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Investigate formation constant of some Amino Acids by *p*-sulphonato-calix (4) arene in Aqueous Solution

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ABSTRACT

The formation constants (log *K*), of the complexes formed between a number of amino acids (glycine , L-valine and L-alanine) with *p*-sulfonatocalix [4] arene at varying temperatures (25± 0.1 to 65 ± 0.1 °C) in aqueous solutions and at natural pH of p-sulphonato-calix [4] arene (pH=3.2) by means of UV-Vis spectrophotometeric technique have been investigated. At this pH the guest molecule is in its cationic and zwitterionic forms. The results revealed that the host is quite capable of complexing with the guest in 1:1 guest-to-host ratio. Regarding the formation constant values, the binding selectivity of the host towards the guests proves in the order (alanine > valine > glycine). The thermodynamic parameters have been assessed and interpreted in matters of the significance of the various interactions responsible for the complexation. A roughly linear relationship between ΔH^o and $T\Delta S^o$ has been observed for the studied complexes and it is discussed.

Keywords: p-Sulphonato-calix [4] arene; glycine; L-valine; L-alanine; Formation constant

INTRODUCTION

The calix-(n)-arenes are one of the three majors groups of organic macrocyclic host compounds in supramolecular chemistry [1]. Both their chemistry [2] and their complexation properties with respect to a wide range of ions [3] and small organic molecules [4] have been widely studied. Calixarenes and their derivatives as a host molecular in supramolecular chemistry have attracted considerable attention in host-guest chemistry owing to their excellent recognition ability [1].

In recent years work has been published on the use of calix-(n)-arenes as molecular skeletons for the development of bio-mimetic systems [5], for the study of their interactions with amino-acids [6, 7], proteins [8] and DNA [9]. Apparently, the outstanding receptor properties of functional calixarenes make them highly promising materials for sensor technology [10], radioactive waste management [11], pharmaceutical science [12], and analytical application [13, 14].

The water soluble *p*-sulphonatocalix (n) arenes (n=4, 6, 8) were synthesized mainly by Shinkai *et al.* [15] and Ungaro *et al.* [16] are able to recognize compounds of biological interest in aqueous solutions. The complexation properties of water-soluble calixarenes towards organic ions [4], amino acids[17],

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small neutral organic molecules, such as alcohols, ketones and nitriles[18] in aqueous solution have been extensively verified by ^{1}H NMR spectroscopy, calorimetric and microcalorimetric titration [19, 20]. The obtained results display that the inclusion capabilities of the investigated hosts are correlated with their conformational properties [18]. The studies have expressed that *p*-sulphonatocalix (4) arene is able to complex α-amino acids by inserting the aromatic or aliphatic group into the calix- arene cavity [17]. The water-soluble *p*-sulphonated calix (*n*) arenes (SC*n*A, *n* = 4, 6, 8) derivatives display wider applications in supramolecular chemistry science in that they allow the study of host-guest interactions in a solvent where most biological processes take place[4, 21-23].

The amino acids, as fundamental constituents of large and diverse categories of biological macromolecules evince attractive targets in the supramolecular chemistry. It is well known that the properties of the amino acids in aqueous solution is of utmost significance in developing the synthesis processes, their purification and separation, as well as in elucidating the principles of transport through biological membranes [24].

The complexation of basic amino acids arginine and lysine by *p*-sulphonatocalix (4) arene by means of ^{1}H NMR spectroscopy [25] and microcalorimetry [26] has witnessed that have been formed 1 : 1 complexes between these amino acids and calixarene in water. In a similar reasoning, the study of the complexation of *p*-sulphonatocalix (4) arene with some amino acids as guests by the use of reversed- phase high-performance liquid chromatography (RP-HPLC) and ^{1}H NMR experiments has been reported [27]. The results obtained suggest that variant interactions, like as hydrophobic, ion-pairing, aromatic-aromatic and electrostatic may occur between the amino acids under study and *p*-sulphonatocalix (4) arene. Depending on a macrocyclic cavity size, binding sites, solvent used and substituents at upper or lower rim, calixarenes are suitable receptors for cations [28-31], anions[32], neutral[33] and chiral [33] molecules. Binding properties of these compounds were extensively studied by UV-Vis spectrometry, NMR, calorimetric, potentiometric and conductometric titrations, chromatographic methods, mass spectrometry, vibrational and luminescence spectroscopy [35]. In organic-calixarene complexes, noncovalent interactions, such as hydrogen bonds, π-hydrogen bonds, hydrophobic interactions, and cation-π and CH-π interactions are the main driving forces allowing stable complexes to form in the liquid and solid states [2, 36].

In this work, the complexation of glycine, L-alanine and L-valine by water soluble calixarene: *p*-sulphonatocalix (4) arene in aqueous solution via UV-Vis spectrophotometric technique has been explored. The formation constants, enthalpies and entropies of complexation have been evaluated. There exist no significant differences between the values of formation constants of amino acid complexes formation with the calixarene under study.

MEASUREMENTS

2.5 ml of p-Sulphonato calix (4) arene solution ($2 \times 10^{-3} - 2.5 \times 10^{-3}$ mol L^{-1}) was titrated at different temperatures with stepwise addition of amino acids solution (1.0×10^{-2} mol L^{-2}), All in water solvent. The UV-Vis spectra of the mixtures undergo small changes at 260-310 nm, but the measured absorbances were sufficient to allow the treatment of the data with the

computer program. All the measurements were carried out at (25± 0.1 to 65 ± 0.1^0 C) using a spectrophotometer (UV-Vis perkin Elmer Lambda 25) scanning spectrophotometer with a Pentium IV computer using 10 mm quartz cells. The system was thermostated at (25± 0.1 to 65 ± 0.1^0 C) by circulating water from an isothermal bath. In all cases the procedure was repeated at last five times and the resulting average values and corresponding deviations from the average are shown in the text and tables.

RESULTS AND DISCUSSIONS

The complex $L_pSC_{4\,q}$ form is characterized by its stoichiometry, *p* and *q*, where L and SC_4 demonstrate each amino acid and p-sulphonato calix (4) arene, respectively. In order to designate the formation constant of complexation, *K*, Eq. 1 is defined,

$$pL + qSC4 \rightleftharpoons L_pSC_{4\,q} \qquad (1)$$

$$K = [L_pSC_{4\,q}] / [L]^p[SC_4]^q$$

Absorbance, *A*, was measured by successive addition of an amino acid solution to the sulphonato calix (4) arene solution, see experimental section. The absorption bands of the sulphonato calix (4) arene decrease upon addition the amino acid solution in all cases. The changes of the absorbance are the result of dilution due to the titration procedure and complex formation, for the extinction coefficient of the complex is different from that of the sulphonato-calix (4) arene. Treatment of the spectrophotometric data (250-350 nm with an interval of 1 nm) obtained during the titrations was conducted with the computer program Squad [37, 38].

Specifying of the formation constant was carried out using the method described previously [30, 31]. All proposed complex species existing in substantial concentrations were checked over a reasonable range of data. As expected, polynuclear complexes were systematically rejected by the computer program. Taking into account a binuclear complex alone or together with the mononuclear one does not improve the goodness of the fit and even leads to the rejection of the model. The ultimately chosen model, formed by LSC_4, resulted in a satisfactory numerical and graphical fitting for all systems. The average values of the formation constants of the 1:1 complex species in divergent wavelengths and at different temperatures are listed in Table 1. The study was performed in aqueous solution without a buffer solution so as to avoid any influence on the formation of the complex.

The interesting curves resulting from the spectrophotometric titration of p-sulphonato-calix (4) arene with glysine, L-alanine and L-valine are shown in Figure 2. The Fig. indicates a sharp break point when the concentration of amino acid to the sulphonato-calix (4) arene ratios reaches unity representing the formation of stable complexe. In this case, the extrapolating of the slopes for the amino acid to sulphonato-calix (4) arene ratio correspond to 1:1 complex stoichiometry in the point of intersections. The dependence of formation constant and thermodynamic parameters (ΔH° and ΔS°) on the host and guest structures provides a tool to elucidate the factors governing the complexation.

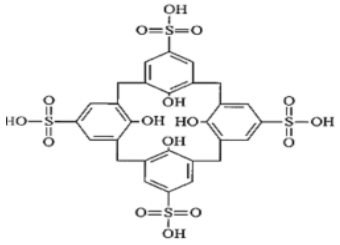

Fig.1. The chemical Structure of *p*-sulphonato-Calix (4) arene.

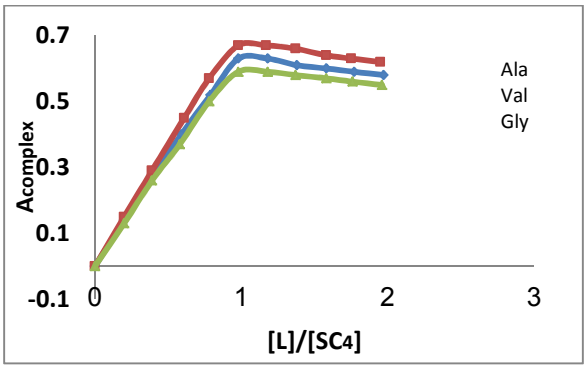

Fig. 2. Spectrophotometric titration plots, $A_{complex}$ versus the mole ratio of the guests to p-sulphonato-calix(4)arene at 25 ± 0.1 °C, 281 nm, and pH = 3.2.

Calixarenes and their derivatives have been known to be able to form non-covalent inclusion complexes with various guest molecules through many interactions, such as the electrostatic interaction, cation–π interactions, hydrogen bonding, van der Waals and hydrophobic interactions [39]. The other literature suggested that, electrostatic interaction was thought to serve a pivotal part in the inclusion process [40]. It is seen from Table 1 that SC4 forms relatively strong complexes with the guest molecules in this work. The host–guest formation constant decreases on the increase of the temperature (from 25 ± 0.1 to 65 ± 0.1 °C) in all cases. This could be for the sake of weekly electrostatic interaction of the guest molecules at high temperature. It can thus be concluded that amino acids are included in the calixarene cavity at 25°C in contrast to 65°C which remains outside the cavity. It is well known that the following species of the amino acids exist in solution at pH=3.2. The guest molecules have their cationic and zwitterionic forms. Hence, favorable interactions between the positively charged amino acid and the negatively charged SC4 are involved at the upper rim of SC4. In effect, in the absence of this particular repulsion the guest at 25°C can penetrate more deeply into the calixarene cavity and so give stronger complexes. The values of ΔH° and ΔS° determined from the slope and the intercept of the straight line of $\log_{10}K$ versus 1/T, and are listed in Table 2. These findings suggest that the binding of SC4 by the guest molecule in water is enthalpy-driven. The results obtained are compared with those drawn in the scientific literatures through other techniques, in this particular case through calorimetric titration, NMR and HPLC techniques. Likewise, no significant differences are noted among the values of the formation constants for the studied complexes.

One can see from Table 1 that *p*-sulphonatocalix (4) arene forms relatively strong complexes with the amino acids studied in present work. The amino acid, glycine, containing no side chain presents a low value of stability constant, log K = 2.78 by means of UV-Vis spectrophotometric titration comparing with the amino acids under study. We reported also a large value of association constant for the complexation of L-Ala (logK= 2 .84) with *p*-sulphonatocalix (4) arene. Same as L-Ala, the L-Val does reveal the high value for formation constant (log K = 2.82). In the conditions of this work, the favorable interactions between the positively charged amino acid and the negatively charged sulphonatocalix (4) arene are involved. One can also see from Table 1 that by UV-Vis spectrophotometric titration a large value of formation constant has been obtained for those amino acids than ^{1}HNMR and HPLC techniques.

Table 1. Average values of $\log_{10} K$ for p-sulphonato-calix (4) arene-gly, ala, and val at different Temperatures together with formation constants of some other amino acids with SC_4 reported in the literature for comparison

Guest	Temperature/°C	$\log_{10} K$	Referenc
Gly	25	2.78 ± 0.03	This work
Gly	35	2.66 ± 0.06	This work
Gly	45	2.52 ± 0.04	This work
Gly	55	2.40 ± 0.05	This work
Gly	65	2.32 ± 0.07	This work
L-Ala	25	2.84 ± 0.06	This work
L-Ala	35	2.75 ± 0.05	This work
L-Ala	45	2.59 ± 0.04	This work
L-Ala	55	2.39 ± 0.03	This work
L-Ala	65	2.32 ± 0.08	This work
L-Val	25	2.82 ± 0.05	This work
L-Val	35	2.73 ± 0.04	This work
L-Val	45	2.65 ± 0.06	This work
L-Val	55	2.42 ± 0.03	This work
L-Val	65	2.38 ± 0.06	This work
Gly		2.74	[41]
		2.26	[27]
L-Ala		3.22	[41]
		2.82	[27]
L-Val		3.20	[41]
		1.20	[17]
L-Leu		3.08	[41]
		1.70	[17]
L-Phe		3.14	[41]
		1.80	[17]
		2.77	[27]
		3.13	[41]
L-Trp		1.40	[17]
		3.18	[27]

By comparing the formation constants obtained by UV-Vis spectrophotometric titration with those determined by RP-HPLC [27], NMR [17] calorimetric titration [41] and microcalorimetry [26], the results are quite different. Direct comparison is difficult owing to the differences in conditions such as pH, solvent polarities and experimental methodology (microcalorimetry, calorimetric titration, RP-HPLC, NMR).

Table 2. The values of the thermodynamic parameters ΔH° and $T\Delta S^{\circ}$ for the complexes of some amino acids with *p*–sulphonatocalix (4) arenes in aqueous solution at 25° C

Amino acids	$-\Delta H°$ (kJ/mol)	$-\Delta G°$ (kJ/mol)	$-T\Delta S°$ (kJ/mol)	References
Gly	42.32± 0. 5	15.86± 0.6	27.19± 0. 4	This work
	38.3		22.7	[41]
L-Ala	47.96± 0. 8	16.21± 0.5	32.49± 0. 6	This work
	30.4		12.0	[41]
L-Val	41.23± 0. 5	16.09± 0.8	25.73± 0. 8	This work
	46.7		28.5	[41]
L-Leu	51.7		34.2	[41]
L-Phe	36.0		18.1	[41]
L-Trp	33.4		15.6	[41]
L-Thr	28.9		10.7	[41]
L-Lys	20.4		-1.8	[41]

The values of ΔH obviously arise from electrostatic interactions between the protonated amino group of the amino acids and the sulphonato groups of the calixarenes. The complex formation is favored by enthalpic contributions and disfavored by entropic contributions. This effect is compensated by the reaction entropy. With the increase of the molecular size of the amino acids, the values of the reaction entropy decrease. One of the most momentous parameters betraying the nature of the intermolecular host– guest interaction is the enthalpy change of a reaction. The enthalpy change evolves from several factors comprising electrostatic interactions, hydrogen bonding, and van der Waals forces. The entropy change also encompasses several factors. In an entropy-driven reaction, the entropy gain is possibly due to the loss of the arrangement of water molecules originally surrounding the organic molecules in a highly ordered state. Nevertheless, in an enthalpy-driven reaction, the entropy loss is possibly in view of the freezing of motional freedom of the guest molecule as a result of association with the host species.

Table 2 denotes that the binding of SC_4 by ala is more exothermic than val and gly, and the entropy change decreases from ala to val, indicating more stable complexes between SC_4 and the smaller guest molecule, in accordance with the previous discussion. Further, the ΔG° of complexations between SC_4 and gly, ala or val are not very different from each other, Table 2. This stands out that the factors governing the complexation of the guests are feasibly the same.

In Figure 3, we have plotted TΔS° against ΔH° for complexation of guest molecules (Glycine, L-Alanine and L-Valine) with the host molecule SC_4. A roughly linear relationship is observed

between the values obtained in this work and those reported in the literature employing manifold methods to pinpoint the formation constants and the thermodynamics parameters. Such a linear relationship bodes that the change in $T\Delta S^{\circ}$ is commensurate to the corresponding change in ΔH° [7,42]. For justification of results, it is not unreasonable to think that, as the host–guest interactions become stronger, the degrees of freedom of the resulting complex will be significantly reduced by virtue of the increased rigidity of the system. As a result, as the host–guest interactions become weaker, the corresponding enthalpic lack will be partially compensated by a simultaneous entropic gain in the wake of the greater degrees of freedom of the resulting complex.

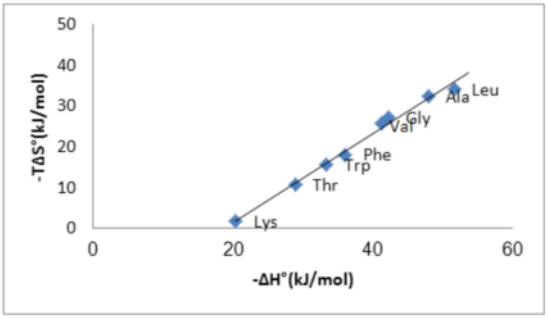

Fig. 3. The plot of $T\Delta S^{\circ}$ versus ΔH° for the binding of p-sulphonato-calix (4)arene with some guest molecules.

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