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NMR Investigation of the complexation of *(S)*-2-isopropyl-1-(*o*-nitrophenyl)sulfonyl)aziridine with β-cyclodextrin

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Abstract: Aziridines are known to undergo hydrolysis in the presence of cyclodextrins, whereas the latter are largely investigated as potential vectors of biologically active compounds. Despite this easy cyclodextrin-induced cleavage of aziridines in aqueous medium, it was of interest to find out a model aziridine derivative that would be sufficiently water-stable and form a stable complex with β-cyclodextrin in aqueous medium, so that it could be used as a reference in future formulations or vectorization work. Among compounds we have investigated, we found out that only (*S*)-2-isopropyl-1-(*o*-nitrophenyl)sulfonyl)aziridine complied with the above-mentioned solubility and stability requirements. NMR studies of the inclusion complex of this derivative with β-cyclodextrin provided useful parameters related to the stoichiometry of the complex and the association constant Ka. The geometry of the complex was assessed by 2D-ROESY experiments, suggesting a deep insertion of the aziridine into the cavity of β-cyclodextrin.

Keywords: ^{1}H NMR, 2D-ROESY, Job's method, β-cyclodextrin, aziridine solubility.

Introduction

Up to now, major interest in cyclodextrin (CDs) research has been fuelled by commercial targets, and many of the published reports on NMR studies about interactions of small molecules with cyclodextrin have mainly focused on pharmaceuticals[1]. This is because formulations with cyclodextrins proved to be efficient in providing a way to increase the solubility, the stability and/or other relevant physico-chemical properties of drugs at the same time[2].

Among three-membered heterocycles, aziridines form a group of natural and/or synthetic organic compounds that constitute a particularly versatile class of molecules as related both to their chemical reactivity and biological properties[3,4]. We focused on synthetic sulfonyl aziridines, and we found that these compounds constituted a class of high interest because of their reactivity and biological activity[5].

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Therefore, we explored the literature in order to find easily available compounds[6-10] that could allow us have an insight in the complexation of aziridines with β-cyclodextrin.

We investigated the encapsulation of those synthetic derivatives in commercial β-cyclodextrin (βCD), using NMR techniques with a view to establishing the stoichiometry of the complexes, calculating the association constant and determining some dynamic aspects of the complexation process[11]. It was of interest to find a model aziridine derivative that would withstand the induced hydrolysis catalysed by βCD, so that it could serve in future investigations related to formulation and transport of biologically active aziridines of interest within our laboratory [12].

A number of investigations can be found in the literature about βCD complexes with different compounds, the majority being of pharmaceutical interest[13]. The results and conclusions can hardly be extended to other classes of compounds, however. Thus, complexes of epoxides and *N*-tosylaziridines have been oxidised in the presence of 2-iodoxybenzoic acid in water by Rao and co-workers to access α-hydroxyketones and α-aminoketones[14]. Previously, the same group also observed that cyclodextrins catalyse aziridine ring opening by means of supramolecular catalysis[15]. Other groups focused on modified cyclodextrin-induced host-guests effects[16]. An attempt to determine parameters of those complexes was made by Beijnen and co-workers, but resulted in the formation of amino-alcohols because of the βCD-induced hydrolysis of aziridines[17].

To the best of our knowledge, there are no previous studies about the encapsulation of *N*-sulfonyl aziridines by cyclodextrins to provide complexes with accessible NMR and physico-chemical characteristics, as those provided in this paper. In view of this, the major challenge to us was to prepare an aziridine with a well-balanced structural compromise between hydrophobic and hydrophilic groups in order to provide both enough solubility and ring-stability in water. In this work, we have used commercial β-cyclodextrin (Fig.1) as a host model, based on the fact that its internal diameter allowed an efficient complexation of medium-sized aromatic compounds and heterocyclic derivatives.

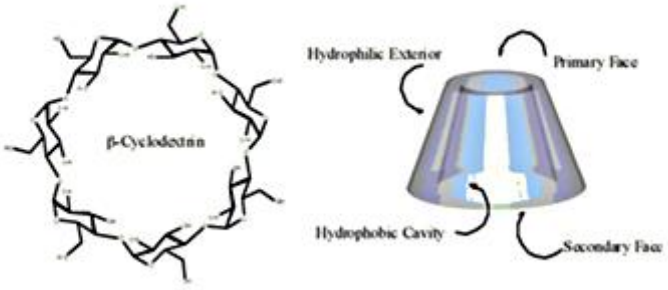
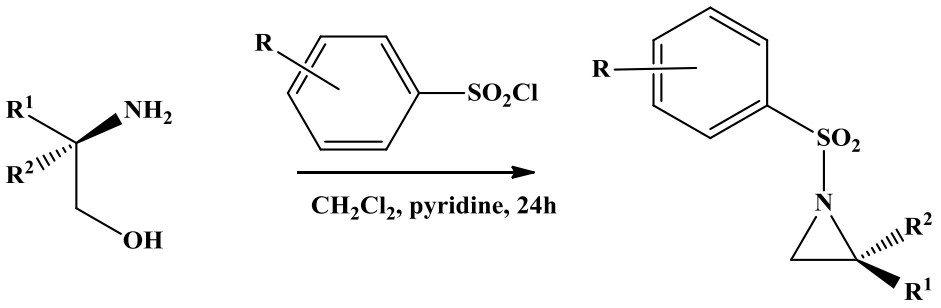


Figure 1: Structure of β-cyclodextrin.

Therefore, we have synthesized some known sulfonyl aziridines according to the literature, and we have examined their potential to insert into βCD. It is worth mentioning that many synthetic schemes of aziridines can be found in the literature. We chose to perform our syntheses beginning from commercial chiral 1,2-amino alcohols[6,8b] as shown in Scheme 1 and in Table 1. As a matter of fact, this procedure was rapid and straightforward, avoiding the tedious protection of amino alcohols. What is more, it guaranteed the retention of the stereochemistry of the amino alcohol in the final aziridine[6a]. Besides, identification of our synthetic compounds could be easily checked for consistency with published data.



Scheme 1: Synthesis of aziridines

Furthermore, we assumed that the stereochemistry of those known chiral aziridines could promote diastereomeric interactions with the βCD glucopyranose unit stereocenters to ensure a unique inclusion pattern of guest compound versus the host.

Table 1. Solubility and stability of aziridines (Az) in water: + stable / or soluble; -not soluble/or not stable/ Preparation references

Az	R	R_1	R_2	Solubility	Stability minutes	References
1	o-NO_2	H	i-C_3H_7	+	120	5a
2	p-NO_2	H	i-C_3H_7	-	60	6
3	p-Me	H	i-C_3H_7	-	30	7
4	p-Me	H	Me	+	60	7b, 8
5	p-NO_2	H	Me	+	30	6a, 6c
6	o-NO_2	H	Me	+	30	9
7	p- NO_2	H	Ph	-	180	6a
8	o- NO_2	H	Ph	-	180	10

Before the complexation studies, all of the compounds were checked for their stability in aqueous medium (Table 1), 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 complex 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.

In the process of NMR spectroscopic assessment, the sampling time was shortened to two, then one minute in order to ensure the best accuracy possible. As shown in Table 1, as far as stability was concerned, nitrobenzenesulfonyl-derivatives offered the best features. However, entries 1, 4, 5, and 6 are the more interesting in terms of both good water-stability and solubility in the presence of βCD, with the best overall pattern shown by entry 1. Phenyl-substituted aziridines offer the best stability, but with poor solubility, the latter being detrimental to their selection as models. Therefore, only (*S*)-2-isopropyl-1-(*o*-nitrophenyl)sulfonyl)aziridine **1** (AZ**1**)[5] (Fig. 2) fulfilled all the above-mentioned criteria and was chosen as our model compound.

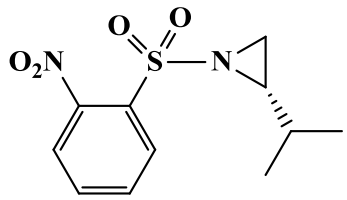


Figure 1: (*S*)-2-Isopropyl-1-(*o*-nitrophenyl)sulfonyl)aziridine **1** (AZ**1**).

Results and Discussion

Stoichiometry and binding constants

Stoichiometry and binding constants are the usual quantitative descriptors of the binding of a guest compound to a host, and NMR techniques are routinely used to measure these parameters as far as guest-host complexes formation is concerned. The terms of reference for such studies are either fast-exchange or slow-exchange phenomena. In the fast exchange regime, which compares well with our work, the observed NMR frequencies are defined as the mole fraction weighted average between the frequencies in the native form and the bound form of the observed molecule. For example, when the proton to be analysed is located on the host molecule, the chemical shift is given by the following equation:

$$\delta_{obs} = X_H\delta_H + X_{HG}\delta_{HG}$$

Wherein δ_{obs} is the chemical shift of the observed nucleus in the experiment, δ_H the chemical shift of the unbound host molecule and δ_{HG} is the chemical shift of the host in the complex. Besides, X_H and X_{HG} are the mole fractions of host molecule in the bound and the unbound states. In this case, the analysis was more complicated than for the slow exchange regime, because the chemical shifts in the complex could not be observed. This problem could be overcome by NMR titration, obtaining information on chemical shifts over a wide range of solutions of different compositions[18].

One of the first methods used for the determination of the stoichiometry of inclusion complexes was Job's method, also known as the continuous variation method[19,20]. For the experiment, we used stock solutions with equimolecular concentrations of Host (βCD) and Guest (AZ**1**), according to the protocol of this method. The samples were prepared by mixing various volumes of these solutions in such a way that the total concentration [βCD] + [AZ**1**] remained constant and the molar fraction of AZ**1**, varied in the range from 0 to 1. Using NMR analysis, the experimental data for the characterization of complexes were the observed variations of chemical shifts of both βCD and AZ**1**[21].

Therefore, we needed an accurate identification of protons that were sensitive to complexation in order to determine the stoichiometry of the AZ**1**-βCD complex. The binding of AZ**1** to βCD was evidenced by a shielding of internal cyclodextrin H-3 and H-5 protons. The chemical shifts of the remaining H-1, H-2 and H-4 protons of the same host were not altered, as shown in Figure 3. While this work was in progress, this behaviour was also observed by S. Mashood and co-workers in their structural elucidation of βCD-xylazine complex[22].

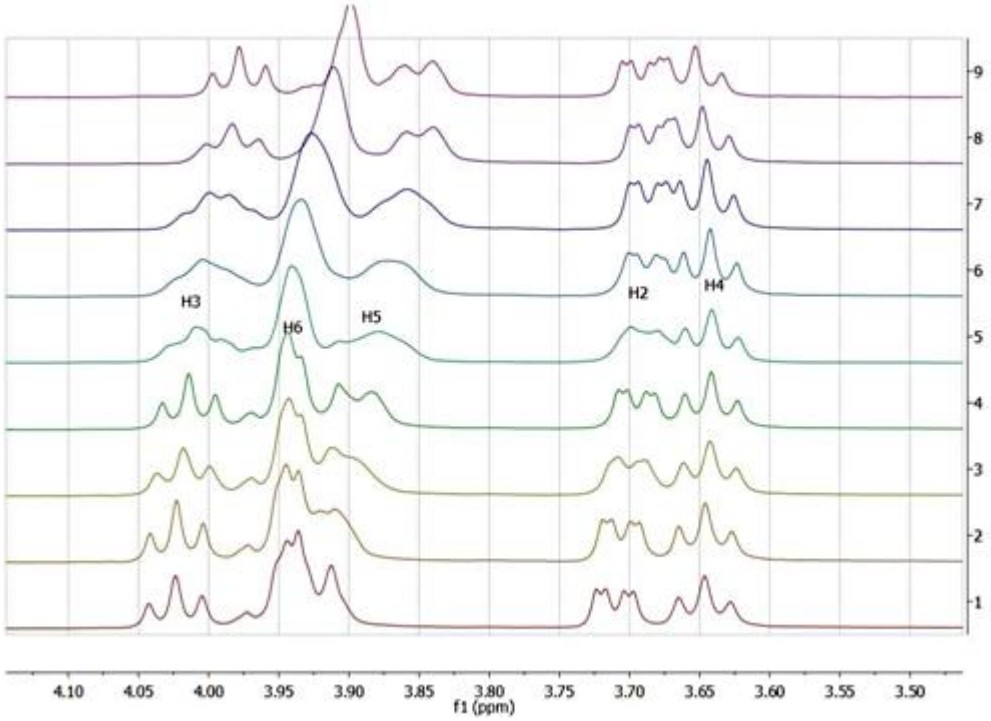


Figure 3: Expanded regions of ^{1}H NMR spectra (500 MHz, D_2O): chemical shift variations of H-3, H-6, H-5, H-2 and H-4 protons of βCD in the complex.

This selective and exclusive effect of complexation on the βCD internal protons is generally taken as good evidence for an interaction, where AZ**1** is encapsulated in the hydrophobic core of the βCD. It can be attributed to the magnetic anisotropy associated with the aromatic ring of the nitrophenyl group inside the hydrophobic cavity of βCD[21]. No distinct chemical shifts were observed for free and bound states of the host and guest molecules, but only one set of signals was found for each species when the AZ1/βCD ratio was modified. This observation was in good agreement with previously described systems regarding NMR fast-exchange limits [23,24].

The stoichiometry of the complex was determined by using the method of continuous variation[25,26]. Chemical shifts differences for βCD H-5 protons were used to draw the plot, and the stoichiometry was determined by plotting ratios of βCD.Δδ(βCD H-5) against ratios of βCD (Fig. 4) to afford a maximum at ratio βCD = 0.5, which meant a 1:1 complex ratio between AZ**1** and βCD.

The same result was provided when chemical shifts differences of βCD H-3 were plotted against molar fractions of the same compound. In this situation, we observed that the magnitude of Δδ(βCD H-5) was greater than Δδ (βCD H-3), giving evidence for a deep inclusion of AZ**1** inside the βCD core.

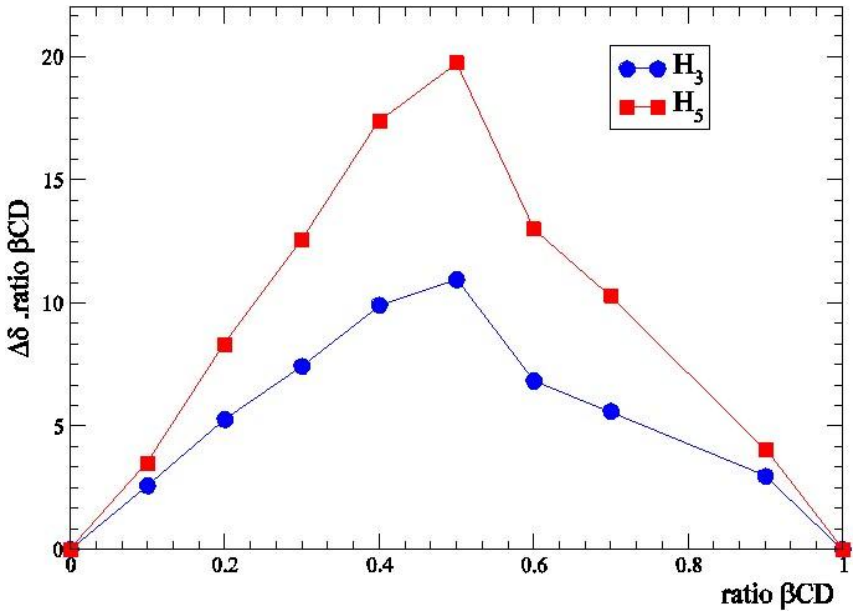


Figure 4: Job's Plot for the complex

Calculation of Ka.

The quantitative measurement of the complexation-induced shifts (CIS) of the AZ**1**-βCD complex at 25°C is represented by the value of the equilibrium constant governing the formation of the inclusion complex (**Table 2**).

There are many ways to calculate the value of Ka such as Graphical (or linearization) or Curve fitting methods. The first one was designed to produce a linear relationship between δ_{obs} and Ka, so that NMR data could be treated graphically. The four methods Benesi-Hildebrand's (Hanna-Ashbaugh) treatment[27], Scatchard's (Foster-Fyfe)[28], Scott's plot[29] and Rose-Drago's method[30] are well known for the graphical treatment of data. Curve fitting methods do not require any approximation for the calculation of Ka. We used the CLAK program that allowed a good assessment of Ka (382 mol^{-1})[31].

Table 2: CIS = Observed increments induced on chemical shifts of βCD H_3 and H_5 as a result of complexation with aziridine. CIS are related to concentrations of both βCD and AZ1.

βCD (mmol)	AZ1 (mmol)	$\Delta\delta_{obs}H_3$	$\Delta\delta_{obs}$ H_5
7.89	0.0	0.0	0.0
7.101	0.789	3.3	4.5
6.312	1.578	10.8	14.6
5.523	2.367	8.0	14.7
4.734	3.156	11.4	21.7
3.945	3.945	21.9	39.5
3.156	4.734	24.8	43.5
2.367	5.523	24.8	41.9
1.578	6.312	26.4	41.6
0.789	7.101	25.8	35.0

The inclusion complex structure.

One source of structural information might be the individual chemical shift modifications of protons of both guest and host. This parameter is referred to as the complexation-induced shift, as already mentioned above (CIS, or Δδ). Therefore, modifications of chemical shifts of

βCD H-3 and H-5 protons provide good evidence for the formation of an internal AZ**1**-βCD complex.

More detailed information concerning the geometry of these inclusion complexes could be derived from the evidence of the spatial neighbourhood between AZ**1** and βCD protons. This was achieved by investigating dipolar interactions using a 2D ROESY NMR experiment[32]. This technique proved to be the most sensitive for the structural analysis of inclusion complexes of βCD formed in solutions[33]. As was done in many other situations related to inclusion complexes in water, a 300 milliseconds (300 ms) mixing time was selected to provide reliable dipolar cross-peaks with a minimal contribution of scalar transfer[34,35].

The 2D-ROESY spectrum of the AZ**1**/βCD mixture (1:1) is depicted in Figure 5a. It shows strong ^{1}H-^{1}H cross peaks of the aromatic and aliphatic protons of AZ**1** with βCD H-3 and/or H-5 protons. These cross peaks along with the lack of correlation peaks with the protons on the outer-surface (H-2 and H-4), confirm the encapsulation of AZ**1** inside the cavity of βCD.

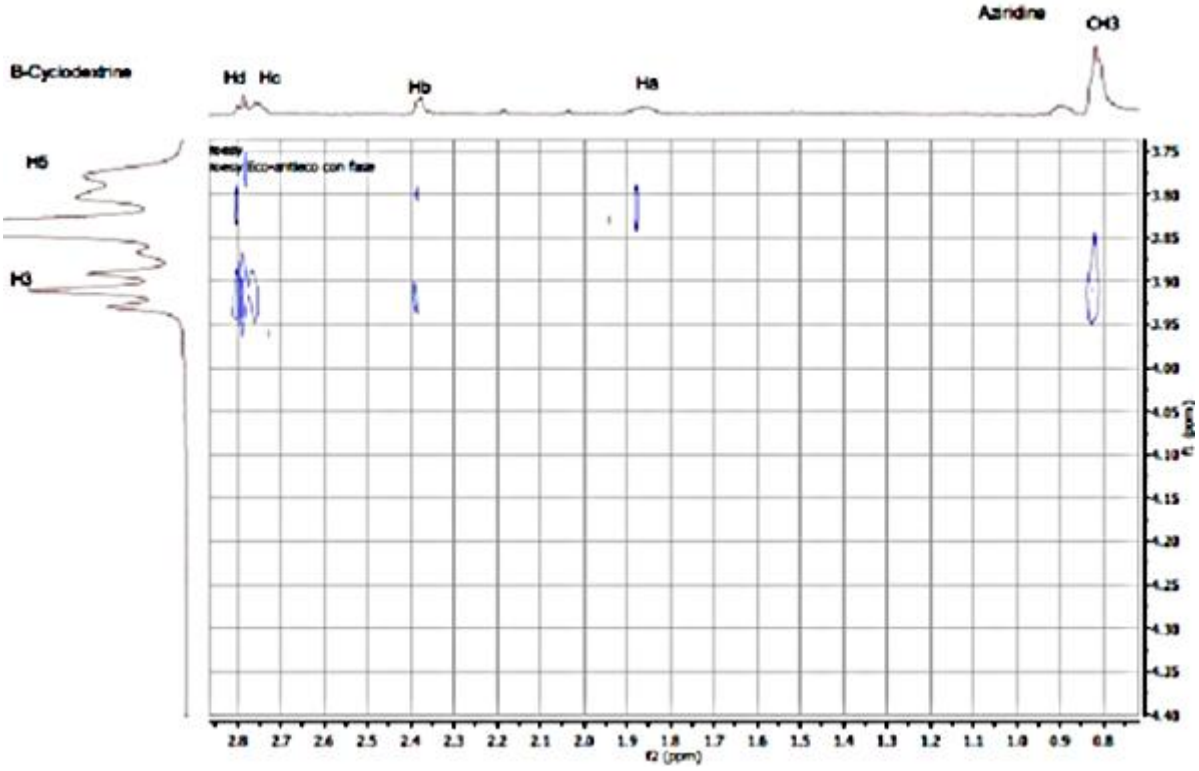


Figure 2a. Partial contour plots of ROESY experiment (mixing time: 300 ms, 500 MHz); inclusion complex βCD-AZ**1** (5 mmol^{-1}) in D_2O, at 298 °K: areas of **Az1** aliphatic (a) and aromatic protons (b).

The 2D spectrum showed several intermolecular cross-peaks between βCD H-3 and H-5 protons and protons of the aromatic ring of (nitrophenyl)sulfonyl group of AZ**1** (H1', H2', H3'and H4'), giving evidence for the inclusion of this group inside the hydrophobic cavity (Figure 5b).

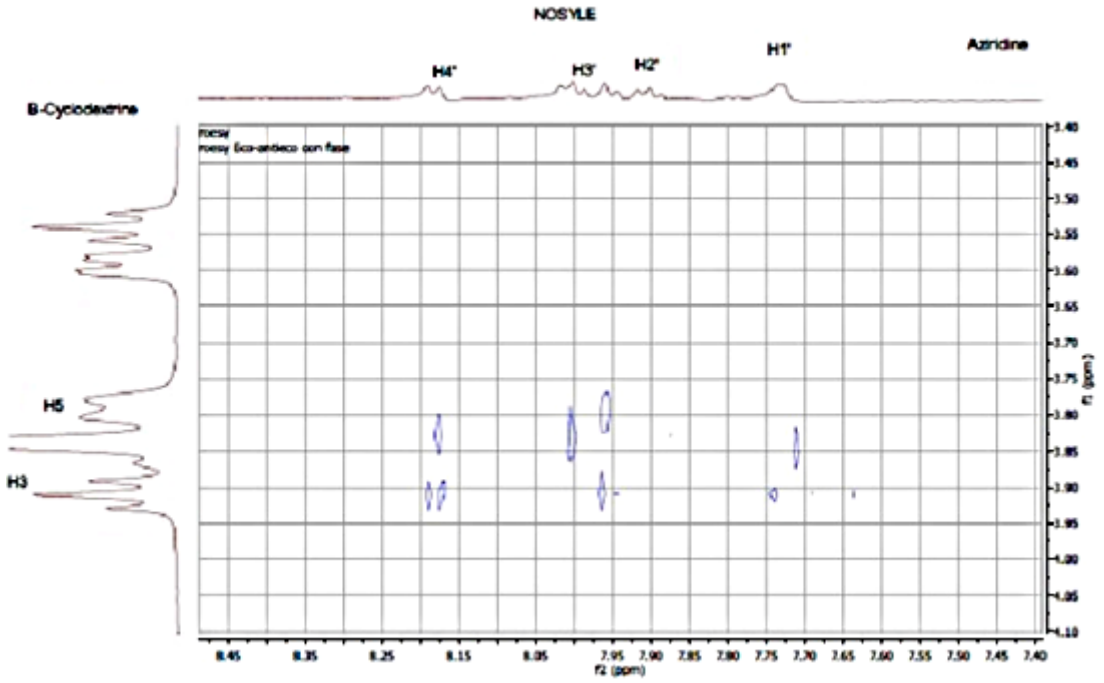


Figure 3b. Partial contour plots of ROESY experiment (500 MHz, mixing time: 300 ms), inclusion complex βCD/AZ**1** (5 mM^{-1}) in D_2O, at 298K: areas of aliphatic protons (a) and aromatic protons (b) of aziridine.

Additional dipolar correlations were found between protons on the aziridine ring (Hb, Hd and Hc) with βCD H-3 and H-5 protons. Finally, methyl protons presented a correlation only with the βCD H-3 proton. This could accounted for by the spatial vicinity of this section of the aziridine with the (nitrophenyl)sulfonyl group, confirming that AZ**1** is deeply inserted into the cavity of βCD by means of its (nitrophenyl)sulfonyl group. We also observed intermolecular cross peaks only with the inner βCD protons, and this observation established intracavity binding without giving evidence for outside contributions.

Therefore, and taking into account the attributions of the NMR analysis, we suggest the following geometry for the structure of our complex (Fig. 6).

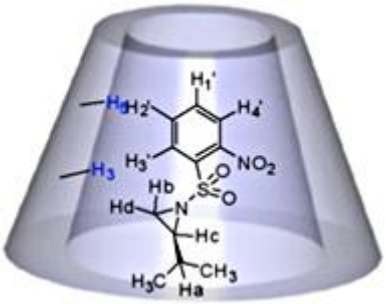


Figure 6: Proposed structure for the inclusion complex AZ**1**-βCD.

Conclusion

We have carried out the first NMR complexation study between a stable aziridine and βCD. The stoichiometry and association constant were determined by Job's method and CLAK program. The spatial relationship between βCD and AZ**1** was assessed using ROESY experiments. Furthermore, NMR studies provided evidence that the interaction was an inclusion phenomenon, but not an association phenomenon, since the changes obtained for βCD signals involved protons that were oriented towards the cavity of the host molecule.

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.

Acknowledgements

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Experimental Section

All the reactions needing anhydrous conditions were performed with dry solvents and carried out under nitrogen. Solvents were purified and dried according to standard procedures. Reagents for synthesis were used as received. I.R spectra were collected from a Mattson Genesis II FTIR. NMR spectra were recorded at 25 °C in $CDCl_3$ (0.004mmol.L^{-1}) on a Bruker 500, 400 or 300 MHz instrument, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) and coupling constant (*J*) values in Hertz (Hz). ROESY spectra were recorded using 500 ms mixing times and computer processing was performed using Mestrenova Software (version 6.2)**.** Column chromatography was performed on silica gel 230-270 mesh (Merck) using CH_2Cl_2, MeOH or mixture of both according to thin layer chromatography (TLC) results.

Preparation of aziridines.

General procedure

Tosyl-, *p*-Nitrobenzensulfonyl- or *o*-Nitrobenzensulfonyl chloride (0.799g, 3.60 mmol) was added in one portion to a suspension of (*S*)-amino alcohol (0.124g, 1.20 mmol) in dry 2:1 CH_2Cl_2/pyridine (3mL) at 0 °C, and the resulting mixture was stirred at room temperature for 4 - 6h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 2 M HCl (3×12 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL), and the organic portions were combined and carefully shaken (**CAUTION**: an undesirable emulsion is produced under vigorous shaking) with 2M KOH aqueous solution (6×30 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed to afford aziridines. Purification was carried out by column chromatography, using CH_2Cl_2 according to previous TLC results. The optical purity was retained in the final product and elemental analysis matched those of the literature.

***(S)*-2-isopropyl-1-(*o*-nitrophenyl)sulfonyl)aziridine 1** (from L-valinol).
(CAS registry number 111 0273-57-8).
Yield 90%, yellow oil, solidifying on standing: mp 64 °C. $[\alpha]_D^{20}$ = + 12.0 (*c* = 1.0 $CHCl_3$). R_f = 0.5 (CH_2Cl_2), IR(cm^{-1}) film: 1540(S=O), 1360(S–O), 1175(C–O), 950(Ph). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 0.84(d, *J* = 6.7Hz, 3H, CH_3), 0.88(d, *J* = 6.9Hz, 3H, CH_3), 1.50(m, 2H, H-3), 1.59(m, 1H, H-2) 1,98(m, 1H, C**H**Me_2), 7.68 (m, 1H, Ph), 8.02(m, 1H, Ph), 8.14(m, 1H, Ph), 8.52(m, 1H, Ph). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.66 (**C**H_3), 35.12(**C**H), 37.98(N-**C**3), 47.26(N-**C**2), 124.16(**C**-Ph), 128.10(**C**-Ph), 131.12(**C**-Ph), 131.86(**C**-Ph), 134.33(**C**-SO_2-), 147.18(**C**-NO_2). Elemental analysis: calcd for $C_{11}H_{14}N_2SO_4$, C 48.8; H 5.2; N 10.4. Found C 49.0; H 5.1; N 10.2.

***(S)*-2-isopropyl-1-(*p*-nitrophenyl)sulfonyl)aziridine 2** (from L-valinol).

White solid; mp 74 °C; Rf= 0.50 (CH_2Cl_2) $[\alpha]_D^{20}$ = +11.2 (*c* =1.0 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85(d, *J* = 6.9Hz, 3H, C**H**$_3$), 0.94(d, *J* = 7.0Hz, 3H, C**H**$_3$), 1.39-1.53(m, 1H, C**H**Me_2), 2.16-2.23(m, 1H, **H**-Az), 2.64-2.76(m, 2H, NC_2-**H**, **H**-Az), 8.16(d, *J* = 9.0Hz, 2H, Ar-**H**), 8.38(d, *J* = 9.0Hz, 2H, Ar-**H**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.5(**C**H_3), 30.1(**C**HMe_2), 33.6(Az-**C**3), 47.0(Az-**C**2), 124.2(Ar-**C**3), 129.3(Ar-**C**2), 144.1(Ar-**C**-SO_2-), 150.6(Ar-**C**-NO_2).. Elemental analysis: calcd for $C_{11}H_{14}N_2SO_4$, C 48.9; H 5.3; N 10.3. Found C 49.0; H 5.2; N 10.4.

(*S*)-2-isopropyl-1-Tosylaziridine 3 (from L-valinol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80(d, *J* = 6.9Hz, 3H, C**H**$_3$), 0.90(d, *J* = 6.8Hz, 3H, C**H**$_3$), 1.37-1.46(m, 1H, C**H**Me_2), 2.43(s, 3H, **H**$_3$C-Ar), 2.49-2.56(m, 1H, Az-**H1**), 2.62(d, *J* = 7.0Hz, 1H,), 7.33(d, *J* = 8.1Hz, 2H, Ar-H), 7.85(d, *J* = 8.1Hz, 2H, Ar-H).). ^{13}C NMR (126MHz, $CDCl_3$) δ 19.5(**C**H_3), 21.4(**C**H_3-Ar), 30.0(**C**HMe_2), 32.9(Az-**C**3), 46.2(Az-**C**2), 128.0(Ar-**C**2), 129.7(Ar-**C**3), 135.0(Ar-**C**-CH_3), 144.5(Ar-**C**-SO_2-). Elemental analysis: calcd for $C_{12}H_{17}NSO_2$: C 60.3; H 7.2; N 5.9. Found C 60.4; H 7.1; H 5.8.

(*S*)-2-methyl-1-tosylaziridine 4 (from L-alaninol).

Transparent liquid. Rf = 0.58 (CH_2Cl_2/MeOH 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20(d, *J* = 6.8Hz, 3H, C**H**$_3$), 2.09(d, J= 5.8Hz, 1H, Az-**H**), 2.44(s, 3H, C**H**$_3$), 2.62(d, *J* = 6.9Hz, 1H, Az-**H**), 2.79(ddq, *J* = 7.0, 6.0, 5.0Hz, 1H, NC**H**Me), 7.34(d, *J* = 8.3Hz, 2H, Ar-**H**), 7.83(d, *J* = 8.3Hz, 2H, Ar-**H**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.8(Ar-**C**H_3), 21.5(**C**H_3), 34.7(Az-**C**2), 36.1(Az-**C**3), 127.9(Ar-**C**2), 129.8(Ar-**C**3), 135.1(Ar-**C**-CH_3), 144.6(Ar-**C**-SO_2-). Elemental analysis: calcd for $C_{10}H_{13}NSO_2$: C 56.9; H 6.2; N 6.6. Found C 57.0; H 6.3; N 6.5

***(S)*-2-methyl-1-(*p*-nitrophenyl)sulfonyl)aziridine 5** (from L-alaninol).

White solid; mp 87 °C, $[\alpha]_D^{20}$ = + 24.5 (*c* = 1.0 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29(d, *J* = 6.0Hz, 3H, C**H**$_3$), 2.13(d, *J* = 5.0Hz, 1H, Az-**H**), 2.75(d, *J* = 7.0Hz, 1H, Az-**H**), 2.89-3.05(m, 1H, NC_2-**H**), 8.15(d, *J* = 8.9Hz, 2H, Ar-**H**), 8.39(d, *J* = 8.9Hz, 2H, Ar-**H**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.4 **C**H_3), 36.1(**C**H_2N), 125.1(Ar-**C**-3), 130.9(Ar-**C**-2), 143.9(Ar-**C**-SO_2-), 146.4(Ar-**C**-NO_2). Elemental analysis: calcd for $C_9H_{10}N_2SO_4$ C 44.6; H 4.1; N 11.6. Found: C 44.8; H 4.0, N 11.7.

***(S)*-2-methyl-1-(*o*-nitrophenyl)sulfonyl)aziridine 6** (from L-alaninol).

Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32(d, J = 5.6Hz, 3H, C**H**$_3$), 2.83(d, J = 7.0Hz, Az-C**H**$_2$), 3.00-3.04(m, 1H, Az-C**H**Me), 7.68-8.25(m, 4H, Ar-**H**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.1(**C**H_3), 24.0(Az-**C**2), 38.1(Az-**C**3), 125.1(C-**C**NO_2), 130.0(Ar-**C**6), 132.9(Ar–**C**4), 134.2(Ar-**C**1), 136.9(Ar-**C**5), 146.4(Ar-**C**-NO_2). Elemental analysis: calcd for $C_9H_{10}N_2SO_4$ C 44.6; H 4.1; N 11.6. Found: C 44.7; H 4.2, N 115.

(*S*)-1-((*p*-nitrophenyl)sulfonyl)-2-phenylaziridine 7 (from L-(+)-α-phenylglycinol).

White solid; mp 121°C, $[\alpha]_D^{20}$= + 77.9 (*c* = 1.0 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51(d, *J*= 5Hz, 1H, Az-**H**), 3.09(d, *J* = 7.0Hz, 1H, Az-**H**), 3.89(dd,*J* = 7.1, 4.7Hz, 1H, N-C**H**), 7.19-7.39(m, 5H, Ph), 8.20(d, *J* = 9.0Hz, 2H, Ar-**H**), 8.39(d, *J* = 9.0Hz, 2H, Ar-**H**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.6(Az-**C**3), 41.9(Az-**C**2), 124.4(Ph-**C**4), 127.7(Ar-**C**2), 127.9(Ph-**C**2), 128.3(Ph-**C**3), 129.2(Ar-**C**3), 144.0(Ar-**C**-SO_2-), 150.6(Ar-**C**-NO_2). Elemental analysis: calcd for $C_{14}H_{12}N_2SO_4$. C 55.3; H 3.9; N 9.2. Found C 55.2; H 4.0; N 9.3.

(*S*)-1-((*o*-nitrophenyl)sulfonyl)-2-phenylaziridine 8 (from L-(+)-α-phenylglycinol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51(d, J= 5.0 Hz, 1H, NCH), 3.11(d, J= 7.0Hz, 1H, Az-H), 3.92(d, J=5Hz, 1H, Az-H), 5.30(m, 5H, Ph), 7.68-8.2(m, 4H, Ar). ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.64(Az-**C**3), 42.83(Az-**C**2), 124.23(Ar-**C**3), 126.47(Ph-**C**4), 127.5(Ph-**C**2), 128.1(Ar-**C**6), 128.61(Ph-**C**3), 130.85(Ar-**C**4), 131.93(Ar-**C**5), 134.19(Ar-**C**SO_2-), 148.57Ar-**C**NO_2). Elemental analysis: calcd for $C_{14}H_{12}N_2SO_4$. C 55.3; H 3.9; N 9.2. Found C 55.0; H 4.1; N 9.5.

Inclusion procedure: aziridine 1- βCD.

Solutions for NMR titration were prepared by mixing 7.89 mM mother solutions of AZ**1** and βCD to provide a series of solutions with a ratio ranging from 1 to 0. The solutions to be analyzed were kept at a constant concentration (7.89 mM) with a total volume steady at 500µl. This solution was sonicated for 10 min and subsequently analyzed by NMR. All NMR data were collected at 25 °C on a Bruker 500 MHz. The 2D data were obtained with a flip angle (90° pulse = 9.7 µs), and acquisition time of 16 s and a relaxation delay of 1s. Conditions for ^{1}H NMR data were flip angle (90° pulse = 9.7 µs), acquisition time (AT) = 4 s, numbers of scans (NS) = 16 and a relaxation delay of 1s.

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