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Infrared spectroscopic study of Inclusion Complex Of aziridine with amphiphiphilic Cyclodextrin

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Abstract: In this work, interactions between components of solid amphiphilic β-cyclodextrin – *aziridine* (ACD –AZ) nclusion complex were confirmed by the IR spectroscopy data. It was established that the vibrations and bends of the guest molecule are restricted and shifted through it encapsulation into the amphiphilic-β-cyclodextrin (ACD) cavity. The inclusion complex with 1:1 molar ratio was prepared by a kneading method. Fourier transform infrared spectroscopy (FTIR), confirmed the formation of the inclusion complex.
Keywords: Aziridines, ampiphilic cyclodextrin, host-guest system, IR spectroscopy, Job's method.

I. Introduction

Aziridines 1 represent an important class of compounds that exhibit anticancer, antibacterial, and/or antimicrobial and antileishmanial activities [2-5]. Some among them behave as potential protease inhibitors [6,7]. Therefore, an assumption might be made that the presence of an aziridine moiety in natural as well as synthetic compounds structures is essential to the observed activities [8]. The biological activity of aziridines is highly related to the establishment of covalent bond with DNA [9]. In a previous work we reported the synthesis of aziridinyl derivatives10 that had antitumor activities against breast cancer cells [11]. Such behaviour was likely due to their capacity to strengthen and modulate the immune system [12]. We have, already reported the synthesis of several aziridines [13], which we replaced the amino acids phtaloyl protecting group with a phosphonate[14] moiety and, surprisingly, the biological activity of the novel phodphonates aziridines shifted from antiviral to an antibacterial one [15].

Thus, going on with our efforts to use the biologically active aziridines that are insoluble and instable in water by pharmaceutical formulation with cyclodextrins (CDs) as vector in vivo16, is a difficult problem since aziridines are known to undergo hydrolysis in the presence of CDs. Despite this easy cyclodextrin-induced cleavage of aziridines ring in aqueous medium [17-22], it was of interest for us to find out a model aziridine derivative, that would be complexed out of water medium and form a stable complex with CDs, so that it could be used as a reference in future formulations or vectorization work.

The solubilization of aziridines at the molecular level as inclusion complexes inside native CDs is a good alternative but we still have the problem of instability after short time. Native CDs are therefore widely used as solubilizers and excipients, masking the physicochemical properties of the guest molecule (poor water solubility, stability problems, or undesired side effects) [23-30]. However, since ring opening of aziridine AZ (Figure 1) takes place too readily upon dilution, inclusion complexes in simple water-soluble CD are not effective for our aziridine structure, as we showed with our previous

results [31]. Complexation of AZ with amphiphilic cyclodextrins (ACD) (Figure 2) has been the aim of our groups, so we already developed the (ACD) (Figure 2) [32], mainly to improve satability and solubility of our aziridines while maintaining the ability to form inclusion complexes.

The concept of amphiphilic cyclodextrins is based on modulation of the hydrophobic /hydrophilic balance of their construction as well as of their self-assembly properties through grafting of single or multiple substituents on the primary, secondary or both faces of native cyclodextrins [33-40]. An important feature for the drug delivery field comes from the fact that the majority of amphiphilic cyclodextrins are considered to be non-hemolytic and non-cytotoxic [41-44].

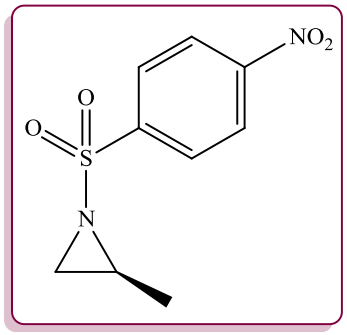

Figure 1 : Guest molecule (AZ) .

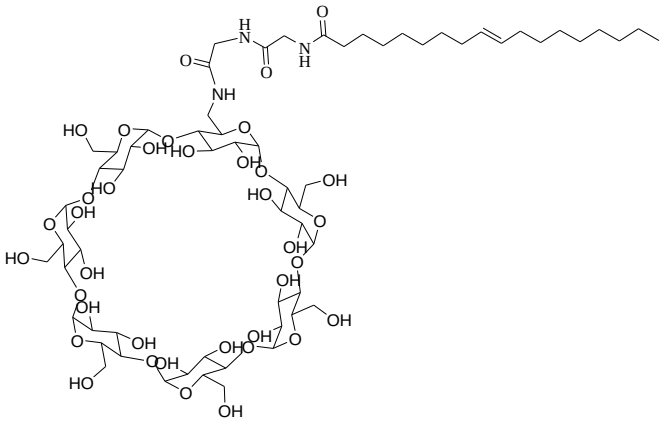

Figure 2: Amphiphilic cyclodextrin(ACD)

II. **Experimental Section**

All the reactions with dry solvents were carried out under dry nitrogen. THF was dried over sodium /benzophenone and freshly distilled before use; CH_2Cl_2 was distilled and dried over phosphorus pentoxide (P_2O_5). I.R spectra were collected from a Mattson Genesis II FTIR. Melting points were determined on an Electrothermal T1A F3.15A instrument. Column chromatography was performed on silica gel 230-270 mesh (Merck) using CH_2Cl_2, MeOH and ether. Elemental analysis was performed only for solids on a LECO CHN 900 instrument.

III. Results and Discussion

1. IR spectral study of aziridine (AZ), (ACD) and "ACD - AZ" inclusion complex :

Inclusion complex formation may be confirmed by IR spectroscopy because bands resulting from the included "guest" molecule are generally shifted or their intensities are altered [44]. But, before the of our complexation studies, all of our aziridines [31] were checked for their stability in aqueous medium, also because the complexation and transport of drugs in water is of interest in living organisms. Therefore, a survey conducted in water would provide enough information for future formulation or studies in this field. The stability of each aziridine was monitored by NMR analysis of an aliquot of the corresponding solution, carried out every five minutes, searching for the appearance of a hydroxyl signal in the region of 3-3.5ppm. When the latter was observed, this gave evidence for the opening of the aziridine.

Based on the two criteria mentioned before, structure of aziridine (Fig.1) chosen this time is completely soluble in water and at the same time unstable since it opens easily as we mentioned in our previous study of complexation of aziridine in aqueous medium [31].

1.2. Protocol of inclusion in pasty fashion:

The **ACD-AZ** inclusion complex was prepared by using the kneading method [45]. Both compounds (ACD and aziridine) were mixed with molar ratio of 1: 1 and thoroughly ground in a mortar for 60 minutes, until a homogeneous mixture in the form of a paste. Ethanol was added at the end of milling process. The precipitate thus formed was removed from the mortar, placed in a bottle and left

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in an oven at a temperature of 70 ° C for 15 min and then for several days in the open air, in order to remove ethanol.

Figure 3: a) First step before mixing; b) Second step, after mixing the guest and host molecules; c) Adding ETOH.

This product will then be characterized by Fourier transform infrared (FTIR), as it is a very useful tool for proving the existence of an inclusion complex because it accompanied by changes in their IR spectra as compared with the individual components (free AZ and ACD).

1.3. IR spectral study of aziridine

In the IR spectrum of AZ (Figure 4) the valence vibrations of the C-H bonds on AZ ring with maxima at 2973,51 and 2928,38 cm^{-1} of free AZ became 2974,05 and 2887,25 cm^{-1}, respectively, in the IR spectrum of inclusion complex (Fig. 5) . From this we can concluded, no significant changes are registered, so it clear that ring of aziridine is not encapsulate inside the cavity of ACD. The band of valence vibrations of the NO_2 bond in the aromatic group is observed at 1528,05 and 1349,58 cm^{-1} (sharp signal due to NO_2 group) of free AZ witch drastically reduces its intensity and sharpness in the complex as we can see in the IR spectrum of inclusion complex, led us to the conclusion that the encapsulation of the aromatic ring deeply in it cavity. In addition the absorption bands with maxima at 1454,03 and 1400,96 cm^{-1} belong to the valence vibrations of the C=C bonds of the nitro-benzene ring, is shifted to *1450 and 1410* cm^{-1}, due to the inclusion of the nitro-benzene into the ACD cavity. The small shift might be owing to the effect of inner microenvironment and non-covalent interaction of ACD hydroxyls on AZ. From this spectral analysis it can be concluded that the most sensitive functional groups, involved in the complexation process, are the aromatic groups [46,47]

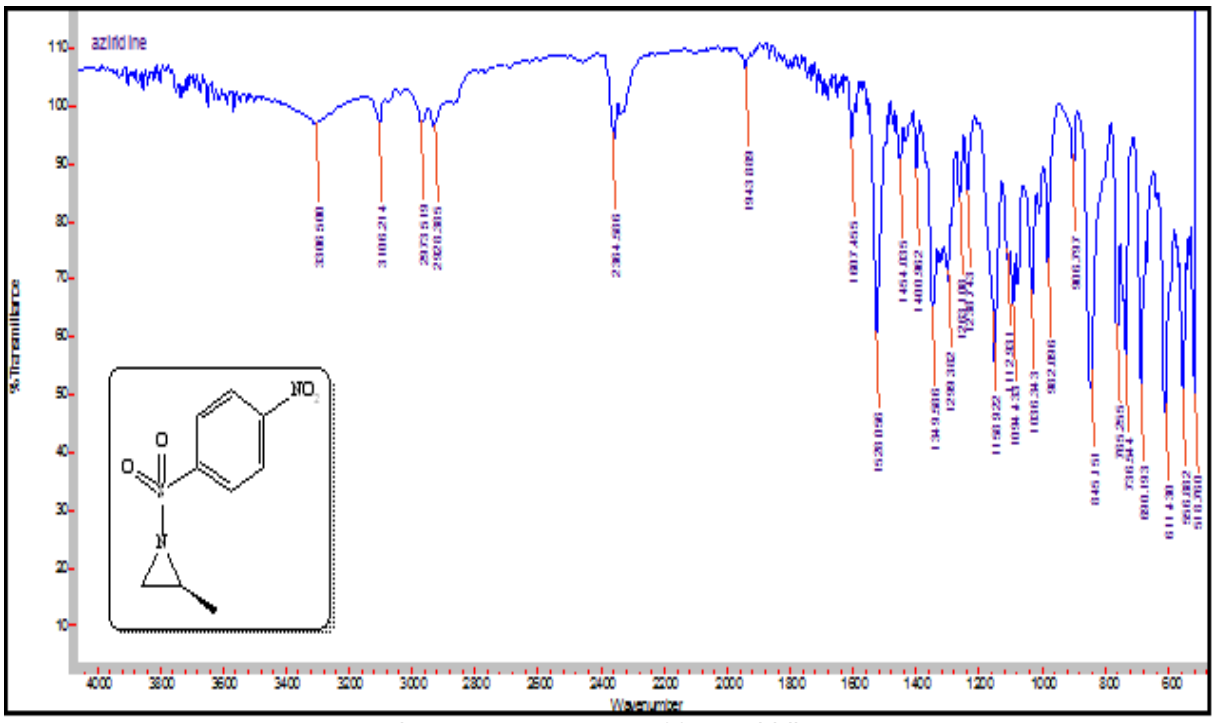

Figure 4: IR spectrum of free aziridine.

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The valence vibrations of the S=O and S-O bond in the sulfoxyde group connected with nitro-benzene ring are observed at 1299,38 and 982,09 cm^{-1} of free AZ and became restricted with Δδ = -37,09 and -32. Finally, the bands of the deformation vibrations of the C-H bonds in the nitro-benzene ring are registered at 845,15 and 816,89 cm^{-1}, respectively before and after the inclusion which proves more that the inclusion occurred with aromatic part f AZ structure [48]. Table 1 illustrates the IR peaks of AZ and its ACD inclusion complex.

Table 1 : Chart of absorption bands intensities of aziridine and complex.

Group	***Aziridine (cm^{-1})***	***inclusion Complexe (cm^{-1})***	***Δcm^{-1}***	***Aziridine bands intensity***	***Complex absorption bands***
v [CH] des CH_3 and CH_2 asymmetric	*2973,51*	*2974,05*	***+ 0,54***	*w*	*w*
v [CH] des CH_3 and CH_2 symmetric	*2928,38*	*2887,25*	***-41,13***	*w*	*s*
v [NO_2]	*1528,05*	-	/	*m*	/
v [NO_2]	*1349,58*	-	**/**	*m*	/
v [C=C] aromatic	*1454,03*	*1450*	***-4,03***	*w*	*m*
v [C=C] aromatic	*1400,96*	*1410*	***+ 9,04***	*w*	*m*
v [S=O]	*1299,38*	*1262,29*	***-37,09***	*m*	*w*
v [S-O]	*982,09*	*950,07*	***-32,02***	*w*	*w*
v [C-H] aromatic	*845,15*	*816,89*	***-28,26***	*m*	*w*

W:weak; m: medium; S: strong.

1.4. IR spectral study of ACD

In the IR spectrum of ACD (Figure 6) the wide band is registered with the absorption maximum at 3322,21 cm^{-1}, which is caused by the valence vibrations of the O-H bonds in the primary hydroxyl groups (C–6 - OH) connected by the intermolecular hydrogen bonds or in the secondary hydroxyl groups connected by the intramolecular hydrogen bonds (the C – 2 - OH group of one glucopyranose unit and C–3 - OH group of the adjacent glucopyranose unit) [49]. Also, in the IR spectrum of ACD the absorption band with maximum at 2926,76 and 2849,62 cm^{-1} is observed. It belongs to the valence vibrations of the C-H bonds in the CH and CH2 groups of ACD and the pendant group dipeptido-lipide.

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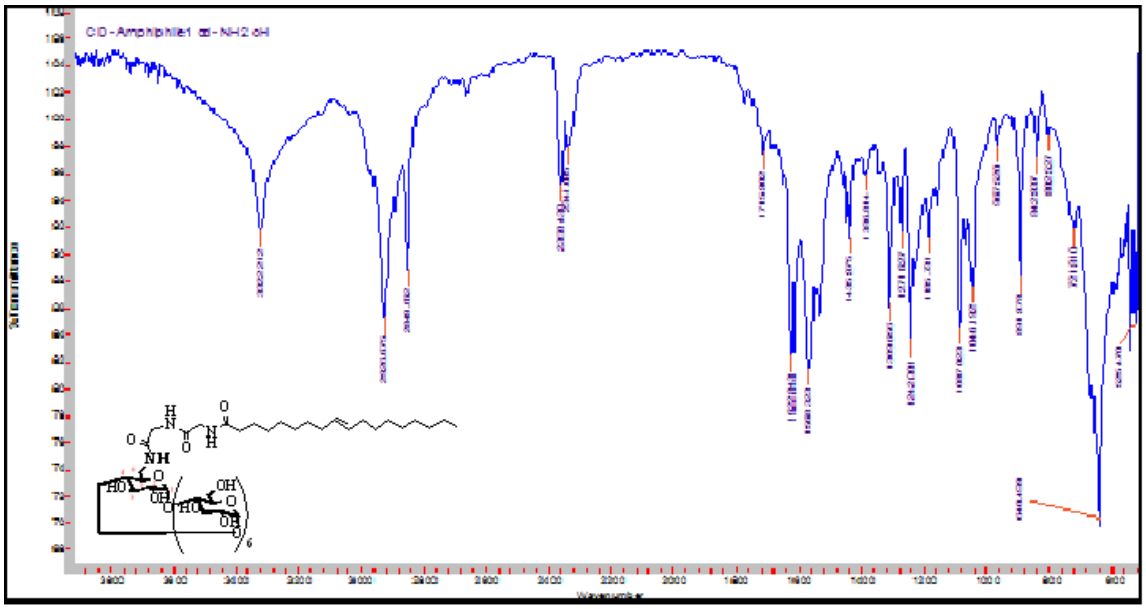

Figure 5: IR spectrum of free amphiphilic Cyclodextrine ACD.

The deformation vibrations of the C-H bonds in the primary and secondary hydroxyl groups of ACD (1410-1250 cm^{-1}), and in the interval 1200-1030 $cm^{-1}$the absorption bands of the valence vibrations of the C-O bonds in the ether and hydroxyl groups of ACD (1080 and 1027 cm^{-1}) are registered. The absorption bands in the region 950 - 700 cm^{-1} belong to the deformation vibrations of the C-H bonds and the pulsation vibrations in glucopyranose cycle. The bands of the valence vibrations of the C=O (1622,84, 1568,32 and 1545 cm^{-1}) of the dipeptido-lipide group of free ACD (Figure 6) is shifted to higher wavenumber in spectral pattern of the inclusion complex (Figure 7) and registered at 1653,45 cm^{-1} for the first and completely disappeared for the two other. At the same time, the band of the valence vibrations of the C=C bonds at 1435,97 cm^{-1} of the free ACD of the peptido-lipide group is shifted to lower wavenumber and observed at 1418,78 cm^{-1}. The band of the deformation vibrations of the CH_2 in ACD free of the peptido-lipide group registered at 642 cm^{-1} have disappeared in the IR spectrum of inclusion complex, which proves the possibility of another mode of inclusion occurred, the intra-complexation of the pendant group inside the cavity of ACD. Table 2 illustrates the IR peaks of ACD and its AZ inclusion complex.

Table 2 : Chart of absorption bands intensities of amphiphilic (ACD) and complex.

Group	***amphiphilic CD (cm^{-1})***	***Inclusion complex (cm^{-1})***	***Δcm^{-1}***	***ACD amphiphilic CD***	***Inclusion complex***
v [OH] et v [NH] amide	*3322,21*	*3400*	***+77,79***	*m*	*m*
v [CH_2] asymmetric	*2926,76*	*2974,5*	***+47,74***	*s*	*w*
v [CH_2] symmetric	*2849,62*	*2887,25*	***+37,63***	*s*	*w*
v [C=O]	*1622,84*	*1653,45*	***+30,61***	*m*	*w*
v [C=O]	*1568,32*	-	***/***	*m*	*/*
v [C=O]	*1545*	-	***/***	*w*	*/*
v [C=C]	*1435,97*	*1418,78*	***-17,19***	*w*	*w*
v [C-O]	*1242,00*	*1262,29*	***+20,29***	*m*	*w*
v [C-C]	*1185,73*	*1154,06*	***-31,67***	*w*	*w*
v [OH] deformation	*1087,023*	*1079,46*	***-7,563***	*m*	*m*
v [CH_2] du synthon deformation	*642*	-	***/***	*s*	*/*

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1.5. IR spectral study of inclusion complex "ACD-AZ"

The formation of inclusion complex of CD and a guest substance is accompanied by changes in their IR spectra as compared with the individual components [50-55]. The IR spectrum of the inclusion complex "ACD –AZ" (Figure 7) differs from the IR spectra of AZ (Figure 5) and ACD ((Figure 6). Significance differences in OH, CH and CO vibration modes are found. Peaks are not only shifted after complex formation, but the shapes of peaks are also change. The sharp peak of OH in ACD becomes broad in inclusion complex.

The absorption bands of the valence vibrations of the C-O bonds in the ether and hydroxyl groups of ACD in the interval 1200 – 1030 cm^{-1} are slightly broadened for the inclusion complex. Moreover, the absorption bands of the valence vibrations of the C = C bonds in the Nitro-benzene ring are shifted to 1410 and 1518 cm^{-1}. The peak at 1242 cm^{-1} in the spectrum of CD which belongs to the deformation vibrations of the C–H bonds in the hydroxyl groups is shifted to the 1262 cm^{-1} and greatly broadened. These results indicate that the vibrations and bends of the "guest" molecule are restricted through encapsulation of *AZ* into the CD cavity and formation of the inclusion complex. Table 3 illustrates the IR peaks of ACD-AZ inclusion complex

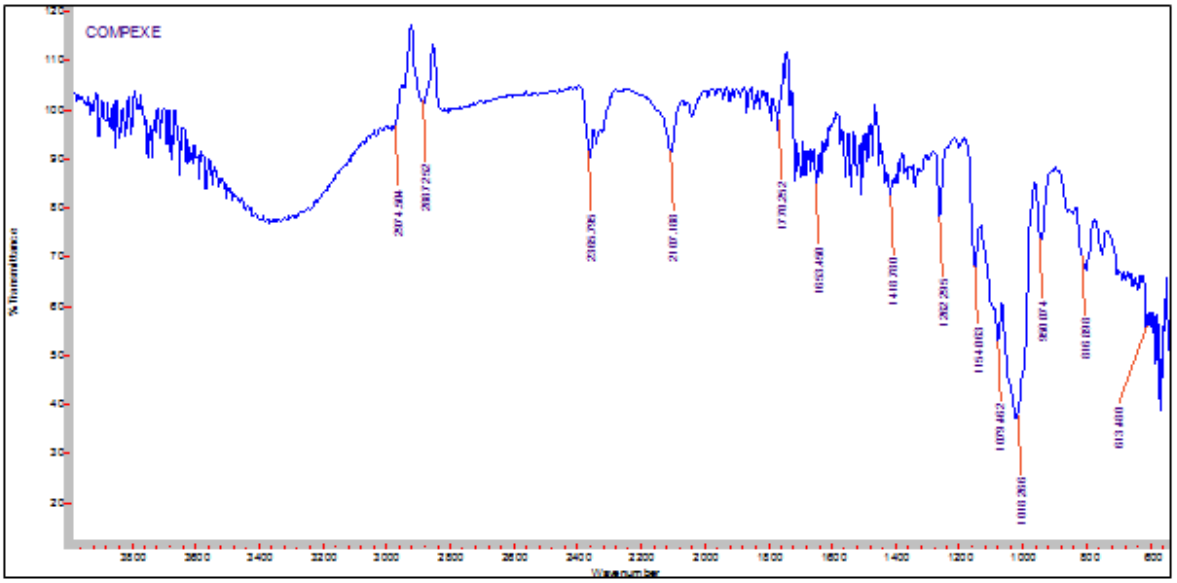

Figure 6 : IR spectrum of the inclusion complex.

2. Proposal geometry of inclusion complex "ACD-AZ"

Although it is difficult to give an inclusion complex geometry, without resorting to the most sensible method that is ROESY, we will issue as assumptions, based for first on our IR results. Essentially the complex IR spectrum that reflects the disappearance of the band characteristic of the CH2 deformation of oleic acid groups that appeared in the spectrum of pure amphiphilic CD to 642 cm^{-1}.

This observation suggests predict the encapsulation of the aliphatic chain of oleic acid rather than the aromatic group of aziridine, which has the conjugation since it is less hydrophobic than the long chain, which gives an intra-complexing energetically favored to intere-complexation. But we can not exclude the existence of the second opportunity for the inclusion of aziridine in question, small percentage, we therefore propose the following two structures:

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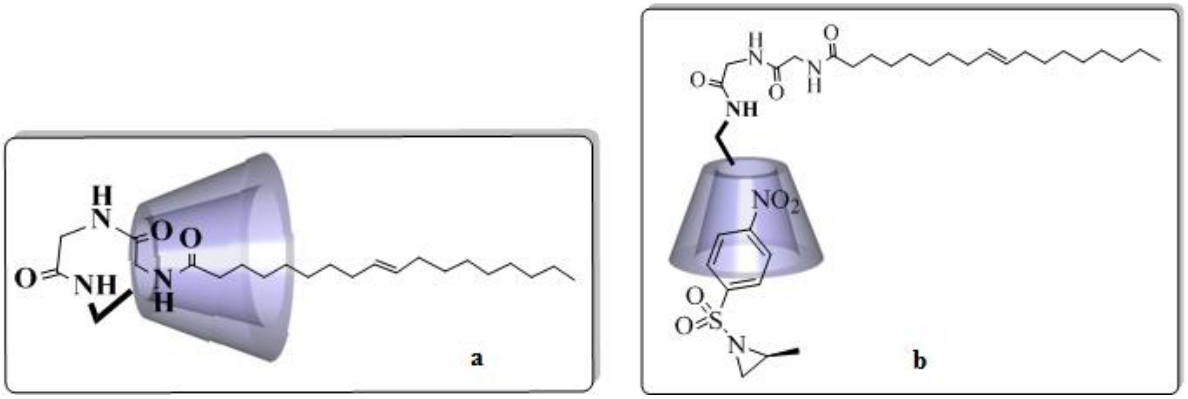

Figure 7: a) geometry of intracompex ; b) geometry of inlusion complex "ACD-AZ".

The CD derivatives with a suitable pendant group can form self-inclusion complexes intramolecularly or intermolecularly as shown above. Binding of an external guest molecule to the CD cavity of the self-included complexes transfers the included pendant group to the outside of the CD cavity.

IV. Conclusion

In this work, the 1:1 inclusion complex of AZ and A*CD* has been prepared and intermolecular interactions between them studied. The significant difference in FTIR of complex reveals clear evidence for inclusion phenomena. The way parameters were determined in this work can serve for future investigations related not only to design new aziridines of biological interest, but also to formulation of existing aziridine-containing drugs.

Based on the results obtained, we can conclude that the methods proposed in this work are effective for obtaining a complex (β-CD:aziridin), l'IR confirm the formation of a complex of inclusion.

Therefore, it is suggested that the inclusion complex between AZ with other modified (β-CD) like those having polar and ionic functional groups attached to the (β-CD) molecule (at either C-3 or C-6), and with the linked cyclodextrins be investigated. Finally other more accurate and sensitive techniques such as HNMR, or CNMR can be used for the determination of the stability constant of the inclusion complexation.

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