complex Table 1. From Figure 1, we notice that the diffraction pattern of the elaborated product is different from that of the picrate and β-cyclodextrin which confirms the obtaining of the complex.

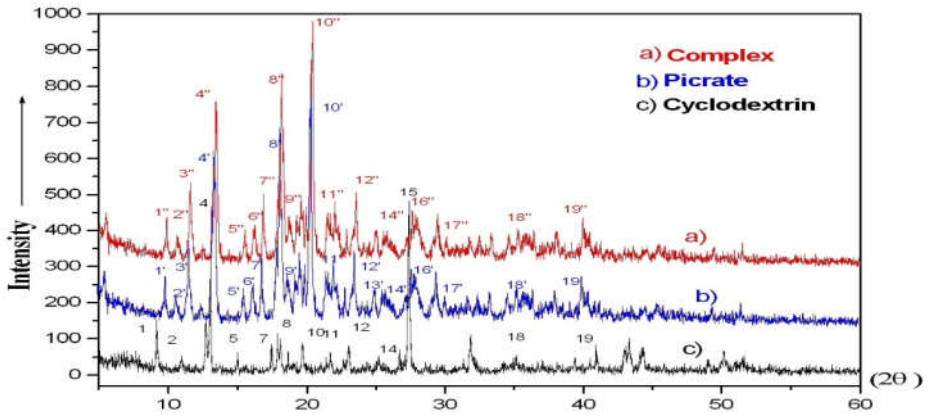


Figure 1. Experimental XRD patterns of **a)** the complex, **b)** the picrate and **c)** the β-CD.

Table 1. Summary of DRX results.

Intensities	Physical mixture	Complex
Strong	8, 13, 17	8’,13’, 17’
Weak	1, 2, 3, 4, 5, 6, 7, 9, 12, 14, 16, 19	1’,2’,3’,4’, 5’,6’,7’,9’,12’,14’,16’,19’ (5’,6’et 7’)
Appear	Disappearance of peaks	21, 22, 23, 24
Disappear	10, 15	Disappearance of peaks

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC)

The thermogravimetric analysis (TGA), the differential thermal analysis (DTA) and the differential scanning calorimetry (DSC) of β inclusion compound are represented in this section (Figure 2a and 2b).

The complex

TG curve of the complex gave evidence that upon heat treatment the complex undergoes chemical changes. The complex is stable up to 230 °C. A remarkable weight loss (50.523%) occurred at around 250 °C. Meanwhile, the DTA curve shows an endothermic peak without loss of mass at about 230 °C. Fusion is directly followed by decomposition and combustion (exothermic phenomenon) with a significant loss of mass (Figure 2a). However the DSC thermogram of complex shows two peaks: one peak at 132.7 °C probably due to the loss of water and the second peak corresponds to melting point of complex (Figure 2b).

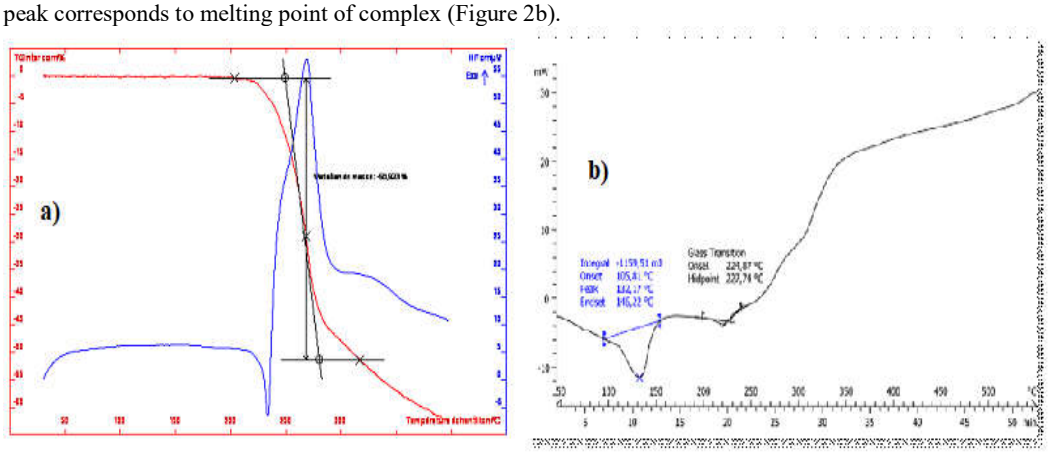


Figure 2. **a)** The thermogravimetric analysis (DTA- TGA) of inclusion compound (complex); **b)** Differential scanning calorimetry of inclusion compound (complex).

Picrate

TG curve of picrate shows a weight loss at 272 °C (60.69%) which may be attributed to the melting point. This weight loss corresponds to the beginning of the degradation of the initial organic molecule to 235 °C. However, the appearance of an exothermic peak around 279 °C corresponds to the decomposition (combustion) of the picrate. Finally, the DSC curve confirms that the melting point of the picrate is equal to 234 °C.

Cyclodextrin

TG curve of cyclodextrin shows two successive weight losses 12.13%, 64.81% respectively at 116 °C and 342 °C. The first weight loss belongs to the removal of 8 water molecules from the 5-cyclodextrin. The second weight loss suggests the decomposition of the macromolecule from 310 °C which also gives a viscous product that after evaporation leads to the departure of 40 water molecules. However, the appearance of an endothermic peak around 300 °C without weight loss on the TG curve, confirms that the melting point obtained is in great agreement with the value given in the literature data (290 °C) [21].

Absorption spectra

Absorption spectral data of picrate and inclusion complex in the mixture of water and ethanol (C = 0.25 10^{-4} mol L^{-1}) are listed in Table 2. Absorption spectra of picrate, inclusion complex and β-CD showed significant differences. The difference between them confirms the formation of picrate–β-CD inclusion complex. The UV spectrum of the filtrate in the mixture of water /ethanol

and at the C = 0.25 10^{-4} mol. L^{-1} was shown to be nearly identical with the UV spectrum of the inclusion complex, then we can suggest that the solution still contains picrate and β-CD with 1:1 molar ratio (guest:host).

Table 2 Absorption spectral data of picrate and inclusion complex.

	λ_{max} (nm)	Absorbance	ε (L mol cm^{-1})
3-Amino-1,2,4-Triazole	220	0.803	642.40
	280	0.228	182.40
Picrate	245	0.370	296.00
	354	0.459	367.00
Complex (β-CD + Picrate)	274	0.460	368.00
	382	0.156	124.80

Infrared spectral studies

In comparison with picrate, the symmetrical/asymmetrical NH_2, +NH stretching in the region vibrations (3451.39 cm^{-1}, 3341.05 cm^{-1}, 3171.35 cm^{-1}) respectively are largely affected upon formation of the inclusion compound 3423 and 2922 cm^{-1}.

The symmetrical/asymmetrical NO_2 (1300, 1500 cm^{-1}) are also affected by the complexation (1336, 1514 cm^{-1}). The C=C bending vibration of aromatic (1450, 1500, and 1600 cm^{-1}) is also blue shifted to 1348.60, 1427.92, 1640.50 cm^{-1}, respectively. In comparison with β-CD, the C–O vibration of primary and secondary alcohol were in the region (1100, 1050 cm^{-1}) respectively these are largely affected in the complex (1080, 1028 cm^{-1}). The intensity diminishing in the inclusion compound FTIR spectrum can prove the inclusion because the inclusion complex between the cyclodextrin host and the guest causes the change of the microenvironment of the guest, host and the formation of hydrogen bonding between the heteroatom of the guest and the primary hydroxyl group at the edge of the β-CD cavity. These reasons induce a decrease of the value of the absorption of stretching and bending vibration modes of different groups such as C–O (alcohol), +NH,C=C, NO_2 group. All the frequencies of different group were affected by the complexation. This finding indicates that picrate is included in the β-CD cavity.

^{1}H NMR spectrum

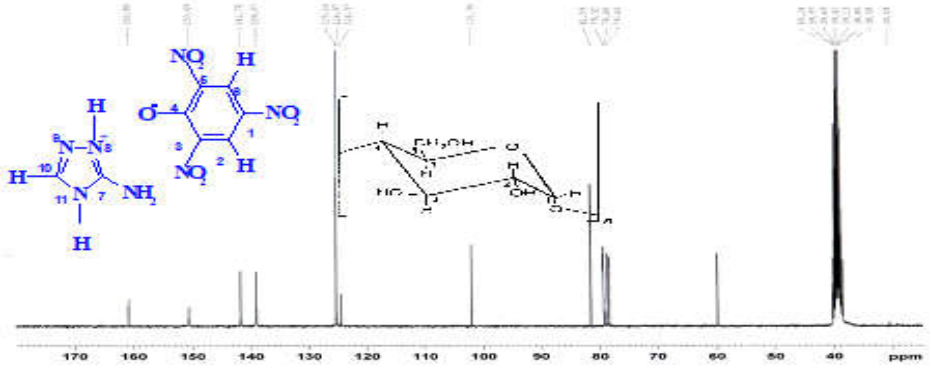
The ^{1}H NMR has proved to be a useful tool in the study of cyclodextrin inclusion complex [22-24]. Direct evidence for the formation of picrate and the inclusion complex can be obtained by ^{1}H NMR and ^{13}C NMR spectra. The information gained from NMR spectroscopy relies on the observation of selective line broadening and/or chemical shift of displacement of ^{1}H NMR spectral signals

We notice, that chemical shifts of picrate protons were changing after complexation. According to the spectrum complex, $H_{4,3,5}$ undergo a very limited shift due to their very strong interaction (hydrogen bonding) with the host molecule (β-CD). $H_{1,2}$ of picrate demonstrate a weak displacement which confirms the interaction (bonding of Van der Waals) with the external OH of β-CD. The chemical shifts of $H_{4,3,5}$, $H_{1,2}$ and H6 located in the hydrophobic cavity of β-CD were also significantly affected by the protons H3 and H5 of the host molecule because of the intermolecular interaction (formation of hydrogen bonding) between picrate and that of β-CD. The ^{1}H NMR spectrum of picrate in DMSO-d_6 has revealed that picrate has four types of protons. The $H_{3,4,5}$ appears as a broad singlet at 7.90; $H_{1,2}$ appears as a singlet at 8.27, the H_6 appears as a singlet at 8.57. The significant distinction, between the ^{1}H NMR spectra of picrate, β-CD and the inclusion complex of picrate with β-CD in DMSO-d6 confirm that the inclusion complex was formed. The chemical shift change is defined as the difference in chemical shift in the presence

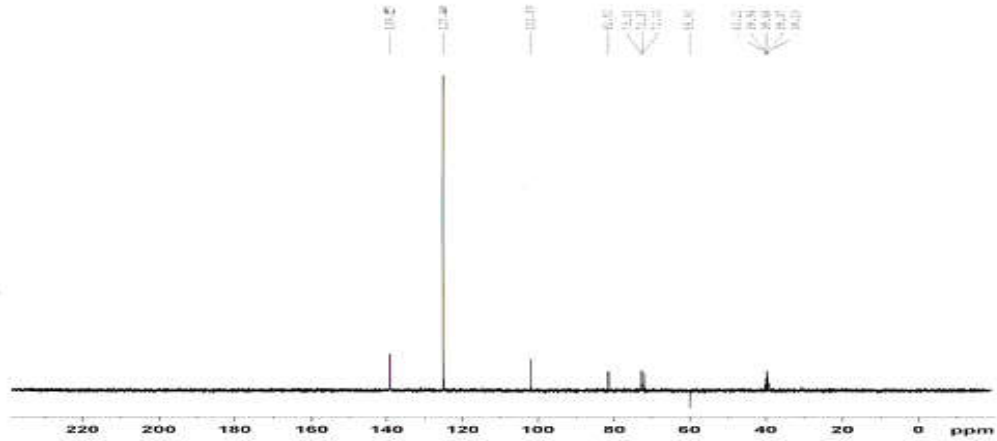
and absence of the other molecules [25]. The value of chemical shifts for different protons in β-CD, picrate and the inclusion complex were listed in Table 3.

^{13}C NMR spectrum

The ^{13}C NMR spectrum of inclusion complex in DMSO-d6 confirms the formation of the complex. In the inclusion complex there are 12 types of carbons, six types of β-CD: C1–C6 and six types of picrate (Table 3). The chemical shift for different types of carbons in the complex were obtained by the ^{13}C spectrum (Figure 3a). The chemical shift of the carbon (C6) was obtained by the ^{13}C spectra dept 135 (Figure 3b).



a)



b)

Figure 3. **a)** ^{13}C NMR spectra in DMSO-d6 of the inclusion complex; **b)** ^{13}C NMR spectra in DMSO-d6 of the inclusion complex (Dept 135).

Table 3. The chemical shifts and their changes upon complexation for β-CD, picrate and inclusion complex protons are presented, where Δ δ = δ complex - δ free guest.

Protons	δ (ppm) of free compound	δ (ppm) upon complexation	Δδ ppm
β-Cyclodextrin protons			
$H_{2,4}$	3.38-3.29	3.34-3.41	0.04
$H_{5,3,6a,6b}$	3.60	3.59-3.63	0.01
OH_6	4.49	3.65	0.84
H_1	4.80	3.68	1.12
OH_3	5.69	4.86	0.83
OH_2	5.75	4.87	0.88
Picrate protons			
$H_{3,4,5}$	7.90	7.95 et 8.02	-0.05 et -0 .12
$H_{1,2}$	8.20	8.32	-0.12
H_6	8.57	8.62	-0.05

Table 4. Chemical shifts δ of carbons in β-CD in free host, picrate in free host and inclusion complex.

carbons	δ (ppm) of free compound	δ (ppm) upon complexation
Carbons in β-CD		
$C_{6\,(CD)}$	59.87	60
$C_{3\,(CD)}$	72.34	78.37
$C_{2\,(CD)}$	71.93	78.81
$C_{5(CD)}$	72.94	79.25
$C_{4(CD)}$	81.52	81.59
$C_{1(CD)}$	101.91	101.96
Carbons in picrate		
$C_{3,5}$	124.82, 124.59	124.25, 124.97
$C_{2,6}$	125.33, 125.35	125.37
C_{10}	139.07	139.07
C_4	141.77	141.76
C_7	150.79	150.69
C_1	160.98	160.88

Determination of the complex stoichiometry

Determination of stoichiometry of the inclusion complex by NMR

In our case of complexation study, we determined the stoichiometry of the complex. Many spectroscopic methods were performed to highlight the phenomenon of the complexation between the β-cyclodextrin and the picrate. However, the ^{1}H NMR method remains a valuable tool for this study. The complexation study by ^{1}H NMR spectroscopy shows the integration of the H_1 proton of β-cyclodextrin and the H_4 proton picrate which indicates that during the formation of the complex (β-cyclodextrin/picrate) it has a stoichiometry of the (1:1).

Determination of stoichiometry of the inclusion complex and the apparent formation constant by UV-Vis

In order to determine the stoichiometry and the apparent formation constant for the obtained inclusion complex we maintained the concentration of picrate constant and the concentration of β-CD is varied. The absorbance of solutions were measured at 275 nm. We can deduce that the

absorbance value increased with increasing β-CD concentration while, the concentration of picrate is the same. Which shows that the solubility of guest molecule (picrate) increases upon forming the inclusion complex. Stoichiometric ratio of inclusion complex calculated by NMR is 1:1. This value will be proved if a linear relationship is obtained from the reciprocal plot of 1/A vs. 1/[β-Cd] based on the Hildebrand-Benesi Equation 1 [26]. Reciprocal plots that determine the stoichiometry ratio of the inclusion formation is shown in Figure 4 shows a good linearity with a correlation factor of R^2= 0.990. This result confirms the formation of the inclusion complex between β -CD and picrate with a stoichiometry of 1:1.

This reciprocal plot clearly confirms the stoichiometry ratio for the inclusion formation between picrate and β-CD which is 1:1. Using the reciprocal plot from Figure 4 we have determined the apparent formation constant. The constant stability (k) for the host–guest inclusion complex was calculated and proved to be equal to $1.2.10^4$ (mol/L) at 25 °C. The higher value of the formation constant of β -CD/picrate inclusion complex suggests that β-CD forms stable inclusion complex with picrate molecule and reveals the presence of strong interactions between the host and the guest [27].

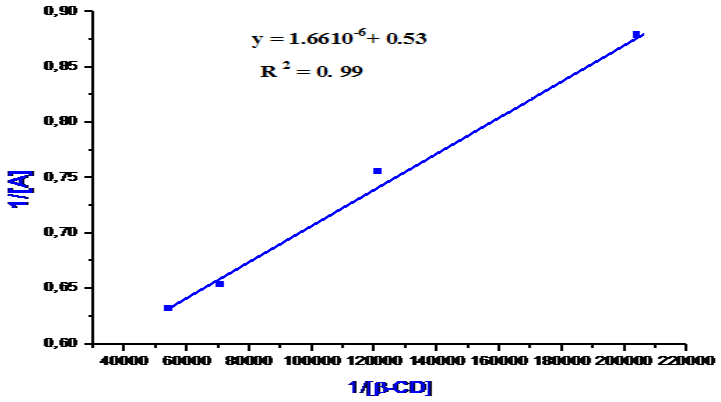


Figure 4. Reciprocal plot for 1/A against 1/[β-Cyd] of picrate-β-CD inclusion complex.

Influence of pH on the complexation yield of inclusion complex

Effect of acid pH

During the complexation process of the picrate by the cyclodextrin, the intial pH is equal to pH_i = 3.1 indicating an acid environment. Then, we add a dilute solution of chlorohydric acid (0.01 $mol.L^{-1}$) until the pH becomes equal to pH_f = 2. When the pH varies from 3.1 to 1, λ_{max} decreases in the same line, however, ε and the solubility of the complex in the reaction mixture will increase Furthermore, we deduce that the acidic environment leads to the reduction of the reaction yield (Table 5). This decrease is due to the protonation of NH in NH^+ which has a non-located doublet in 3-amino-1,2,4-triazole. According to the moderation law for a system in chemical equilibrium state, any perturbation in one of the equilibrium factors moves it in the direction which tends to moderate the modification.

Effect of basic pH

During the complexation of the picrate by the cyclodextrin, the initial pH of the reaction is equal to pH_i = 3.1. When we add a dilute solution of tetrabutylammonium hydroxide (0.01 mol. L^{-1}) the

pH rises to pH_f = 7.32. Complexation in a basic environment increases the reaction yield. The base allows then the deprotonation of the hydrogen of the endocyclic nitrogen of the 3-amino-1,2,4-triazole. Finally, we deduce the influence of the pH on the enhancement of the reaction yield (Table 5).

Table 5. Absorption spectra of complex in ethanol at different pH acid and basic.

pH	λ_{max} (nm)	Absorbance	ε (L. mol^{-1}.cm^{-1})	Yield
	274	0.46	368	
pH = 3.1	382	0.156	124.8	70%
	260	0.512	409.6	
pH = 2	375.5	0.608	486.4	45%
pH = 1	255	0.693	554.4	32%
	210	0.924		
pH = 7.32	359	0.770	616.0	79%
	208	0.750		
pH = 9.95	354	0.729	583.2	85%

CONCLUSION

In this work we have synthesized an inclusion complex between b-CD and AT with stoichiometry 1:1 was obtained. The complex was characterized using UV visible, DRX, TGA, DTA, ^{1}H NMR and ^{13}C NMR. We studied the influence of pH on the complexation. We have determined the apparent formation constant. The value of apparent formation constant was 1.2×10^4 L.mol^{-1}.

ACKNOWLEDGMENTS

Authors thank the ministry of high education and scientific research of Tunisia for the financial support of this work.

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