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INTRODUCTION

L'intérêt des complexes Host-Guest en pharmacologie et en médecine fait l'objet de très nombreux travaux scientifiques. L'aspect thermodynamique de la formation de ces espèces, intervient entre autres, dans l'amélioration de la solubilité des biomolécules (complexes d'inclusion), dans la mesure de la force de leur interaction avec le milieu biologique (complexes de transfert de charge) et dans l'imagerie médicale (complexes organométalliques

Nombreuses sont les molécules organiques qui présentent une activité biologique in vitro, mais sont relativement inactives in vivo en raison de leurs hydrosolubilités insuffisantes, ce qui limite la biodisponibilité de la biomolécule et sa migration à travers les membranes biologiques.

L'un des moyens pour combler cette lacune et contourner ce problème est l'insertion de ces molécules dans les cavités des macromolécules. Parmi les macromolécules qui se proposent, notre attention s'est portée sur la β-cyclodextrine (β-CD) native ou modifiée.

Les propriétés des molécules ainsi encapsulées totalement ou même partiellement se améliorées de manière significative.

L'étude thermodynamique permet de confirmer la formation des complexes en solution et de caractériser la force de l'interaction par le biais des constantes de stabilité et des grandeurs thermodynamiques d'activation. Les contributions des études structurales des complexes solides et de de modélisation moléculaire permettent de voir s'il y ait inclusion totale ou partielle et de faire ressortir les sites d'interaction entre le hôte et l'invité. Les mesures de la lipophilie (facteur de Hansh) des biomolécules nues et encapsulées montrent dans quelle mesure l'hydrosolubilité s'est améliorée suite à la formation des complexes d'inclusion .

L'interaction d'une biomolécule donnée avec le milieu biologique, pourrait être estimée moyennant la formation des complexes de transfert de charge. Le degré de l'interaction est analogiquement déterminé par une étude thermodynamique de la complexation de certaines biomolécules avec les substances actives interagissent avec des accepteurs π (TCNE , DDQ, Chloroaniline) et des accepteurs σ (iode , brome).

Dans les études sur les biomolécules, il est intéressant de savoir le mécanisme de leur décomposition dans un milieu physiologique. Ce milieu est caractérisé par une température de 37°C et un pH de 7 fixé par une système tampon phosphaté.

En subissant l'hydrolyse catalysée, les biomolécules donnent naissance aux principales espèces responsables de l'interaction avec le milieu biologique. Les études cinétiques permettent d'accéder à telles informations.

La dernière partie du sujet concerne la synthèse et la caractérisation des complexes solides à base de Re et Rh utilisés en imagerie médicale.

1. TRAVAUX PUBLIES

1.1 A spectrophotometric and thermodynamic study of the charge-transfer complexes of N-aryl-N'-isopropyloxycarbonylsulfamides with DDQ and TCNE.

Abstract:

Molecular charge-transfer complexes of three N-aryl-N'-isopropyloxycarbonylsulfamidesderivatives with π acceptors tetracyanoethylene (TCNE), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), were studied by using zero and second order derivative UV spectrophotometry in different solvents at four different temperatures within the range of 20-35°C.The stoichiometriesofthe complexes were found to be 1:1 ratio between donors and acceptors usingJob's method. The data were analyzed in terms of their stability constant (K), molar extinction coefficient (ε_{CT}), thermodynamic standard reaction quantities ($\Delta G^0, \Delta H^0, \Delta S^0$), oscillator strength (*f*), transition dipole moment (μ_{EN}) and ionization potential (I_D).

The results show that the stability constant (K) for the complexes was found to be dependant upon the nature of electron acceptor, electron donor, and polarity of usedsolvents.

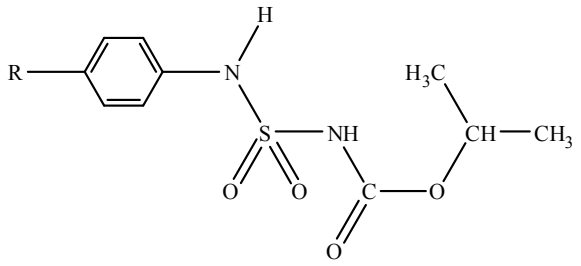
Key words: N-aryl-N'-isopropyloxycarbonylsulfamides; DDQ; TCNE; Charge-transfer complexes; Second order derivative UVspectrophotometry; Stability studies.

1.Introduction

Charge–transfer (CT) complexes that originate from a weak interaction between electron donor and acceptor molecules in biomolecular equilibrium or in model compounds intramolecular interaction have been an important topic of research in physical chemistry and biochemistry for many decades [1-4].Charge-transfer complexation is of great importance in chemical reactions, including addition, substitution, condensation [5], biochemical and bioelectrochemical energy transfer processes [6], biological systems, and drug–receptor binding mechanisms[7]. The important role is also played by the charge- transfer complexes in the quantitative estimations of drugs [8,9].

The properties of charge-transfer (CT) complexes formed in the reaction of electron acceptors with donors containing nitrogen, sulfur, oxygen atoms, have growing importance in recent years [10-22]. N-aryl-N'-isopropyloxycarbonylsulfamides are compounds which containin their molecular structures a sulfamoyl moiety as pharmacophore. They have been primarily used as important synthetic intermediates in the generation of unsymmetricsulfamides [23,24] and sulfahydantoins [25]. They have been studied as acyl-CoA: cholesterolO-acyl-transferase (ACAT) inhibitors [26], and showed a broad range of inhibitory activity against several isoforms of carbonic anhydrase [27].

The objective of the present work is to carry out a spectroscopic and thermodynamic study of the complexation of N-aryl-N'-isopropyloxycarbonylsulfamides D1, D2 and D3 **(**Fig.1) with the electron acceptors tetracyanoethylene (TCNE), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), following two procedures: in liquid phase and at the solid state.



D1 R= OCH_3
D2 R= CH_3
D3 R= H

Fig.1 N-aryl-N'-isopropyloxycarbonylsulfamidesused in this study.

Spectrophotometric measurements based on zero and/or second order derivative UV spectrophotometry were used to evaluate in four different solvents (chloroform, methanol, ethanol and acetone), stability constants (K), the molar extinction coefficient (ε_{CT}), thermodynamic standard reaction quantities ($\Delta G^0, \Delta H^0, \Delta S^0$), the oscillator strength (f), the transition dipole moment (μ_{EN})and the ionization potential (I_D). Moreover, the solid complexes were synthesized and characterized by using FT-IR spectroscopy.

2. Experimental

N-aryl-N'-isopropyloxycarbonylsulfamides were synthesized according to literature [28]. π acceptors tetracyanoethylene (TCNE), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were obtained from Aldrich Chemical Co. and were used without modification. The spectroscopic grade solvents (ethanol, methanol, acetone, and chloroform) were purchased fromFluka or Prolabo.

The electronic absorption spectra were recorded in the range 400-220nm using a Jasco UV-530 spectrophotometer equipped with a Jasco EHC-477S thermostat (±0.1 °C) using 1.0 cm matched quartz cells.FT-IR spectra of the reactants and the formed complexes were recorded as KBr pellets using Spectrum one Perkin Elmer FT-IR.

The solid charge –transfer complexes were isolated by taking equimolar amounts of the donor and the acceptor and dissolved separately at room temperature in the minimum volume of a mixture methanol/dichloromethane (1:1, v/v).The two solutions were mixed and the resulting mixture was stirred overnight at room temperature.The resulting solid compound precipitated was first filtered off, washed several times with methanol/dichloromethane mixture to remove any unreacted materials, and finally dried.

3. Results and discussion

3.1 Electronic spectra

In solution, the complexation of N-aryl-N'-isopropyloxycarbonylsulfamides by acceptors (TCNE or DDQ) was demonstrated by spectrophotometry at UV-vis at 20 °C.

The UV-vis spectrum of each of N-aryl-N'-isopropyloxycarbonylsulfamidesstudied was altered in the presence of the acceptor (TCNE or DDQ).Following the progressive addition of acceptor on donor solutions, characteristic phenomena of the charge–transfer complexes formation were noticed: batho or hypsochromic shifts, increase in the intensity of the absorption band or appearance of new absorption bands in a region where neither free donors nor acceptors have any measurable absorption.

As shown in figures 2-3, the absorbance spectra of D1 in solutions containing various amounts of DDQ or TCNE in chloroform, was examined. It was intendedto serve as a model of the three N-aryl-N'-isopropyloxycarbonylsulfamidesderivates studied.

Fig. 2 shows electronic absorption spectra of D1 in chloroform containing various concentrations of DDQ.The donor D1 (4.10^{-4}M) displays a broad absorption band which spreads out from 259 nm to 276 nm.Upon the addition of the DDQ, this band shifts left, increases in intensity and culminates at 268 nm. Moreover, the absorption band at 354 nm increases in intensity. These findings indicate the formation of a charge –transfer complex of D1 with DDQ.

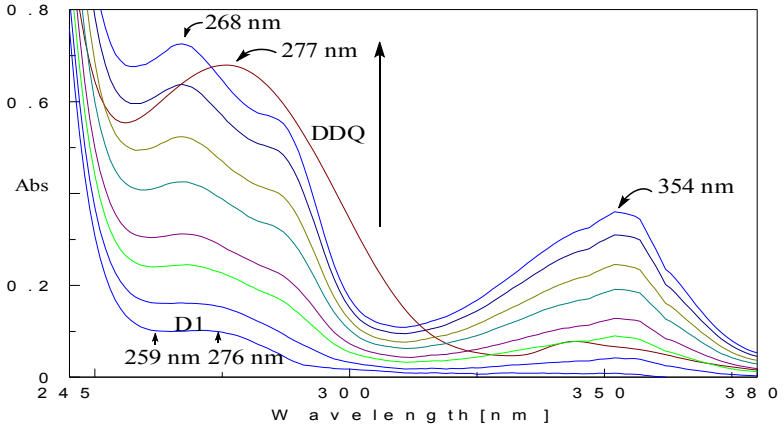


Fig.2 Absorption spectra of D1 (4.10^{-4}M) in chloroform containing various concentration of DDQ.

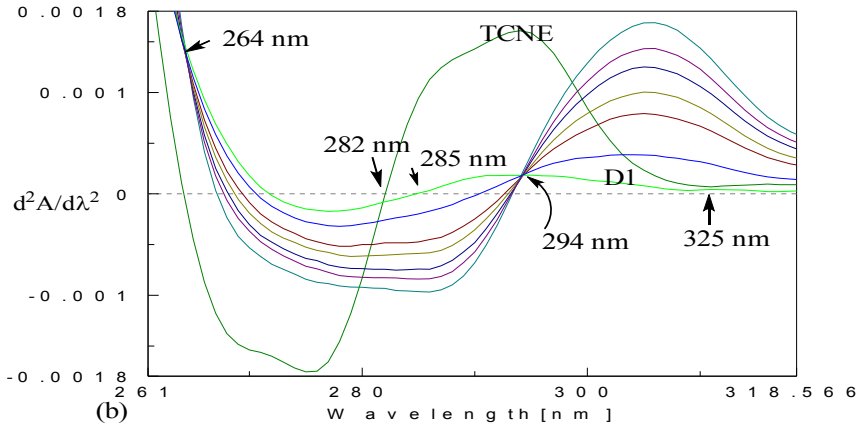


Fig.3 displays absorption spectra of D1 in chloroform with progressive concentrations of TCNE.As the TCNE concentration increases, the absorbance at 267 nm enhances and a new absorption band at 287 nm appearswhich is clearly due to the charge–transfer complex.

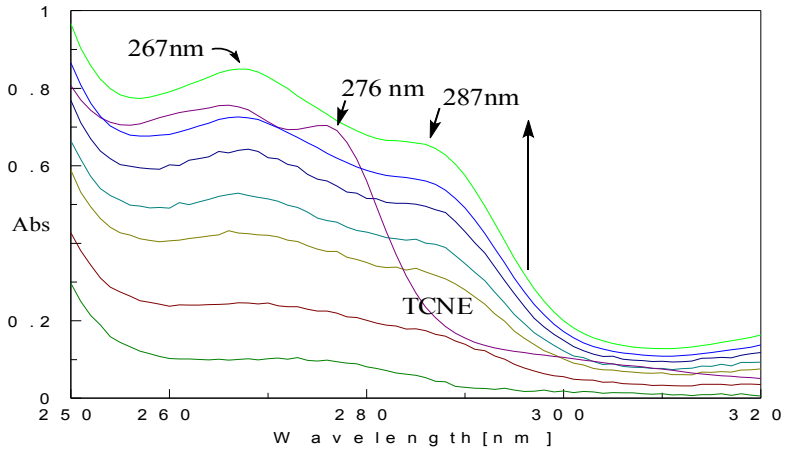


Fig.3 Absorption spectra of D1 (4.10^{-4}M) in chloroform containing various concentration of TCNE.

3.2 **Second order derivative spectra**

Second order derivative UV spectrophotometry was used to eliminate the overlap noticed in the spectra of complexes resulting from the contributions of the absorbance of the acceptor and / or of the donor. In addition, this method emphasizes subtle spectral features of the data by presenting them in a new and visually more accessible way.

As an example, the secondderivative spectra of the charge–transfer complex formation of the same compound already measured by direct spectrophotometry are respectively presented on Fig. 4.

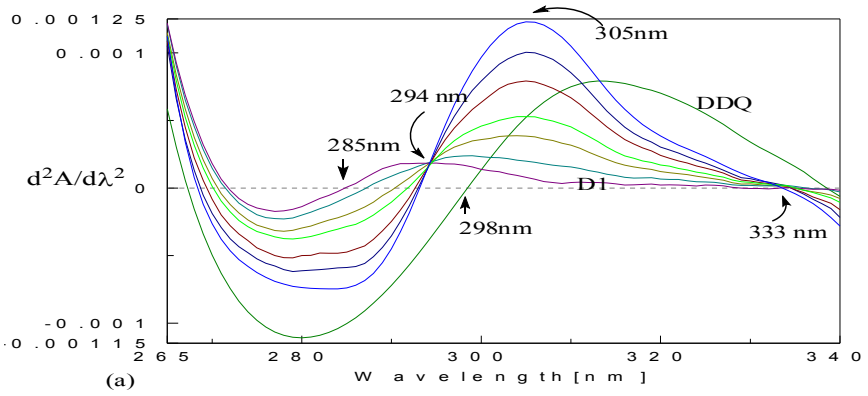


Fig.4 Evolution of second order derivative spectra of D1 (4.10^{-4}M) in chloroform containing various concentration of DDQ (a) and TCNE (b).

The main instrumental parameters that affect the shape of derivative spectra are the wavelength speed, the wavelength increment (Δλ)over which the derivative is obtained, and

the smoothing. These parameters need to be optimized to give well-resolved large peaks, and a larger relatively intense signal.In general,it was noticed that, the noise level decreases with an increase in $\Delta\lambda$ thus decreasing the fluctuation in the derivative spectra.However, if the value of $\Delta\lambda$ is too large, the spectral resolution is very poor [29]. Therefore, the optimum value of $\Delta\lambda$had to be determined by taking into account the noise level and the resolution of the spectra. Some values of $\Delta\lambda$ were tested. As optimal conditions $\Delta\lambda$ = 5 nm and wavelength scanning speed = 200 $nm.min^{-1}$ were selected for second derivative method to give a satisfactory signal to the noise ratio.

Figure 4 shows that, in each case the complexation is better visualized, the bathochromic shifts are more significant and the isosbestic points are clearer.Figure 4(a), reveals a noteworthy difference from the original absorption spectra, sincethe second derivative absorption spectra isosbestic points are clearly observed at 294 nm and 333 nm.

At the zero-crossing wavelength of the spectrum of DDQ (298 nm), the amplitude ($^2d_\lambda$) of the second derivative spectrum is proportional to the concentration of the charge–transfer complex in the solution.

In Fig. 4(b),isosbestic points are observed at 264 nm and 294 nm, and the zero-crossing wavelength of the spectrum of TCNE is at 282 nm. In addition, by neglecting the amplitudes of the donor and the acceptor at 325 nm, this wavelength can be taken as zero –crossing wavelength of the spectrum of donor D1 and the acceptor TCNE. At these points the measured amplitudes are due to the charge–transfer complex.

Moreover, it mustbe emphasized that in chemical equilibria calculations, the main advantage of this method compared with zero-order spectrophometry is the accuracy of the measured $d^2A/d\lambda^2$ .This is of great interest in N-aryl-N'-isopropyloxycarbonylsulfamides – acceptors systems where the difference of absorbance between free and complexed forms is small and/or when the overlapping of spectra is observed.

In this respect, it must be noted that, the zero-crossing method is the approach used in this work for the determination of the stoichiometry of charge- transfer complexes.

At the zero-crossing wavelength of the spectrum of a given acceptor, the amplitude ($^2d_\lambda$) of the second derivative spectrum is proportional to the concentration of the corresponding complex in the solution.

$$^2d_\lambda = d^2A/d\lambda^2 = d^2\left(\varepsilon.l.[\text{complex}]\right)/d\lambda^2 \qquad (1)$$

Where A is the absorbance, l is the path length and ε is the molar extinction coefficient.

The wavelengths, at which the amplitudes of the complexes studied were measured, are 298 nm for complexes with DDQ, and 282 nm in which TCNE is the acceptor.

3.3 **Determination of the composition of the complexes and their stability constants**

On the basis of the above considerations, the amplitudes $^2d_\lambda$ of the different solutions at suitable wavelength were processed by Job's method of continuous variation [30], and thestoichiometries of the complexes studied were determined (Fig 5,6).The results show that, the interaction between each donor and each one of π-acceptor occurs on an equimolar basis (1:1) independently of the solvent nature.

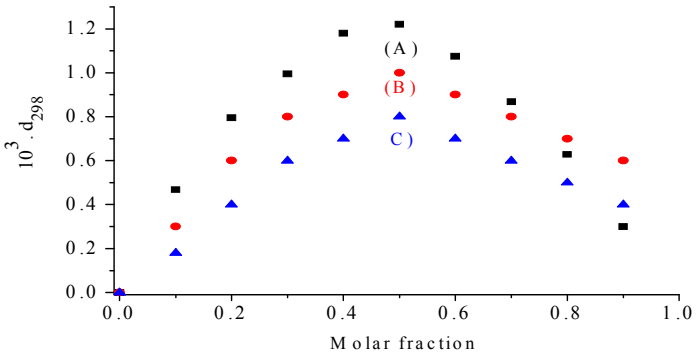


Fig.5 Continuous variation plot for charge - transfer reaction in chloroformbetween DDQ as

acceptor and (A) D1, (B) D2 and (C) D3 as donors

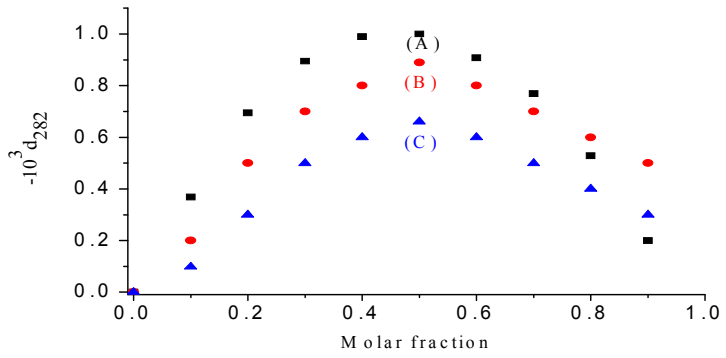


Fig.6 Continuous variation plot for charge - transfer reaction in chloroform between TCNE as acceptor and (A) D1, (B) D2 and (C) D3 as donors.

The stability constants (K) and molar extinction coefficients (ε_{CT}) of the charge – transfer complexes studied have been determined in different solvants at 25 °C, using Benesi Hildebrand [31]equation for cells with 1 cm optical path length:

$$\frac{[A]_0[D]_0}{Abs} = \frac{[D]_0}{\varepsilon_{CT}} + \frac{1}{K\varepsilon_{CT}} \qquad (2)$$

With $Abs = d - d_A^0 - d_D^0$, $[A]_0$ and $[D]_0$ as the initial concentrations of the π-acceptors (DDQ or TCNE) and donors (D1,D2 or D3) respectively. d is the absorbance of the donor-acceptor mixture at some suitable wavelength (λ_{CT})against the solvent as referenceand d_A^0, d_D^0 are the absorbances of the acceptor and donor solutions with the same molar concentrations , as in the mixture at the same wavelength.The quantity $\varepsilon_{CT} = \varepsilon - \varepsilon_A - \varepsilon_D$ refers to the correction of the molar extinction coefficient of the complexand ε_A, ε_D being those of the acceptor and donor respectively at λ_{CT}.K is the stability constant of the complex. Eq. (2) is valid under the condition $[D]_0 >> [A]_0$.The obtained data throughout these calculations are translated by plotting the values of $[D]_0[A]_0/Abs$ against $[D]_0$ values for each donor with each acceptor.For the reaction of D1 and DDQ in chloroform at 25°C, straight line is obtained with a slope of $1/\varepsilon_{CT}$, and the intercept on the ordinate of $1/K\varepsilon_{CT}$ as shown in Fig.7.

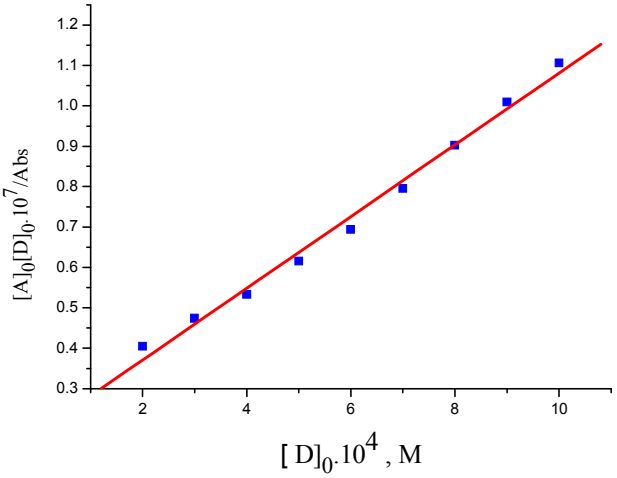


Fig.7 Benesi Hildebrand plot for D1-DDQ complex in chloroform at 25 °C.

The values of K and ε_{CT} associated with allcomplexes arereported in Table 1.

Table1

Stability constants K and molar extinction coefficients ε_{CT} at 25 °C of 1:1N-aryl-N'-isopropyloxycarbonylsulfamides/ acceptorscomplexes at various solvents.

Complexes	Solvent	λ_{CT},nm	K.10^{-3}	ε_{CT}, L.mol^{-1}.cm^{-1}
	Chloroform			
D1-DDQ		268	4594	11264
D2-DDQ		265	4089	9784
D3-DDQ		265	3403	8254
D1-TCNE		267	4473	10654
D2-TCNE		265	3465	9358
D3-TCNE		265	2862	8205
	Acetone			
D1-DDQ		354	2514	6322
D2-DDQ		352	2432	6211
D3-DDQ		352	1524	4562
D1-TCNE		265	2312	4322
D2-TCNE		263	2310	4310
D3-TCNE		260	1322	4020
	Methanol			
D1-DDQ		263	1540	3500
D2-DDQ		270	1510	3200
D3-DDQ		263	1430	2500
D1-TCNE		271	1350	2400
D2-TCNE		265	1256	2250
D3-TCNE		265	1065	2142
	Ethanol			
D1-DDQ		290	1054	3400
D2-DDQ		291	987	3300
D3-DDQ		290	870	3100
D1-TCNE		271	746	3225
D2-TCNE		265	743	3156
D3-TCN*E*		268	650	3154

The values of both of molar extinction coefficients (ε_{CT}) and the stability constants (K) of 1:1 charge-transfer complexes are influenced by the medium polarity, the acceptor nature and the substituted group in the benzene ring of N-aryl-N'-isopropyloxycarbonylsulfamides.

The effect of substitutes on the position and intensity of CT bands, stability constants, and extinction coefficients values, is attributed to substitutions with π-orbital of the benzene ring. The hyper conjugate effect of OCH_3, and inductive effect of CH_3 group, all perturbe resonance in the benzene ring and boost the energy of the donor level and bring it closer to the

LUMO of acceptors, and thus cause an increase in the intensity of charge-transfer complex bands.

The stabilities of the complexes increase with theelectron withdrawing ability of the substitutions in benzene ring of N-aryl-N'-isopropyloxycarbonylsulfamides.Consequently,the stability constantsdecrease in the following order:

D1-DDQ > D2-DDQ > D3-DDQ

D1-TCNE > D2- TCNE > D3- TCNE

3.4 Determination of thermodynamic parameters of CT complexes

In order to have a better understanding of the thermodynamics of the charge-transfer reactions, it is useful to consider the enthalpic (ΔH^0) and entropic (ΔS^0) contributions to these reactions. Evaluation of the stability constants K of the studied complexes at four different temperatures within the range 20-35°C allows the determination of the thermodynamic parameters (ΔH^0, ΔS^0) by a Van 't Hoff plot of lnK vs. 1/T (Eq. 3).

$$\ln K = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} \quad (3)$$

A plot of lnK vs. 1/T for the studied charge-transfer complexes is shown in Fig.8, and all other systems give similar linear plots.In each case the correlation coefficient is 0.96 or above. The enthalpies and entropies of complexation were determined from the slopes and intercepts,respectively.

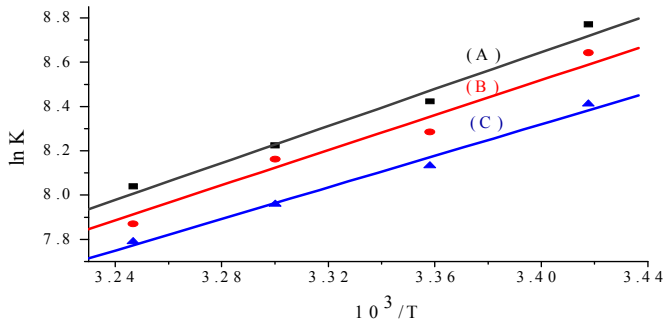


Fig.8.Van't Hoff plots of the complexes of DDQ with D1 (A), D2(B) and D3(C) in chloroform.

The values of standard free energy changes were obtained according to the equation:

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 = -RT \ln K \quad (4)$$

where ΔG^0 is the free energy change of the complex (kJ.mol^{-1}), R is the gas constant (8.314 J.mol^{-1}.K^{-1}), T is the temperature in Kelvin degrees and K is the stability constant (l.mol^{-1}) at room temperature.

The values of thermodynamic parameters listed in Table 2 show that thecharge-transfer reactions are exothermic, and are all thermodynamicallyfavored.

Table 2

Thermodynamic standard reaction quantities of N-aryl-N'-isopropyloxycarbonylsulfamides complexes with DDQ and TCNE in different solvents.

Complexes	Solvent	-ΔG°, (kJ/mol)	-ΔH°, (kJ/mol)	-ΔS°, (J/K.mol)
	Chloroform			
D1-DDQ		48.048	34.638	45.00
D2-DDQ		45.138	32.915	41.02
D3-DDQ		39.005	29.613	31.52
D1-TCNE		47.039	33.987	43.80
D2-TCNE		43.713	31.942	39.50
D3-TCNE		35.399	27.598	26.18
	Acetone			
D1-DDQ		34.426	26.920	25.19
D2-DDQ		32.366	25.840	21.90
D3-DDQ		27.736	22.954	16.05
D1-TCNE		33.246	26.238	23.52
D2-TCNE		31.898	25.540	21.34
D3-TCNE		26.885	22.356	15.20
	Methanol			
D1-DDQ		29.773	23.977	19.45
D2-DDQ		29.683	23.911	19.37
D3-DDQ		28.636	23.312	17.87
D1-TCNE		29.250	23.553	19.12
D2-TCNE		28.361	23.021	17.92
D3-TCNE		27.656	22.456	17.45
	Ethanol			
D1-DDQ		26.456	21.849	15.46
D2-DDQ		25.635	21.350	14.38
D3-DDQ		24.681	20.718	13.30
D1-TCNE		25.192	20.785	14.79
D2-TCNE		25.168	20.751	14.71
D3-TCNE		24.007	20.200	13.38

The values of ΔH^0 and ΔS^0 usually become more negative as the stability constant for the complexes increases.

3.5 Effects of solvents on the formation of CT complexes

The effect of different solvents, namely chloroform, acetone, ethanol and methanol on the stability of charge transfer complexes was also examined. Our measurements indicated that, the chloroform was the most suitable diluting solvent because it has an excellent solvating power for the studied donors and a high absorbance.

The experimental results of the interaction between each donor with each acceptor in different solvents show that the values of stability constants, and spectroscopic properties were markedly affected by the variation of solvent polarity in which measurements were carried out. In the present experiment, K values decrease significantly from chloroform to methanol with an increasing solvents polarity. This may be attributed to the fact that charge transfer complexes had to be stabilized in non-polar solvent [32]. Dissociation of the complexes into D^+-A^- radicals have been found to occur in the ground state [33]. It means that the charge-transfer complexes must be strong in non – polar solvent than polar solvent.

3.6 Determination of ionization potentials of the donor

The ionization potentials of the donor (I_D) in the charge- transfer complexes were calculated using the empirical equation derived by Aloisi and Pignataro [34]:

$$I_D(eV) = 5.76 + 1.53\times10^{-4}\nu_{CT} \text{ for DDQ} \quad (5)$$

$$I_D(eV) = 5.21 + 1.65\times10^{-4}\nu_{CT} \text{ for TCNE} \quad (6)$$

where ν_{CT} is the wavenumber in cm^{-1} of the complex, which was determined in different solvents: choloroform, aceton, methanol and ethanol. Thedetermined values of ionization potentialsare given in Table 3.

3.7 Determination of oscillateur strength (f) and transition dipole (μ_{EN})

From the charge-transfer complexes absorption spectra, we can extract the oscillator strength$f$ whichis estimated on the basic of the formula:

$$f = 4.32\times10^{-9}\int \varepsilon d\nu \quad (7)$$

where $\int \varepsilon d\nu$ is the area under the curve of the molar extinction coefficient of the absorption band in question vs.frequency. As a first approximation:

$$f = 4.32\times10^{-9}\varepsilon_{CT}\Delta\nu_{1/2} \quad (8)$$

where ε_{CT} is the maximum molar extinction coefficient of the band, and $\Delta\nu_{1/2}$ is the half-width, i.e., the width of the band at half the maximum extinction. The observed oscillator strenghts of the CT bands are summarized in Table 3. The values of the calculated oscillator

strengths indicate a strong interaction between the donor-acceptor pair with relative high probabilities of CT transitions. This is also supported by the relatively large heat formation. The extinction coefficient is related to the transition dipole by

$$\mu_{EN} = 0.0952\left[\varepsilon_{CT}\,\Delta\nu_{1/2}/\Delta\nu\right]^{1/2} \qquad (9)$$

where $\Delta\nu \approx \nu_{CT}$ at ε_{CT} and μ_{EN} is defined as $-e\int \Psi_{ex} \sum_i r_i \Psi_g d\tau$.

The observed oscillator strengths of the CT bands and transition dipole are summarized in Table3.

Table 3

Spectral properties of CT complexes of N-aryl-N'-isopropyloxycarbonylsulfamideswith DDQ and TCNE in different solvents.

Complexes	Solvent	$\Delta\nu_{1/2}$, (cm^{-1})	f	μ_{EN} (D)	I_D (eV)
	Chloroform				
D1-DDQ		452 132	22.00	2.9025	11.468
D2-DDQ		458 168	19.36	2.702	11.533
D3-DDQ		350 132	12.48	2.839	11. 533
D1-TCNE		410 123	18.876	2.969	11.389
D2-TCNE		479 156	19.370	2.584	11.436
D3-TCNE		470 145	16.664	2.443	11.436
	Acetone				
D1-DDQ		753 012	20.565	1.466	10.080
D2-DDQ		745 232	19.995	1.464	10.106
D3-DDQ		736 920	14.523	1.262	10.106
D1-TCNE		690 613	12.894	1.462	11.436
D2-TCNE		780 640	14.534	1.456	11.483
D3-TCNE		829 875	14.411	1.299	11.556
	Methanol				
D1-DDQ		310 752	4.698	1.970	11.577
D2-DDQ		366 853	5.071	1.711	11.426
D3-DDQ		300 390	3.244	1.693	11.577
D1-TCNE		500 000	5.184	1.266	11.298
D2-TCNE		488 042	4.744	1.255	11.436
D3-TCNE		478 240	4.425	1.237	11.436
	Ethanol				
D1-DDQ		452 132	6.641	1.532	11.035
D2-DDQ		376 082	5.361	1.655	11.017
D3-DDQ		308 452	4.131	1.772	11.035
D1-TCNE		456 231	6.356	1.537	11.298
D2-TCNE		426 803	5.819	1.555	11.136
D3-TCNE		374 812	5.106	1.689	11.366

3.8 FT-IR spectra

The FT-IR spectra bands of free donors (D1, D2, and D3), free acceptors (DDQ, TCNE), and of their corresponding charge-transfer complexes are shown in Fig. 9-11 , while the assignments of their characteristic FT-IR spectral bands are reported in Tables 4 and 5.

The additional support of the formation of the 1:1 charge-transfer complexes during the reaction of each donor with each acceptor is the presence of the main characteristic FT-IR bands of the donor and acceptor in the spectrum of the product.Interestingly, some shifts in the band wavenumber values and changes in band intensities were noticed. For example, upon the complexation, the vibration frequencies of C=O (1645.70,1558.99, 1630.06 cm^{-1}) and C=C (1458.06,1458.06 and 1448.11cm^{-1}) in charge -transfer complexes with DDQ as acceptor are lower than corresponding ones appearing on the spectra of both free donors and free DDQ. However, the vibration frequencies of C-C in complexes (1196.15, 1176.62 and1186.56cm^{-1}) are higher than those of corresponding free donors (1162.87, 1170.58, and 1170.58cm^{-1}), and free DDQ (1174.03cm^{-1}).

Other characteristic bands of free DDQ($\nu_{C\equiv N} = 2253.82\,cm^{-1}$) and free donors ($\nu_{N-H} = 3262\,cm^{-1}$, $\nu_{SO_2}(\text{symetrics}) = 1344.44, 1455.99$ and $1355.99\,cm^{-1}$), appear at lower vibration frequencies in charge-transfer complexes at $\nu_{C\equiv N} = 2244.13\,cm^{-1}$, $\nu_{N-H} = 3251.95\,cm^{-1}$, $\nu_{SO_2} = 1337.24, 1277.54$ and $1354.29\,cm^{-1}$.

Besides, when TCNE was used as acceptor, the outlined changes in the main characteristic bands of free donors (for example N-H), and free acceptor (forexample $C \equiv N$) upon complexation clearly supports the formation of charge-transfer complexes between donors studied and TCNE.

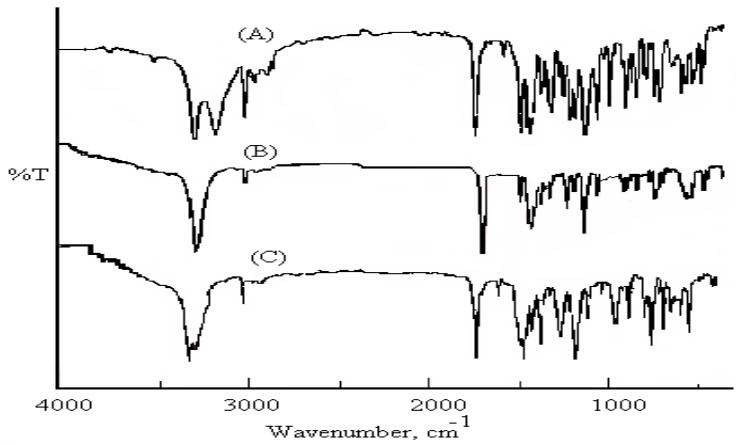


Fig.9 FTIR of free donors D1(A), D2(B) and D3(C).

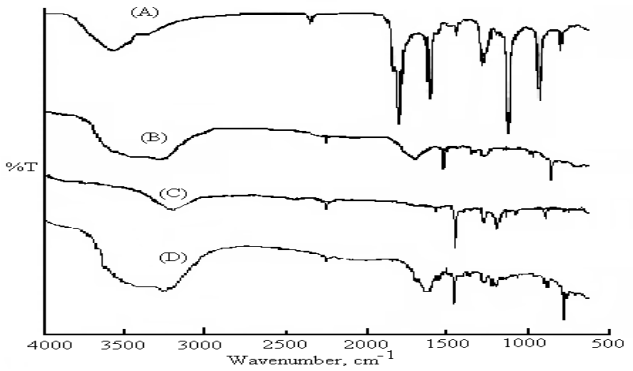


Fig.10 FT-IR of free DDQ (A) and its corresponding charge-transfer complexes D1-DDQ(B), D2-DDQ(C), and D3-DDQ(D).

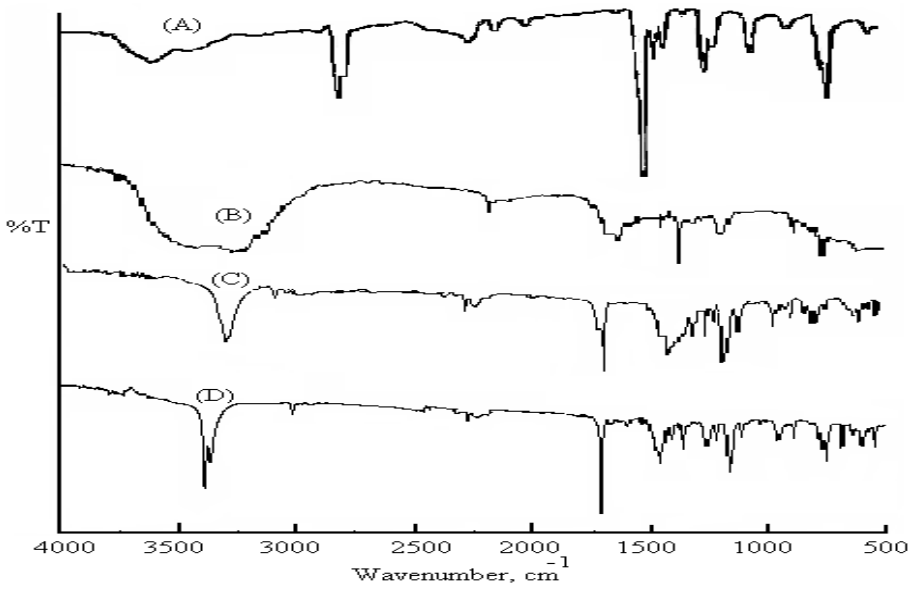


Fig.11 FT-IR of free TCNE (A) and its corresponding CT complexes D1-TCNE(B), D2-TCNE (C), and D3-TCNE (D).

Table 4

Characteristic infrared[a] frequencies (cm^{-1}) and tentative assignments for N-aryl-N'-isopropyloxycarbonylsulfamides, DDQ and their complexes.

DDQ	D1-DDQ	D2-DDQ	D3-DDQ	Assignments
	3251.95br	3212.55brm	3251.95br	ν(N-H)
	3262s			ν(N-H) D1
		3260.07s		ν(N-H) D2
			3275.50s	ν(N-H) D3

2253.82w	2244.13w	2244.13w	2244.13w	ν(C≡N)
1675.07s	1645.70m	1558.99w	1630.06m	ν(C=O)
	1764.90s			ν(C=O) D1
		1710.55 s		ν(C=O) D2
			1710.55s	ν(C=O) D3
1554.92m	1458.06w	1458.06s	1448.11w	ν(C=C)
	1465.63s			ν(C=C) D1
		1509.03m		ν(C=C) D2
			1455.99m	ν(C=C) D3
1174.03s	1196.15w	1176.62m	1186.56w	ν(C-C)
	1162.87s			ν(C-C) D1
		1170.58s		ν(C-C) D2
			1170.58s	ν(C-C) D3
	1337.24w	1277.54m	1354.29w	ν(SO_2)
	1287.49w	1065.74w	1267.59w	
	1344.44m			ν(SO_2)D1
	1101.11m			
		1455.99m		ν(SO_2)D2
		1101.15m		
			1355.99m	ν(SO_2) D3
			1262.66m	
887.35s	770.07m	770.07m	770.07m	ν(C-Cl)

[a]s, strong; w,weak ; m,medium; br, broad.

Table 5

Characteristic infrared frequencies (cm^{-1}) and tentative assignments for TCNE and it's CT complexes with N-aryl-N'-isopropyloxycarbonylsulfamides.

TCNE	D1-TCNE	D2-TCNE	D3-TCNE	Assignments
	3453.80br	3251.95m	3271.85mbr	ν(N-H)
2257.97brw	2224.23w	2254.18w	2224.23w	ν(C≡N)
	1630.06s	1711.08s	1721.03s	ν(C=O)

1535.63m	1438.16m	1458.06 m	1469.48m	ν(C=C)
1146.70m	1166.66ms	1267.59ms	1358.56 m	ν(C-C)
	1347.19w	1156.71m	1156.72w	ν(SO_2)
	1247.69w	1156.71m	1095.59w	

4. Conclusion

Charge-transfer interactions between three N-aryl-N'-isopropyloxycarbonylsulfamides as electron donors, and DDQ and TCNE as π-acceptors were studied by using zero and second order derivative UV spectrophotometry in four different solvents at different temperatures within the range 20-35°C.

The spectroscopic and thermodynamic parameters of 1:1 complexes such, as stability constants (K), molar extinction coefficients (ε_{CT}), ionization potentials (I_D), oscillator strengths (f), and transition dipole moments (μ_{EN}) were estimated. The results revealed that their values were influenced by the medium polarity, the substituent in benzene ring of N-aryl-N'-isopropyloxycarbonyl, and the acceptor nature.

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Host-guest interaction between 3,4-dihydroisoquinoline-2(1*H*)- sulfonamide and β-cyclodextrin: Spectroscopic and molecular modeling studies

Abstract

The inclusion complex of 3,4-dihydroisoquinoline-2(1*H*)-sulfonamide with β-cyclodextrin was investigated experimentally and by molecular modeling studies. The stoichiometric ratio of the complex was found to be 1:1 and the stability constant was evaluated using the Benesi - Hildebrand equation. Estimation of the thermodynamic parameters of the inclusion complex in vacuum showed that it is an enthalpy driven process phase and an enthalpy–entropy co-driven process in aqueous solution, which is in accord with the experimental results.

Semi-empirical calculations using PM3, PM6 and ONIOM2 methods, in vacuum and in water, were performed. The energetically more favorable structure obtained with the ONIOM2 method leads to the formation of intermolecular hydrogen bonds between sulfonamide and β-cyclodextrin. These interactions were investigated using the Natural Bond Orbital (NBO).

Keywords

3,4-Dihydroisoquinoline-2(1*H*)-sulfonamide; β-Cyclodextrin; Inclusion complex; Molecular modeling.

1. Introduction

Cyclodextrin (CD) chemistry has caused much interest, not only due to its applications in pharmaceutical science and technology but also because the inclusion represents an ideal model mimicking enzyme–substrate interactions [1,2]. Furthermore, the study of host -guest interaction may lead to a better understanding of some fundamental topics (i.e. the nature of the hydrophobic and hydrophilic interactions). Cyclodextrins (CDs) are torus shaped water soluble cyclic oligosaccharides composed of relatively non-polar internal cavity [3]. The cyclic oligosaccharide contains six, seven, and eight glucopyranose units and they are called α-CD (cyclohexaamylose), β-CD (cycloheptaamylose) and γ-CD (cyclooctaamylose) [4,5].
Nevertheless, β-CD (Fig. 1) is by far the most widely used compound owing to the optimal size of its internal cavity (8 Å), the most accessibility, and the lowest price for the encapsulation of molecules [6].

The resultant inclusion complexes can induce modification of the physicochemical properties of the 'guest' molecules, particularly in terms of water solubility and solution stability [7–9]. Therefore, it is important to clarify the structures of the inclusion complexes from a viewpoint of enzyme-substrates within the hydrophobic cavities of CDs [10].

The sulfonamide group is considered as a pharmacophore, which is present in number of biologically active molecules, particularly antimicrobial agents [11]. It was shown that sulfonamide moieties can enhance largely the activity of antibacterial agents especially against both Gram-positive and Gram-negative bacteria [12]. Mainly, (3,4-dihydroisoquinoline-2(1*H*)-sulfonamide (SUL) is a variety of modified molecules (Fig. 1) which contains sulfonamide group used in several types of pharmacological agents possessing antibacterial [13,14], antidiabetic [14], antitumor [15], anticarbonic anhydrase [16], anticonvulsant [17] or protease activities inhibitor [18] among others.
However, their poor aqueous solubility has hindered their application in the therapy as pharmaceutical formulations. Furthermore, the sulfonamides exhibit interesting solid state

properties. Among them, the ability to exist in two or more polymorphic forms through the propensity for hydrogen bonding due to the presence of various hydrogen bond donors and acceptors [19].

Hence, the present work is designed to investigate the complexation of sulfonamide/β-CD through spectroscopic techniques. The stoichiometric ratio and stability constant of the complex were studied and its thermodynamic parameters were obtained.

In the second part, we performed a detailed theoretical study focused on the modeling of the molecular interactions of β-CD molecule and the evaluation of the interaction energies. An intensive investigation of the 3D geometry of this complex is carried out using semi-empirical chemical calculations.

2. Experimental

2.1. Materials

The Title compound was synthesized according to the procedure described in the literature [20]. β-CD was purchased from Sigma. All used chemicals were of high purity (analytical grade). Double-distilled water was used throughout. The solutions were prepared just before taking measurements. The concentration of the sulfonamide solutions was ranging from the order of 10^{-3} to 10^{-4} M. The concentration of β-CD was varied from 10^{-3} to 10^{-5} M. The experiments were carried out at room temperature.

2.2 Inclusion complex preparation

To a stirred saturated solution of β-CD in water (2%) was added drop wise a solution of sulfonamide (1 equiv.) in methanol: water system (10:90, v/v). The mixture was stirred vigorously for 24 h at room temperature. The solution became turbid and the resulting solid was separated and dried under vacuum

2.3. Instruments

The electronic absorption spectra were recorded in the range 400–220 nm using a Jasco UV-Vis.V530 spectrophotometer equipped with a Jasco EHC-477S thermostat (±0.1 °C) using 1.0 cm matched quartz cells. FT-IR spectra of the reactants and the formed complex were recorded as KBr pellets using Spectrum one Perkin Elmer FT-IR.

3. Molecular modeling

The theoretical calculations were performed using the Gaussian 09 program [21] and MOPAC 2012 [22]. The structure of sulfonamide was constructed using Hyperchem 7.5 molecular modeling package [23]. The initial structure of β-CD was built with CS Chem3D Ultra (Version8.0) from the crystal structure [24]. Then, the two sulfonamide and β-CD structures were optimized by PM3, PM6 semi-empirical methods (Fig. 1). These geometries were always used in all calculations of host–guest complexes.

In order to simulate the inclusion process, the glycosidic oxygen atoms of the β-CD were placed on the YZ plane and their center was defined as the center of the coordination system. The β-CD was then maintained in this position while the guest molecule was introduced along the X-axis into the cavity of the β-CD.

The relative position between the host and the guest molecule was measured by the distance along the X-axis (Fig. 2) of the sulfonamide with labeled carbon atom to the coordinate center. Two possible orientations of the guest molecule in complex were considered. Then the guest was moved into the β-CD cavity along the X-axis from -7 to +7 Å with 1 Å step. The generated structures at each step were optimized with PM3 and PM6 methods. In order to find an even more stable structure of the complex, the guest molecule was rotated around X-axis by 20° from 0° to 360°.

For the PM3, PM6 optimized equilibrium geometries of the β-CD/SUL complex, DFT/B3LYP and RHF single point calculations with the split-valence 3-21 G* and 6-31G* basis set and thermodynamic analysis were performed in vacuum. The solvent effects on

the conformational equilibrium have been investigated using the PCM model for water (ε = 78.39) as a solvent with PM6 methods.

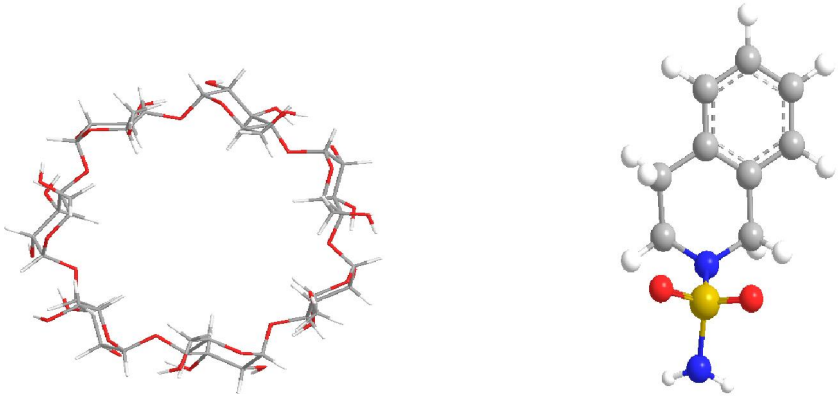

Fig. 1 Geometrical structures of sulfonamide and β-CD optimized at PM3 method.

The more stable complex found by PM3 and PM6 calculations were optimized using a hybrid approach developed by Morokuma and others [25], called the ONIOM method, which means ‘‘Our own N-layer Integrated molecular Orbital and molecular Mechanics’’. This hybrid method allows a partition of the molecular system into two, three or more layers, and distributes the computational methods (MO or MM) among these layers. In the terminology of Morokuma [26, 27], the full system is called ‘‘real’’ and is treated with the two low and high levels given by the theory. Total energy E^{ONIOM} is then expressed by the equation below:

$$E^{ONIOM} = E\ (high;\ model) + E\ (low;\ real) - E\ (low\ -\ model) \quad (1)$$

Finally the interaction between sulfonamide and β-CD structures is quantified on the basis of an NBO population analysis. The NBO calculations were performed using NBO 3.1 program, as implemented in the Gaussian 09 package, to understand various second-order interactions between the filled orbitals of one subsystem and vacant orbitals of another subsystem, which is a measure of the intermolecular delocalization on hyperconjugation [28].

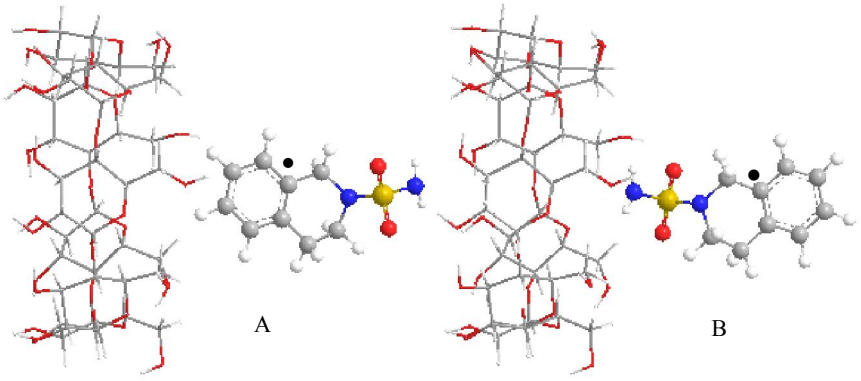

Fig. 2 The proposed structures of the sulfonamide/β-CD complex for (A) orientation 1, and (B) orientation 2.

4. Results and discussion

4.1. Absorption measurements

Fig.3. shows absorption spectra of sulfonamide solution (2.5×10^{-5} M) containing various concentrations of β-CD. Upon the addition of β-CD, the absorption peak at 264 nm increases in intensity. This finding indicates the formation of a new species, probably an inclusion complex.

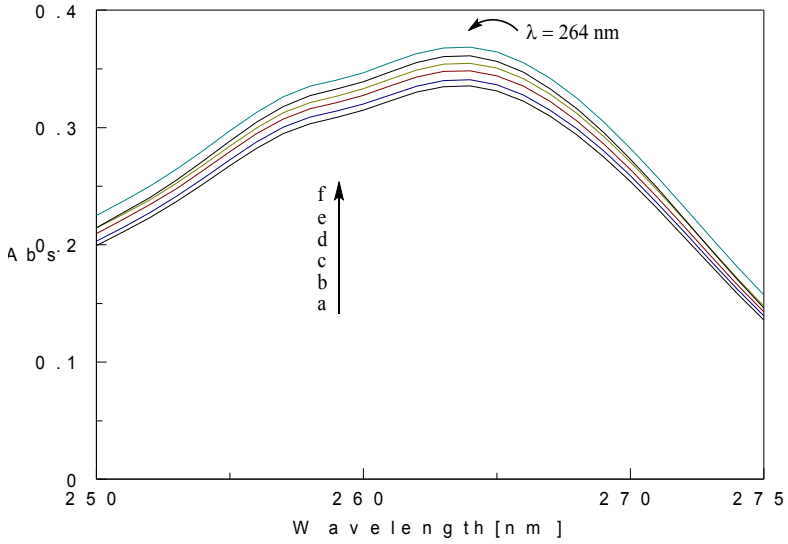

Fig. 3 Absorption spectra of sulfonamide ($2{,}5.10^{-4}$ mol.dm^{-3}) containing various concentration of β-CD: a (0) , b (10^{-5} M), c(4.10^{-5} M), d(6.10^{-5}M), d (8.10^{-5}M), e (10^{-5} M), f ($2{,}5.10^{-4}$ M).

4.2. Stoichiometric of the inclusion complex

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 [29].
The experiments use stock solutions with equimolecular concentrations of Host and Guest components. The samples are prepared by mixing different volumes of these two solutions in such a way that the total concentration [Host]+[Guest] remains constant and the molar fraction of the guest varies in the range 0–1 [30].
A 1:1 ratio of complex was determined for the host- guest interaction (Fig.4).

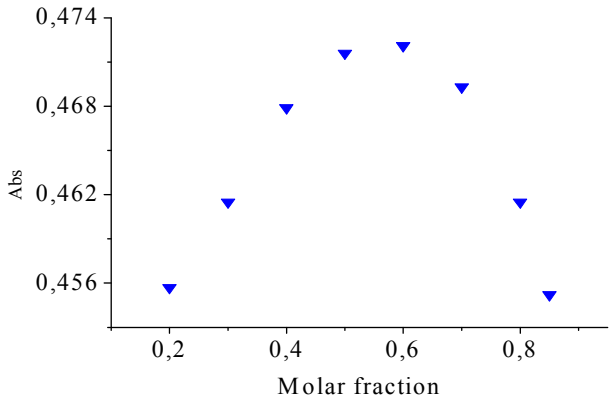

Fig. 4 The plot of Job's method for sulfonamide with β-CD.

4.3 Determination of the composition of the complex and its stability constant

The stability constant (K) of the host-guest complex has been determined in aqueous solution at different temperatures, using Benesi - Hildebrand [31] equation for cell with 1 cm optical path length:

$$\frac{[\beta-CD]_0[SUL]_0}{Abs}=\frac{[SUL]_0}{\varepsilon_C}+\frac{1}{K\varepsilon_C} \qquad (2)$$

With $Abs = d - d^0_{\beta-CD} - d^0_{SUL}$, $[\beta-CD]_0$ and $[SUL]_0$ as the initial concentrations of the cyclodextrin and the guest respectively. 'd' is the absorbance of the β-CD-sulfonamide mixture at some suitable wavelength (λ_{max}) against the water as reference and $d^0_{\beta-CD}$, d^0_{SUL} are the absorbances of the cyclodextrin and sulfonamide solutions with the same molar concentrations, as in the mixture at the same wavelength. The quantity $\varepsilon_C = \varepsilon - \varepsilon_{\beta-CD} - \varepsilon_{SUL}$ refers to the correction of the molar extinction coefficient of the complex and $\varepsilon_{\beta-CD}$, ε_{SUL} being those of the host and guest respectively at λ_{max}. K is the stability constant of the complex. Eq.(2) is valid under the condition $[SUL]_0 >> [\beta-CD]_0$. The obtained data throughout these calculations are translated by plotting the values of $[\beta-CD]_0[SUL]_0/Abs$ against $[SUL]_0$ values. A straight line is obtained with a slope of $1/\varepsilon_C$, and an intercept of $1/K\varepsilon_C$ on the ordinate as shown in (Fig.5).

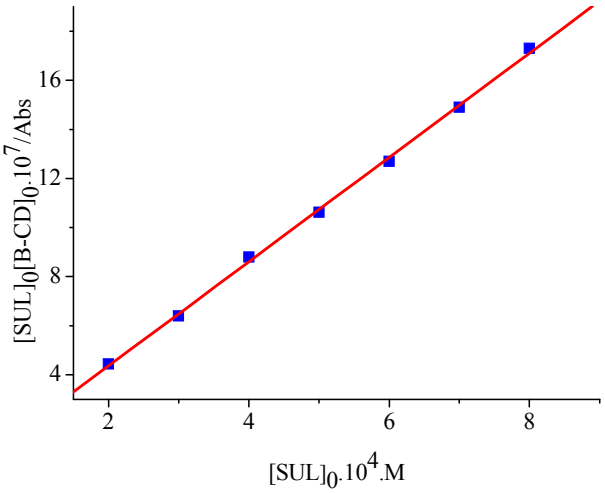

Fig. 5 Benesi Hildebrand plot for sulfonamide/ β-CD complex at 25°C.

Apparent stability constants (K) of the inclusion complex between sulfonamide and β-CD at different temperatures are presented in Table 1**.**

Table 1
Stability constants (K) of the inclusion complex between sulfonamide and β-CD at different temperatures.

Temperature (K)	Linearity (R)	Stability constant
288	0.99924	$1.09 \times 10^5 \pm 220$
293	0.99959	$8.9 \times 10^4 \pm 150$
298	0.99947	$7.3 \times 10^4 \pm 130$
303	0.99935	$5.98 \times 10^4 \pm 120$

4.4. Thermodynamic parameters involved with the formation of the inclusion complex

The thermodynamic parameters such as enthalpy change (ΔH°), entropy change (ΔS°) and free energy change (ΔG°) of the complexation reaction were determined from the van't Hoff plot (Fig. 6) [32, 33]. The temperature dependence of the equilibrium constant was studied at different temperatures (288, 293, 298 and 303 K). The thermodynamic parameters were evaluated using the following equation:

$$\ln K = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \qquad (3)$$

$$\Delta G^\circ = \Delta H^\circ - T\,\Delta S^\circ \qquad (4)$$

Where K and R are the equilibrium, and gas constants, respectively. Calculated thermodynamic parameters from the van't Hoff plot using the above mentioned equations are listed in Table 2.

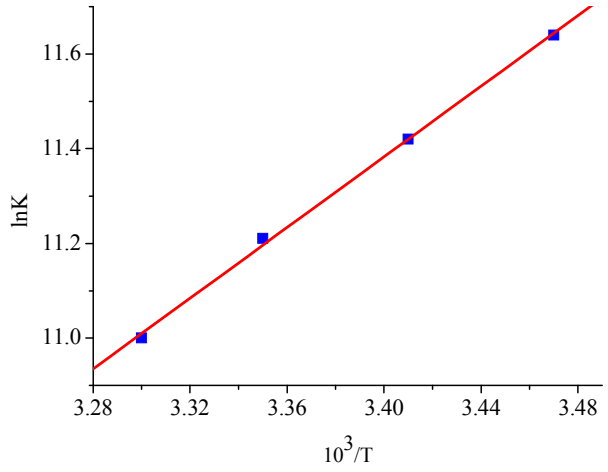

Fig. 6 van't Hoff plot for the inclusion complex of sulfonamide with β-CD in water.

Table 2
Thermodynamic parameters of inclusion complexes between β-CD and sulfonamide.

ΔH° (kcal/mol)	-7.42 ± 0.5

ΔS° (cal/mol.K)	2.58 ± 0.1
ΔG°(kcal/mol)	- 8.13 ± 0.6

It has been generally accepted that the main driving forces for complexation are hydrophobic interactions, van der Waal's interactions, release of high-energy water molecules from β-CD cavity and hydrogen bonding [34]. Hydrophobic interaction essentially involves a favorable positive entropy to gather with a slightly positive enthalpy change, while the other forces involve negative ΔH° and ΔS°. As revealed in Table 1, complexation of sulfonamide with β-CD in aqueous solution is associated by a negative ΔH°, reflecting a spontaneous, exothermic process. The ΔS° positive value is due to the breaking of highly ordered aqueous microenvironments surrounding the hydrophobic part of the guest molecules upon the binding of CD [35]. ΔG° is negative, which suggests that the inclusion process proceeded spontaneously.

Large negative enthalpy (ΔH°) changes are usually attributed to strong van der Waal's interactions and formation of hydrogen bonds between host and guest. These changes indicate a strong size and shape complementarity as well as formation of hydrogen bonds between sulfonamide and β-CD.

4.5. FT-IR spectra

The variation of the shape, shift, and intensity of the IR absorption peaks of the guest or host can provide enough information for the occurrence of the inclusion [34]. FT-IR spectra of sulfonamide (A), β-CD (B), and inclusion complex sulfonamide /β-CD (C) are presented in (Fig. 7). Although, if sulfonamide and β-CD form a inclusion complex, the non-covalent interactions between them such as hydrophobic, van der Waal's interactions and hydrogen bonds will lower the energy of the included part of sulfonamide, reduce the absorption intensities of the corresponding bonds. Based on these considerations, we noticed that the differences between spectra of sulfonamide, and inclusion complex. For example, absence of sulfonamide bands in the region 3500–4000 cm^{-1}, demonstrating that the aniline NH_2, is involved in the interaction process. The intensity and the shape of these bands changed dramatically for the inclusion compound as compared to those for pure sulfonamide and β-CD, indicating the formation of an inclusion complex.

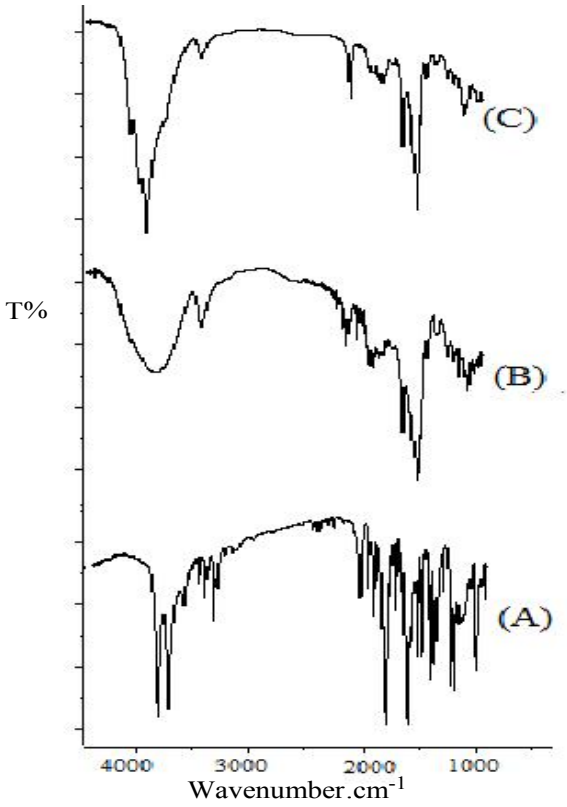

Fig. 7 FT-IR spectra of (A) sulfonamide, (B) β-CD, and (C) the inclusion complex of sulfonamide/β-CD.

4.5. Molecular modeling studies

4.5.1. Semi-empirical results

The energy change occurring with the formation of the sulfonamide/β-CD complex defines the complexation energy $E_{complexation}$ during the inclusion process and makes it possible to find the most stable structure between all the configurations under study. It can be calculated using the below equation (5):

$$E_{complexation} = E_{complex} - \left(E_{free-guest} + E_{free-host}\right) \qquad (5)$$

Where $E_{complex}$, $E_{free-guest}$ and $E_{free-host}$ represent respectively the HF energy of the complex, the free optimized β-CD and the free optimized sulfonamide energy.

The greatest negative values of complexation energies correspond to the most stable complexes formed in vacuum and in water.

Fig.8 depicts the variations of complexation energy in the inclusion process of sulfonamide into β-CD at different distances by considering orientation 1 and 2 from PM3 and PM6, respectively. The variation of the complexation energy during the inclusion process indicated that the complexes adopt inclusion geometry in which the sulfonamide structure is completely embedded inside the β-CD cavity. It can be understood that the guest exactly fitted in the cavity of β-CD.

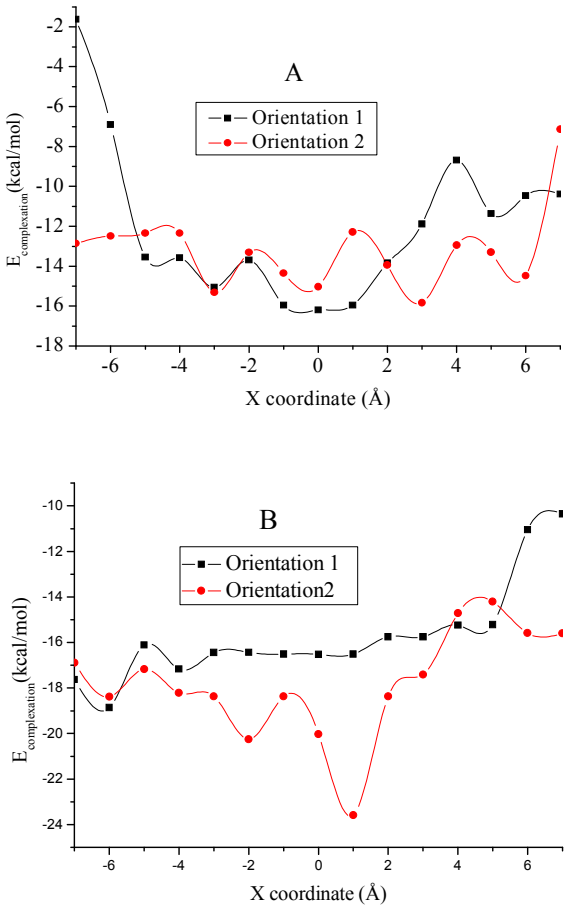

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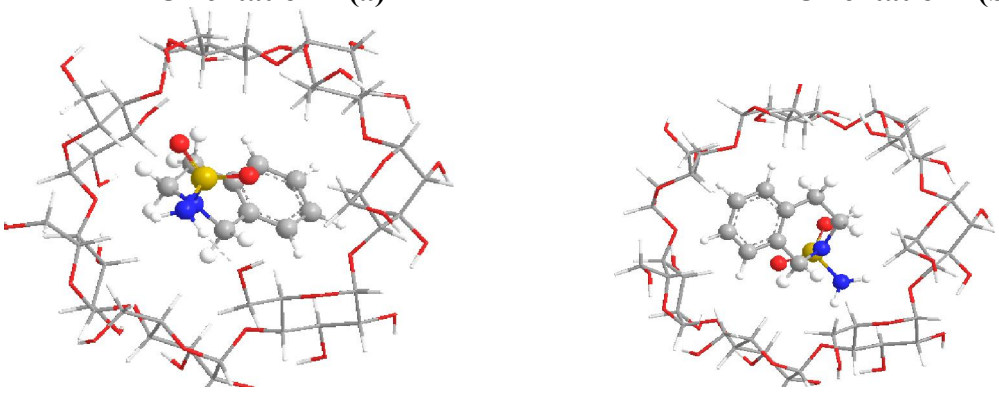
Fig. 8 Complexation energy sulfonamide/β-CD complex versus coordinate X (Å) in vacuum, calculated by PM3 (A) and PM6 (B) methods.

The complex energy value calculated with PM3 is higher than that calculated with PM6. On the other hand the most stable structure of SUL/β-CD is reached at X = 0 and -6 Å for the orientation 1. At this point, the complexation energy is –16.04 and -18.86 kcal/ mol from PM3 and PM6, respectively. For the orientation 2, the optimum position was found at 3 and 1Å, with complexation energy is –15.83 and -23.59 kcal/mol from PM3 and PM6, respectively (Fig. 9).

.

Orientation 1 (a) **Orientation2 (b)**



Orientation 1 (à) **Orientation 2 (b')**

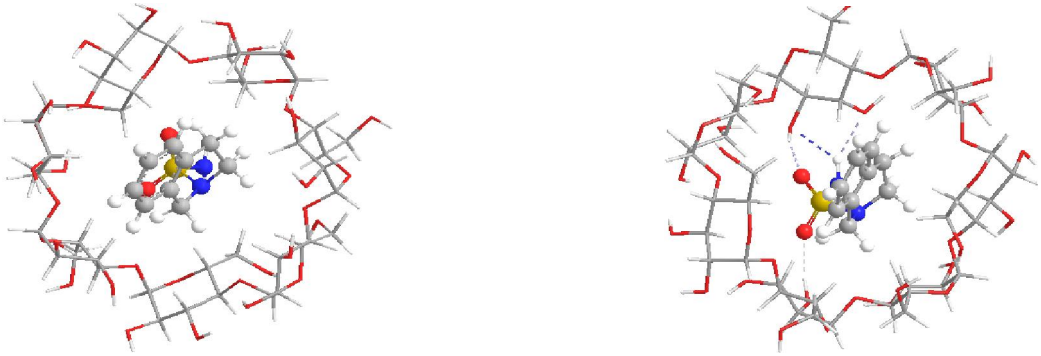
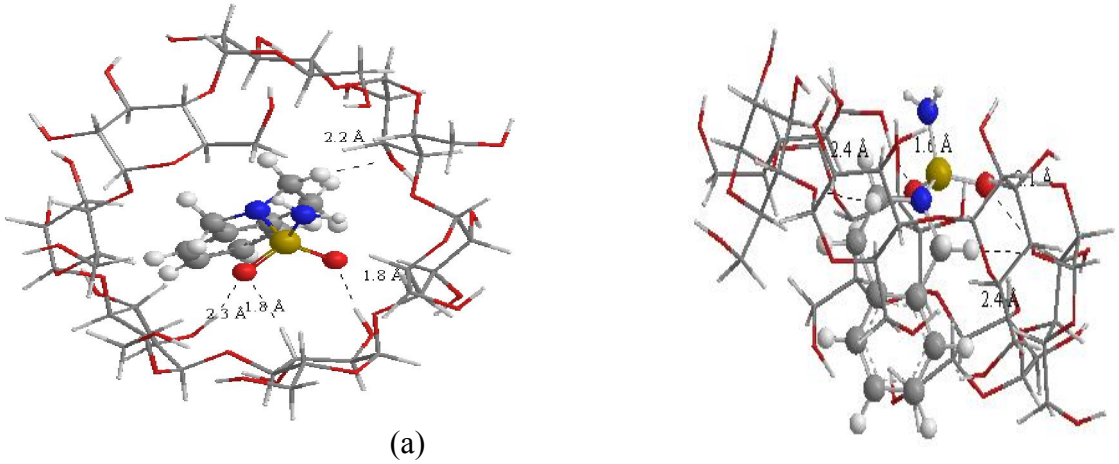


Fig. 9 Geometrical structures of the most stable sulfonamide/β-CD inclusion complexes.a) and b) correspond respectively to orientation 1 and 2 from PM3 calculation. a') and b') correspond respectively to orientation 1 and 2 from PM6 calculation.



(a)

(b)

Fig. 10 Geometrical structures optimized at ONIOM2 for sulfonamide/β-CD complexes: (a) orientation 1 and (b) orientation 2.

The deformation energy is the change in energy of each species as a result of complexation and is the difference between the optimized geometry energy and the energy of the individual components in their complex geometry (E species in complex). These values were determined by decomposing the optimized complex and performing a single point energy calculation on each resulting species (Eq. (6)) [36]. The magnitude of the energy change would be a sign of the driving force towards complexation.

$$E_{deformation}\left(component\right) = E^{SP}_{component} - E_{component} \qquad (6)$$

The energetic features, thermodynamic characteristics of the obtained complex are summarized in Table 3

Table 3

Energies, thermodynamic characteristics calculations using PM3 and PM6 methods for

Energies (kcal/mol)	**SUL**	**β-CD**	**Orientation 1**	**Orientation 2**
In vacuum				
PM3				
E^a	-54.40	-1456.73	-1527.19	-1526.98
$E_{complexation}$			-16.04	-15.83
$E_{deformation}$ (β-CD)			-3.36	-4.45
$E_{deformation}$ (SUL)			1.22	0.54
H°	81.33	-660.66	-586.93	-607.04
ΔH°			-7.59	-27 .71
G°	46.85	-783.64	-653.78	-687.82
ΔG°			83.01	48.97
ΔS°			-0.30	-0.25
PM6				
E^a	-55,01	-1568,16	-1642.03	-1646.76
$E_{complexation}$			-18.86	-23.59
$E_{deformation}$ (β-CD)			2.94	5.38
$E_{deformation}$ (SUL)			1.01	3.77
H°	73.91	-840.47	-817.71	-834.23
ΔH°			-51.15	-67.67
G°	40.08	-968.39	-909.49	-922.32
ΔG°			18.82	5.99
ΔS°			-0.23	-0.24
In water				
PM6				
E^a	-67.54	-1597.82	-1675.51	-1677.63
$E_{complexation}$			-10.15	-12.27
ΔS^c			0.46	0.44

E^a is the HF energy. $\Delta Å = A_{complex} - (A_{\beta-CD} + A_{Sul})$, A=H,G or S at P=1 atm and T=298.15 K. $E_{deformation}$ is the deformation energy. ΔS^c is the entropy change considered the effect of H_2O molecules.

Table 4
Single point energies in kcal/mol of the orientation 1 and 2 calculated at B3LYP/3-21G* and HF/3-21G* in vacuum and in water.

Energies (kcal/mol)	SUL	β-CD	Orientation 1	Orientation 2
In vacuum				
HF/3-21G*				
E^a	-626477.92	-2652869 .20	-3279351.74	-3279551.29
$E_{complexation}$			-4.62	-204.17
HF/6-31G*				
E^a	-629609.28	-2666441.80	-3296039.68	-3295989.12
$E_{complexation}$			11.41	61.96
B3LYP/3-21G*				
E^a	-629248.03	-2667911.83	-3297182.52	-3297124.89
$E_{complexation}$			-22.65	34.97
In water				
HF/3-21G*	-626458.83	-2652926.77	-3279407.81	-3279591.21
E^a			-22.21	-205.61
$E_{complexation}$				
B3LYP/3-21G*	-629221.04	-2667938.23	-3297224.70	-3297169.75
E^a			-65.43	-10.48
$E_{complexation}$				

Investigation of the deformation energy of the guest by PM3 methods (as shown in Table 3), interestingly demonstrated that the SUL molecule for orientation 1 requires slightly more energy for conformation adaptation upon binding within the cavity of β-CD than that of the orientation 2 as indicated by the $E_{deformation}[G]$ of about 1.22 and 0.54 kcal mol^{-1}, respectively. While the guest deformation energy is important in the orientation 2 from PM6 methods (3.77 kcal/mol). This can be supported by the fact that flexibility of the guest structure is an important structural requirement for β-CD upon complexation.

When the solvation effect is taken into consideration, the complexation energy from the PM6 calculation becomes larger than its calculated value in vacuum. This confirms that the orientation 2 is much stable than the orientation 1. On the contrary, the calculated single point energies using HF/3-21G* and B3LYP/3-21G* are lower than corresponding values in vacuum (Table 4).

With regard to the obtained results from statistical thermodynamic calculation at 1 atm and 298.15 K, we noticed that in vacuum both PM3 and PM6 methods predict that, complexation reactions of sulfonamide with β-CD are exothermic judged from the negative enthalpy changes suggesting that these inclusion processes are enthalpy driven in nature.

The theoretically calculated Gibbs free energy change using PM3 and PM6 calculations are positive magnitude, suggesting that the inclusion reaction was non-spontaneous.

As compared to the ΔS° values obtained by experimental methods (2.58 cal/mol.K), this value is completely different in sign and magnitude from the theoretically obtained value. This difference in results is justified by the fact that the solvation of the water molecules by the environment that takes place after inclusion is neglected in our semi empirical calculations. Thus, we must include the solvent effect to rationalize our harmonic frequency calculations.

However, since the inclusion reaction happened in aqueous solution, the influence of water molecules on the inclusion process should be very important and the effect of H_2O molecules mainly concentrates on ΔS by our calculation. Because of the limitation of our computer, it can hardly calculate the interaction of β-CD system in aqueous solution. Fortunately, it is known that there are approximately seven water molecules encapsulated in the cavity of β-CD molecule [24,37,38] and they will be released when the guest molecule enters into the cavity of β-CD. Based on this consideration, a reasonable model is built to calculate ΔS of the inclusion complex in aqueous solution. This model is proposed based on the following assumption: the effect of H_2O molecules on the entropy change of the SUL/β-CD system is mainly determined by the H_2O molecules in the cavity of β-CD and the effect of the H_2O molecules out of the cavity is less important and thus can be negligible.
Therefore, the entropy change values for the hydrated complex were calculated according to:

$$SUL + \beta\text{-CD}.7H_2O \longrightarrow SUL: \beta\text{-CD} + 7H_2O$$

So, the entropy changes in aqueous solution become 467.26 cal/K.mol and 448.38 cal/K.mol (PM3) for orientation 1 and 2 , respectively. This indicates that the formation of the complex becomes an enthalpy–entropy co-driven process in aqueous solution (Table 3).

4.5.2 ONIOM2 calculations

In order to further understand molecular recognition between the guest and the host, we adopted ONIOM2 methods. In this hybrid model study, we submitted the host molecule β-CD to the low level of quantum calculations (PM3 and PM6) since we assumed it provides only an environmental effect and contains the larger number of atoms, while the guest molecule sulfonamide is treated at a high level of calculation (RHF/3-21G*). All calculations were carried out according to procedure reported in the literature [39].
Table 5 emphasizes the computational results of the ONIOM2 study.

The ONIOM2 results show that the energy of orientation 2 from PM6 is more negative, allowing it to be the must preferred orientation.

Table 5

4.5.3 Natural Bond Orbital (NBO) analysis

Inclusion complexes were stably formed via intermolecular weak interactions such as van der Waal's, electrostatic, and hydrogen bond interaction, etc. Hydrogen bond interaction is much stronger than van der Waal's interaction. Two types of hydrogen bonds such as

O–H…..O and C–H….O interactions have been considered. The cut-off criteria of O…O distance for O–H…O interaction were no more than 3.2 Å [40]. The cut-off criteria of C…O distance for C–H….O interaction were no more than 3.5 Å [40]. The angles of hydrogen bonds belonged to 90–180°.

The formation of a hydrogen bonded complex implies that a certain amount of electronic charge is transferred from the proton accepter to the proton donor [41]. Delocalization effects can be identified from the presence of diagonal elements of the Fock matrix in the NBO basis. The strengths of these delocalization interactions $E^{(2)}$ are estimated by second order perturbation theory [42].

The selected electron donor and acceptor orbitals, and their corresponding second-order interaction energies $E^{(2)}$ indicate the intensity of the interaction between the electron donor and acceptor orbitals. Thus, the greater value of $E^{(2)}$, the more tendency of a higher donor orbital [43].

The stabilization energies $E^{(2)}$ calculated using RB3LYP/3-21G* method and the geometric parameters of the established H-bond in the inclusion complex are presented in Table 6. The structures of the energy minimum obtained with ONIOM2 (RHF3-21G* :PM6) method show the presence of several intermolecular hydrogen bond interactions, as shown in (Fig. 10). In the orientation 2, the sulfonamide is included deeply in the β-CD cavity.
In this disposition, the oxygen atom (O73) establishes two hydrogen bonds: the first as proton acceptor (O73···H173–N161) located at 2.3 Å with an angle equal to 137.8° and the second as proton donor (O73–H145···O159) positioned at 1.6 Å with an angle of 151.5°. The interaction energy for the first hydrogen bond (1.68 kcal/mol) was lower than the second (14.25 kcal/mol).

At the same time, several C–H···O hydrogen bonds were established between sulfonamide and β-CD. Sulfonamide plays the role of donor for example the carbon atoms (C154) and (C150) to the oxygen atoms (O60) and (O62) of β-CD (C154–H167···O60 and C150–H164···O62). The interaction energies of these C–H···O hydrogen bond are 1.49 kcal/mol and 0.94 kcal/mol respectively. These values are typical of weak hydrogen bonds according to the values of conventional hydrogen bonding (the C–H···O bond energies were around 0.5–2 kcal/ mol). While atom (O160) of sulfonamide establishes a very strong intermolecular H-bond with hydrogen atom (H133) of O53-H133 bond, and with stabilization energy $E^{(2)}$ equal to 9.09 kcal/mol.

For orientation 1, the guest molecule is partially incorporated in the cavity. In this structure, two strong O···H–O hydrogen bonds are established. The first between oxygen atom (O159) and the hydrogen atom (H139) of the O63–H139 bond located at 1.8 Å with an angle equal to 169.9° with stabilization energy $E^{(2)}$ equal to 6.84 kcal/mol and the second between O160 and hydrogen atom (H136) of the O58-H136 with $E^{(2)}$ equal to 10 kcal/mol .

Table 6
Figure 10

5. Conclusion

The formation of the inclusion complex of sulfonamide with β-CD was analyzed using spectroscopic techniques. The complex was found to present a 1:1 stoichiometry. The formation constants of the complex in water (K) were determined. The thermodynamic parameters, ΔH°, ΔS° and ΔG°, were determined by analyzing the variation of lnK with the inverse of the temperature. The obtained results indicate that the encapsulation process is favored by both negative enthalpy and positive entropy changes. These thermodynamic parameters were also calculated with the PM3 in aqueous solution, which is in accord with the experimental results. Two possible orientations for the inclusion of the sulfonamide in the β-CD were considered, and the orientation 2 was determined to be the most favorable one from PM6 methods in vacuum and in water. ONIOM2 and NBO analysis reveals that intermolecular hydrogen bond is the main driving force of formation of inclusion complex. Finally, it is important to note that the enthalpy and entropy changes suggest that the

formation of the inclusion complex is an enthalpy-driven process in gas phase and an enthalpy–entropy co-driven process in aqueous solution, which is in accord with the experimental results.

Acknowledgements
This paper was supported in part by PNR (08/U24/2011). We acknowledge the Algerian Ministry of Higher Education and Scientific Research and General Direction of Scientific and Technologic research for financial support. We thank Miss Rym MERABET for language assistance.

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2. Travaux soumis pour publication

2.1 Docking theoretical study of N-sulfamoyloxazolidinones with β-cyclodextrin

Abstract

Host-guest interactions of a series of N-sulfamoyloxazolidinones with β-cyclodextrin have been investigated with molecular modeling, using the semi-empirical PM3 method, the quantum hybrid ONIOM/2 method, and NBO analysis. The complexes stabilities are influenced by the orientation and the nature of the substituted group in the phenyl of the guests. The ONIOM/2 method was used to confirm the most favorable inclusion complex structure. In vacuum, the inclusion reaction is an enthalpic process however in aqueous solution the reaction is enthalpic-entropic process. The NBO analysis demonstrate that the hydrogen bonds interactions are of type $C-H\cdots O$ with stabilization energies smaller than 2 kcal/mol indicating that the interactions between β-CD and N-sulfamoyloxazolidinones are weak.

Keywords: N-sulfamoyloxazolidinone; β-cyclodextrin; molecular docking studies; PM3 semi-empirical method; solvent effect; ONIOM calculation , NBO analysis; hydrogen bonds

2.2 Theoretical study of Diclofenac with β-cyclodextrin

Abstract

The inclusion interactions between β-cyclodextrin (β-CD) and diclofenac (DCF) were simulated using the semi-empirical PM3 and ONIOM (B3LYP/3-21g: PM3) methods.

The modeling results showed that the most stable geometry of DCF into β-CD complex is B orientation inclusion, in which the phenyl acetate moiety is included inside the hydrophobic cavity of β-CD. The results showed that the binding energy (BE) and total stabilization energy

(E^{ONIMO}) of B orientation are lower than A orientation, indicating that the B orientation is more stable than the A orientation. Furthermore, it can be deduced from the results obtained by NBO analysis that the main driving forces of DCF/β-CD are weak hydrogen bonding interactions.

Keywords:
Diclofenac,β-cyclodextrin,Inclusion complex, PM3semi-empirical method,ONIOM,NBO

3. Travaux en cours de finalisation

3.1 Evaluation de la capacité complexante de la β-CD avec le Gliclazide : Etude expérimentale et théorique

.

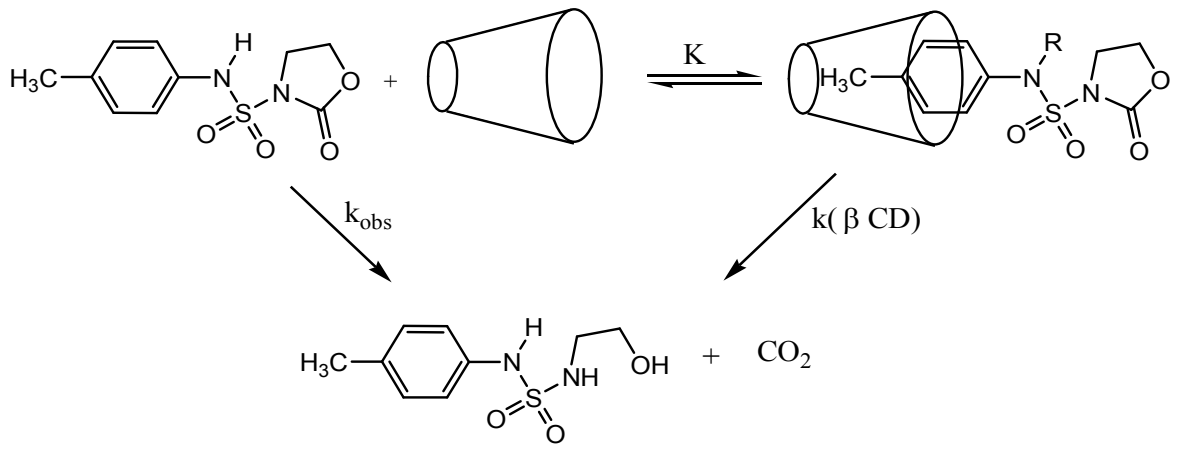
Résumé :

Les cyclodextrines (CD) sont des oligosaccharides cycliques ayant la capacité d'encapsuler entièrement ou au moins en partie, dans leur cavité hydrophobe, une large variété de molécules, formant des complexes d'inclusion. Ce processus d'intégration conduit à des changements dans les propriétés physico-chimiques de l'invité, telles que la solubilité, la vitesse de dissolution et la biodisponibilité.
Le gliclazide (GL) est un sulfamide hypoglycémiant de deuxième génération, largement utilisé pour le traitement des non-diabètes sucré insulino-dépendant. Il a une faible solubilité dans les fluides gastriques, qui détermine un taux de dissolution faible et la variabilité interindividuelle, donc sur sa biodisponibilité.
L'objectif de ce travail est l'évaluation de la capacité complexant d'un CD (B-cyclodextrine) avec le GL.
Le complexe d'inclusion a été étudiée expérimentalement (caractérisation par spectroscopie infrarouge IR et UV-Vis) et par étude de modélisation moléculaire.
Les interactions d'inclusion entre le gliclazide (GL) ont été simulées dans le vide à l'aide de la méthode semi- empirique PM6, ONIOM2 (DFT (B3LYP/6-31G) : PM6), ainsi que (HF/STO-3G) pour les calculs des fréquences
La structure la plus basse énergie obtenu (le complexe préféré) a montré que le groupement sulfonyle est totalement intégré dans le b-CD tandis que le carbamide reste en dehors de la cavité, qui en accord avec les résultats expérimentaux. Cette disposition préférée augmente les interactions intermoléculaires des liaisons H entre le b-CD /GL. Ceci est confirmé par l'analyse NBO.

Mots-clés : *B-cyclodextrine, gliclazide, inclusion, modélisation moléculaire*

3.2 Influence de la β-cyclodextrine sur la cinétique d'ouverture du cycle oxazolidinone.

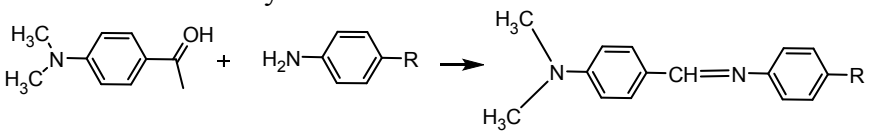
Résumé : Les sulfamoyloxazolidinones, dernière génération des sulfamides, comportent deux pharmacophores ce qui leur confère une activité biologique remarquable. Leur hydrosolubilité limite malheureusement leur biodisponibilité. L'un des moyens utilisé consiste à les insérer des cavités des macromolécules . Notre travail est une contribution à la mise en évidence des complexes d'inclusion par une technique directe : la spectrophotométrie UV-Vis et par une étude indirecte qui consiste à étudier la cinétique d'ouverture de cycle oxazolidinone en milieu basique en présence et en absence de la β cyclodextrine. Les résultats obtenus montrent que le complexe formé en solution est de stoechiométrie 1 :1. L'insertion de la molécule sulfamoyoxazolidinone dans la cavité macromoléculaire lui confère une certaine stabilité vis-à-vis de l'ouverture du cycle oxazolidinone .Comme l'insertion s'effectue par la partie aromatique), un composé comme le Bis (N-oxazolidinone) sulfone ne manifeste aucune influence à la présence de la β cyclodextrine.



Mots- Clés : Sulfamoyloxazolidinones ; cyclodextrines ; ouverture du cycle ; cinétique ; complexes d'inclusion.

3.3 Complexes d'inclusion et cinétique d'hydrolyse des imines : Etude expérimentale et théorique

Les imines d'intérêt ont été synthétisées selon le schéma réactionnel suivant :



(6 heures en reflux dans le MeOH)

I_1: R= Cl I_2: R=CH_3
I_3: R=NO_2 I_4: R=OCH_3
I_5: R=H

Ces composés sont généralement jaunes se présentent sous forme de paillettes, aiguilles et poudres, recristalisables dans le méthanol ou l'éthanol. Leurs points de fusion sont compris entre 100 et 200 °C. Ils sont solubles dans les solvants polaires, donnent des spots jaunes en CCM à la température ambiante et ils sont révélés à la vapeur d'iode.
Ces imines sont caractérisées en FTIR par les bandes de vibration à 1600-1620 cm^{-1} pour la liaison imine(C=N) et à1580-1595cm^{-1} pour les liaisons (C=C), ainsi que celles qui dues aux groupements (CH_3 aliphatiques)à 2800-3000cm^{-1}.

Visualisation de l'interaction avec la cyclodextrine

La complexation en solution a été suivie par spectroscopie UV-Visible à 20°C. La concentration des solutions utilisées de la β-CD (ou la 2HP β-CD) et des imines sont de l'ordre 10^{-5} M dans deux solvants le méthanol et le diméthylformamide. Les imines sont solubles dans les solvants polaires mais elles subissent le phénomène de protonation. Ce qui justifie le choix de solvants avancés.
L'interaction entre les molécules des imines et la cyclodextrine native ou modifiée se traduit par modifications dans des les allures spectres.
Pour chaque imine I_1-I_5 étudié, le spectre UV-visible est altéré par addition progressive de la β-CD native ou de la 2HP β-CD aux solutions d'invités.
La formation des complexes d'inclusion est caractérisée par un changement dans le maximum d'absorption, la diminution de l'absorbance de façon significative et l'apparition d'un point isobestique.
La figure montre le spectre d'absorption du composé I_2 (10^{-5}M) dans le DMF contenant des concentrations variées de β-CD.
L'addition de β-CD á la solution de l'invité I_2 produit une diminution de l' absorbance avec un changement dans le maximum d'absorptions à λ_{max} = 354 nm et l'apparition d'un point isobestique á λ = 278nm.

Détermination de la stoechiométrie

La stoechiométrie des complexes a été déterminée par la méthode des rapports molaires. En traçant les valeurs de l'absorbance en fonction des rapports molaires, le point d'inflexion correspond au rapport formé.

Les résultats montrent que le rapport molaire imines :CD est 1 :1 indépendamment de la nature de la molécule invitée.

Détermination des constantes de stabilité.

Les constantes de stabilité des complexes d'inclusion formés avec les imines et la β-CD ou la 2HP β-CD ont été déterminées par la méthode de Benessi-Hildebrand dans deux solvants différents (MeOH et DMF) à 20 °C.

Détermination des paramètres thermodynamiques

Les propriétés de complexation dépendent étroitement de la structure des molécules hôtes et invitées. Il est donc essentiel d'étudier les propriétés de la reconnaissance moléculaire pour toutes les molécules hôtes et invitées.

Les paramètres thermodynamiques (ΔG, ΔH, ΔS) associés à la formation du complexes d'inclusion entre la série de base de schiff I_1-I_5 et les deux hôtes(β-CD ,2HPβ-CD)ont été évalués moyennant les mesures spectrophotométriques à six températures différentes (10 , 15, 20, 25 , 30 et 35°C) dans deux solvants différents (MeOH ,DMF).

Au sein d'une même série les composés possédant les structures similaires, subissent un mécanisme réactionnel commun et le phénomène de compensation enthalpie – entropie est parvenu [6]. Dans la thermodynamique de la réaction d'inclusion de CD avec des molécules invitées, la variation d'enthalpie joue un rôle prédominant dans la variation de l'énergie libre et le processus d'inclusion qualifié de *processus sous contrôle enthalpique*.

La variation d'entropie dépend du degré de confusion du système. Généralement la diminution d'enthalpie est en faveur d'une réduction de l'enthalpie libre, et l'augmentation d'entropie entraîne également une réduction de ΔG.

Etude de l'influence de β-CD sur la cinétique d'hydrolyse des imines

L'hydrolyse de base des imines est largement étudiée par plusieurs auteurs . Le mécanisme global est une addition d'une molécule d'eau sur la double liaison C=N, suivie de la régénération des composés initiaux qui ont permis leur formation (composé carbonylé et l'amine corresponde) :.

$$\text{imine} + \text{eau} \rightleftarrows \text{amine} + \text{aldéhyde}$$

La réaction est du pseudo premier ordre.

Dans cette partie, nous étudions la cinétique d'hydrolyse des imines à différents PH en absence et en présence de la β-CD. Cette étude a pour but de mise en évidence de formation des complexes entre ces imines et la β-CD de manière indirecte, et de déterminer l'effet de β-CD sur la stabilité de ces imines (inhibition ou accélération d'hydrolyse) .

Bien que l'hydrolyse des imines subisse une catalysé généralisée, nous avons choisi uniquement les pH où en plus de l'hydrolyse , la complexation des imines est très favorisée (grande affinité de la cylodextrine pour les molécules neutres), ce qui justifie l'utilisation des solutions tampons pH=7.2 et pH=8.

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