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INCLUSION COMPLEXES BETWEEN β-CYCLODEXTRIN AND BIRADICALS WITH A RIGID AROMATIC SKELET

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The interaction of β-cyclodextrin with three biradicals composed of two TEMPOs linked by aromatic skelets (benzyl, dibenzofuran and diphenyl) was subjected to an EPR study at room temperature. Binding constants for inclusion complexes formed were evaluated considering both 1:1 and 1:2 stoechiometry and the variation of the rapports between heights of the central line and the one at high field in EPR spectra with concentration of cyclodextrin.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides with α-D-glucose units connected through α (1-4) linkages, characterized by a toroidal shape and a relatively hydrophobic cavity. Therefore, cyclodextrins can form stable inclusion complexes of the host-guest type with various molecules and ions. Among them, β-cyclodextrin (β-CD), with seven glucopiranose units, is the most widespread. Geometrical parameters of β-CD (internal diameters 0.78 nm and external one 1.53 nm, depth 0.78 nm) determine the capacity to form more stable compounds with organic molecules comparatively with those of α-CD.[1-3] Cyclodextrines were used as cyclic components for supramolecular structures[4] with various applications in drug delivery, catalysis, or separations.

There are many physicochemical methods for determination of the stoechiometry and stability constants for complexes of CDs with guests: microcalorimetry,[5] NMR spectroscopy,[6] surface tension measurements[7] or most widely used UV-Vis and fluorescence spectroscopy.[8]

EPR spectroscopy is suitable for studying supramolecular interactions as this technique is sensitive to local structure in the vicinity of spin labels and molecular dynamics on the nanosecond timescale. EPR can be used if either the host or the guest molecules are paramagnetic.

CDs complexes with different types of paramagnetic compounds (stable free radicals, as TEMPO derivatives,[9-12] or short lived organic radicals[13,14]) were studied by EPR spectroscopy during the last three decade. Some spin-labelled cyclodextrins (SL-CDs) were synthesized considering the possibility to apply EPR spectroscopy in studying supramolecular complexes of CDs with different diamagnetic compounds. Paramagnetic moieties covalently attached to cyclodextrin form intramolecular complexes which affect the guest properties of naturally and therefore SL-CDs are suitable as reporters in studying large supramolecular assemblies of CDs.[15,16]

There are some EPR studies about interaction of CDs with flexible biradicals[17,18] or formation of paramagnetic rotaxane obtained by reaction of sebacoyl chloride with amino-TEMPO with α-CD trapped between paramagnetic moieties.[19]

In this paper are presented the results regarding interaction of CDs with less flexible biradicals (paramagnetic moieties are linked by aromatic skelets – Fig. 1) obtained by EPR measurements. The binding constants between biradicals **1-3** were evaluated by analyzing the changes of their EPR paramaters spectra with concentration of β-CD.

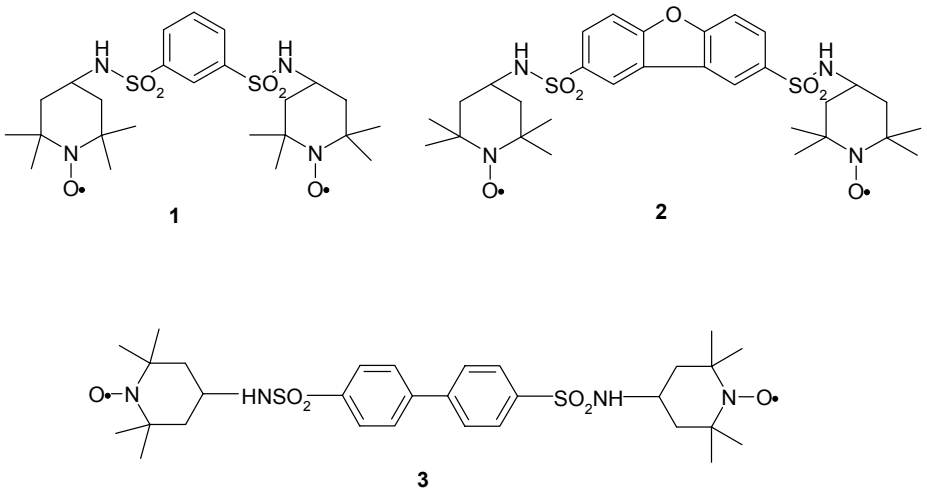

Fig. 1 – Chemical structures of biradicals used in this study.

EXPERIMENTAL

α- and β-CDs were purchased from Fluka. Benzen-1,3disulfonyl chloride, dibenzofuran-2,8-disulfonyl chloride and biphenyl-4,4'-disulfonyl chloride, 4-Amino-TEMPO were purchased from Aldrich. The solvents were supplied by Aldrich or Chimopar. Synthesis of biradicals: **1**-**3** was carry out in each case by reaction of corresponding disulfonyl chloride with 4-amino-TEMPO and was described previously.[20]

The EPR spectra of **1**-**3** were recorded in water (in the absence or the presence of α- or β-CD at concentrations up to 10^{-2} M) and DCM solutions at room temperature on a Jeol Jes FA 100 spectrometer. The general settings used were the following: center field 3356 G, sweep field 80 G, frequency 100 kHz, gain in the range 100- 200 sweep time 480 s, time constant 0.3 s, modulation width 1 G, microwave power 1 mW.

Concentrations of CDs in water were: 10^{-4}, 3×10^{-4}, 6×10^{-4}, 10^{-3}, 3×10^{-3}, 6×10^{-3}, 10^{-2} M.

For the EPR measurements, 2 μl of a biradical solution in ethanol 10^{-2} M were put in a sample tube and the solvent was evaporated. Then 200 μl of water or CD solution was added. The solution was taken in a capillary tube.

RESULTS AND DISCUSSION

EPR spectra of mono nitroxide type radicals show three lines separated by hyperfine splitting constant (a_N) due to interaction between unpaired electron and ^{14}N nucleus. The a_N value is sensitive to the solvent polarity. In the case of biradicals, due to spin-spin interactions between unpaired electrons (characterized by exchange coupling constant, J) is possible to observe additional lines in EPR spectra in liquid solutions. Exchange interactions are strongly depended on the solvent polarity, distance between paramagnetic moieties and molecular flexibility, or interactions with other species in solution.[21] In Fig. 2 are presented EPR spectra of radicals **1**-**3** in dichloromethane solution (3×10^{-4} M) recorded at room temperature. All spectra presented in Fig. 2 show additional lines (in case of **1** and **2** two lines and in case of **3** four lines) comparatively with a monoradical spectra because there is a fast exchange interaction and J is much greater than a_N. In case of biradical **3**, the EPR spectrum suggests that the molecular conformation may have a strong effect on the exchange interactions. The aromatic rings present in the structure of **3** can rotate around central C-C bond, generating different conformations. The spin-spin interaction between unpaired electrons seems to be sensitive in case of biradical **3** to the conformations adopted, so different J values characterize them.

There are some models which explain spin exchange in nitroxide biradicals.[22] The bridges between paramagnetic moieties in compounds **1** – **3** are not flexible, being an aromatic skelet, and the spin spin interactions by collisions are less possible (especially in case of **2** and **3**). However, from EPR spectra of these biradicals recorded in DCM (Fig. 2) and in water (Figs. 3-5) it can be observed that intensities of intermediary lines are high. The mechanism of exchange interactions might be in these situations through the core of sigma bonds and possible even the aromatic π-bonds have a contribution.

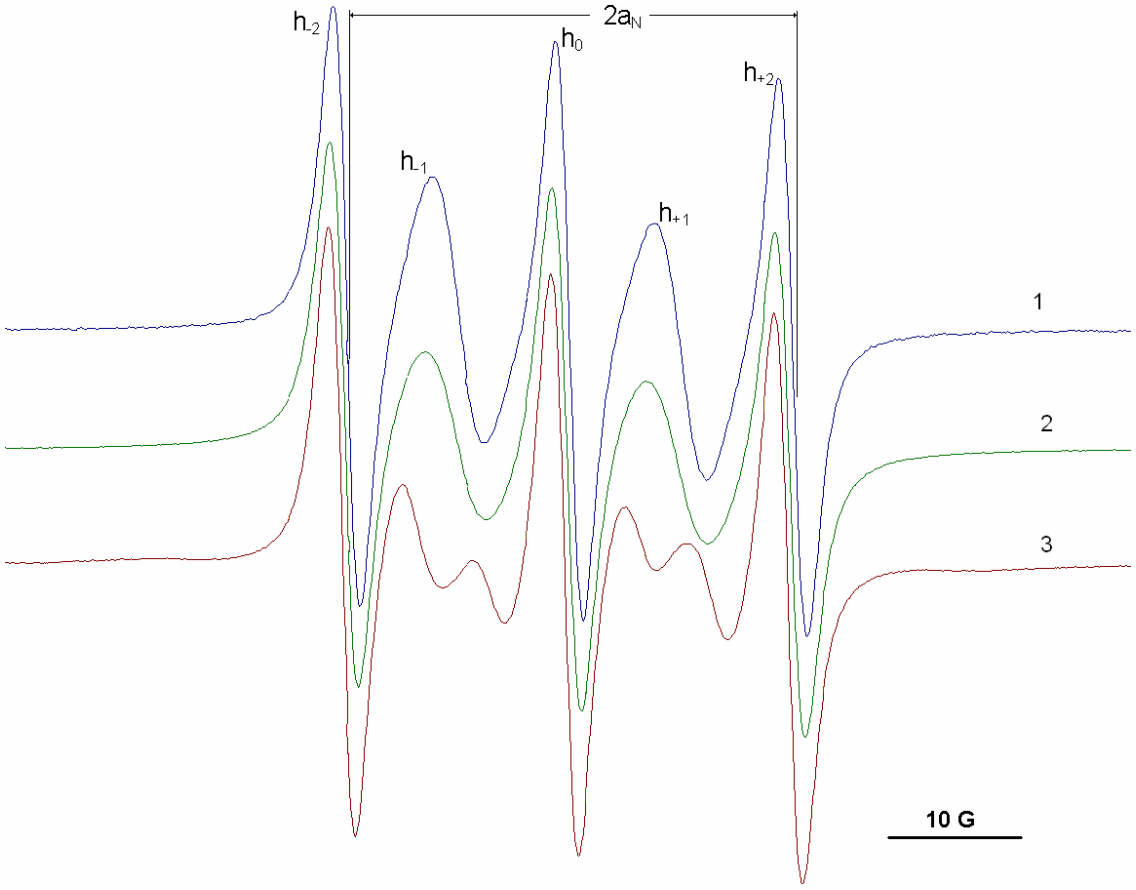

Fig. 2 – EPR spectra of radicals **1-3** in DCM (concentration of diradical was $5x10^{-4}$ M) .

EPR spectra of biradicals **1-3** (Figs. 3-5) in water solution shown five lines, but exchange interactions are weaker then in DCM because water is more polar solvent comparatively with DCM. Table 1 shows the rapports between heights of central line (h_0) and heights of lines due to exchange interactions (h_{-1} or h_{+1} – Fig. 2) and a_N values for EPR spectra recorded in water and in DCM.

The distance between TEMPO units increases from **1** to **3** and therefore the rapport h_0/h_{+1} decrease from **1** to **3** in both solvents. Meantime, the hyperfine splitting values are higher in water then in DCM. It can be noticed that in water solution the tumbling motion of radicals is slowly, as the heights of the last line in EPR spectra is considerably smaller than of central line. The presence of CDs leads to a slower motion of radicals as concentration increases which proves formation of inclusion complexes. On the same time, the formation of inclusion complexes leads to the decreasing of spin-spin exchange interactions. However, in the presence of α-CD the changes in EPR spectra were observable at concentration 10^{-1} M, but in this case the viscosity effect is taken into account.

The polarity of cyclodextrin cavity is lower then water polarity and formation of inclusion complexes with paramagnetic moieties inside determine smaller a_N values, as CD concentration increases. At 10^{-2} M concentration of β-CD the a_N values for biradicals spectra are: 16.85 G (**1**), 16.88 G (**2**) and 16.87 G (**3**).

By adding adamantine amine (10^{-1} M) as a competitive guest to the solutions which contain biradicals **1-3** and β-CD 10^{-2} M, the EPR spectra became similar with those in water solution proving that biradicals were released from the complex. The adamantine derivative was choosing considering the strong binding constants which characterize complexes between β-CD and adamantine derivatives.[23]

β-CDs inclusion complexes formed in solution with biradicals 1-3 can be characterised by different stoechiometries, as a function of CD concentration. Binding constants were evaluated for biradical / β-CD complexes from variation of the rapports h_{+2}/h_0 (see Fig. 2) with β-CD concentration, assuming both 1:1 and 1:2 stoechiometry (suggested in Fig. 6).

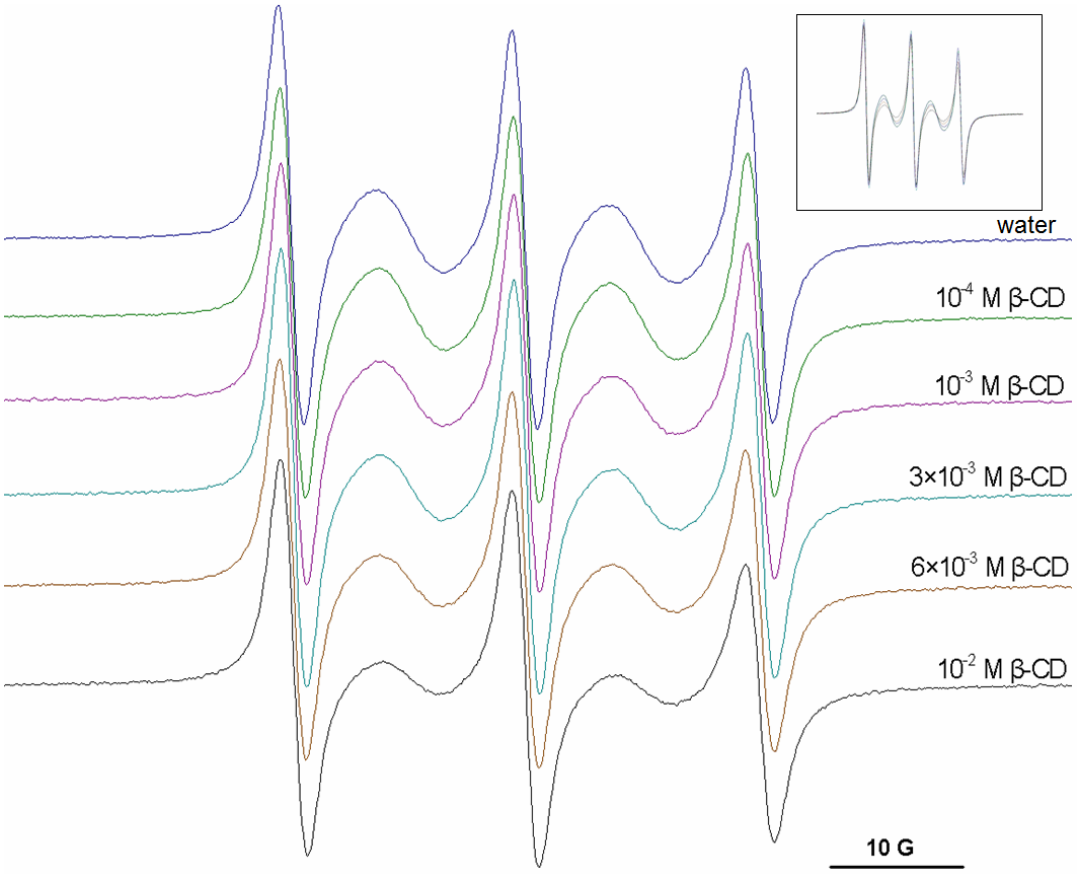

Fig. 3 – EPR spectra of **1** in pure water and solution of β-CD, (in the icon superposed spectra).

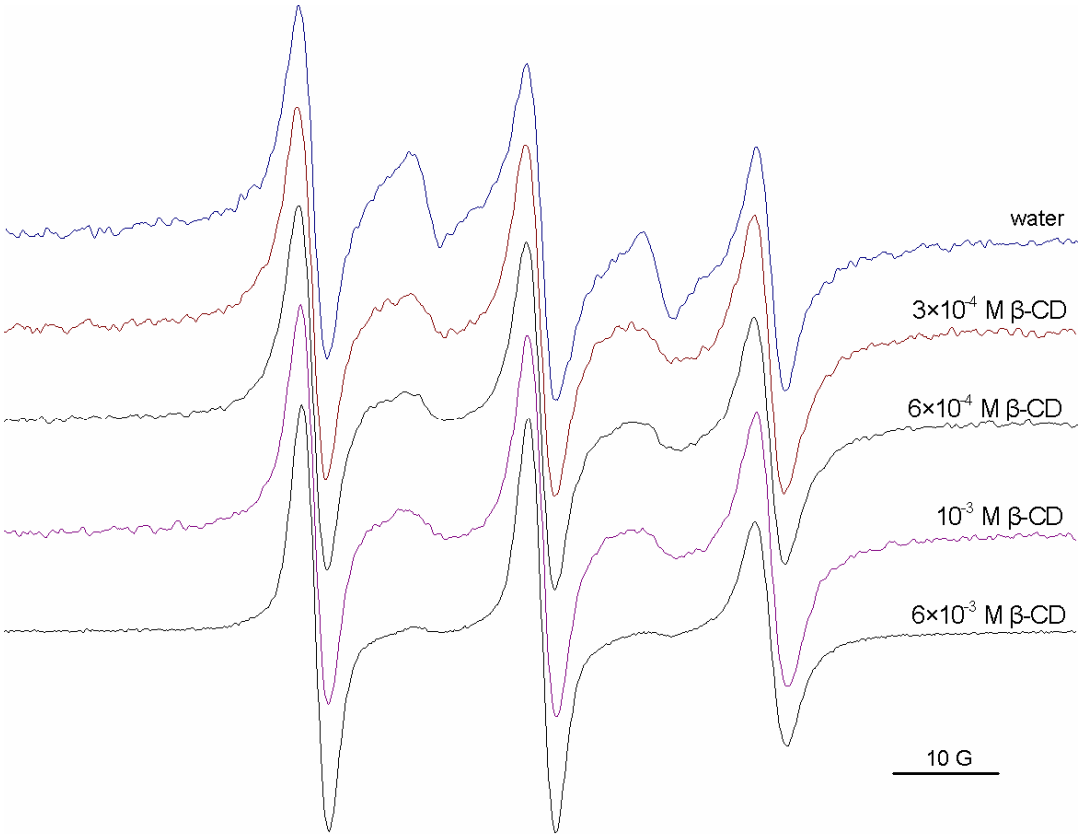

Fig. 4 – EPR spectra of **2** in pure water and in β-CD solution.

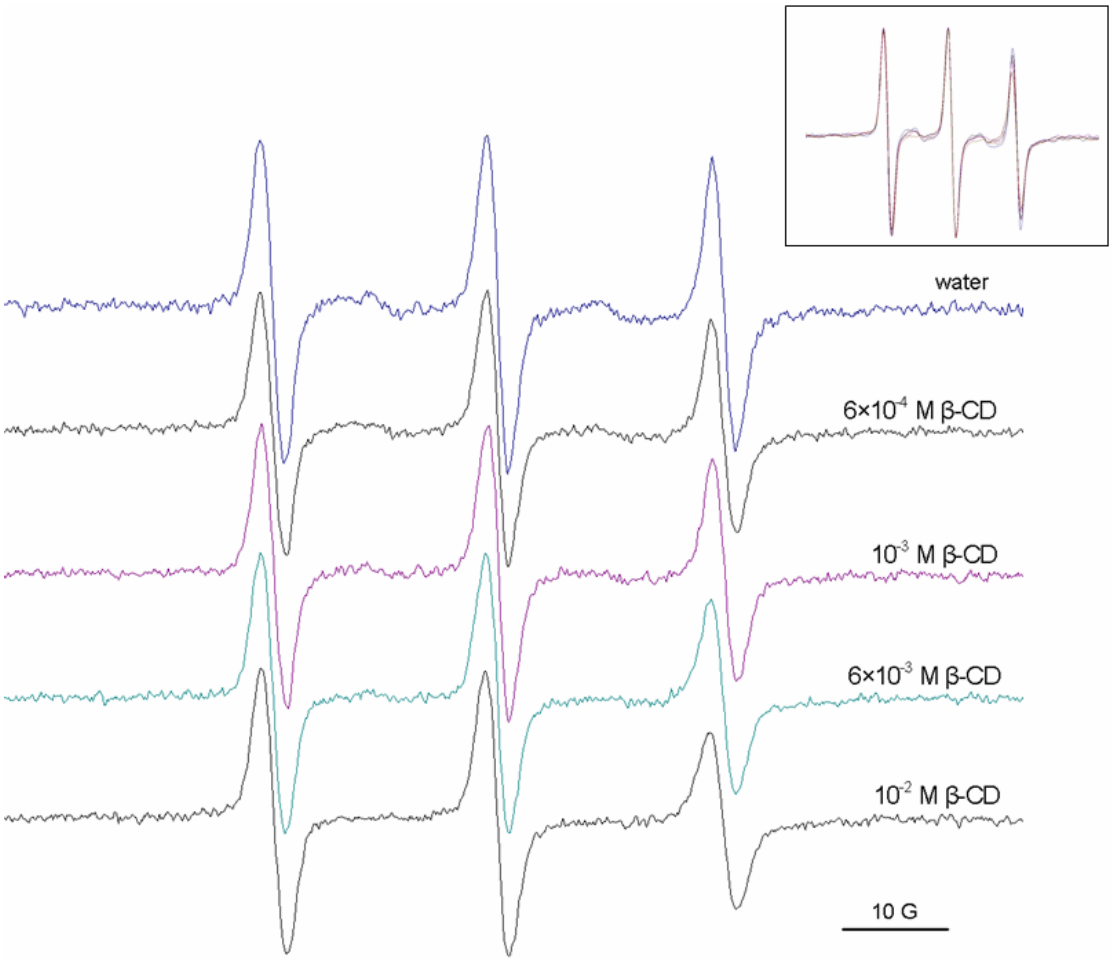

Fig. 5 – EPR spectra of **3** in pure water and in solution of β-CD, (in the icon superposed spectra).

Table 1

EPR parameters of biradicals **1-3** in water and DCM

Compound	h_0/h_{+1} (in DCM)	h_0/h_{+1} (in water)	a_N in DCM (G)	a_N in water (G)
1	0.44	0.19	15.65	16.98
2	0.31	0.26	15.64	16.99
3	0.22	0.05	15.68	16.99

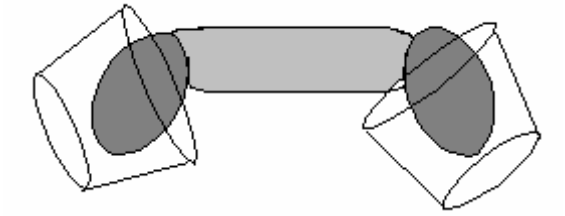

Fig. 6 – Schematic representation of biradical/β-CD inclusion complex with 1:2 stoechiometry (dark grey – paramagnetic moiety, light grey aromatic linkage).

At low concentration of β-CD, the stoechiometry 1:1 stoechiometry is more probably, while at higher concentrations of β-CD the 1:2 stoechiometry can be taken in account. A linear relationship between h_{+2}/h_0 and the concentration of the complex in solution was assumed (eq. 1).

$$\frac{h_{+2}}{h_0} = a[R] + b[RCD] \quad (1)$$

where: a and b are constants, [R] concentration of free biradical, [RCD] concentration of inclusion complex. In case of 1:1 stoechiometry, concentration of free biradical in solution is described by equation 2:

$$[R] = \frac{(K[R_0] - K[b-CD_0] - 1) + \sqrt{(K[R_0] - K[b-CD_0] - 1)^2 + 4K[R_0]}}{2K} \quad (2)$$

Where $[R_0]$ is initial concentration of biradical, $[b\text{-}CD_0]$ is the initial concentration for each experiment, K is equilibrium constant.

Values a, b and K were estimated after the fitting was closer to the experimental curves. In case of 1:2 stoechiometry simulated curves were determined by finding appropriate values for a, b and K corresponding to minimal deviation from experimental curves. Equations 3 and 4 were taken into account in the case of 1:2 stoechiometry.

$$[R] = \frac{\frac{h_{+2}}{h_0} - b[R_0]}{a-b} \quad (3)$$

$$[b-CD_0] = \frac{\frac{4K(\frac{h_{+2}}{h_0} - b[R_0])}{(a-b)[R_0]} - 4\frac{\frac{h_{+2}}{h_0} - b[R_0]}{(a-b)^2 K} + \sqrt{4K\frac{\frac{h_{+2}}{h_0} - b[R_0]}{a-b}[R_0] - 4K\frac{\frac{h_{+2}}{h_0} - b[R_0]}{(a-b)^2}}}{\frac{2K(a-b)}{\frac{h_{+2}}{h_0} - b[R_0]}} \quad (4)$$

Fig. 7 presents the simulated and experimental curves obtained in case of biradicals 1-3 for 1:1 and 1:2 stoechiometries suggesting that the stoechiometry of inclusion complexes varies with concentration of β-CD and with the structure of each biradical.

In case of 1:1 stoechiometry values of binding constant are 3.3×10^2, 1.5×10^3, and 1.6×10^3 $l\times mol^{-1}$. For a 1:2 stoechiometry the values of binding constant are: 8×10^5 $l^2\times mol^{-4}$ (**1**), 1.3×10^6 $l^2\times mol^{-2}$ (**2**) and 7.5×10^6 $l^2\times mol^{-2}$ (**3**). These values of binding constants are not in contradiction with the data reported in literature[12] for interaction of TEMPO with β-CD (about 10^3 $l\times mol^{-1}$ order of magnitude for 1:1 complex). In case of biradical **1** binding constant is considerably lower comparatively with biradicals **2** and **3** and this fact can be explained by closer position of TEMPO moieties.

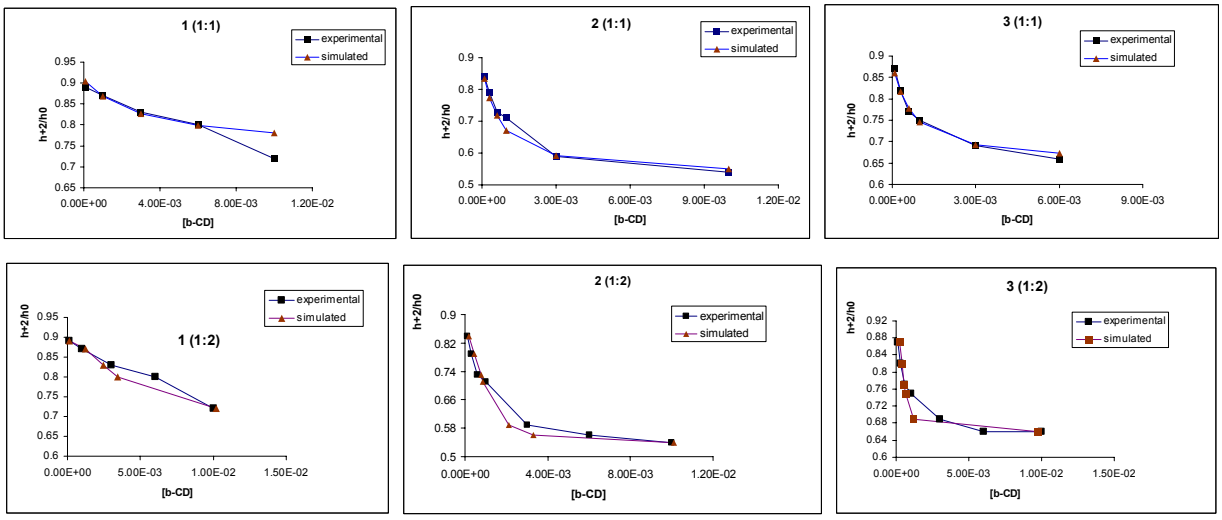

Fig. 7 – Experimental h_{+2}/h_0 values and fitted curves as a function of [β-CD] for inclusion complexes in case of 1:1 and 1:2 stoechiometry.

CONCLUSION

In conclusion, the interaction of β-CD with compounds bearing two paramagnetic moieties linked by a rigid aromatic skelet was evidenced by EPR spectroscopy. The EPR spectra of biradicals revealed that spin-spin interactions between unpaired electrons are sensitive to the presence of CD molecules and by analizing the changes of parameters spectra is possible to evaluate the binding constants.

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